Review

Melatonin: therapeutic potential for stroke and other neurodegenerative diseases

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ABSTRACT

Neurodegenerative diseases are a serious health issue globally. High morbidity and mortality of these disorders lead to researchers further exploring more effective preventive and therapeutic remedies to combat these devastating diseases. An important strategy is to delay the progression of these debilitating diseases. The prevalence of neurodegenerative disease increases with aging which not only results in neuronal deterioration, but also causes the brain ischemia leading to stroke, and death. Melatonin, a potent endogenous antioxidant mainly secreted by the pineal gland, has often used in the treatment of neuropathologies with great success. Herein, we review the current evidence documenting melatonin's therapeutic effects on neurodegenerative and brain ischemic diseases; we also summarize the known molecular mechanisms of its protective actions.

Key words: Melatonin, neurodegenerative diseases, ischemic stroke, multiple sclerosis, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease

1. INTRODUCTION

Neurodegenerative diseases, characterized by irreversible and progressive loss of neurons, not only a major threat to human health, but also cause an enormous financial burden for health care systems across the world (1). Genetic alterations, obesity, inflammation and age are the most prevalent risk factors for the development of neurodegenerative diseases (2). These degenerative conditions are accompanied by locomotor deficits, memory loss and cognitive impairments, and share multiple biological processes including protein modification, oxidative stress, proteostasis, neuroinflammation, reduced neurogenesis and elevated cell loss (3-5). Ischemic stroke, a life-threatening and a global concerning event, is characterized by a sudden blood flow interruption following an embolism or thrombosis that occludes a cerebral vessel

supplying in a specific brain area (6). Ischemic stroke is a leading cause of disability and death in the world. Of note, one out of six individuals will have a stroke in their lifetime, and approximately 14 million of people suffer from stroke annually worldwide (7). There is no effective treatment for these disorders, and current therapies merely alleviate the symptoms. Therefore, novel and more effective therapeutic modalities are urgently required (8).

Melatonin (N-aceyl-5-methoxytryptamine), a multifunctional molecule mainly produced by the pineal gland in vertebrates, possesses many beneficial properties for health. The production of melatonin drops as a consequence of aging and also has lower levels in some diseases such as neurological disorders; this indicates that melatonin decline may contribute to the progression or development of human diseases as has been proposed by researchers (9-11). In addition to its role in the regulation of circadian rhythms and sleep, melatonin exhibits several biological actions including anti-apoptotic and anti-inflammatory activities, and protection against free radicals, all of which have been documented in experimental models of neurodegenerative diseases (12, 13). The current review summarizes the available data on protective potential of melatonin in reference to its delaying or preventing progressive neurological diseases.

2. CEREBRAL ISCHEMIA-REPERFUSION AND ISCHEMIC STROKE: WHAT HAPPENS IN THE BRAIN?

Ischemia-reperfusion injury is a common feature of ischemic stroke, which occurs when blood supply is restored after a period of ischemia. It is a pathological condition characterized by an initial restriction of blood supply in tissues or organs followed by the subsequent restoration of perfusion and concomitant reoxygenation. In its classic manifestation, occlusion of the arterial blood supply is caused by an embolus and results in a severe imbalance of metabolic supply and demand, causing tissue hypoxia (14). During brain ischemia-reperfusion, an increased reactive oxygen species (ROS) production causes a change in the reactivity of the vessels which damages vascular endothelial cells as well as the blood-brain barrier (15). Furthermore, ROS cause disability and degeneration of organelle and cell membranes through induced lipid peroxidation of unsaturated fatty acids (16). The accompanying cerebral edema, neuronal cell apoptosis, inflammation and the infarct size enlargement causes extensive brain tissue injury with the death of neurons and glia leading to debilitation and possible death of the individuals (17). Ischemia and reperfusion also activate various cell death programs, which are categorized as necrosis, apoptosis or autophagy-related cell death (18).

3. MELATONIN AND ISCHEMIA-REPERFUSION OF THE BRAIN: ROLES AND OPPORTUNITIES

Cerebral ischemia-reperfusion injury (CIRI) is a common disorder in hypertensive, diabetic and elderly individuals. After ischemic stroke, pathological damages may occur following inappropriate blood reflow with high mortality and disability rates (19). However, the efficient therapies beyond 6 hours after stroke onset are not currently available (20). Cerebral ischemia-reperfusion injury is a complex pathophysiologic event, which is associated with the mitochondrial dysfunction, inflammation, excitotoxicity, oxidative stress, and apoptosis (21, 22). Among these changes, oxidative stress caused by excessive ROS generation which results in lipid peroxidation, DNA damage, protein dysfunction and neuronal death plays an essential role in cerebral ischemia-reperfusion injury (CIRI) (23). To date, numerous attempts have been made to mitigate neuronal injury caused by CIRI; however, few efficient therapeutic options are currently available (24). It is well-known that CIRI precedes the actual infarction and morbidity; hence, the identification of the safe and effective therapeutic modalities to interrupt

the pathological processes of these life-threating events is essential. Several cellular processes including autophagy (25), apoptosis (26), neuro-inflammation and oxidative stress involved in the pathogenesis of CIRI have been identified (27).

Melatonin with the properties of anti-apoptosis, anti-inflammation, anti-oxidation, and circadian rhythm regulation has been suggested being a protective molecule against ischemic brain injury (28, 29). It has been reported that melatonin enhances the therapeutic impact of plasma exosomes on cerebral ischemia-mediated inflammation and inflammation-dependent pyroptosis *via* the TLR4/NF-κB pathway, indicating that melatonin administration influences the production of neural substances that have beneficial effects on CIRI. Melatonin downregulates exosomal miR-199a-5p and miR-100-5p to directly regulate TLR4, indicating the modulatory effects of melatonin on exosomal miRNAs (30). Melatonin also alleviates CIRI by activating OPA1-associated mitochondrial fusion. Moreover, it maintains the optimal neurophysiology, reduces N2a cell death, and corrects cellular energy metabolic disorders. Elevated OPA1-associated mitochondrial fusion inhibits mitochondrial oxidative stress and mitochondrial apoptosis. Conversely, OPA1 loss abolishes melatonin protective effects on N2a cell viability as well as mitochondrial homeostasis (31)**.**

Yang *et al*. showed that melatonin protects CIRI through suppressing neuronal oxidative stress, inflammation, autophagy, and apoptosis (32). The role of endoplasmic reticulum (ER) stress involving in brain ischemic reperfusion damages has been previously reported (26, 33); melatonin inhibits ER stress-mediated neuron cell death in cultured neurons and rat brains after ischemic reperfusion. Melatonin enhances survival of neurons in the penumbra of neural lesions and decreases infarction size in ischemia-reperfusion rats. It regulates protein levels through downregulating the expression of ER stress-related proteins including CHOP, ATF4, p-eIF2α, and p-PERK after ischemia-reperfusion (34). Melatonin exhibits a potent antioxidant activities in diverse *in vitro* and *in vivo* models of neurodegenerative diseases *via* scavenging free radicals and enhancing gene expression of antioxidant enzymes including glutathione peroxidase (GPx) and superoxide dismutase (SOD) (35). In line with this, Saleh and colleagues showed that melatonin restores antioxidant enzymes levels to the normal state in brains of ischemic/reperfusion rats (36).

Upon re-establishment of the blood supply, melatonin decreases reperfusion-mediated enhancements in pro-MMP-9 and MMP-9 enzyme activities, the expression of MMP-9 protein and *in situ* gelatinolytic activity 24 hours after transient ischemia in brain of rats. Melatonin-mediated reduction in MMP-9 expression and activity are associated with reduced blood clot leakage and infarct maturation of the ischemic brain, ameliorating neurological outcomes (37). The therapeutic roles of melatonin on CIRI are summarized in table 1. It appears that this molecule is a suitable candidate for therapy of ischemia-reperfusion injury. This field is in desperate need of clinical trials to test the efficacy of melatonin.

4. MELATONIN'S ROLE IN THE TREATMENT OF ISCHEMIC STROKE: KEY POINTS

As noted, stroke is a leading cause of morbidity and mortality (38). Stroke is a broad term indicating a variety of abnormalities caused by hemorrhage or occlusion of one of the main arteries which supply blood to the brain (39). Of note, disability associated with stroke results in considerable economic, social and emotional burden on individuals and society. It is estimated that, by the year 2030, the number of deaths due to stroke will reach 12 million and patients surviving from the stroke will increase to 70 million (40). Stroke exists in three main types including ischemic stroke, hemorrhagic stroke, and transient ischemic stroke; among them ischemic stroke is responsible for 85% of all cases, which is the second leading cause of mortality in the world (41, 42). However, except for the use of tissue plasminogen activator

during a short therapeutic window, few effective therapies can prevent the brain damage in the patients (43-45); therefore, identification of safe and effective neuroprotective treatments is a crucial and urgent task for researchers (46).

We have noticed an interest relationship between stroke and melatonin, i.e., patients with stroke have reduced levels of melatonin, indicating the possible role of this deficiency in the pathogenesis of the stroke (47). More importantly, melatonin has been shown a therapeutic option for stroke. Prophylactic melatonin application (10 mg/kg/day, i.p., 7 days) significantly alleviates ischemic injury and enhances the survival rate during 2 weeks post-ischemia with its neuroprotective effect by suppressing autophagy and ER stress (28). Zou and co-workers reported that treatment with melatonin (15 mg/kg/day; three times) 0.5 hour before photothrombotic stroke onset remarkably decreased the infarction volume at 72 hours post-stroke in the COX-1-gene wild-type mice. Melatonin may mediate its beneficial effects through enhancing penumbral cerebral blood flow. Thus, melatonin may exert some of its protective effect by enhancing and/or maintaining the activity of COX-1-gene during ischemia (48).

Melatonin increases neurogenesis and improves neuronal survival, even when applied one day after stroke (49). Melatonin preserves brain architecture integrity as well as neurological functions mainly *via* modulating oxidative stress and inflammatory signaling pathways (50). After transient global cerebral ischemia, chronic use of melatonin did not preserve hippocampal CA1 pyramidal neurons, but did improve ischemia-mediated cognitive impairments through remyelination *via* up-regulating the expression of ERK1/2 in oligodendrocytes and restoring glutamatergic synapses in the ischemic CA1 region (51). Kawada *et al*. shows that combination of suvorexant and ramelteon (a melatonin receptor agonist), rather than a GABA receptor agonist, improves subjective sleep quality without delirium induction in patients with acute stroke (52). Recently, an increasing number of studies have successively demonstrated that melatonin's neuroprotection against ischemic stroke derives from its inhibition of mitochondrial cytochrome C release (53) and the decrease of inflammatory responses (54). Overall, melatonin has therapeutic potential against ischemic stroke; however, the large scale of clinical trials should be encouraged and the underlying mechanisms should be clarified. Table 1 summarizes current data on melatonin therapy in the treatment of ischemic stroke**.**

5. MELATONIN, AN MOLECULE FOR THROMBOLYTIC THERAPY: A ROAD TO CLINICAL PRACTICE

The current treatment for acute ischemic stroke is still confined to thrombolysis and supportive therapy that benefits only a small proportion of stroke patients. As mentioned previously, melatonin has a variety of actions that may be helpful for acute stroke. Melatonin preserves the BBB permeability, attenuates the oxidative/nitrosative damage of ischemic neurovascular unit, and decreases a risk of hemorrhagic transformation accompanying the tPA-induced thrombolysis following ischemic stroke in mice (37). Exogenous melatonin effectively attenuates post-ischemic MMP-9 expression and activation, and reduces the reperfusion-induced hemorrhagic transformation and brain damage following a cerebral ischemic–reperfusion insult (55). Findings indicate that melatonin decreases acute ischemic brain damage, brain edema and hemorrhagic transformation, and may be a suitable add-on medicine to thrombolytic therapy for ischemic stroke patients (55). In mice treated with tissue plasminogen activator (t-PA), melatonin increases neuronal survival after 30 minutes middle cerebral artery occlusion through suppression of caspase-3 activity; however, t-PA itself significantly reduces the degree of injury (56). In an *in vivo* study, at 6 hours after photo-irradiation, either melatonin or t-PA, or a combination therapy with both melatonin and t-PA, did not significantly influence brain infarction, in comparison to controls. Subjects treated with t-PA had enhanced hemorrhagic formation, and these events were efficiently reversed by co-

therapy with melatonin. Therefore, melatonin ameliorates the postischemic damage of the BBB permeability and reduces the risk of adverse hemorrhagic transformation after t-PA therapy for ischemic stroke (57). The findings further support melatonin's pleural neuroprotective actions and indicate that melatonin may be suited either as a single treatment or an add-on substance to thrombolytic therapy for ischemic stroke patients.

