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Nanocurcumin: A Chemistry-Oriented Review of Nanoformulation Strategies and Therapeutic Application Against Sleep Deprivation-Induced Pathologies

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ABSTRACT: Sleep deprivation disrupts both rapid eye movement (REM) and non-rapid eye movement (NREM) sleep, contributing to neurological, metabolic, and immune dysfunction through oxidative stress, chronic inflammation, and neuronal damage. Although curcumin, the principal polyphenolic compound of Curcuma longa, possesses well-established antioxidant, anti-inflammatory, and neuroprotective properties, its therapeutic application is restricted by poor aqueous solubility, low bioavailability, rapid metabolism, and limited blood brain barrier penetration. Advances in nanotechnology have enabled the development of nanocurcumin formulations that significantly improve the physicochemical stability, solubility, bioavailability, controlled release, and targeted delivery of curcumin. This review provides a chemistry-oriented overview of nanocurcumin as a promising therapeutic strategy for sleep deprivation-induced pathologies. Particular emphasis is placed on formulation approaches, nanoparticle synthesis, physicochemical characterization, and the relationship between nanomaterial properties and biological performance. The molecular mechanisms underlying nanocurcumin-mediated neuroprotection, including modulation of oxidative stress, inflammatory signaling, apoptosis, mitochondrial dysfunction, and immune responses, are critically discussed. Current evidence supporting its therapeutic potential in neurodegenerative diseases, glioma, neuropathic pain, cognitive impairment, and immune dysfunction associated with sleep deprivation is also summarized. Furthermore,

challenges related to formulation reproducibility, long-term stability, biosafety, large-scale manufacturing, regulatory approval, and clinical translation are highlighted. By integrating natural product chemistry, nanotechnology, and targeted drug delivery, this review demonstrates the potential of nanocurcumin as an innovative nanotherapeutic and identifies future directions for the development of effective interventions against sleep deprivation-associated disorders.

1. INTRODUCTION

The plants have always played a significant role in medicine and human health. Among them, herbal plants have garnered global interest due to their natural therapeutic properties. One such plant is turmeric, which belongs to the ginger family (Zingiberaceae) [1,2]. The primary active compound extracted from its rhizome is curcumin, a fat-soluble polyphenolic pigment known for its vibrant yellow colour [3]. Curcumin has been extensively studied and has demonstrated numerous health benefits, including potent antioxidant, anti-inflammatory, and anti-apoptotic effects. These properties contribute to its ability to influence multiple molecular pathways, thereby protecting various body organs and systems [4]. Historically, turmeric holds a revered place in traditional medicine systems, especially Ayurveda, where it is recognized for its healing properties and spiritual significance in Hinduism. Curcumin, the bioactive compound in turmeric, has shown a wide range of biological actions, including growth-promoting, antiparasitic, hepatoprotective, bactericidal, and antioxidant effects [5]. For thousands of years, it has been used in Indian and Chinese traditional medicine to treat wounds and a variety of ailments, showcasing its therapeutic versatility. In modern applications, curcumin is commonly used not only as a culinary spice but also as a natural food colorant, especially in Southeast Asian cuisines [6]. Beyond its culinary uses, curcumin continues to draw significant scientific interest for its potential in treating a broad spectrum of conditions. Studies have highlighted its efficacy in combating cardiovascular diseases, liver disorders, obesity, cancer, inflammatory diseases, and even aspects of aging [3]. **Figure 1** illustrates the diverse applications of curcumin, emphasizing its promise as a natural, multifunctional agent in both preventive and therapeutic contexts.

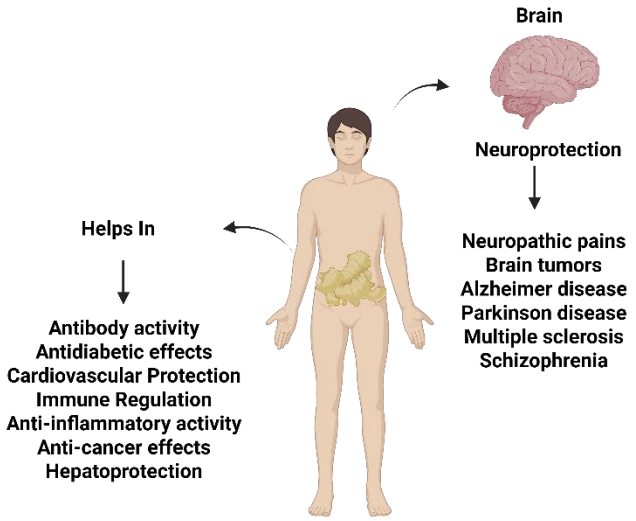

Figure 1: Application of curcumin in the treatment of different illnesses.

Sleep is a vital physiological process essential for the survival and proper functioning of all living organisms. It is broadly categorized into two types: Rapid Eye Movement (REM) sleep and Non-Rapid Eye Movement (NREM) sleep [7]. Both stages play crucial roles in maintaining behavioural, mental, and physiological balance. Sleep deprivation has been linked to a variety of acute and chronic health conditions, including premature death, increased brain excitability, arthritis, Alzheimer's disease, and Parkinson's disease. In both humans and animals, lack of sleep is associated with adverse effects such as irritability, anxiety,

confusion, and other cognitive disturbances [8]. Excessive daytime sleepiness may lead to narcolepsy, characterized by abnormal REM sleep, hypnagogic hallucinations, and sleep paralysis. These symptoms disrupt normal sleep-wake patterns and are associated with altered levels of hypocretin, a key neuropeptide involved in sleep regulation [9]. Additionally, narcolepsy is often accompanied by increased levels of proinflammatory cytokines, such as TNF-α, IL-1, and IL-6, during the day [10]. There is evidence linking elevated body mass index (BMI) and increased levels of inflammatory cytokines to narcoleptic symptoms. TNF-α, in particular, plays a role in both sleep regulation and inflammation. IL-6, which is known to increase fatigue and sleepiness, is also associated with metabolic disturbances related to hypocretin deficiency and may contribute to obesity [11]. A study by Hinge-Selch (1998) measured cytokine levels of IL-1β, IL-1ra, IL-2, IL-6, TNF-α, and TNF-β in plasma, as well as in nitrogen-stimulated monocytes and lymphocytes from narcoleptics, Hemocyte Cytotoxic Activity (HCA) patients, and healthy controls. It was found that only IL-6 was significantly secreted, with no evidence of T-cell abnormalities. Animal studies further support the role of cytokines in sleep modulation [12]. Proinflammatory cytokines, including IL-1 and TNF-α, are recognized for their role in facilitating NREM sleep in rats. IL-6, although frequently linked to disease, has also been detected during NREM sleep in both humans and animals [13]. It appears that during stages 1 and 2 of REM sleep, IL-6 secretion occurs, along with increased levels of TNF-α and human growth hormone (hGH). In narcoleptics, there may be alterations in hGH secretion patterns. REM sleep is also associated with neurogenesis and significant changes in the neurochemical and hormonal environment [14]. These changes include increased plasma cortisol levels, which contribute to the stress response observed during REM sleep. Despite the growing body of research, the impact of REM sleep on different organs remains poorly understood. One notable study in mice investigated the effects of REM sleep deprivation on the liver and examined the potential therapeutic benefits of curcumin [15]. The results were promising, suggesting that curcumin may mitigate some of the adverse effects of REM sleep loss. This opens the door to further exploration into how REM sleep affects other organs and whether curcumin or similar compounds might offer protective benefits, leading to the development of new therapeutic strategies.