6. THERAPEUTIC EFFECT OF MELATONIN ON NEURODEGENERATIVE AND NEUROLOGICAL DISEASES

Reduced melatonin levels are found in the blood and cerebrospinal fluid of Alzheimer's patients, even during the early onset of the disease (58). Decreased local melatonin synthesis in neuronal and immune cells, as well as in the glia and gut, may be critical for the etiology and management of Parkinson's disease (58). Clinical trials have investigated the role of melatonin supplementation in the alleviation of symptoms of Alzheimer's disease (59). The vast majority of clinical investigations support the beneficial effects of melatonin on cognitive impairment and sleep disorders (60-63). The cognitive impairment is a crucial symptom of neurodegenerative diseases. Animal study has also shown that melatonin attenuates isoflurane-mediated ER-stress and neuroapoptosis in the hippocampus, and reduces the serum levels of neuroinflammatory factors in newborn rats, leading to improved spatial memory and learning. Furthermore, suppression of the SIRT1/Mfn2/PERK pathway by lentivirus transfection results in the reduction of melatonin's neuroprotective effects (64). Sun *et al*. reported that beneficial actions of melatonin in improving spatial learning and memory probably involve downregulation of BACE1 and mitophagy (65)**.** Therapeutic effects of melatonin on the treatment of neurodegenerative diseases will be discussed below.

6.1. Alzheimer diseases.

Alzheimer's disease (AD), characterized by progressive memory loss and cognitive impairment, is the most prevalent age-related neurodegenerative disease. Alzheimer's disease is the cause of 60 to 80% of all dementias (66) and is significantly more common in females than in males. Around 35.6 million people are predicted to have AD worldwide, with 4.6 million new cases diagnosed each year (67). The chance of having the disease increases every five years after the age of 60; these rates rose from about 0.17% per year at age 65 to 0.71, 1.0, and 2.92% per year at ages 75, 80, and 85, respectively (68, 69). The primary etiology of AD is unknown and several factors including genetics, age, gender, and diet have a role in its development (70, 71).

The extracellular amyloid plaques and intracellular neurofibrillary tangles (NFT), the former predominantly in the form of β-amyloid (Aβ) and the latter in the form of hyperphosphorylated tau, may be considered its most outstanding pathological biomarkers. Irregular homeostasis of Aβ is a primary factor and often the initiator of AD. In other words, the accumulation of Aβ peptides, also referred to as senile plaques, due to the imbalance between their formation and removal results in the oxidative stress and subsequent inflammation and apoptosis in neural cells (72-74).

Melatonin as a small molecule easily crosses blood-brain barrier, where it binds to its receptors, MT1 and MT2 (75), and also has antioxidant action independents of its receptors (76). Studies have shown that melatonin levels in AD patients are lower than normal individuals of a similar age (77-79). The age-related drop in melatonin levels may associated with the progression of AD (80, 81). Studies using the APP695 transgenic mouse AD model have suggested that melatonin administration improves learning and memory impairment (82). Ample studies indicate that melatonin may be an effective treatment for AD pathology in the

early stages of the disease due to its antioxidant and antiapoptotic effects (83, 84). Moreover, researches have demonstrated that melatonin may reduce Aβ production, independent of its antioxidant effects.

In AD, Aβ peptides are derived from the aberrant cleavage of the amyloid precursor protein (APP) (85). Evidence has revealed that melatonin may reduce Aβ formation (86) by modulating cAMP level (87, 88), to interfere APP gene expression. Melatonin promotes non-amyloidogenic processing and α-secretase function. MT1 and MT2 activation by melatonin stimulates the Gq/ PLC/ PKC, Gi/ PI3K / PDK1/ PKC and Gs/ cAMP/ PKA signaling pathways and resulting in ERK1 phosphorylation which, then, phosphorylates CREB and Oct-1 enhances ADAM10 transcription and lowers Aβ overproduction (89). In addition, melatonin, as a stimulator of SIRT1 (90, 91), may trigger ADAM10 expression, promote non-amyloidogenic processing, and protect against excess Aβ generation (86, 92, 93).

Melatonin modulates the two major regulators of Aβ synthesis. First, melatonin promotes the expression of PIN1, a cis-trans peptidyl-prolyl isomerase, which is a crucial factor in inhibiting Aβ formation; as a result, to inhibit amyloidogenic process. Studies have suggested that melatonin treatment increases the expression of PIN1 mRNA and protein in a dose-dependent manner and lowers Aβ production (94). Second, melatonin inhibits the amyloidogenic process by blocking GSK-3 phosphorylation. Studies reveal that GSK-3β is overproduced in the brains of patients with AD, and this production rises with age. Strong evidence suggests that impaired GSK-3β regulation impacts Aβ formation and tau hyperphosphorylation in AD (87). Melatonin inactivates GSK-3 and lowers Aβ formation by activating and phosphorylating PKC. To achieve this, melatonin interacts with the MT2 to activates the PLC / DAG / PKC pathway (87). The PKC activation also inhibits Aβ formation by promoting α-secreted non-amyloidogenic APP processing (87). The PKC protein is oxidative stress-sensitive and an oxidizing environment may inactivate this signaling molecule. Therefore, as an antioxidant, melatonin prevents PKC inactivation by reducing oxidative stress (86).Tau hyperphosphorylation is another major pathogenic feature in the pathophysiology of AD, which contributes to the disruption of tau binding to microtubules and the subsequent alterations in the stability of microtubules; melatonin attenuates Tau hyperphosphorylation by inhibiting GSK-3β (75).

Melatonin, on the other hand, increases the glymphatic CSF/interstitial fluid (ISF) exchange system. The glymphatic system is an active water exchange process in the extracellular space (ECS) in the brain; it serves the same purpose as the lymphatic system in other tissues (95). CSF/ISF exchange is assisted by aquaporin-4 (AQP4) which are abundantly expressed in astrocyte perivascular end feet (96, 97). This system helps to clean Aβ peptides and Tau proteins from brain. Studies have revealed that Aβ peptide elimination increases considerably during sleep (98), and failure of Aβ clearance, as a cause of sleep disturbance, might exacerbate the progression of AD. This is also applied to the tau protein. Studies have found that in a murine traumatic brain injury model, AQP4 depletion increases neurofibrillary tangle formation and the accumulation of extracellular tau (99). Moreover, glymphatic Aβ clearance is augmented when AD transgenic mice receive melatonin treatment (100).

Clinical research has shown that melatonin levels are lowered in AD patients compared to healthy subjects (101) and treatment with melatonin alleviates mild cognitive impairment (83, 84). Theoretically speaking, the beneficial effects of melatonin in inhibiting AD disease is evidence, especially in experimental animals; nevertheless, further large scale of clinical trials are required to determine efficacy of melatonin in the treatment of AD patients.

6.2. Parkinson disease.

Parkinson's disease (PD) is the second most common neurodegenerative disease, affecting about 1.8% of people over 65; the number of PD patients is expected to double by 2030 (102, 103). Several underlying factors, including age, sex, socioeconomic conditions, and genetics are involved in development of Parkinson's disease (103). Symptoms of the disease include motor (tremors, swallowing difficulty, rigidity, hypokinesia, bradykinesia, and postural instability) and non-motor (cognitive and sleep disturbances) dysfunctions (104). The major pathogenic cause of the disease is the reduction in dopaminergic neurons in the substantia nigra (SN) (73) and striatum (103, 104). Motor symptoms arise after the loss of 3/4 of the dopaminergic cells in the SN (105). In addition, increased inflammatory factors including NF-κB, IL-1, IL-6 (106), Cox-2, TNF-α, iNOS, and INF-γ (107, 108) in glial cells and elevated oxidative stress due to excessive free radical generation following mitochondrial damage play an essential roles in the progression of the disease (109-111).

A reduction in melatonin MT1 and MT2 density in certain regions of the brain, such as in the amygdala and SN, is common in patients with PD (106). In experimental PD model , melatonin increases the concentration of nigral and striatal dopamine (112); it also reportedly prevents the depletion of dopamine and disruption of dopaminergic neurons (113) and neurotoxins-induced dopaminergic neuron death (114, 115). Moreover, Ozsoy *et al*. 2015 demonstrated an elevation in the activity of superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) and reduction in the malondialdehyde (MDA) level and death of dopaminergic neurons after melatonin treatment in the SN of rats with PD model induced by 6-OHDA (116). Administration of melatonin also reduces oxidative stress in the mouse model of PD resulting from administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (117), a frequently-used drug to induce PD-like signs. A significant reduction in the MPP (+)-induced oxidative stress has been reported after treatment of cortical neurons with melatonin (118). Regarding melatonin's capacity to suppress free radicals, transfer electrons, and repair damaged biomolecules, it may effectively protect neurons and glial cells from the oxidative stress pathway in PD.

In vitro and *in vivo* studies have demonstrated that melatonin reduces DNA fragmentation and mitochondrial deficiency in PD models (112, 118-120). Moreover, melatonin decreases P-p53, Bax, and caspase 9 expression (113) and increases Bcl-2 and p53 levels (121), leading to the inhibition of the apoptosis pathway. Melatonin limits neuroinflammation by inhibiting COX-2 activity in the mouse model of PD induced by MPTP (117). In addition, López *et al*. (152) have found that in MPTP-induced PD mice, melatonin prevents the rise of iNOS, as a pathologic hallmark of PD-associated neuroinflammation (122). Over-expression of α-synuclein is strongly associated with PD pathogenesis (123, 124). α-Synuclein accumulation and fibril formation cause apoptosis, dopaminergic nerve terminal damage *via* caspase activation (125-127). The protective effect of melatonin on α-synuclein-induced damage to dopaminergic neurons in the SN has been observed in animal models (114). Melatonin prevents α-synuclein assembly and fibril formation (128) by suppressing protofibril development and instability in precursor fibrils (114, 128).

The expression of AQ4 is significantly reduced in PD patient brains compared to the healthy individuals (129). The AQ4 water channels have an essential role in lowering CSF α-synuclein levels (130). As mentioned previously, melatonin preserves the function of glymphatic system and increases AQ4 expression (86); hence, it has a favorable effect on PD patients. Based on the data obtained from experimental models of Parkinsonism, it can be concluded that melatonin have the potential to suppress the progression of this neurodegenerative disorder (131). However, further clinical trials are required to definitively prove the beneficial effects of melatonin on PD patients.

6.3. Amyotrophic lateral sclerosis.

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder, characterized by progressive death of motor neurons in the ventral horn of the spinal or bulbar level. This neurodegenerative disorder is categorized in two forms including non-hereditary form, which is the most common (90–95%) and the familial-type of ALS (FALS), associated with genetic dominant inheritance factor which constitutes the remaining 5–10% of the ALS cases. Muscle weakness, twitching, and cramping are the most common symptoms of ALS, leading to muscle impairment (11). Due to the role of oxidative stress in the pathogenesis of ALS, melatonin, as an antioxidant and free-radical scavenger, is suggested to be a beneficial treatment for patients with ALS (9). The impact of melatonin on progression and overall survival of ALS has been investigated through a Cox proportional hazards ratio model which determined the effect of melatonin on time to death. As secondary outcomes, the effect of melatonin on standardized ALS functional rating scale (sALSFRS) and percentage of predicted forced vital capacity (FVC) scores has been investigated by linear mixed effects regression models. The rate of annualized hazard death has been significantly reduced in melatonin users compared to the non-melatonin users [HR=0.241 (95% CI 0.088 – 0.659), p=0.0056]. Furthermore, the rate of decline in the sALSFRS score and change in the percentage of predicted FVC score was slowed in melatonin treated patients compared to the patients did not receive melatonin (9). Considering the positive outcomes with the use of melatonin in ALS, further research of melatonin is warranted to investigate its possible efficacy in treating this deadly disease.