Despite the remarkable pharmacological activities of curcumin, its therapeutic translation remains limited by poor aqueous solubility, rapid metabolism, low systemic bioavailability, and inadequate penetration across the blood-brain barrier. Nanotechnology-based formulations have emerged as promising strategies to overcome these limitations by improving stability, targeted delivery, controlled release, and tissue distribution. Therefore, this review focuses on the chemistry of nanocurcumin formulations, their physicochemical characteristics, molecular mechanisms of neuroprotection, and their therapeutic potential against sleep deprivation-induced disorders.

MECHANISMS OF SLEEP DEPRIVATION-INDUCED DAMAGE

Sleep is a fundamental physiological process that supports metabolic balance, cognitive integrity, immune function, and emotional regulation. Disruption of sleep, particularly prolonged deprivation of both REM and NREM phases, induces multifactorial damage to neural and systemic physiology. The mechanisms through which sleep deprivation exerts harmful effects are complex and interrelated, involving oxidative stress, inflammation, impaired neurogenesis, hormonal imbalance, and immune dysregulation. One of the primary consequences of sleep deprivation is oxidative stress. Sleep is known to regulate redox homeostasis; its absence leads to increased production of reactive oxygen species (ROS) and a reduction in antioxidant enzyme activity, such as superoxide dismutase (SOD) and catalase (CAT) [16]. ROS accumulation damages cellular lipids, proteins, and DNA, particularly in the brain, where antioxidant defenses are comparatively limited [17]. This oxidative insult has been implicated in the pathogenesis of neurodegenerative diseases, including Alzheimer's and Parkinson's disease. Neuroinflammation is another key mechanism activated by sleep deprivation. Evidence shows that sleep loss results in the activation of microglia and astrocytes, leading to elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β) [18]. Chronic neuroinflammation disrupts neuronal signaling and contributes to cognitive dysfunction and mood disorders. Moreover, cytokine-induced damage can compromise the integrity of the blood-brain barrier, further exacerbating neuronal vulnerability [19]. Additionally, sleep facilitates the clearance of neurotoxic waste through the glymphatic system, a glia-dependent pathway for cerebrospinal fluid (CSF) exchange. During sleep, especially NREM phases, CSF flow increases, allowing efficient clearance of metabolites like β-amyloid and tau proteins. Sleep deprivation impairs this clearance mechanism, leading to the accumulation of these proteins, which are key contributors to neurodegenerative pathology [20]. Hormonal dysregulation is a systemic effect of sleep deprivation, characterized by elevated cortisol levels, reduced melatonin secretion, and altered insulin sensitivity [21]. These hormonal changes impair glucose metabolism, contribute to systemic inflammation, and may disrupt circadian regulation. Melatonin, which also has antioxidant and neuroprotective roles, becomes insufficient under conditions of sleep loss, diminishing its protective capacity [22].

Furthermore, sleep deprivation impairs immune function by reducing the activity of natural killer (NK) cells, inhibiting lymphocyte proliferation, and altering cytokine profiles [23]. This immunosuppression increases vulnerability to infections, slows wound healing, and may contribute to chronic inflammatory diseases. Studies have also linked poor sleep with autoimmune flare-ups and reduced vaccine efficacy [24]. On a cellular level, mitochondrial dysfunction plays a critical role. Sleep deprivation reduces mitochondrial respiration efficiency and increases mitochondrial ROS production, compromising ATP synthesis and cellular energy status. This dysfunction particularly affects neurons, which are highly dependent on mitochondrial integrity for synaptic transmission and plasticity [25]. In summary, sleep deprivation activates a cascade of detrimental processes that affect the brain and peripheral organs. Understanding these mechanisms is essential for developing targeted interventions, including emerging therapeutics like nanocurcumin, which may mitigate some of these pathological effects through antioxidant and anti-inflammatory mechanisms.

Nanotechnology strategies for curcumin delivery

Curcumin, the primary bioactive constituent of Curcuma longa (turmeric), is well-established for its extensive pharmacological properties, encompassing anti-inflammatory, antioxidant, anticancer, neuroprotective, and immunomodulatory actions [26]. Despite these promising properties, curcumin's clinical utility has been severely hampered by its poor bioavailability, resulting from low aqueous solubility, rapid metabolism, and systemic elimination [27]. Conventional curcumin is poorly absorbed in the gastrointestinal tract, extensively metabolized in the liver, and excreted rapidly, leading to low plasma and tissue concentrations [28]. To overcome these limitations, nanotechnology-based delivery systems have emerged as transformative tools in enhancing the therapeutic potential of curcumin. Nanocurcumin, a nano formulation of curcumin, encapsulates curcumin within nanocarriers such as liposomes, polymeric nanoparticles, micelles, and solid lipid nanoparticles. These carriers improve the solubility, stability, and cellular uptake of curcumin while protecting it from premature degradation [29]. Several studies have confirmed that nanocurcumin exhibits significantly enhanced bioavailability and biological activity compared to its free form. For instance, Shaikh et al. demonstrated that nanocurcumin increased systemic availability nearly nine-fold in animal models compared to free curcumin [30]. Furthermore, nanocurcumin can cross the blood-brain barrier (BBB) more efficiently, which is crucial in treating neurological disorders such as Alzheimer's disease, glioma, and sleep deprivation-induced neurodegeneration [31]. Nanocurcumin's therapeutic efficacy is due not only to improved pharmacokinetics but also to its increased ability to influence molecular pathways implicated in oxidative stress, inflammation, and apoptosis. It suppresses NF-κB, COX-2, and pro-inflammatory cytokines including TNF-α and IL-6, while increasing antioxidant enzymes like HO-1 and glutathione peroxidase [32]. This makes nanocurcumin especially effective in mitigating pathologies associated with chronic inflammation and oxidative damage. Moreover, nanocurcumin's immunomodulatory effects are of particular relevance in conditions such as sleep deprivation, which is known to impair immune responses. By modulating T-cell proliferation, macrophage activity, and cytokine secretion, nanocurcumin supports immune homeostasis in compromised states [33]. Recent preclinical studies have also demonstrated nanocurcumin's neuroprotective potential. In rodent models of cognitive impairment and neuroinflammation, nanocurcumin administration improved memory performance, reduced oxidative damage, and preserved neuronal integrity [34]. These findings highlight nanocurcumin as a promising candidate for addressing sleep-related cognitive decline and neuroinflammatory disorders. In conclusion, nanocurcumin represents a therapeutic breakthrough in natural product-based medicine. By addressing the bioavailability limitations of native curcumin and enhancing its systemic and central nervous system delivery, nanocurcumin opens new avenues for treating a wide range of conditions, including those exacerbated by sleep deprivation. Continued research into optimized formulations, long-term safety, and human clinical trials will be essential for translating these benefits into mainstream medical practice.

Mechanisms of Action- section to explain how nanocurcumin counteracts sleep deprivation

Nanocurcumin, the nano-encapsulated form of curcumin, holds considerable promise in mitigating the detrimental effects of sleep deprivation. Its enhanced bioavailability, improved tissue targeting, and multifunctional molecular activity make it a particularly effective therapeutic agent. The mechanisms by which nanocurcumin exerts its neuroprotective and systemic benefits in the context of sleep deprivation include its ability to cross the blood-brain barrier (BBB), inhibit the NF-κB inflammatory pathway, and modulate oxidative stress and immune responses. One of the major limitations of conventional curcumin in treating neurological conditions is its poor penetration of the BBB. The BBB is a selective barrier that tightly regulates the passage of substances from the bloodstream into the central nervous system (CNS). Sleep deprivation has been shown to impair BBB integrity, making the brain more susceptible to neurotoxins and inflammatory insults [35]. Nanocurcumin

overcomes this challenge through its small particle size (typically <200 nm) and lipid-based or polymeric encapsulation, which enhances its permeability and retention in brain tissue [36]. Studies have shown that nanocurcumin reaches higher concentrations in the brain than free curcumin and remains there for longer durations [37]. This property is critical for sleep-deprived states, where oxidative and inflammatory processes are particularly active in regions such as the hippocampus and prefrontal cortex, which are responsible for memory and emotional regulation. One of the key molecular pathways activated during sleep deprivation is the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway. This transcription factor is responsible for initiating the expression of several pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β, which are elevated during both acute and chronic sleep loss [38]. These cytokines not only promote systemic inflammation but also exacerbate neuronal damage, cognitive decline, and mood disturbances. Nanocurcumin has been shown to effectively suppress NF-κB activation by preventing the degradation of IκB (inhibitor of NF-κB), thereby blocking its translocation to the nucleus [39]. This leads to a downregulation of inflammatory gene expression and protects neurons from cytokine-induced injury. In animal models of neuroinflammation and sleep deprivation, nanocurcumin administration significantly reduced levels of IL-6 and TNF-α, while improving cognitive performance and reducing neuronal apoptosis [40]. Sleep deprivation induces the accumulation of reactive oxygen species (ROS), leading to oxidative stress and mitochondrial dysfunction. Nanocurcumin counters this by scavenging free radicals and upregulating endogenous antioxidant enzymes, including superoxide dismutase (SOD), catalase, and glutathione peroxidase [41]. This antioxidative action protects the neuronal membrane, DNA, and mitochondrial function, thus preserving cognitive function and synaptic integrity in sleep-deprived states. In addition to reducing inflammation and oxidative damage, nanocurcumin modulates immune cell activity, particularly microglia and astrocytes, which play a key role in neuroimmune interactions during sleep loss. It promotes an anti-inflammatory microglial phenotype (M2), supports neurogenesis, and reduces glial scarring [42].

STUDY SURVEY

Surveying a variety of research and review papers related to sleep deprivation, it becomes evident that most existing studies heavily focus on the neurological impacts of inadequate sleep. Topics such as cognitive decline, emotional instability, and disruptions in neurochemical pathways are well-explored in the scientific literature. However, there is a noticeable gap in studies that investigate how sleep deprivation, particularly during the REM phase, affects other vital organs and physiological systems. This observation prompted the development of a focused inquiry to explore immunological changes during REM sleep, assess the effects of nano-curcumin on REM sleep [43], investigate the involvement of proinflammatory cytokines during this sleep phase, and evaluate the correlation between nano-curcumin and immunomodulation during REM sleep. To address this, a series of relevant studies was reviewed. One such study was conducted by Atul Kumar Pandey et al. in 2011, where the researchers investigated the effects of REM sleep deprivation on liver function in male Wistar rats [44, 45]. Using the flowerpot method, a common technique for REM sleep deprivation, the rats were prevented from entering REM sleep while still being allowed NREM sleep. The study employed a wide range of experimental procedures, including immune transferase measurement, gel electrophoresis and densitometry, Edman sequencing, MALDI–TOF mass spectrometry, RNA isolation, and TaqMan real-time PCR. Additionally, cytokine and chemokine levels were analyzed, followed by statistical evaluation. The results showed a marked increase in liver enzymes such as AST and ALT, indicating liver damage likely due to ruptured hepatocytes [45]. These findings highlight the vulnerability of liver tissue to prolonged REM sleep loss, suggesting a broader systemic impact beyond the brain. Another study by M. L. Okun et al. in 2004 examined the role of cytokines and endocrine factors in narcolepsy, a disorder characterized by excessive daytime sleepiness and symptoms such as hypnagogic hallucinations, sleep paralysis, and cataplexy. This research delved into the possible involvement of inflammatory cytokines triggered by dysfunction in the hypocretin (orexin) system, an essential neuropeptide involved in maintaining sleep-wake stability [46, 47]. The study emphasized that low hypocretin levels may initiate or worsen inflammatory processes, particularly through the action of proinflammatory cytokines such as TNF-α and IL-6. These findings offer valuable insight into how immune and endocrine dysregulation could contribute to the development and progression of sleep disorders like narcolepsy. A third study by Ali Noorafshan et al. in 2017 explored the protective effects of curcumin on mice subjected to REM sleep deprivation. In this experiment, the researchers assessed various physiological and neurological outcomes, such as changes in body weight, memory function, and structural alterations in the hippocampus, specifically in the CA1 and dentate gyrus (DG) regions [48]. Mice that were deprived of REM sleep without curcumin treatment exhibited significant weight loss, impaired memory, and a reduction in both hippocampal volume and total cell count. Conversely, mice treated with curcumin maintained their body weight, demonstrated improved memory, and showed increased hippocampal volume and cell numbers [49]. These results indicate that

curcumin may offer a neuroprotective effect during REM sleep deprivation, potentially through its anti-inflammatory and antioxidant properties. Together, these studies underscore the multifaceted consequences of REM sleep deprivation on bodily systems and emphasize the need for more research into its systemic effects. Furthermore, the promising results of nano-curcumin treatment open new avenues for therapeutic strategies aimed at mitigating the damage caused by disrupted REM sleep. As such, future research should expand beyond the neurological domain to consider how sleep, immunity, metabolism, and organ health are intricately linked [50, 51].

RELATIONSHIP BETWEEN SLEEP AND THE IMMUNE SYSTEM

It is widely recognized that sleep plays a critical role in maintaining the body's immune defences [52]. A lack or complete loss of sleep can significantly weaken the immune system, making the body more vulnerable to a variety of diseases. Historical studies dating back to the 19th century have demonstrated the lethal consequences of prolonged sleep deprivation [53]. For example, in early experiments conducted on dogs, it was observed that complete sleep deprivation eventually led to death. Similar outcomes have been documented in more recent studies using mice, where the deprivation of REM sleep resulted in death within a few weeks. These findings underscore the essential nature of sleep for survival and physiological stability [54]. The sleep-wake cycle, along with emotional regulation and cognitive functioning, is primarily governed by the medial prefrontal cortex (mPFC) in conjunction with the hippocampus. This neural network plays a crucial role in processing emotions, regulating mood, and forming memories [55]. The interconnected activity between these regions is essential for balanced psychological and cognitive health. Research suggests that adults require approximately 7 to 8 hours of sleep per night to support metabolic homeostasis and maintain optimal physical and mental health [56]. Both REM and NREM sleep are essential for immune regulation. However, disturbances in these sleep phases can disrupt immune function, leading to imbalances in proinflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP). These inflammatory markers are closely associated with various health conditions when chronically elevated [57]. Furthermore, inadequate sleep quality, short sleep duration, and dysfunction in the autonomic nervous system have been linked to increased risk factors for atherogenesis. These risks include hormonal imbalances, immune dysfunction, oxidative stress, systemic inflammation, metabolic disturbances, and impaired endothelial function. Together, these factors contribute to the progression of cardiovascular and metabolic diseases, highlighting the complex and far-reaching impact of sleep on overall health [58]. The factors that must be considered when studying the complex relationship between sleep and immune function are illustrated in **Figure 2**. These factors include the duration and method of sleep deprivation, the specific time points for specimen collection, the type of immune assay used, and the circadian rhythm of the subject. Additional considerations involve the species being analyzed, environmental conditions, age, and health status of the subjects, psychosocial stress levels, and the methodologies used for sleep assessment [59]. All these elements play critical roles in determining the outcomes of sleep-immune interaction studies and highlight the need for well-controlled experimental designs. Research exploring the bidirectional relationship between sleep and immune responses often uses experimental approaches to uncover causal connections. These studies typically involve manipulating either sleep patterns or immune parameters to observe subsequent changes. Such experimental setups are essential for understanding how alterations in sleep can impact immune function, and vice versa. For example, depriving subjects of sleep allows researchers to evaluate changes in cytokine levels, stress hormones, and other immune markers, while immune challenges (like exposure to pathogens) can help assess how immune activation affects sleep architecture [60]. Sleep is not only a basic biological necessity but also a key indicator of overall well-being. Normal, high-quality sleep is essential for healthy memory consolidation and optimal brain function. This is because multiple interconnected neural circuits within the brain actively participate in regulating sleep processes [61]. In modern society, however, sleep deprivation (SD) has become a growing public health concern. Prolonged sleep deprivation impairs long-term potentiation and disrupts key molecular pathways associated with memory formation, ultimately leading to cognitive decline and mental fatigue [62]. Additionally, sleep deprivation hinders the clearance of harmful metabolites that naturally accumulate in the brain, contributing to the onset and progression of several neurological disorders. These include neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and the increased risk of cerebrovascular conditions like stroke [63]. Moreover, chronic sleep deprivation disrupts immune balance, thereby worsening the underlying mechanisms of immune-related neurological disorders such as Multiple Sclerosis (MS) and gliomas. It can be concluded that sleep deprivation has widespread negative effects on various proteins, genes, and molecular pathways, contributing to the pathophysiology of numerous neurodegenerative and immune-related disorders [64].