6.4. Multiple sclerosis.

Multiple sclerosis (MS) is a neuroinflammatory, chronic, autoimmune demyelinating disorder of the CNS which usually appears in young adults; the condition influences millions of people, either as patients or as care givers across the world (132). Its clinical manifestations are variable including sensory and visual impairments, coordination and motor disturbances, and pain, spasticity, fatigue, and cognitive defects (133). Multiple sclerosis is related to numerous pathophysiological mechanisms such as oxidative stress, multiple leukocytes infiltration, altered immune system, chronic inflammation, breaching of the BBB as relapsing-remitting (RR) episodes, demyelination leading to neuronal and axonal damage, remyelination and repair systems activation (134-136). A combination of autoimmune, environmental, and genetic factors contributes to the risk of developing MS (137). Currently, several immunosuppressive and immunomodulatory therapies are available to regulate immune responses of patients. However, these treatments have limited curative effects and are also associated with serious side effects. Thus, it is essential to explore safe and effective complementary and/or alternative therapeutic approaches. It has been observed that the pineal calcification caused low melatonin level are associated with the increased incidence of MS in patients, particularly in those with some degree of brain atrophy (138). Of note, the levels of urine 6-sulphatoxymelatonin levels (the major melatonin metabolite) are lower in MS patients compared to healthy subjects, indicating the possible involvement of melatonin in MS pathogenesis (139). The therapeutic effect of melatonin on MS has been investigated in animal studies and human trials. Melatonin considerably decreases the clinical scores of experimental autoimmune encephalomyelitis (EAE) as well as the demyelinating plaques number. Moreover, melatonin reduces the mRNA expression of the regulatory enzyme of kynurenine pathway, indoleamine 2,3-dioxygenase 1 (140).

Pyruvate dehydrogenase (PDH) is a crucial modulatory enzyme in energy metabolism and catalyzes the pyruvate to form acetyl-coenzyme A (141-143). Pyruvate dehydrogenase kinase (PDK) is able to negatively modulate PDH activity through phosphorylation of one of its

subunits. PDK possesses four identified tissue-specific isozymes, sharing 70% DNA sequences (144). The combination of melatonin and disopropylamine dichloroacetate, a PDK4 inhibitor, has been shown to have beneficial effects on cerebral metabolism and remyelination in animal model of MS. This co-therapy seems to have better effect to inhibit pro-inflammatory and increase anti-inflammatory cytokines than melatonin treatment alone and promotes the recovery of the expression of the decreased oligodendrocytic markers in EAE. This co-treatment also restores PDC function while decreasing the lactate levels (145). To target the memory defects in MS, melatonin shows its therapeutic effects by upregulating cAMP-response element-binding protein to increase the gene expression of the postsynaptic density protein 95 and synapse-associated synaptophysin in the prefrontal cortex (146). A result from a 6-month clinical trial shows that melatonin significantly decreases the serum levels of pro-inflammatory cytokines including TNF-α and IL-1β, and oxidative stress in RR-MS patients (147). In a pilot study, Jallouli *et al*. have reported that acute nocturnal melatonin (6 mg) ingestion is safe for increasing mobility, fall risk and postural balance in RR-MS patients, probably by ameliorating cognitive function and sleep quality (147). In a case report, a patient with MS treated with pharmacological doses of melatonin for several years exhibited remarkable improvement in all aspects of the disease (148). Hsu and colleagues also showed that the use of melatonin significantly ameliorates the mean total sleep time in MS patients (149). Table 1 summarizes current evidence on the therapeutic roles of melatonin in neurodegenerative diseases including MS.

6.5. Huntington disease.

Huntington's disease (HD) is a devastating genetic neurodegenerative disease, affecting 8 to 10 persons per 100,000 people globally. There is no effective treatment for this neurodegenerative disorder. HD is characterized by progressive motor disorders, cognitive impairment, psychiatric problems, dementia, depression, and weight loss (150). The recurrence of cytosine-adenine-guanine (CAG)c sequence in exon 1 is the primary cause of HD, which initially affects the striatum and then the cortex (151). Until recently, the definite function of the Huntington protein remained unknown (152).

In HD, oxidative stress plays a key role in the pathology of neuronal degeneration and damage (153-156). Reactive oxygen species induce the DNA damage with high levels of 8-hydroxydeoxguanosine in the putamen of HD patients (157). To date, treatment of HD with emphasis on antioxidant protection seems partially effective. Melatonin is effective in lowering oxidative damage in the central nervous system due to its ability to rapidly passing the blood-brain barrier. Antioxidant properties of melatonin are multiple including directly scavenging free radicals, inducing mitochondrial and neuronal nitric oxide synthase activity by binding to the calcium-calmodulin complex and increasing activities of antioxidant enzymes such as SOD, GPx and catalase (158-161).

Melatonin has profound protective effect on mutant Huntington (mutant-htt) ST14A cells, an *in vitro* model of HD (53, 156, 162). 3-nitropropionic acid, a mitochondrial complex II inhibitor, accurately induces the neurochemical, histological, and clinical characteristics of HD and is therefore utilized as an experimental model of HD (163, 164). In a 3-nitropropionic acid-induced rat model of HD, melatonin delayed the symptoms of HD through its antioxidant actions (165).

Melatonin may also prevent the release of cytochrome c from mitochondria into the cytoplasm and the activation of mutant Htt-induced caspase-1, hence suppressing mitochondrial and cell death pathways. A relation has been observed between MT1 receptor expression and development of HD (166, 167). Mutant Huntington-mediated toxicity leads to the loss of MT1 receptors. The deficiency of MT1 receptors sensitizes neurons to cell death,

while overexpression of these receptors protects neurons. Furthermore, MT1 receptor expression decreases as HD progresses, and melatonin administration delays the reduction of these receptors. Melatonin also delays disease onset and death in R6/2 mice (CAG repeated 110-115 times); this effect of melatonin is mediated by the activation of MT1 receptors (166, 167).

The accumulation of intracellular calcium, which causes mitochondrial dysfunction, and the stimulation of the N-methyl-D-aspartate (NMDA) receptor are other means to induce HD-like pathogenesis (168). Kainic acid is the most commonly used excitotoxic agents to induce HD models in both rodent and primate. Melatonin diminishes the neuronal excitotoxicity generated by kainic acid *in vivo* and *in vitro* conditions by decreasing lipid peroxidation and free radical production caused by interaction of kainic acid with NMDA receptors (169). In summary, considering the positive preliminary findings, additional basic and clinical research should be pursued to further clarify the effects of melatonin treatment on HD.

6.6. Traumatic brain injury.

Traumatic brain injury (TBI) is a leading cause of long-term disability and mortality in young adults. The devastating consequences of TBI on emotion, executive functioning, and cognition have been well established (170). The increased evidence suggests that TBI is a risk factor for neurodegenerative diseases such as Alzheimer's disease(171) . Currently, there are no Food and Drug Administration (FDA)-approved medicines for treatment of TBI (172). Melatonin has many potential beneficial effects as a treatment for TBI (173). Melatonin is the most colloquially known sleep aid sold as the form of food supplement (174). Melatonin is produced in pineal gland at night to configuration of circadian rhythm, but, it also has pleiotropic effects including anti-inflammatory, antioxidant, and cell cycle-modulating properties (175). In this review, we summarize the role of melatonin in preventing post-TBI neurodegeneration, particularly focusing on melatonin's potential to reduce the risk of cognitive impairment after TBI. The available data highlight its neuroprotective and anti-inflammatory effects. Melatonin reduces neuroinflammation and edema, late-phase activation of nuclear factor-kappa light chain enhancer of activated B cells (NFkB) and activator protein 1 (AP-1) to the basal level while promotes the activity of SOD and GPx to protect cerebral tissue from oxidative stress (176). Studies on adult mice have shown that melatonin at specific doses decreases lipid peroxidation levels and promotes antioxidant activity following TBI (176). Melatonin preserves hippocampal neurons following brain trauma and limits deficits in spatial memory as identified by performance in a water maze task (173).

Furthermore, in addition to its inhibitory effects on inflammatory processes following TBI, melatonin appears to indirectly influence cognitive function by regulating sleep-wake cycles (177). Melatonin exhibits neuroprotective effects through its anti-inflammatory and antioxidant function to reduce the excessive neuronal reactions occurring after TBI in human brain (172). The proposed include, as noted, its ability to attenuate pro-inflammatory NF-kB signaling, scavenge free radicals, decrease apoptotic cell death, and reduce the expression of abnormal proteins such as Aβ and p-tau (172). A reduction in such secondary injury processes may result in decreased risk of developing neurodegenerative diseases such as Alzheimer's disease following TBI (178). Beyond the direct anti-inflammatory and antioxidant actions of melatonin, the receptor-mediated actions are also involved in the protection against TBI as well (179).

Although evidence suggests melatonin's ability to reduce post-TBI cognitive decline as measured by subject performance on memory tasks, the longitudinal data on whether melatonin decreases the risk of developing dementia after TBI is lacking. Thus, research into the role of the long-term protective actions of melatonin in individuals suffering with TBI is warranted.

6.7. Spinal cord injury.

Spinal cord injury (SCI) often results in the loss of sensory and motor function (180). In severe cases, SCI leads to paralysis and death. In patients with SCI, primary injury from the initial trauma is followed by a secondary injury cascade of cellular and molecular events (181). The secondary injury exacerbates neurologic damage and enhances loss of function. This secondary injury may be caused by the production of ROS and reactive nitrogen species (RNS) which damage protein, DNA, and cell membranes. The consequences of the secondary injury include mitochondrial dysfunction, neurotransmitter accumulation, disruption of the blood-brain barrier and blood-spinal cord barrier (BSCB), apoptosis, excitotoxicity, and inflammatory and immune processes (181). Melatonin exerts neuroprotective effects for the secondary pathophysiological processes associated with SCI (182). Melatonin regulates the altered levels of MDA, glutathione (GSH), SOD and myeloperoxidase (MPO) after SCI and manages them back to the normal levels (183). Melatonin may also protect tissues from secondary injury of SCI through other biological actions such as inhibition of inflammation, apoptosis, and attenuation of edema (184). Therapeutic potential and underlying mechanisms of melatonin for SCI are reduction of oxidative stress, regulation of nitric oxide synthase (NOS), anti-inflammation, promoting BSCB repair, inhibition of apoptosis and attenuation of edema (184). The bulk of studies illustrating the beneficial actions of melatonin in reducing the severity and improving recovery from SCI come from experiments in animals; clearly, what is needed are clinical trials specifically designed to examine the efficiency of melatonin on SCI patients.

7. REGENERATIVE ACTIVITIES OF MELATONIN IN THE RECOVERY OF NERVE INJURIES

The peripheral nervous system relays information between the CNS and peripheral receptors located throughout the body (185). Most peripheral nerve injuries (PNI) are secondary to toxicity from local anesthetics, surgical resection, or trauma. Severe neuropathic pain is one of the morbidities that occurs following PNI (186, 187). Application of novel strategies is required to improve the recovery of injured nerves.

Melatonin exhibits beneficial potentials in neuroregeneration after PNI (188). Melatonin promotes the migration and proliferation of Schwann cells *via* the Shh signaling pathway after PNI, leading to the peripheral nerve regeneration (189). Sciatic nerve damage causes a remarkable decline in nerve conduction velocity. According to the findings from a recent investigation, melatonin considerably increases the nerve conduction velocity and promotes the histological regeneration, as well as accelerates sciatic functional recovery compared to a control group receiving placebo (190). Melatonin also enhances functional recovery after end-to-side neurorrhaphy (191). Liu and colleagues (192) showed that animals with melatonin treatment displays increased β3-tubulin and GAP43 expression one month after end-to-side neurorrhaphy. Melatonin also promotes neurite outgrowth and increases the expression of melatonin receptors as well as β3-tubulin in mouse neuroblastoma N2a cells. Moreover, melatonin suppresses the activation of calmodulin-dependent protein kinase II (CaMKII); thus, β3-tubulin remodeling may involve CaMKII-induced Ca^{2+} signaling (192).