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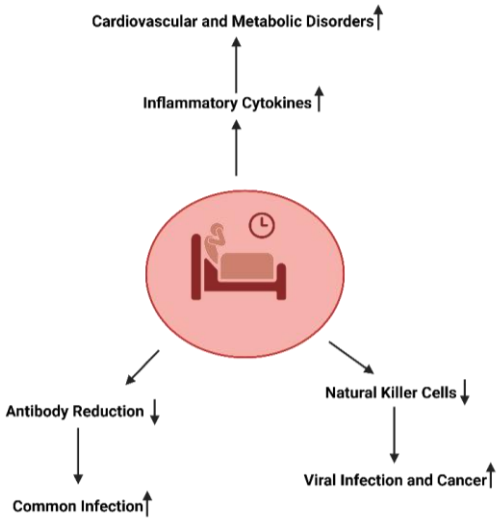

Figure 2: Shows different kinds of sleep-deprived diseases caused due to the manifestation of sleep deprivation.

In today's modern society, sleep-related disorders and disruptions to the circadian rhythm have become increasingly common [65]. These disturbances not only affect day-to-day functioning but are also strongly linked to the body's immune responses [66]. Research indicates a strong correlation between circadian rhythms, sleep quality, and the regulation of immune functions, as shown in **Figure 3**. Individuals who consistently get less sleep often experience fatigue, reduced cognitive and physical performance, and lowered immune resilience [67]. On average, 7 to 8 hours of sleep per night is considered essential for maintaining optimal health and performance. Immunologically, sleep deprivation has significant effects. Studies have shown that biological suppression of interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α) can lead to a reduction in non-rapid eye movement (NREM) sleep [68]. Conversely, elevated levels of these cytokines increase NREM sleep while reducing rapid eye movement (REM) sleep. Under normal physiological conditions, the sleep-wake cycle and circadian rhythms help regulate a balanced immune response, promoting an anti-inflammatory state during the day and a pro-inflammatory state during the night [69].

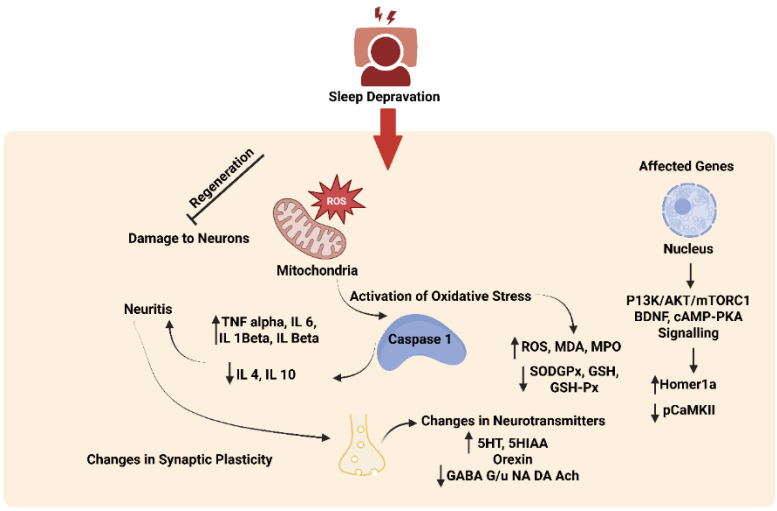

Figure 3. Potential mechanism for the effect of potential sleep deprivation on memory function.

Mild immune activation has been observed to enhance NREM sleep and suppress REM sleep, whereas severe immune reactions, often characterized by excessive cytokine production, lead to disturbances in both NREM and REM sleep patterns. Luísa de Sousa Nogueira Freitas et al. (2020) cited research by Watson (2017), which emphasized that athletes may require 9 to 10 hours of total sleep time (TST) for optimal physical recovery. The role of sleep in protein synthesis and degradation is also

crucial [70]. Studies have demonstrated that adequate sleep significantly reduces muscle breakdown and supports the body's regenerative processes, while sleep deprivation, both partial and total, negatively impacts these functions [71]. Moreover, sleep affects the circulation and function of immune cells. During nocturnal sleep, leukocyte counts in the blood decrease, while their presence in lymphatic tissues increases, enhancing immune surveillance. Cytokines like IL-2, derived from T-cells, are also regulated by sleep and play an essential role in adaptive immune defense [72]. Sleep plays a pivotal role in athletic recovery as well. Lack of sleep can severely impair skeletal muscle repair due to hormonal imbalances and altered cytokine levels. Biomarkers such as AST, ALT, and LDH, indicative of muscle damage, tend to rise in response to sleep deprivation [71]**.** This occurs through several physiological disturbances, including endocrinological imbalances, immune system activation, oxidative stress, inflammation, and endothelial dysfunction. The biological consequences of inadequate sleep in athletes suggest that insufficient sleep may lower levels of testosterone and growth hormone, both of which are crucial for muscle repair [73]. This decline may inhibit the activation of PI3K, subsequently reducing the phosphorylation of Akt and switching off the mTOR pathway, a key regulator of protein synthesis. This leads to impaired activation of S6K1 and Bmal, reduced expression of heat shock proteins (HSPs), increased reactive oxygen species (ROS), and elevated cortisol levels. Collectively, these changes inhibit the secretion of insulin-like growth factor-1 (IGF-1), further dampening the PI3K pathway and activating proteins such as REDD1, 4EBP1, and FOXO, all of which contribute to reduced muscle protein synthesis and repair [74]. Moreover, insufficient sleep affects the integrity of sphingolipid morphology on cell membranes, disrupting inflammatory signaling. This includes increased levels of IL-6, IL-1β, TNF-α, prostaglandin activation, and ubiquitination pathways. Simultaneously, protective mediators such as IL-10, Annexin A1 (AnxA1), Lipoxin A4 (LXA4), and resolvins (RvE and RvD) are found to decrease. These disruptions collectively impair IGF-1 secretion, reduce insulin sensitivity, and hinder overall protein synthesis [75]. The downstream result is a reduced capacity for muscle recovery and a higher risk of musculoskeletal injuries.

NANOCURCUMIN AND REM SLEEP

Curcumin's powerful antioxidant and anti-inflammatory effects have made it a popular candidate for neuroprotection. Curcumin combats oxidative stress, which is an imbalance between ROS production and the body's antioxidant defences [76]. Research indicates that SD significantly increases free radicals while simultaneously weakening the oxidative defence system. This imbalance disrupts the body's homeostasis, leading to oxidative damage, chronic inflammation, and eventually the degeneration of critical biological tissues, especially in the brain [77]. Sleep deprivation is associated with a multitude of neurological complications. Prolonged lack of sleep has been shown to trigger DNA damage responses and neuronal death, hinder neuronal plasticity, reduce hippocampal glycogenesis, and diminish dendritic spine density and length in several brain regions. These changes are closely linked to cognitive decline, mood disturbances, memory impairments, depression, and even psychotic disorders. A disrupted sleep–wake cycle interferes with normal brain functioning and may contribute to long-term structural and functional brain abnormalities [78]. Turmeric, the source of curcumin, contains three major curcuminoids: curcumin, demethoxycurcumin, and bisdemethoxycurcumin. These components are known to regulate inflammation, modulate cell proliferation, and control apoptosis [79]. The antioxidant and anti-inflammatory characteristics of curcumin make it a powerful compound in managing diseases driven by chronic inflammation, such as cancer, atherosclerosis, Alzheimer's disease, and other metabolic disorders. This stress stems from excessive ROS production, including free radicals and reactive metabolites, overwhelming the body's antioxidant defences and causing damage to lipids, proteins, and DNA [76]. ROS plays a central role in modulating both upstream and downstream pathways of NF-ϰB and TNF-α, both of which are key mediators of inflammatory responses. Among the various types of ROS, hydroxyl radicals are considered the most damaging due to their high reactivity.

Table1. Comparing curcumin vs. nanocurcumin in terms of bioavailability, efficacy in sleep models, and clinical outcomes

Parameter	*Curcumin*	*Nanocurcumin*	*References*
Bioavailability	*Poor bioavailability due to limited solubility, fast metabolism, and elimination.*	*Enhanced solubility, prolonged systemic retention, 5–10× higher plasma levels than curcumin*	[80-83]
Blood-Brain Barrier (BBB) Penetration	*Limited BBB penetration*	*Improved BBB permeability due to nanoparticle size and lipid carriers*	[81,84,85]

Efficacy in Sleep Deprivation Models	*Modest reduction in oxidative stress and inflammation in preclinical models*	*Significant reduction in pro-inflammatory cytokines, oxidative stress, and neuronal apoptosis*	[85–87]
Cognitive Outcomes in Sleep-Impaired Rodents	*Partial protection of memory and learning functions*	*Stronger protection against memory loss, better synaptic preservation*	[85–88]
Antioxidant Activity	*Inhibits lipid peroxidation; induces some antioxidant enzymes*	*Greater ROS scavenging; robust upregulation of SOD, CAT, and GSH levels*	[80,87,88]
NF-κB Pathway Inhibition	*Moderate inhibition in vitro; limited in vivo due to poor uptake*	*Potent NF-κB pathway suppression in CNS and peripheral tissues*	[83,85,87]
Clinical Translation	*Limited due to poor systemic levels and short half-life*	*Better pharmacokinetics and patient compliance in early clinical studies*	[81–83,89]

Although curcumin has demonstrated exceptional potential in various biological and pharmacological applications, it suffers from poor bioavailability and low water solubility, which limits its effectiveness in clinical settings. To address these limitations, nano-curcumin formulations have been developed, significantly enhancing curcumin's absorption and efficacy as shown in **Table 1** [90]. A study by Mehdi Maghbooli et al., 2019, revealed that nanomicelle curcumin notably improved sleep quality and quality of life (QoL) in patients with Parkinson's disease, compared to a placebo group [91]. Additionally, Yang's research suggested that curcumin facilitates brain recovery in the hippocampus of rodents, while Issuriya's findings confirmed that curcumin prevented hippocampal cell death induced by dexamethasone in rats [92]. Although the precise mechanisms by which curcumin preserves memory and prevents structural degeneration in the hippocampus and dentate gyrus (DG) require further exploration, current evidence suggests that these effects are largely due to curcumin's ability to mitigate oxidative stress [93]. REM sleep deprivation (REM-SD) is believed to impair spatial memory and alter hippocampal architecture. While numerous studies have shown that novel object recognition tasks can be either hippocampus-dependent or independent, depending on the experimental protocol, it remains uncertain whether changes in hippocampal volume directly correlate with behavioural performance in such tasks. Since the 1970s, numerous foundational studies have established a strong correlation between poor sleep quality and various psychological factors, particularly in the context of chronic stress and mental strain [94]. One major biological pathway linking sleep disturbances with psychological dysfunction is inflammation, especially through the activity of proinflammatory cytokines. These cytokines, including interleukin-1β (IL-1β), IL-6, tumor necrosis factor-alpha (TNF-α), IL-17, and others, are primarily produced by activated immune cells such as microglia [95]. They play a crucial role in initiating and amplifying the acute phase response (APR), a fundamental component of the body's inflammatory defence system. Moreover, increases in C-reactive protein (CRP), a sensitive inflammatory biomarker, have been shown to predict fatigue and reduced vitality in community-dwelling adults [96]. These findings collectively suggest that both systemic inflammation and sleep disruption can significantly contribute to physical exhaustion and possibly diminish an individual's overall quality of life and immune resilience. In a study conducted by Atul Kumar Pandey et al., 2011, it was observed that the levels of proinflammatory cytokines, including IL-1β, IL-6, and IL-12 (p70), increased significantly on the fourth and ninth days of REMSD when compared to the control group [45]. These cytokines, which are pivotal messengers of the peripheral immune system, not only regulate the expression of acute phase proteins such as A1I3 but also influence sleep regulation itself. Total sleep deprivation has been associated with a significant rise in IL-1β and IL-6 levels, reinforcing previous reports that identified IL-6 as a primary mediator of the APR, with IL-1β contributing indirectly via IL-6 pathways. Sleep, particularly slow-wave sleep (SWS), plays a fundamental role in supporting the adaptive immune response [97]. During immune activation, antigen-presenting cells (APCs) capture and process invading antigens, presenting them to T helper (Th) cells. This interaction forms a temporary "immunological synapse", initiating a cascade of immune reactions. The release of interleukin-12 (IL-12) by APCs promotes a Th1 immune response, supporting cytotoxic T cell activation and stimulating B cells to produce antigen-specific antibodies [98]. Ultimately, this leads to the formation of long-lasting immunological memory. Hormonal fluctuations during sleep also play a role in immune regulation. SWS and the circadian rhythm together promote a pro-inflammatory hormonal environment, characterized by increased secretion of growth hormone and prolactin, and decreased levels of cortisol, a stress hormone with anti-inflammatory effects [99]. These hormonal shifts are essential in enhancing the early stages of adaptive immune activation, particularly within lymph nodes, where immune memory formation begins. Similar to the neurobehavioral memory processes within the central nervous system, immunological memory development can also be conceptualized in stages encoding, consolidation, and recall. In both systems, sleep, especially deep sleep phases, plays a critical role in the consolidation phase,

ensuring robust memory formation. These parallels between neural and immune memory underscore the multifaceted importance of sleep, not only for cognitive function but also for immune system performance and resilience.