8. MELATONIN AND MICROGLIA POLARIZATION IN NEUROLOGICAL DISEASES

Microglia are resident immune cells in the central nervous system (CNS), contributing to the maintenance of CNS homeostasis in the normal condition. Microglia can drastically alter

their phenotypes and functions (pro-inflammation, anti-inflammation as examples) in response to microenvironmental changes. Microglia play an important role in inflammatory processes after ischemic stroke. Modulating microglia polarization from pro-inflammatory phenotype to anti-inflammatory state has been suggested as a potential therapeutic approach in the treatment of ischemic stroke (193).

Retinoic acid-related orphan nuclear receptor alpha (RORα) is a crucial circadian nuclear receptor with a modulatory impact on immune responses. RORα has been identified as a natural ligand of melatonin (194). Melatonin (20 mg/kg) significantly enhances the RORα levels and protects dopamine neurons, with reduced inflammation and promoted anti-inflammatory M2-like phenotype in the microglia of PD model (195). In the early stage of SCI, melatonin (50 mg/kg) inhibits pro-inflammatory responses and promotes M2 polarization of microglia in the spinal cord, contributing to functional recovery (196). Melatonin (20 mg/kg) lowers brain damage and reduces brain infarct through shifting microglia phenotype from pro-inflammatory to anti-inflammatory polarity by regulating STAT3 signaling pathway (197). Melatonin has been reported to effectively abrogate cellular inflammatory responses by reducing migration of the circulatory neutrophils and macrophages/monocytes into the ischemic brain and by decreasing local microglial activation within the ischemic hemisphere after transient focal cerebral ischemia in rats (198). Microglial necroptosis also plays an important role in the pathogenesis of intracerebral hemorrhage (ICH). Melatonin inhibits ICH-induced microglial necroptosis through inhibiting the expression of receptor-interacting protein 3 (RIP3) by regulating the deubiquitinating enzyme A20 expression (10). However, the effect of melatonin specifically on microglia polarization after stroke and underlying mechanisms remain unknown.

9. NEUROPROTECTIVE EFFECTS OF COMBINED THERAPY OF MELATONIN WITH MESENCHYMAL STEM CELL: A NEW AVENUE FOR FUTURE RESEARCH

Mesenchymal stem cells (MSCs) are multipotent cells that are isolated from various tissues such as dental tissue, placenta, periosteum, bone marrow, muscle, adipose tissue, and others (199, 200). For restoring organ and tissue functions, MSCs have recently emerged as promising sources; however, there are several potential safety risks for their clinical use such as potential tumorigenicity, sensitivity to toxic environments, senescence, and an availability (201). MSC-based therapy is promising with the potential of organ regeneration (202). Implantation of a sufficient number of active MSCs can restore the function of a damaged organ caused by sepsis, high glucose, drugs, ischemia, wounding, and other pathological circumstances (203-206). However, the MSCs lifespan is restricted by the harsh microenvironment, which hence results in an insufficient availability of cells (207).

Melatonin administration preserves the function of MSCs both *in vivo* and *ex vivo*. Melatonin generally serves as a cell-protective and homeostatic molecule protecting MSCs from aging, ischemia, apoptosis, inflammation, and oxidative stress, therefore, preserves their viability and differentiation in diverse tissues and organs (208, 209). Recently, a large number of studies have shown that melatonin-treated MSCs have therapeutic potential in a spectrum of disorders including neurological diseases. Zhang *et al.* (210) reported that melatonin and adipose-derived stem cells (ADSCs) co-treatment increases number of lysosomes and autophagosomes, and the expression of beclin-1 and LC3-II/LC3-I proteins in the recipients . Moreover, this combination enhances myelin regeneration and motor neuron number as well as decreased atrophy of the gastrocnemius muscle. The results have also shown that this combination promotes peripheral nerve regeneration through autophagic process (210). Currently, Liu and colleagues (211) evaluated the beneficial effects of melatonin-pretreated

MSCs in an animal model of SCI. They find that extracellular vesicles (EVs) derived from melatonin-pretreated MSCs (MEVs) boosts motor behavioral recovery and microglia polarization from M1 to M2 phenotype, as well as suppresses oxidative stress compared to the non-treated EVs. Additionally, proteomics analysis shows that ubiquitin-specific protease 29 (USP29) is markedly enhanced in MEVs, and USP29 knockdown declined MEVs-mediated beneficial properties *in vitro* and *in vivo*. The data indicates that melatonin stabilizes USP29 mRNA to produce its protective effect.

Pretreatment of MSCs with melatonin facilitates MSCs survival and, thus, reduces AD complications to improve cognition and memory. In a recent study, bone marrow derived MSCs (BMSCs) were separated from femural and tibial bones of the rat and pretreated with melatonin (5μM) for 24 hours. Both melatonin-treated BMSCs are intravenously transplanted into rats and they are found to transmigrate to the brain tissues. Melatonin-treated BMSCs significantly boosts memory, cognition and learning in comparison with non-melatonin treated BMSCs (212). The similar results have been observed by Nasiri *et al*. They have observed that intravenously transplanted ADSCs migrate into the brain of rats; however, the melatonin-treated ADSCs produce better outcomes as to the memory, cognition and learning than the non-treated ADSCs. Furthermore, a more significant enhancement in Aβ deposition clearance as well as in microglial cells reduction are observed in animals with melatonin-treated ADSCs compared to the non-treated ADSCs (213).

In the case of cerebral ischemia, Tang and co-workers have reported that melatonin pretreated MSCs have higher survival rate *in vitro* and lower apoptosis after transplantation into the ischemic brain of animals than the non-treated MSCs. Melatonin-treated MSCs transplantation can effectively reduce cerebral infarction and ameliorated neurobehavioral outcomes. Neurogenesis and angiogenesis are significantly increased in rats with melatonin-treated MSCs. Melatonin also elevates the p-ERK1/2 level in MSCs, which is inhibited by luzindole, a melatonin receptor antagonist. U0126, an inhibitor of ERK phosphorylation, can reverse the protective effects of melatonin, indicating that melatonin contributes to the improved MSC survival and functions *via* activating the ERK1/2 signaling pathway (214). Promising therapeutic potentials of melatonin-stem cell combination should be further examined by trials in several neurodegenerative diseases where cell loss is a major factor.

Table 1. Summarized data on therapeutic effects and signaling pathways of melatonin on neurodegenerative diseases

Disease	Dose	Targeting pathways	Effect (s)	*Model*	Ref.
Cerebral ischemia-reperfusion injury	-	PERK-EIF2α	Enhanced autophagy in brain vessel endothelial cells preserved ER function reduced refractory stress granules.	*In vivo*	(215)
	25-50 mg	TNF-α, Nrf-2, HO-1, NF-κB p65, bax, bcl-2	Intranasal administration of melatonin loaded in lipidic nanocapsules increased antioxidant, anti-apoptotic and anti-inflammatory effects.	*In vivo*	(216)
	-	-	Intranasal administration of melatonin loaded in polymeric nanocapsules reduced hippocampal inflammation and oxidative stress.	*In vivo*	(217)
	10, 20, 40 mg/kg	Bax and Caspase-3, IL-1*β*, IFN-*γ*, NF-*κ*B p65, MDA, ROS, JNK/FoxO3a/Bim	Anti-inflammatory, antioxidant and anti-apoptosis effect.	*In vivo*	(218)
	-	GSK-3β, RIP1K	Ameliorated axonal regeneration and decreased infarct volume.	*In vivo*	(219)
	-	SIRT1-BMAL1	Enhanced cell survival, anti-apoptosis and antioxidant effects, and increased autophagy.	*In vivo*	(220)

	15 mg/kg	α7nAchR	Protective impact on ischemia/reperfusion-mediated BBB damage.	*In vivo*	(221)
	5, 10 mg/kg	Akt-SIRT3-SOD2	Ameliorated cerebral infarct volume, neurological deficit, brain edema, and cell viability. Decreased ROS generation, mitochondrial swelling and cytoplasmic cytochrome *c* release.	*In vivo*	(222)
	400, 1200, 2400 μg/kg	MDA	Reduced ultrastructural damages in white and gray matter.	*In vivo*	(223)
	10 mg/kg	MDA, NO, IL-1β, TNF-α, NF-kB, COX2	Attenuated the cerebral ischemic injury.	*In vivo*	(36)
	10 mg/kg	TNF-α, IL-6, IL-10	Anti-inflammatory effect.	*In vivo*	(224)
	20, 30, 50 mg/kg	NOX-1, NOX-2, p22phox, TNF-α, NF-κB, MMP-9, Bax, caspase-3, PARP	Decreased infarct volume and increased antioxidant, anti-apoptosis and anti-inflammatory effects.	*In vivo*	(225)
	20 mg/kg	SIRT3	Reduced cell apoptosis and neurological dysfunction.	*In vivo*	(226)
	10, 20 mg/kg	Yap-OPA1	Decreased infarct area and neuron death.	*In vivo*	(31)
	10 mg/kg	RORα	Reduced cerebral apoptosis, infarct volume, ER stress and nitrative/oxidative stress.	*In vivo*	(227)
	5 mg/kg	GSHPx, SOD, LC3II/LC3I, MDA, P62, IL-10, miR-26a-5p, NRSF TNF-α, IL-6	Increased antioxidant, anti-apoptotic, anti-autophagic and anti-inflammatory effects.	*In vivo, in vitro*	(32)
Ischemic stroke	20 mg/kg	STAT3	Decreased brain infarct, neurologic functions and increased anti-inflammatory effects.	*In vivo, in vitro*	(197)
	10 mg/kg	ERK1/2, VGLUT-1	Improved cognitive function.	*In vivo*	(51)
	5, 10 mg/kg	doublecortin, ki67, adamts20, adam11	Increased endogenous neurogenesis and cell proliferation and exerted antioxidant and anti-inflammatory effect.	*In vivo*	(228)
	10 mg/kg	MuRF1, MAFbx, IGF-1	Prophylactic and therapeutic effect on muscle atrophy.	*In vivo*	(229)
	5 mg/kg	-	Decreased BBB permeability and risk of hemorrhagic formation after t-PA therapy.	*In vivo*	(57)
	10 mg/kg	SIRT1, Bcl2, Bax	Reduced infarct volume, brain edema, and increased neurological scores.	*In vivo*	(230)
	20, 50 mg/kg	HMBG1, TLR2, TLR4, TRAF6, NF-κB, IL-1β, IL-6, TNF-α/IFN-γ, JNK	Improved neurological functions through inhibiting oxidative stress and inflammation.	*In vivo*	(50)
	50 mg/kg	MMP-9	Attenuated BBB disruption.	*In vivo*	(231)
Multiple sclerosis	0.1 mg/kg	AhR, IDO-1	Decreased the number of demyelinating plaques and the EAE clinical score.	*In vivo*	(140)
	6 mg	-	Improved functional mobility, postural balance and fall risk *via* enhancing sleep quality and cognitive functions.	Human	(232)
	0.5, 3 mg	-	Improved sleep quality.	Human	(149)
	1 mg/kg	GSH, TNF-α	Increased antioxidant and anti-inflammatory effects.	*In vivo*	(233)
	80 mg/kg	CREB, synaptophysin, PSD-95	Ameliorated the memory defects caused by cuprizone toxicity.	*In vivo*	(146)
	3 mg	IL-1β	Increased anti-inflammatory effect.	Human	(234)
	80 mg/kg	GSH, SOD, CAT, IL-1β, TNF-α	Increased antioxidant and anti-inflammatory effects to improve locomotor activity.	*In vivo*	(235)
	10 mg/kg	PDK-4, IL-4, IL-10, IL-1β, TNF-α	Increased anti-inflammatory effect.	*In vivo*	(236)
	25 mg	IL-1β, TNF-α, IL-6, LPO, NOC	Increased anti-inflammatory and antioxidant effect.	Human	(147)
	1 mM	SIRT1, CAT, MnSOD	Increased antioxidant effect.	*In vitro*	(237)

	0.1 mM	Th1, Th22	Increased anti-inflammatory effect.	*In vitro*	(238)
Huntington's disease	50, 100, or 150 µg	*Cwo, Cry, Cyc, Per, Tim, Clk*	Ameliorated eclosion behavior and locomotion ability.	*In vivo*	(239)
	2, 4 mg/kg	GSH, MDA, CAT, SOD	Decreased 3-NPA-mediated weight loss, impaired locomotion, learning-memory, motor coordination and increased antioxidant effect.	*In vivo*	(240)
	10, 20 mg/kg	-	Restored 3-NP-mediated loss of dendritic spines in the cortex and striatum, and the decrease in cerebellar granule cell, but not hippocampal CA1 neuronal arborization.	*In vivo*	(241)
	5, 20 mg/kg	SOD	Antioxidant effect.	*In vivo*	(242)
ALS	-	LC3II/LC3I, SIRT1, Beclin-1, p62	Reversed the ALS-mediated short survival time, rotating rod latency decrease and weight loss. Induced autophagy.	*In vivo*	(243)
	-	-	Reduced annualized hazard death rate.	Human	(9)
	30mg/kg, 10 l/g	Rip2/caspase-1, cytochrome c, caspase-3	Delayed disease onset, mortality, neurologic deterioration and inhibited motor neuron death and ventral horn atrophy.	*In vivo*	(244)
	0.5 mg/mL, 50 µM, 300 mg	Protein carbonyl	Attenuated glutamate-mediated cell death of cultured motoneurons. Delayed disease progression and prolonged survival Increased antioxidant effect.	*In vivo, in vitro*	(245)
Traumatic brain injury	200 mg/kg	-	Reduced brain edema	*In vivo*	(246)
	10 mg/kg	iNOS, MMP-2, MMP-9	Reduced brain edema and infraction, astrocytes infiltration and CCI-induced oxidative stress.	*In vivo*	(247)
	5, 20 mg/kg	MDA, SOD, GPx	Decreased BBB permeability, brain edema and ICP Increased veterinary coma scale.	*In vivo*	(248)
	10mg/kg	Nrf2-ARE	Improved cortical neuronal degeneration, brain edema and antioxidant effect.	*In vivo*	(249)
	10 mg/kg	TNF-α, mTOR, p70S6K, S6RP, IL-1β	Restrained microglial activation and increased anti-inflammatory effect.	*In vivo*	(250)
	5, 10 mg/kg	GPx, β-carotene, vitamin C, and E	Increased antioxidant effect.	*In vivo*	(251)
	5 mg/kg	caspase-3 and -9, ROS	Increased antioxidant effect and decreased intracellular free Ca(2+).	*In vivo*	(252)
	5, 10, 20 mg/kg	GFAP	Decreased astrogliosis and increased antioxidant effect.	*In vivo*	(253)
	10 mg/kg	Bax, cytochrome c,	Induced autophagy and inhibited apoptosis.	*In vivo*	(254)
	4 mg/kg	p38, ERK-1/2, SAPK/JNK-1/2, iNOS	Melatonin/memantine combination decreased brain injury and DNA fragmentation.	*In vivo*	(255)
	5 mL/kg	mTOR, IL-1β	Activated mitophagy and inhibited inflammation.	*In vivo*	(256)
	10 mg/kg	KCC2, BDNF, p-ERK	Decreased brain edema, neurological deficits and improved cortical neuronal apoptosis.	*In vivo*	(257)
	5, 20 mg/kg	IL-10, TNF-α, IL-1ß, IL-6	Increased anti-inflammatory effect.	*In vivo*	(258)
	2 mg	-	Improved sleep quality.	Human	(259)
	20 mg/kg	p-NF-κB, p-AMPK, p-CREB	Improved energy depletion and protected against brain injury.	*In vivo*	(260)
	10 mg/kg	PGC-1α, Bax, Drp1	Decreased mitochondrial fission, oxidative damage, brain edema and improved mitochondrial fusion	*In vivo*	(261)
	10 mg/kg	Ferritin H	Inhibited neuronal ferroptosis.	*In vivo*	(262)
	15 mg/kg	SOD, MDA,	Enhanced cerebral blood flow, the neuron regeneration in the cortex and antioxidant as well as anti-apoptotic effects.	*In vivo*	(263)
	10 mg/kg	ERK1/2, JNK1/2, p38MAPK, caspase-3, Bcl-2, Bax	Ameliorated exploratory and locomotor activities, neuronal apoptosis and enhanced neuron numbers.	*In vivo*	(264)
	-	-	Promoted cognitive function and inhibited astrocyte reactivation.	*In vivo*	(265)

	10 mg/kg	circPtpn14, miR-351-5p, 5-LOX	Reduced ER stress and ferroptotic impacts.	*In vivo, in vitro*	(266)
	10 mg/kg	PKA/CREB	Reversed TBI-mediated anxiety-like behavior, reduced neuronal apoptosis and the number of activated astrocytes and in the amygdala mediated by TBI.	*In vivo*	(267)
	10 mg/kg	HO-1/CREB	Decreased TBI-mediated enhanced immobility time in the force swim test, reduced time spent sniffing the novel rat in 3-chambered social test.	*In vivo*	(268)
	10 mg/kg	-	Protected synaptic function.	*In vivo*	(269)
Parkinson's disease	10, 20, 30 mg/kg	GSH	Protective effect against nigral dopamine loss and replenished the striatal dopamine loss and increased antioxidant effect.	*In vivo*	(270)
	20 mg/kg	Tyrosine hydroxylase	Improved motor function and inhibited the striatal degeneration.	*In vivo*	(271)
	4 mM	hLRRK2	Ameliorated long-term memory deficits and modulated calcium channel.	*In vivo, in vitro*	(272)
	10 mg	hs-CRP, PPAR-γ, TAC, GSH, TNF-α	Decreased the Unified Parkinson's disease rating scale and increased antioxidant and anti-inflammatory effects.	Human	(273)
	25 mg	BMAL1	Alteration in levels of the clock genes.	Human	(274)
	10 mg/kg	NLRP3	Prevented neurotoxicity, improved motor dysfunction, decreased microglial activation and increased anti-inflammatory effect.	*In vivo, in vitro*	(275)
	25 mg	Complex I, CAT, carbonyl groups	Restored respiratory control ratio and increase antioxidant effect.	Human	(276)
	20 mg/kg 50 μM	RORα	Enhanced anti-inflammatory M2-like phenotype in the microglia.	*In vivo, in vitro*	(195)
	-	HSP70, Bax, Bcl2, caspase-3, HSF1	Increased antioxidant and anti-apoptotic effects.	*In vitro*	(277)
	20 mg/kg	Caspase-3, GSH	Enhanced the number of neurons in striatum and in substantia nigra and increased antioxidant effect.	*In vivo*	(278)
Alzheimer's disease	10 mg/kg	Caspase-3	Reduced proteinopathy, cognitive decline, restored the autophagy flux, increased antioxidant and anti-inflammatory effects, prevented.	*In vivo*	(279)
	0.2, 0.5, 1 μM	DAPK1, Pin1	Reduced tau phosphorylation and accumulation, promoted microtubule assembly and neurite outgrowth.	*In vitro*	(280)
	30 mg/kg	VEGF	Improved learning, memory and microvessel abnormality in the hippocampus and cerebral cortex.	*In vivo*	(281)
	80 mg/kg	Creb1, Bdnf	Ameliorated spatial memory.	*In vivo*	(282)
	10 mg/kg	miR-504-3p, p39/CDK5	Decreased neurofibrillary tangles and neuronal loss.	*In vivo*	(283)
	10 μM	Caspase-1, NLRP3, IL-18, Parkin, p62, TFEB, IL-1β	Promoted mitophagy.	*In vitro*	(284)
	10 mg/kg	Mcoln1	Attenuated Aβ pathology, restored mitophagy, improved cognition.	*In vivo*	(285)
	-	IRP2, LRP1, IDE	Inhibited metal ion dyshomeostasis, oxidative stress, neuroinflammation, γ-secretase, tau hyperphosphorylation.	*In vivo*	(286)
	10 μM	Ca^{2+}, caspase-3, ROS	Increased antioxidant and anti-apoptotic effects by TRPA1 channels.	*In vitro*	(287)
	0.04 mg/kg	-	Slowed down an enhancement in anxiety and deterioration of reference memory.	*In vivo*	(288)
Spinal cord injury	12.5 mg/kg	PI3K/AKT/mTOR	Reduced apoptosis, enhanced autophagy and locomotor function recovery.	*In vivo*	(289)
	50 mg/kg	TNF-α, IL-6, IL-1β	Increased anti-inflammatory effect.	*In vivo*	(196)
	10 mg/kg	Monocyte chemotactic protein 1	Improved intestinal integrity and locomotor performance in antibiotic-treated mice.	*In vivo*	(290)
	12.5 mg/kg	NLRP3	Attenuated apoptosis, alleviated SCI through decreasing spinal cord water content.	*In vivo*	(291)
	12.5 mg/kg 40 μM	Wnt/β-catenin, caspase-3, Bcl-2, Bax	Inhibited neural cell apoptosis and promoted locomotor recovery.	*In vivo, in vitro*	(292)

	50 mg/kg	-	Enhanced spinal cord blood flow as well as oxygen saturation.	*In vivo*	(293)
	10 mg/kg	IL-1β	Increased anti-inflammatory effect.	*In vivo*	(294)
	10 mg/kg	Nissl bodies	Improved permeability of blood-spinal cord barrier, rescued blood vessels.	*In vivo*	(295)
	30 mg/kg	NF-κB, iNOS	Increased anti-inflammatory effect.	*In vivo*	(296)
	10 mg/kg	MDA, GSH, MPO, GSSG, occludin, ZO-1	Enhanced the decreased blood flow and reduced SCI-mediated permeability of capillaries, as well as antioxidant effect.	*In vivo*	(297)
	30 mg/kg 60 μM	MDA, SOD, GPx, NLRP3, Nrf2/ARE	Increased antioxidant and anti-inflammatory effect.	*In vivo, in vitro*	(298)
	15 mg/kg	PI3K-AKT1	Synergistic effect with half-dose methylprednisolone to improve acute SCI.	*In vivo*	(299)
	10 mg/kg	SIRT1/AMPK, Beclin-1	Activated autophagy and inhibited apoptosis.	*In vivo*	(300)
	10 mg/kg	Bax, GFAP, caspase-3, Bcl-2, IL-1β, iNOS, TNF-α	Attenuated astrogliosis and microgliosis and improved anti-inflammatory effect		(301)

10. CONCLUSIONS AND FUTURE PERSPECTIVES

Neurodegenerative diseases cause an enormous financial burden for health care systems over the world. Although there have been notable advances in the development of effective therapies for these devastating disorders, mortality rate of them are still considerably high. This makes researchers manage to find alternatives and/or complementary treatments for neurodegenerative diseases. As discussed herein, melatonin has numerous well-documented neuroprotective effects; these include anti-oxidant, anti-inflammatory and anti-apoptotic activities. Furthermore, melatonin has recently been shown as a promising agent for nerve regeneration, and its combination with stem cell therapy is a promising therapeutic method for the treatment of neurodegenerative diseases. With the information at hand, the authors urge further experimental and especially clinical studies to clarify the utility of melatonin and its effectiveness and safety for neurologically-compromised patients.

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AUTHORSHIP

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CONFLICT OF INTEREST

The authors declare that they have no competing interests

REFERENCES

1. Mecca AP & van Dyck CH (2021) Alzheimer's & Dementia: The Journal of the Alzheimer's Association. *Alzheimer & dement.* **17** (2): 316.
2. Mitchell KJ (2011) The genetics of neurodevelopmental disease. *Curr. Opin. Neurobiol.* **21**(1): 197-203.