CONCLUSION

Sleep is a vital physiological process required for maintaining metabolic balance, cognitive function, immune competence, and cellular homeostasis. Chronic SD, defined as insufficient or disrupted sleep over an extended period, is a growing public health concern with profound implications for physical and mental health. The mechanisms through which SD exerts damage span multiple biological systems and are increasingly recognized as key contributors to various pathological conditions. One of the central mechanisms of SD-induced damage involves oxidative stress and mitochondrial dysfunction. During normal sleep, the body clears ROS and repairs oxidative damage. However, lack of sleep impairs mitochondrial bioenergetics and increases ROS production, leading to DNA damage, lipid peroxidation, and protein misfolding. This oxidative burden is especially detrimental to high-energy organs such as the brain and heart. Neuroinflammation is another critical pathway. SD activates microglial cells in the central nervous system, increasing the production of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6. These inflammatory mediators compromise synaptic plasticity, disrupt neurotransmitter homeostasis, and damage the blood-brain barrier, contributing to cognitive decline, mood disorders, and increased susceptibility to neurodegenerative diseases like Alzheimer's and Parkinson's. At the hormonal level, SD alters the hypothalamic-pituitary-adrenal (HPA) axis, leading to elevated cortisol levels and dysregulation of melatonin and growth hormone secretion. Chronic cortisol elevation promotes catabolism, impairs memory consolidation, and increases visceral fat deposition, raising the risk of metabolic syndrome, insulin resistance, and type 2 diabetes. Sleep deprivation also disrupts the immune system, suppressing NK cell activity, altering T-cell responses, and reducing antibody production. This immunosuppression heightens vulnerability to infections and reduces vaccine efficacy. Simultaneously, the body enters a state of chronic low-grade inflammation, which is a shared mechanism in the pathogenesis of cardiovascular diseases, cancer, and autoimmune disorders. At the genomic level, SD impacts gene expression and epigenetic regulation, particularly in clock genes and those involved in stress responses and metabolism. Studies show that even a single night of total SD alters the expression of hundreds of genes, including those regulating circadian rhythm, DNA repair, and apoptosis. Moreover, telomere shortening and increased expression of DNA damage markers such as 8-oxodG have been observed, linking SD with premature aging and cellular senescence. Synaptic homeostasis is another sleep-regulated process impaired by SD. The synaptic homeostasis hypothesis suggests that sleep is necessary to downscale synaptic strength accumulated during wakefulness. Without this resetting, excessive excitatory activity may lead to excitotoxicity and impair memory encoding and learning. Therefore, the damage induced by sleep deprivation is profound, multi-systemic, and cumulative. It disrupts redox balance, triggers neuroinflammation, destabilizes hormonal and immune networks, and induces genetic and epigenetic changes that compromise cellular integrity. These mechanistic pathways do not act in isolation but rather intersect, amplifying the systemic burden of chronic sleep loss. The silent erosion caused by inadequate sleep often goes unnoticed until it manifests in serious health outcomes, including neurodegeneration, cardiovascular diseases, metabolic disorders, and immune dysfunction. In an age defined by constant connectivity and diminishing rest, prioritizing sleep is no longer a luxury; it is a biological imperative. Addressing sleep deprivation must become a central pillar in public health strategies, clinical care, and personal well-being to prevent its long-term consequences and restore resilience at both the individual and societal levels.

Author Contribution

PT wrote the manuscript. RD implemented the idea of figures, which RK drew. RD, SK, and RK proofread it. All authors read and approved the final manuscript

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Conflict of Interest

The authors declare that they have no conflict of interest.

REFERENCES

[1] Ballester, Pura et al. "Antioxidant Activity in Extracts from *Zingiberaceae* Family: Cardamom, Turmeric, and Ginger." *Molecules (Basel, Switzerland)* vol. 28,10 4024. 11 May. 2023, doi:10.3390/molecules28104024

[2] Akaberi, Maryam et al. "Turmeric and Curcumin: From Traditional to Modern Medicine." *Advances in experimental medicine and biology* vol. 1291 (2021): 15-39. doi:10.1007/978-3-030-56153-6_2
[3] Sharifi-Rad, Javad et al. "Turmeric and Its Major Compound Curcumin on Health: Bioactive Effects and Safety Profiles for Food, Pharmaceutical, Biotechnological and Medicinal Applications." *Frontiers in pharmacology* vol. 11 01021. 15 Sep. 2020, doi:10.3389/fphar.2020.01021
[4] Islam, Md Rezaul et al. "Targeted therapies of curcumin focus on its therapeutic benefits in cancers and human health: Molecular signaling pathway-based approaches and future perspectives." *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie* vol. 170 (2024): 116034. doi:10.1016/j.biopha.2023.116034
[5] Fuloria, Shivkanya et al. "A Comprehensive Review on the Therapeutic Potential of *Curcuma longa* Linn. in Relation to its Major Active Constituent Curcumin." *Frontiers in pharmacology* vol. 13 820806. 25 Mar. 2022, doi:10.3389/fphar.2022.820806
[6] Li, Hong et al. "Curcumin, the golden spice in treating cardiovascular diseases." *Biotechnology advances* vol. 38 (2020): 107343. doi:10.1016/j.biotechadv.2019.01.010
[7] Institute of Medicine (US) Committee on Sleep Medicine and Research. *Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem*. Edited by Harvey R Colten et. al., National Academies Press (US), 2006. doi:10.17226/11617
[8] Bishir, Muhammed et al. "Sleep Deprivation and Neurological Disorders." *BioMed research international* vol. 2020 5764017. 23 Nov. 2020, doi:10.1155/2020/5764017
[9] Chavda, Vishal et al. "Narcolepsy-A Neuropathological Obscure Sleep Disorder: A Narrative Review of Current Literature." *Brain sciences* vol. 12,11 1473. 30 Oct. 2022, doi:10.3390/brainsci12111473
[10] Mohammadi, Soheil et al. "Cytokines in narcolepsy: A systematic review and meta-analysis." *Cytokine* vol. 131 (2020): 155103. doi:10.1016/j.cyto.2020.155103
[11] Vgontzas, A N et al. "Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity." *The Journal of clinical endocrinology and metabolism* vol. 82,5 (1997): 1313-6. doi:10.1210/jcem.82.5.3950
[12] Yang, Qiao et al. "Association between cytokines and fatigue in patients with type 1 narcolepsy." *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia* vol. 120 (2024): 102-106. doi:10.1016/j.jocn.2024.01.007
[13] Hogan, Dale et al. "Interleukin-6 alters sleep of rats." *Journal of neuroimmunology* vol. 137,1-2 (2003): 59-66. doi:10.1016/s0165-5728(03)00038-9
[14] Chennaoui, Mounir et al. "Sleep and the GH/IGF-1 axis: Consequences and countermeasures of sleep loss/disorders." *Sleep medicine reviews* vol. 49 (2020): 101223. doi:10.1016/j.smrv.2019.101223
[15] Nicolaides, Nicolas C., et al. "HPA Axis and Sleep." *Endotext*, edited by Kenneth R Feingold et. al., MDText.com, Inc., 24 November 2020.
[16] Silva RH et al. Sleep deprivation induces oxidative stress in rat hippocampus. Neurochem Res. 2004;29(3):579–585.
[17] Everson CA et al. Sustained sleep deprivation leads to brain oxidative damage. Am J Physiol. 1994;266:R1211–R1217.
[18] Zielinski MR et al. Chronic sleep restriction elevates brain interleukin-1β and tumor necrosis factor-α levels. Neuroscience. 2014;274:318–326.
[19] Hurtado-Alvarado G et al. Sleep loss as a factor to induce cellular and molecular inflammatory variations. Clin Dev Immunol. 2013;2013:801341.
[20] Xie L et al. Sleep drives metabolite clearance from the adult brain. Science. 2013;342(6156):373–377.
[21] Spiegel K et al. Impact of sleep debt on metabolic and endocrine function. Lancet. 1999;354(9188):1435–1439.
[22] Reiter RJ et al. Melatonin as an antioxidant: under promises but over delivers. J Pineal Res. 2016;61(3):253–278.
[23] Irwin MR et al. Sleep loss reduces natural killer cell activity and interleukin-2 levels. Psychosom Med. 1996;58(6):493–500.
[24] Besedovsky L et al. Sleep and immune function. Pflugers Arch. 2012;463(1):121–137.
[25] Brown MK, Naidoo N. The role of oxidative stress in sleep deprivation-associated injury. NeuroMolecular Med. 2010;12(4):307–320.
[26] Aggarwal BB, Sung B. Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets. *Trends Pharmacol Sci*. 2009;30(2):85–94.
[27] Anand P et al. Bioavailability of curcumin: problems and promises. *Mol Pharm*. 2007;4(6):807–818.
[28] Ireson CR et al. Characterization of metabolites of the chemopreventive agent curcumin in human and rat hepatocytes and in the rat in vivo. *Cancer Res*. 2001;61(3):1058–1064.