3. Moreno-Jiménez EP, *et al.* (2019) Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease. *Nat. Med.* **25** (4): 554-560.
4. Dugger BN & Dickson DW (2017) Pathology of Neurodegenerative Diseases. *Cold Spring Harbor perspect. Biol.* **9** (7).
5. Gitler AD, Dhillon P, & Shorter J (2017) Neurodegenerative disease: models, mechanisms, and a new hope. *Dis. Model. Mech.* **10** (5): 499-502.
6. Taoufik E & Probert L (2008) Ischemic neuronal damage. *Current pharmaceutical design* 14(33):3565-3573.
7. Shakir R & Norrving B (2017) Stroke in ICD-11: the end of a long exile. *Lancet* **389** (10087): 2373.
8. Gribkoff VK & Kaczmarek LK (2017) The need for new approaches in CNS drug discovery: Why drugs have failed, and what can be done to improve outcomes. *Neuropharmacology* 120:11-19.
9. Bald EM, Nance CS, & Schultz JL (2021) Melatonin may slow disease progression in amyotrophic lateral sclerosis: Findings from the Pooled Resource Open-Access ALS Clinic Trials database. *Muscle Nerve* **63** (4): 572-576.
10. Lu J, *et al.* (2019) Melatonin suppresses microglial necroptosis by regulating deubiquitinating enzyme A20 after intracerebral hemorrhage. *Front. Immunol.* **10**: 1360.
11. Zarei S, *et al.* (2015) A comprehensive review of amyotrophic lateral sclerosis. *Surg. Neurol. Int.* **6**: 171.
12. Vriend J & Reiter RJ (2015) Melatonin feedback on clock genes: a theory involving the proteasome. *J. Pineal Res.* **58** (1): 1-11.
13. Slats D, Claassen JA, Verbeek MM, & Overeem S (2013) Reciprocal interactions between sleep, circadian rhythms and Alzheimer's disease: focus on the role of hypocretin and melatonin. *Ageing Res. Rev.* **12** (1): 188-200.
14. Pan J, Konstas AA, Bateman B, Ortolano GA, & Pile-Spellman J (2007) Reperfusion injury following cerebral ischemia: pathophysiology, MR imaging, and potential therapies. *Neuroradiology* **49** (2): 93-102.
15. Wang Y, Luo J, & Li SY (2019) Nano-curcumin simultaneously protects the blood-brain barrier and reduces m1 microglial activation during cerebral ischemia-reperfusion injury. *ACS Appl. Mater. Interfaces* **11** (4): 3763-3770.
16. Xing P, Ma K, Wu J, Long W, & Wang D (2018) Protective effect of polysaccharide peptide on cerebral ischemia-reperfusion injury in rats. *Mol. Med. Rep.* **18** (6): 5371-5378.
17. Wu L, *et al.* (2020) Targeting Oxidative Stress and Inflammation to Prevent Ischemia-Reperfusion Injury. *Front. Mol. Neurosci.* **13**: 28.
18. Liu Y, Qu X, Yan M, Li D, & Zou R (2022) Tricin attenuates cerebral ischemia/reperfusion injury through inhibiting nerve cell autophagy, apoptosis and inflammation by regulating the PI3K/Akt pathway. Hum. Exp. Toxicol. **41**: 9603271221125928.
19. Park HR, *et al.* (2018) Protective Effects of Spatholobi Caulis Extract on Neuronal Damage and Focal Ischemic Stroke/Reperfusion Injury. *Mol.Neurobiol,* **55** (6): 4650-4666.
20. Lu Z, *et al.* (2018) Curcumin protects cortical neurons against oxygen and glucose deprivation/reoxygenation injury through flotillin-1 and extracellular signal-regulated kinase1/2 pathway. *Biochem. Biophys. Res. Commun*. **496** (2): 515-522.
21. Millar LJ, Shi L, Hoerder-Suabedissen A, & Molnár Z (2017) Neonatal hypoxia ischaemia: mechanisms, models, and therapeutic challenges. *Front. Cell. Neurosci.* **11**: 78.

22. Lee RHC, *et al.* (2018) Cerebral ischemia and neuroregeneration. *Neural Regen. Res.* **13** (3): 373-385.
23. Thornton C, *et al.* (2017) Cell Death in the developing brain after hypoxia-ischemia. *Front. Cell. Neurosci.* **11**: 248.
24. Leiva-Salinas C, *et al.* (2016) Prediction of early arterial recanalization and tissue fate in the selection of patients with the greatest potential to benefit from intravenous tissue-type plasminogen activator. *Stroke* **47** (2): 397-403.
25. Huang YG, *et al.* (2019) Autophagy: novel insights into therapeutic target of electroacupuncture against cerebral ischemia/ reperfusion injury. *Neural Regen. Res.* **14** (6): 954-961.
26. Nakka VP, Gusain A, Mehta SL, & Raghubir R (2008) Molecular mechanisms of apoptosis in cerebral ischemia: multiple neuroprotective opportunities. *Mol. Neurobiol.* **37** (1):7-38.
27. Wong CH & Crack PJ (2008) Modulation of neuro-inflammation and vascular response by oxidative stress following cerebral ischemia-reperfusion injury. *Curr. Med. Chem.* **15** (1): 1-14.
28. Feng D, *et al.* (2017) Pre-ischemia melatonin treatment alleviated acute neuronal injury after ischemic stroke by inhibiting endoplasmic reticulum stress-dependent autophagy via PERK and IRE1 signalings. *J. Pineal Res.* **62** (3).
29. Sinha K, Degaonkar MN, Jagannathan NR, Gupta YK (2001) Effect of melatonin on ischemia reperfusion injury induced by middle cerebral artery occlusion in rats. *Eur. J. Pharmacol.* **428** (2): 185-192.
30. Wang K, *et al.* (2020) Melatonin enhances the therapeutic effect of plasma exosomes against cerebral ischemia-induced pyroptosis through the TLR4/NF-κB pathway. *Front. Neurosci.* **14**: 848.
31. Wei N, Pu Y, Yang Z, Pan Y, & Liu L (2019) Therapeutic effects of melatonin on cerebral ischemia reperfusion injury: Role of Yap-OPA1 signaling pathway and mitochondrial fusion. *Biomed. Pharmacother.* **110**: 203-212.
32. Yang B, *et al.* (2020) Melatonin plays a protective role by regulating miR-26a-5p-NRSF and JAK2-STAT3 pathway to improve autophagy, inflammation and oxidative stress of cerebral ischemia-reperfusion injury. *Drug Des. Devel. Ther.* **14**: 3177-3188.
33. Tajiri S, *et al.* (2004) Ischemia-induced neuronal cell death is mediated by the endoplasmic reticulum stress pathway involving CHOP. *Cell Death Differ.* **11** (4): 403-415.
34. Lin YW, *et al.* (2018) Melatonin protects brain against ischemia/reperfusion injury by attenuating endoplasmic reticulum stress. *Int. J. Mol. Med.* **42** (1): 182-192.
35. Wang X (2009) The antiapoptotic activity of melatonin in neurodegenerative diseases. *CNS Neurosci. Ther.* **15** (4): 345-357.
36. Saleh DO, Jaleel GAA, Al-Awdan SW, Hassan A, Asaad GF (2020) Melatonin suppresses the brain injury after cerebral ischemia/reperfusion in hyperglycaemic rats. *Res. Pharm. Sci.* **15** (5): 418-428.
37. Hung YC, *et al.* (2008) Melatonin decreases matrix metalloproteinase-9 activation and expression and attenuates reperfusion-induced hemorrhage following transient focal cerebral ischemia in rats. *J. Pineal Res.* **45** (4): 459-467.
38. Mathers CD, Boerma T, Ma Fat D (2009) Global and regional causes of death. *Br. Med. Bull*. **92**: 7-32.
39. Hossmann KA (2012) The two pathophysiologies of focal brain ischemia: implications for translational stroke research. *J. Cereb. Blood Flow Metab.* **32** (7):1310-1316.
40. Feigin VL, *et al.* (2014) Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet* **383 (**9913): 245-254.

41. Flynn RW, MacWalter RS, Doney AS (2008) The cost of cerebral ischaemia. *Neuropharmacology* **55** (3): 250-256.
42. Pandya RS, *et al.* (2011) Central nervous system agents for ischemic stroke: neuroprotection mechanisms. *Cent. Nerv. Syst. Agents Med. Chem*. **11** (2):81-97.
43. Jin Y, *et al.* (2015) The shh signaling pathway is upregulated in multiple cell types in cortical ischemia and influences the outcome of stroke in an animal model. *PloS one* **10** (4): e0124657.
44. Wali B, Ishrat T, Won S, Stein DG, & Sayeed I (2014) Progesterone in experimental permanent stroke: a dose-response and therapeutic time-window study. *Brain* **137** (Pt 2):486-502.
45. Canazza A, Minati L, Boffano C, Parati E, Binks S (2014) Experimental models of brain ischemia: a review of techniques, magnetic resonance imaging, and investigational cell-based therapies. *Front. Neurol.***5**:19.
46. Jin R, Zhu X, Li G (2014) Embolic middle cerebral artery occlusion (MCAO) for ischemic stroke with homologous blood clots in rats. *J. Vis. Exp*. **91**: 51956.
47. Ritzenthaler T, *et al.* (2013) Dynamics of oxidative stress and urinary excretion of melatonin and its metabolites during acute ischemic stroke. *Neurosci. Lett.* **544**: 1-4.
48. Zou LY, Cheung RT, Liu S, Li G, Huang L (2006) Melatonin reduces infarction volume in a photothrombotic stroke model in the wild-type but not cyclooxygenase-1-gene knockout mice. *J. Pineal Res.* **41** (2): 150-156.
49. Kilic E, *et al.* (2008) Delayed melatonin administration promotes neuronal survival, neurogenesis and motor recovery, and attenuates hyperactivity and anxiety after mild focal cerebral ischemia in mice. *J.Pineal Res.* **45** (2): 142-148.
50. Chen KH, *et al.* (2020) Melatonin against acute ischaemic stroke dependently via suppressing .both inflammatory and oxidative stress downstream signallings. *J. Cell. Mol. Med*. **24** (18): 10402-10419.
51. Chen BH, *et al.* (2018) Melatonin improves vascular cognitive impairment induced by ischemic stroke by remyelination via activation of ERK1/2 signaling and restoration of glutamatergic synapses in the gerbil hippocampus. *Biomed. Pharmacother*. **108**: 687-697.
52. Kawada K, Ohta T, Tanaka K, Miyamura M, Tanaka S (2019) Addition of suvorexant to ramelteon therapy for improved sleep quality with reduced delirium risk in acute stroke patients. *J Stroke Cerebrovasc. Dis.* **28** (1): 142-148.
53. Wang X, *et al.* (2009) Methazolamide and melatonin inhibit mitochondrial cytochrome C release and are neuroprotective in experimental models of ischemic injury. *Stroke* **40** (5): 1877-1885.
54. Yawoot N, Govitrapong P, Tocharus C, Tocharus J (2021) Ischemic stroke, obesity, and the anti-inflammatory role of melatonin. *BioFactors* **47** (1): 41-58.
55. Tai SH, *et al.* (2010) Melatonin inhibits postischemic matrix metalloproteinase-9 (MMP-9) activation via dual modulation of plasminogen/plasmin system and endogenous MMP inhibitor in mice subjected to transient focal cerebral ischemia. *J. Pineal Res.* **49** (4): 332-341.
56. Kilic E, Kilic U, Yulug B, Hermann DM, Reiter RJ (2004) Melatonin reduces disseminate neuronal death after mild focal ischemia in mice via inhibition of caspase-3 and is suitable as an add-on treatment to tissue-plasminogen activator. *J. Pineal Res.* **36** (3): 171-176.
57. Chen TY, *et al.* (2006) Melatonin attenuates the postischemic increase in blood-brain barrier permeability and decreases hemorrhagic transformation of tissue-plasminogen activator therapy following ischemic stroke in mice. *J. Pineal Res.* **40** (3): 242-250.