[29] Yallapu MM et al. Nano-curcumin: a promising therapeutic advancement for treatment of cancer. *Mol Pharm*. 2012;9(1):1–11.
[30] Shaikh J et al. Enhanced bioavailability and pharmacodynamic activity of curcumin using solid lipid nanoparticles. *Colloids Surf B Biointerfaces*. 2009;68(2):505–510.
[31] Tsai YM et al. Curcumin and its nano-formulation: the kinetics of tissue distribution and blood-brain barrier penetration. *Int J Pharm*. 2011;416(1):331–338.
[32] Kunnumakkara AB et al. Curcumin targets multiple signaling pathways and genes for cancer prevention and therapy. *Front Pharmacol*. 2017;8:18.
[33] Banerjee A et al. Curcumin nanoparticles enhance the anti-inflammatory and antioxidant effects in LPS-induced macrophages. *Front Immunol*. 2020;11:538.
[34] Ghosh S et al. Nanocurcumin ameliorates cognitive dysfunction and neuroinflammation in diabetic rats: a comparative study with curcumin. *Front Pharmacol*. 2021;12:653940
[35] Hurtado-Alvarado G et al. Sleep loss as a factor to induce cellular and molecular inflammatory variations. *Clin Dev Immunol*. 2013;2013:801341.
[36] Tsai YM et al. Curcumin and its nano-formulation: the kinetics of tissue distribution and blood-brain barrier penetration. *Int J Pharm*. 2011;416(1):331–338.
[37] Shaikh J et al. Enhanced bioavailability and pharmacodynamic activity of curcumin using solid lipid nanoparticles. *Colloids Surf B Biointerfaces*. 2009;68(2):505–510.
[38] Zielinski MR et al. Chronic sleep restriction elevates brain interleukin-1β and TNF-α levels. *Neuroscience*. 2014;274:318–326.
[39] Kunnumakkara AB et al. Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. *Cancer Lett*. 2008;269(2):199–225.
[40] Ghosh S et al. Nanocurcumin ameliorates cognitive dysfunction and neuroinflammation in diabetic rats: a comparative study with curcumin. *Front Pharmacol*. 2021;12:653940.
[41] Reiter RJ et al. Melatonin as an antioxidant: under promises but over delivers. *J Pineal Res*. 2016;61(3):253–278.
[42] Banerjee A et al. Curcumin nanoparticles enhance anti-inflammatory and neuroprotective effects in LPS-induced microglial activation. *Front Immunol*. 2020;11:538
[43] Baranwal, Navya et al. "Sleep physiology, pathophysiology, and sleep hygiene." *Progress in cardiovascular diseases* vol. 77 (2023): 59-69. doi:10.1016/j.pcad.2023.02.005
[44] Kumar R, Pandey A, Vibhuti A et al. Unlocking Mysteries: Exploring the Dynamic Interplay among Sleep, the Immune System, and Curcumin in Contemporary Research. Sleep Science 2024 (efirst). doi:10.1055/s-0045-1802321
[45] Pandey, Atul Kumar, and Santosh Kumar Kar. "REM sleep deprivation of rats induces acute phase response in liver." *Biochemical and biophysical research communications* vol. 410,2 (2011): 242-6. doi:10.1016/j.bbrc.2011.05.123
[46] Okun, M L et al. "Exploring the cytokine and endocrine involvement in narcolepsy." *Brain, behavior, and immunity* vol. 18,4 (2004): 326-32. doi:10.1016/j.bbi.2003.11.002
[47] Barateau, Lucie et al. "Narcolepsy." *Journal of sleep research* vol. 31,4 (2022): e13631. doi:10.1111/jsr.13631
[48] Noorafshan, Ali et al. "Restorative effects of curcumin on sleep-deprivation induced memory impairments and structural changes of the hippocampus in a rat model." *Life sciences* vol. 189 (2017): 63-70. doi:10.1016/j.lfs.2017.09.018
[49] Silva, R H et al. "Role of hippocampal oxidative stress in memory deficits induced by sleep deprivation in mice." *Neuropharmacology* vol. 46,6 (2004): 895-903. doi:10.1016/j.neuropharm.2003.11.032
[50] Karthikeyan, Adhimoolam et al. "Nanocurcumin: A Promising Candidate for Therapeutic Applications." *Frontiers in pharmacology* vol. 11 487. 1 May. 2020, doi:10.3389/fphar.2020.00487
[51] Panzarini, Elisa et al. "Novel Therapeutic Delivery of Nanocurcumin in Central Nervous System Related Disorders." *Nanomaterials (Basel, Switzerland)* vol. 11,1 2. 22 Dec. 2020, doi:10.3390/nano11010002
[52] Besedovsky, Luciana et al. "The Sleep-Immune Crosstalk in Health and Disease." *Physiological reviews* vol. 99,3 (2019): 1325-1380. doi:10.1152/physrev.00010.2018
[53] Garbarino, Sergio et al. "Role of sleep deprivation in immune-related disease risk and outcomes." *Communications biology* vol. 4,1 1304. 18 Nov. 2021, doi:10.1038/s42003-021-02825-4
[54] Villafuerte, Gabriel et al. "Sleep deprivation and oxidative stress in animal models: a systematic review." *Oxidative medicine and cellular longevity* vol. 2015 (2015): 234952. doi:10.1155/2015/234952

[55] Goldstein, Andrea N, and Matthew P Walker. "The role of sleep in emotional brain function." *Annual review of clinical psychology* vol. 10 (2014): 679-708. doi:10.1146/annurev-clinpsy-032813-153716
[56] Desai, Dev et al. "Exploring the Role of Circadian Rhythms in Sleep and Recovery: A Review Article." *Cureus* vol. 16,6 e61568. 3 Jun. 2024, doi:10.7759/cureus.61568
[57] Ibarra-Coronado, Elizabeth G et al. "The Bidirectional Relationship between Sleep and Immunity against Infections." *Journal of immunology research* vol. 2015 (2015): 678164. doi:10.1155/2015/678164
[58] Kadoya, Manabu, and Hidenori Koyama. "Sleep, Autonomic Nervous Function and Atherosclerosis." *International journal of molecular sciences* vol. 20,4 794. 13 Feb. 2019, doi:10.3390/ijms20040794
[59] Besedovsky, Luciana et al. "Sleep and immune function." *Pflugers Archiv : European journal of physiology* vol. 463,1 (2012): 121-37. doi:10.1007/s00424-011-1044-0
[60] Garbarino, Sergio et al. "Role of sleep deprivation in immune-related disease risk and outcomes." *Communications biology* vol. 4,1 1304. 18 Nov. 2021, doi:10.1038/s42003-021-02825-4
[61] Palagini, Laura et al. "Sleep, insomnia and mental health." *Journal of sleep research* vol. 31,4 (2022): e13628. doi:10.1111/jsr.13628
[62] Chen, Pinqiu et al. "The Devastating Effects of Sleep Deprivation on Memory: Lessons from Rodent Models." *Clocks & sleep* vol. 5,2 276-294. 15 May. 2023, doi:10.3390/clockssleep5020022
[63] Wankhede, Nitu L et al. "Sleep deprivation-induced shifts in gut microbiota: Implications for neurological disorders." *Neuroscience* vol. 565 (2025): 99-116. doi:10.1016/j.neuroscience.2024.11.070
[64] Dash, Umesh Chandra et al. "Oxidative stress and inflammation in the pathogenesis of neurological disorders: Mechanisms and implications." *Acta pharmaceutica Sinica. B* vol. 15,1 (2025): 15-34. doi:10.1016/j.apsb.2024.10.004
[65] Sun, Shi-Yu, and Gui-Hai Chen. "Treatment of Circadian Rhythm Sleep-Wake Disorders." *Current neuropharmacology* vol. 20,6 (2022): 1022-1034. doi:10.2174/1570159X19666210907122933
[66] Morey, Jennifer N et al. "Current Directions in Stress and Human Immune Function." *Current opinion in psychology* vol. 5 (2015): 13-17. doi:10.1016/j.copsyc.2015.03.007
[67] Al-Abri, Mohammed A et al. "Circadian Rhythm, Sleep, and Immune Response and the Fight against COVID-19." *Oman medical journal* vol. 38,2 e477. 31 Mar. 2023, doi:10.5001/omj.2023.38
[68] Besedovsky, Luciana et al. "Sleep and immune function." *Pflugers Archiv : European journal of physiology* vol. 463,1 (2012): 121-37. doi:10.1007/s00424-011-1044-0
[69] Irwin, Michael R. "Sleep disruption induces activation of inflammation and heightens risk for infectious disease: Role of impairments in thermoregulation and elevated ambient temperature." *Temperature (Austin, Tex.)* vol. 10,2 198-234. 21 Aug. 2022, doi:10.1080/23328940.2022.2109932
[70] de Sousa Nogueira Freitas, Luísa et al. "Sleep debt induces skeletal muscle injuries in athletes: A promising hypothesis." *Medical hypotheses* vol. 142 (2020): 109836. doi:10.1016/j.mehy.2020.109836
[71] Morrison, Matthew et al. "Sleep, circadian biology and skeletal muscle interactions: Implications for metabolic health." *Sleep medicine reviews* vol. 66 (2022): 101700. doi:10.1016/j.smrv.2022.101700
[72] Garbarino, Sergio et al. "Role of sleep deprivation in immune-related disease risk and outcomes." *Communications biology* vol. 4,1 1304. 18 Nov. 2021, doi:10.1038/s42003-021-02825-4
[73] Chu, Brianna, et al. "Physiology, Stress Reaction." *StatPearls*, StatPearls Publishing, 7 May 2024.
[74] Glaviano, Antonino et al. "PI3K/AKT/mTOR signaling transduction pathway and targeted therapies in cancer." *Molecular cancer* vol. 22,1 138. 18 Aug. 2023, doi:10.1186/s12943-023-01827-6
[75] Mullington, Janet M et al. "Sleep loss and inflammation." *Best practice & research. Clinical endocrinology & metabolism* vol. 24,5 (2010): 775-84. doi:10.1016/j.beem.2010.08.014
[76] Sharifi-Rad, Javad et al. "Turmeric and Its Major Compound Curcumin on Health: Bioactive Effects and Safety Profiles for Food, Pharmaceutical, Biotechnological and Medicinal Applications." *Frontiers in pharmacology* vol. 11 01021. 15 Sep. 2020, doi:10.3389/fphar.2020.01021
[77] Lobo, V et al. "Free radicals, antioxidants and functional foods: Impact on human health." *Pharmacognosy reviews* vol. 4,8 (2010): 118-26. doi:10.4103/0973-7847.70902
[78] Havekes, Robbert et al. "Sleep deprivation causes memory deficits by negatively impacting neuronal connectivity in hippocampal area CA1." *eLife* vol. 5 e13424. 23 Aug. 2016, doi:10.7554/eLife.13424

[79] Zhang, Huiying Amelie, and David D Kitts. "Turmeric and its bioactive constituents trigger cell signaling mechanisms that protect against diabetes and cardiovascular diseases." *Molecular and cellular biochemistry* vol. 476,10 (2021): 3785-3814. doi:10.1007/s11010-021-04201-6
[80] Anand P et al. Bioavailability of curcumin: problems and promises. *Mol Pharm*. 2007;4(6):807–818.
[81] Ireson CR et al. Characterization of curcumin metabolism and challenges for delivery. *Cancer Res*. 2001;61(3):1058–1064.
[82] Shaikh J et al. Enhanced pharmacodynamic activity of curcumin using solid lipid nanoparticles. *Colloids Surf B*. 2009;68(2):505–510.
[83] Yallapu MM et al. Curcumin nanoformulations: a promising future for improving therapeutic efficacy. *Mol Pharm*. 2012;9(1):1–11.
[84] Tsai YM et al. The kinetics of tissue distribution and BBB penetration of curcumin nanoformulation. *Int J Pharm*. 2011;416(1):331–338.
[85] Ghosh S et al. Nanocurcumin ameliorates cognitive dysfunction and neuroinflammation in diabetic rats. *Front Pharmacol*. 2021;12:653940.
[86] Silva RH et al. Sleep deprivation induces oxidative stress in rat hippocampus. *Neurochem Res*. 2004;29(3):579–585.
[87] Banerjee A et al. Curcumin nanoparticles reduce neuroinflammation and oxidative damage in LPS-induced models. *Front Immunol*. 2020;11:538.
[88] Xu Y et al. Nanocurcumin enhances memory and reduces oxidative stress in aging mice. *Pharmacol Biochem Behav*. 2020;196:172971.
[89] Amalraj A et al. Clinical efficacy and safety of curcumin nanoformulations: a review. *J Tradit Complement Med*. 2017;7(3):339–355.
[90] Karthikeyan, Adhimoolam et al. "Nanocurcumin: A Promising Candidate for Therapeutic Applications." *Frontiers in pharmacology* vol. 11 487. 1 May. 2020, doi:10.3389/fphar.2020.00487
[91] Yang, Xuemei et al. "Curcumin promotes neurogenesis of hippocampal dentate gyrus via Wnt/β-catenin signal pathway following cerebral ischemia in mice." *Brain research* vol. 1751 (2021): 147197. doi:10.1016/j.brainres.2020.147197
[92] Chang, Yu-Hsien. "Curcumin as a potential therapeutic agent for Parkinson's disease: a systematic review." *Frontiers in pharmacology* vol. 16 1593191. 22 Apr. 2025, doi:10.3389/fphar.2025.1593191
[93] Nam, Sung Min et al. "Effects of curcumin (Curcuma longa) on learning and spatial memory as well as cell proliferation and neuroblast differentiation in adult and aged mice by upregulating brain-derived neurotrophic factor and CREB signaling." *Journal of medicinal food* vol. 17,6 (2014): 641-9. doi:10.1089/jmf.2013.2965
[94] Institute of Medicine (US) Committee on Sleep Medicine and Research. *Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem*. Edited by Harvey R Colten et. al., National Academies Press (US), 2006. doi:10.17226/11617
[95] Rengasamy, Manivel et al. "A chicken and egg scenario in psychoneuroimmunology: Bidirectional mechanisms linking cytokines and depression." *Journal of affective disorders reports* vol. 6 (2021): 100177. doi:10.1016/j.jadr.2021.100177
[96] Sproston, Nicola R, and Jason J Ashworth. "Role of C-Reactive Protein at Sites of Inflammation and Infection." *Frontiers in immunology* vol. 9 754. 13 Apr. 2018, doi:10.3389/fimmu.2018.00754
[97] Krueger, James M et al. "Cytokines in immune function and sleep regulation." *Handbook of clinical neurology* vol. 98 (2011): 229-40. doi:10.1016/B978-0-444-52006-7.00015-0
[98] Pobor, G et al. "B lymphocyte activation upon exclusive recognition of major histocompatibility antigens by T helper cells." *European journal of immunology* vol. 14,3 (1984): 222-7. doi:10.1002/eji.1830140305
[99] Al-Abri, Mohammed A et al. "Circadian Rhythm, Sleep, and Immune Response and the Fight against COVID-19." *Oman medical journal* vol. 38,2 e477. 31 Mar. 2023, doi:10.5001/omj.2023.38