58. Srinivasan V, Pandi-Perumal SR, Cardinali DP, Poeggeler B, Hardeland R (2006) Melatonin in Alzheimer's disease and other neurodegenerative disorders. *Behav. Brain Funct.* **2** (1): 15.
59. Srinivasan V (2002) Melatonin oxidative stress and neurodegenerative diseases. *Indian J. Exp. Biol*. **40** (6): 668-79
60. Duffy JF, Wang W, Ronda JM, & Czeisler CA (2022) High dose melatonin increases sleep duration during nighttime and daytime sleep episodes in older adults. *J. Pineal Res.* **73** (1): e12801.
61. Hadi F, *et al.* (2022) Safety and efficacy of melatonin, clonazepam, and trazodone in patients with Parkinson's disease and sleep disorders: a randomized, double-blind trial. *Neurol. Sci.* **43** (10): 6141-6148.
62. Xu H, *et al.* (2020) Efficacy of melatonin for sleep disturbance in middle-aged primary insomnia: a double-blind, randomised clinical trial. *Sleep Med.* **76**: 113-119.
63. Yuge K, *et al.* (2020) Long-term melatonin treatment for the sleep problems and aberrant behaviors of children with neurodevelopmental disorders. *BMC psychiatry* **20** (1): 445.
64. Fang X, Han Q, Li S, Luo A (2022) Melatonin attenuates spatial learning and memory dysfunction in developing rats by suppressing isoflurane-induced endoplasmic reticulum stress via the SIRT1/Mfn2/PERK signaling pathway. *Heliyon* **8** (9): e10326.
65. Sun C, *et al.* (2020) Long-term oral melatonin alleviates memory deficits, reduces amyloid-β deposition associated with downregulation of BACE1 and mitophagy in APP/PS1 transgenic mice. *Neurosci. lett.* **735**: 135192.
66. DeTure MA & Dickson DW (2019) The neuropathological diagnosis of Alzheimer's disease. *Mol. Neurodegener.* **14** (1): 32.
67. Mohammadi F, *et al.* (2020) Anticonvulsant effect of melatonin through ATP-sensitive channels in mice. *Fundam. Clin. Pharmacol*. **34** (1): 148-155.
68. Hollingworth P, Harold D, Jones L, Owen MJ, Williams J (2011) Alzheimer's disease genetics: current knowledge and future challenges. *Int. J. Geriat. Psychiatry* **26** (8): 793-802.
69. Mayeux R,Stern Y (2012) Epidemiology of Alzheimer disease. *Cold Spring Harbor Perspect. Med.* **2** (8): a006239.
70. Leszek J, Sochocka M, & Gąsiorowski K (2012) Vascular factors and epigenetic modifications in the pathogenesis of Alzheimer's disease. *J. Neurol. Sci.* **323** (1): 25-32.
71. Mustapic M, *et al.* (2012) Alzheimer's disease and type 2 diabetes: the association study of polymorphisms in tumor necrosis factor-alpha and apolipoprotein E genes. *Metab. Brain Dis.* **27** (4): 507-512.
72. Nilsson P, Saido TC (2014) Dual roles for autophagy: Degradation and secretion of Alzheimer's disease Aβ peptide. *BioEssays* **36** (6): 570-578.
73. Raghavan NS, *et al.* (2020) Association between common variants in RBFOX1, an RNA-binding protein, and brain amyloidosis in early and preclinical alzheimer disease. *JAMA Neuro.* **77** (10): 1288-1298.
74. Reddy PH, Oliver DM (2019) Amyloid beta and phosphorylated tau-induced defective autophagy and mitophagy in alzheimer's disease. *Cells* **8** (5):488.
75. Chen D, Zhang T, Lee TH (2020) Cellular mechanisms of melatonin: insight from neurodegenerative diseases. *Biomolecules* **10** (8): 1158.
76. Reiter RJ, *et al.* (2022) Melatonin in ventricular and subarachnoid cerebrospinal fluid: Its function in the neural glymphatic network and biological significance for neurocognitive health. *Biochem. Biophys. Res. Commun.* **605**: 70-81.
77. Feng Z, *et al.* (2004) Melatonin alleviates behavioral deficits associated with apoptosis and cholinergic system dysfunction in the APP 695 transgenic mouse model of Alzheimer's disease. *J. Pineal Res.* **37** (2): 129-136.

78. Mahlberg R, *et al.* (2008) Pineal calcification in Alzheimer's disease: an in vivo study using computed tomography. *Neurobiol. Aging* **29** (2):203-209.
79. Ozcankaya R, Delibas N (2002) Malondialdehyde, superoxide dismutase, melatonin, iron, copper, and zinc blood concentrations in patients with Alzheimer disease: cross-sectional study. *Croat. Med. J.* **43** (1): 28-32.
80. Wu Y-H, *et al.* (2003) Molecular changes underlying reduced pineal melatonin levels in alzheimer disease: Alterations in preclinical and clinical stages. *J. Clin. Endocrinol. Metab.***88** (12): 5898-5906.
81. Wu Y-H, Swaab DF (2005) The human pineal gland and melatonin in aging and Alzheimer's disease. *J. Pineal Res.* **38** (3):145-152.
82. Deng Y-q, Xu G-g, Duan P, Zhang Q, Wang J-z (2005) Effects of melatonin on wortmannin-induced tau hyperphosphorylation. *Acta Pharmacol. Sin.* **26** (5): 519-526.
83. Cardinali DP, *et al.* (2012) Therapeutic application of melatonin in mild cognitive impairment. *Am. J. Neurodegener. Dis.* **1** (3):280.
84. Furio AM, Brusco LI, Cardinali DP (2007) Possible therapeutic value of melatonin in mild cognitive impairment: a retrospective study. *J. pineal Res.* **43** (4): 404-409.
85. Lahiri DK (1999) Melatonin affects the metabolism of the β-amyloid precursor protein in different cell types. *J. Pineal Res.* **26** (3): 137-146.
86. Li Y, Zhang J, Wan J, Liu A, Sun J (2020) Melatonin regulates Aβ production/clearance balance and Aβ neurotoxicity: A potential therapeutic molecule for Alzheimer's disease. *Biomed. Pharmacother.* **132**: 110887.
87. Mayo JC, *et al.* (2005) Anti-inflammatory actions of melatonin and its metabolites, N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK) and N1-acetyl-5-methoxykynuramine (AMK), in macrophages. *J. Neuroimmunol.* **165** (1-2): 139-149.
88. Lee RKK, Knapp S, Wurtman RJ (1999) Prostaglandin E₂ Stimulates Amyloid Precursor Protein Gene Expression: Inhibition by Immunosuppressants. *J. Neurosci.* **19** (3): 940.
89. Shukla M, *et al.* (2015) Melatonin stimulates the nonamyloidogenic processing of βAPP through the positive transcriptional regulation of ADAM10 and ADAM17. *J. Pineal Res.* **58** (2):151-165.
90. Chang H-M, Wu U-I, Lan C-T (2009) Melatonin preserves longevity protein (sirtuin 1) expression in the hippocampus of total sleep-deprived rats. *J. Pineal Res.* **47** (3): 211-220.
91. Cristòfol R, *et al.* (2012) Neurons from senescence-accelerated SAMP8 mice are protected against frailty by the sirtuin 1 promoting agents melatonin and resveratrol. *J. Pineal Res.* **52** (3): 271-281.
92. Albani D, *et al.* (2009) The SIRT1 activator resveratrol protects SK-N-BE cells from oxidative stress and against toxicity caused by α-synuclein or amyloid-β (1-42) peptide. *J. Neurochem.* **110** (5): 1445-1456.
93. Wang J, *et al.* (2010) The role of Sirt1: At the crossroad between promotion of longevity and protection against Alzheimer's disease neuropathology. *Biochim. Biophys. Acta* **1804** (8): 1690-1694.
94. Chinchalongporn V, Shukla M, Govitrapong P (2018) Melatonin ameliorates Aβ42-induced alteration of βAPP-processing secretases via the melatonin receptor through the Pin1/GSK3β/NF-κB pathway in SH-SY5Y cells. *J. Pineal Res.* **64** (4): e12470.
95. Bitar RD, Torres-Garza JL, Reiter RJ, Phillips WT (2021) Neural glymphatic system: Clinical implications and potential importance of melatonin. *Melatonin Res.* **4** (4): 551-565.
96. Jessen NA, Munk ASF, Lundgaard I, Nedergaard M (2015) The glymphatic system: a beginner's guide. *Neurochem. Res.* **40** (12): 2583-2599.

97. De Lima VR, *et al.* (2010) Influence of melatonin on the order of phosphatidylcholine-based membranes. *J. Pineal Res.* **49** (2): 169-175.
98. Boespflug EL, Iliff JJ (2018) The emerging relationship between interstitial fluid–cerebrospinal fluid exchange, amyloid-β, and sleep. *Biol. psychiatry* **83** (4): 328-336.
99. Iliff JJ, *et al.* (2014) Impairment of glymphatic pathway function promotes tau pathology after traumatic brain injury. *J. Neurosci.* **34** (49):16180-16193.
100. Pappolla M, *et al.* (2018) Melatonin treatment enhances Aβ lymphatic clearance in a transgenic mouse model of amyloidosis. *Curr. Alzheimer Res.* **15** (7):637-642.
101. Mishima K, *et al.* (1999) Melatonin secretion rhythm disorders in patients with senile dementia of Alzheimer's type with disturbed sleep–waking. *Biol. Psychiatry* **45** (4):417-421.
102. Elbaz A, Carcaillon L, Kab S, Moisan F (2016) Epidemiology of Parkinson's disease. *Rev. Neurol.* **172** (1): 14-26.
103. Elbaz A, Moisan F (2008) Update in the epidemiology of Parkinson's disease. *Curr. Opin. Neurol.* **21** (4): 454-460.
104. Connolly BS, Lang AE (2014) Pharmacological treatment of Parkinson disease: a review. *JAMA* **311** (16): 1670-1683.
105. Chung KK, *et al.* (2001) Parkin ubiquitinates the α-synuclein–interacting protein, synphilin-1: implications for Lewy-body formation in Parkinson disease. *Nat. Med.* **7** (10): 1144-1150.
106. Adi N, *et al.* (2010) Melatonin MT1 and MT2 receptor expression in Parkinson's disease. *Med. Sci. Monit.* **16** (2): BR61-BR67.
107. Michel PP, Hirsch EC, Hunot S (2016) Understanding dopaminergic cell death pathways in Parkinson disease. *Neuron* **90** (4): 675-691.
108. Tan SH, *et al.* (2019) Emerging pathways to neurodegeneration: Dissecting the critical molecular mechanisms in Alzheimer's disease, Parkinson's disease. *Biomed. Pharmacother.* **111**: 765-777.
109. Allan CL, Behrman S, Ebmeier KP, Valkanova V (2017) Diagnosing early cognitive decline—when, how and for whom? *Maturitas* **96**: 103-108.
110. Furuya M, *et al.* (2012) Marked improvement in delirium with ramelteon: five case reports. *Psychogeriatrics* **12** (4): 259-262.
111. Zhang W, *et al.* (2016) Exogenous melatonin for sleep disorders in neurodegenerative diseases: a meta-analysis of randomized clinical trials. *Neurol. Sci.* **37** (1): 57-65.
112. Patki G, Lau Y-S (2011) Melatonin protects against neurobehavioral and mitochondrial deficits in a chronic mouse model of Parkinson's disease. *Pharmacol. Biochem. Behav.* **99** (4): 704-711.
113. Singhal NK, Srivastava G, Patel DK, Jain SK, Singh MP (2011) Melatonin or silymarin reduces maneb- and paraquat-induced Parkinsons disease phenotype in the mouse. *J. Pineal Res.* **50** (2): 97-109.
114. Brito-Armas J, *et al.* (2013) Melatonin prevents dopaminergic cell loss induced by lentiviral vectors expressing A30P mutant alpha-synuclein. Histol. Histopathol. **28** (8): 999-1006.
115. Datieva V, Rosinskaia A, Levin O (2013) The use of melatonin in the treatment of chronic fatigue syndrome and circadian rhythm disorders in Parkinson's disease. *Zhurnal nevrologii i psikhiatrii imeni SS Korsakova* **113** (7 Pt 2): 77-81.
116. Ozsoy O, *et al.* (2015) Melatonin is protective against 6-hydroxydopamine-induced oxidative stress in a hemiparkinsonian rat model. *Free Radic. Res.* **49** (8): 1004-1014.
117. Ortiz GG, *et al.* (2013) Fish oil, melatonin and vitamin E attenuates midbrain cyclooxygenase-2 activity and oxidative stress after the administration of 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine. *Metab. Brain Dis.* **28** (4): 705-709.

118. Chuang JI, *et al.* (2016) Melatonin prevents the dynamin-related protein 1-dependent mitochondrial fission and oxidative insult in the cortical neurons after 1-methyl-4-phenylpyridinium treatment. *J. Pineal Res.* **61** (2): 230-240.
119. Antolín I, *et al.* (2002) Protective effect of melatonin in a chronic experimental model of Parkinson's disease. *Brain Res.* **943** (2):163-173.
120. Chen ST, Chuang JI, Hong MH, Li EIC (2002) Melatonin attenuates MPP+-induced neurodegeneration and glutathione impairment in the nigrostriatal dopaminergic pathway. *J. Pineal Res.* **32** (4): 262-269.
121. Yildirim FB, *et al.* (2014) Mechanism of the beneficial effect of melatonin in experimental Parkinson's disease. *Neurochem. Int.* **79**: 1-11.
122. Lopez A, *et al.* (2017) Mitochondrial impairment and melatonin protection in parkinsonian mice do not depend of inducible or neuronal nitric oxide synthases. *PloS one* **12** (8): e0183090.
123. Eller M & Williams DR (2011) α-Synuclein in Parkinson disease and other neurodegenerative disorders. *Clin. Chem. Lab. Med.* **49** (3): 403-408.
124. Zarranz JJ, *et al.* (2004) The new mutation, E46K, of α-synuclein causes parkinson and Lewy body dementia. *Ann. Neurol.* **55** (2):164-173.
125. Lee FJ, Liu F, Pristupa ZB, Niznik HB (2001) Direct binding and functional coupling of α-synuclein to the dopamine transporters accelerate dopamine-induced apoptosis. *FASEB J.* **15** (6): 916-926.
126. Masliah E, *et al.* (2000) Dopaminergic loss and inclusion body formation in α-synuclein mice: implications for neurodegenerative disorders. *Science* **287** (5456):1265-1269.
127. Saha AR, *et al.* (2000) Induction of neuronal death by α-synuclein. *Eur. J. Neurosci.* **12** (8): 3073-3077.
128. Chang AM, *et al.* (2012) Human responses to bright light of different durations. *J. Physiol.* **590** (13): 3103-3112.
129. Hoshi A, *et al.* (2017) Expression of aquaporin 1 and aquaporin 4 in the temporal neocortex of patients with Parkinson's disease. *Brain Pathol.* **27** (2): 160-168.
130. Schirinzi T, *et al.* (2019) CSF α-synuclein inversely correlates with non-motor symptoms in a cohort of PD patients. *Parkinsonism Relat. Disord*. **61**: 203-206.
131. Naskar A, *et al.* (2013) Melatonin synergizes with low doses of L-DOPA to improve dendritic spine density in the mouse striatum in experimental Parkinsonism. *J. Pineal Res.* **55** (3): 304-312.
132. Wallin MT, *et al.* (2019) Global, regional, and national burden of multiple sclerosis 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* **18** (3):269-285.
133. Compston A, Coles A (2008) Multiple sclerosis. *Lancet* **372** (9648):1502-1517.
134. Ohl K, Tenbrock K, Kipp M (2016) Oxidative stress in multiple sclerosis: Central and peripheral mode of action. *Exp. Neurol.* **277**: 58-67.
135. Bielekova B & Martin R (2004) Development of biomarkers in multiple sclerosis. *Brain* **127** (Pt 7): 1463-1478.
136. Haider L, *et al.* (2016) The topograpy of demyelination and neurodegeneration in the multiple sclerosis brain. *Brain* **139** (Pt 3): 807-815.
137. Miller ED, Dziedzic A, Saluk-Bijak J, Bijak M (2019) A review of various antioxidant compounds and their potential utility as complementary therapy in multiple sclerosis. *Nutrients* **11** (7): 1528.
138. Sandyk R, Awerbuch GI (1994) The relationship of pineal calcification to cerebral atrophy on CT scan in multiple sclerosis. *Int. J. Neurosci.* **76** (1-2): 71-79.

139. Gholipour T, *et al.* (2015) Decreased urinary level of melatonin as a marker of disease severity in patients with multiple sclerosis. *Iran J. Allergy Asthma. Immunol.* **14** (1): 91-97.
140. Jand Y, *et al.* (2022) Melatonin ameliorates disease severity in a mouse model of multiple sclerosis by modulating the kynurenine pathway. *Sci. Rep.* **12** (1): 15963.
141. Devasagayam TP, *et al.* (2004) Free radicals and antioxidants in human health: current status and future prospects. *J. Assoc. Physicians. India* **52**: 794-804.
142. Hayyan M, Hashim MA, AlNashef IM (2016) Superoxide Ion: Generation and Chemical Implications. *Chem. Rev.* **116** (5): 3029-3085.
143. Woolbright BL, Rajendran G, Harris RA, Taylor JA 3rd (2019) Metabolic flexibility in cancer: Targeting the pyruvate dehydrogenase kinase:Pyruvate dehydrogenase axis. *Mol. Cancer.Ther.* **18** (10): 1673-1681.
144. Yagi K, *et al.* (2015) Therapeutically targeting tumor necrosis factor-α/sphingosine-1-phosphate signaling corrects myogenic reactivity in subarachnoid hemorrhage. *Stroke* **46** (8): 2260-2270.
145. Ghareghani M, Farhadi Z, Rivest S, Zibara K (2022) PDK4 inhibition ameliorates melatonin therapy by modulating cerebral metabolism and remyelination in an EAE demyelinating mouse model of multiple sclerosis. *Front. Immunol.* **13**: 862316.
146. Alghamdi BS, AboTaleb HA (2020) Melatonin improves memory defects in a mouse model of multiple sclerosis by up-regulating cAMP-response element-binding protein and synapse-associated proteins in the prefrontal cortex. *J. Integr. Neurosci.* **19** (2): 229-237.
147. Sánchez-López AL, *et al.* (2018) Efficacy of melatonin on serum pro-inflammatory cytokines and oxidative stress markers in relapsing remitting multiple sclerosis. *Arch. Med. Res.* **49** (6):391-398.
148. López-González A, *et al.* (2015) Melatonin treatment improves primary progressive multiple sclerosis: a case report. *J. Pineal Res.* **58** (2): 173-177.
149. Hsu WY, *et al.* (2021) Effects of melatonin on sleep disturbances in multiple sclerosis: A randomized, controlled pilot study. *J. Exp. Transl. Clin.* **7** (4): 20552173211048756.
150. Kandel ER, *et al.* (2000) *Principles of neural science* (McGraw-hill New York).
151. Bates GP, *et al.* (2015) Huntington disease. *Nat. Rev. Dis. Primers* **1** (1): 15005.
152. Ross CA, Tabrizi SJ (2011) Huntington's disease: from molecular pathogenesis to clinical treatment. *Lancet Neurol.* **10** (1):83-98.
153. Sánchez-López F, *et al.* (2012) Oxidative stress and inflammation biomarkers in the blood of patients with Huntington's disease. *Neurol. Res.* **34** (7): 721-724.
154. Tasset I, *et al.* (2013) Extremely low-frequency electromagnetic fields activate the antioxidant pathway Nrf2 in a Huntington's disease-like rat model. *Brain Stimul.* **6** (1): 84-86.
155. Túnez I, *et al.* (2011) Important role of oxidative stress biomarkers in Huntington's disease. *J. Med. Chem.* **54** (15): 5602-5606.
156. Rigamonti D, *et al.* (2000) Wild-type huntingtin protects from apoptosis upstream of caspase-3. *J. Neurosci.* **20** (10): 3705-3713.
157. Browne SE, *et al.* (1997) Oxidative damage and metabolic dysfunction in Huntington's disease: selective vulnerability of the basal ganglia. *Ann. Neurol.* **41** (5): 646-653.
158. Kaur C, Ling E-A (2008) Antioxidants and neuroprotection in the adult and developing central nervous system. *Curr. Med. Chem.* **15** (29): 3068-3080.
159. Reiter RJ, *et al.* (2000) Pharmacology and physiology of melatonin in the reduction of oxidative stress in vivo. *Neurosignals* **9** (3-4):160-171.

160. Srinivasan V, *et al.* (2005) Role of melatonin in neurodegenerative diseases. *Neurotox. Res.* **7** (4): 293-318.
161. Tan D-X, *et al.* (2003) Antioxidant strategies in protection against neurodegenerative disorders. *Expert Opin. Ther. Pat.* **13** (10):1513-1543.
162. Rigamonti D, *et al.* (2001) Huntingtin's neuroprotective activity occurs via inhibition of procaspase-9 processing. *J. Biol. Chem.* **276** (18):14545-14548.
163. Schulz JB & Beal MF (1994) Mitochondrial dysfunction in movement disorders. *Curr. Opin. Neurol.* **7** (4): 333-339.
164. Southgate G, Daya S (1999) Melatonin reduces quinolinic acid-induced lipid peroxidation in rat brain homogenate. *Metab. Brain Dis.* **14** (3): 165-171.
165. Christofides J, *et al.* (2006) Blood 5-hydroxytryptamine, 5-hydroxyindoleacetic acid and melatonin levels in patients with either Huntington's disease or chronic brain injury. *J. Neurochem.* **97** (4): 1078-1088.
166. van Wamelen DJ, *et al.* (2013) Suprachiasmatic nucleus neuropeptide expression in patients with Huntington's disease. *Sleep* **36** (1):117-125.
167. Wang X, *et al.* (2011) The melatonin MT1 receptor axis modulates mutant Huntingtin-mediated toxicity. *J. Neurosci.* **31** (41): 14496-14507.
168. Gunata M, Parlakpinar H, & Acet HA (2020) Melatonin: A review of its potential functions and effects on neurological diseases. *Rev. Neurol.* **176** (3): 148-165.
169. Reiter RJ, *et al.* (1999) Melatonin as a pharmacological agent against neuronal loss in experimental models of Huntington's disease, Alzheimer's disease and parkinsonism. *Ann. N. Y. Acad. Sci.* **890** (1): 471-485.
170. Ahmed S, *et al.* (2017) Traumatic brain injury and neuropsychiatric complications. *Indian. J. Psychol. Med.* **39** (2): 114-121.
171. DeKosky ST. Asken BM (2017) Injury cascades in TBI-related neurodegeneration. *Brain Inj.* **31** (9): 1177-1182.
172. Blum B, Kaushal S, Khan S, Kim JH, Villalba CLA (2021) Melatonin in Traumatic brain injury and cognition. *Cureus* **13** (9):e17776.
173. Ozdemir D, *et al.* (2005) Effect of melatonin on brain oxidative damage induced by traumatic brain injury in immature rats. *Physiol. Res.* **54** (6): 631-637.
174. Naeser MA, *et al.* (2016) Transcranial, red/near-infrared light-emitting diode therapy to improve cognition in chronic traumatic brain injury. *Photomed. Laser Surg.* **34** (12): 610-626.
175. Mediavilla MD, Sanchez-Barcelo EJ, Tan DX, Manchester L, Reiter RJ (2010) Basic mechanisms involved in the anti-cancer effects of melatonin. *Curr. Med. Chem.* **17** (36): 4462-4481.
176. Osier N, *et al.* (2018) Melatonin as a therapy for traumatic brain Injury: A review of published evidence. *Int. J. Mol. Sci.* 19 (5): 1539.
177. Capizzi A, Woo J, & Verduzco-Gutierrez M (2020) Traumatic brain injury: An overview of epidemiology, pathophysiology, and medical management. *Med. Clin. North Am.* **104** (2):213-238.
178. Beck JG, *et al.* (2008) The impact of event scale-revised: psychometric properties in a sample of motor vehicle accident survivors. *J. Anxiety Disord.* **22** (2): 187-198.
179. Barlow KM, Esser MJ, Veidt M, Boyd R (2019) Melatonin as a Treatment after traumatic brain injury: a systematic review and meta-analysis of the pre-clinical and clinical literature. *J. Neurotrauma* **36** (4): 523-537.
180. Gómez RM, *et al.* (2018) Cell therapy for spinal cord injury with olfactory ensheathing glia cells (OECs). *Glia* **66** (7): 1267-1301.
181. Hewson DW, Bedforth NM, Hardman JG (2018) Spinal cord injury arising in anaesthesia practice. *Anaesthesia* **73** Suppl 1: 43-50.

182. Yang L, *et al.* (2016) Melatonin for Spinal Cord Injury in Animal Models: A Systematic Review and Network Meta-Analysis. *J. Neurotrauma* 33(3):290-300.
183. Ghaisas MM, Ahire YS, Dandawate PR, Gandhi SP, Mule M (2011) Effects of combination of thiazolidinediones with melatonin in dexamethasone-induced insulin resistance in mice. *Indian J. Pharm. Sci.* **73** (6): 601-607.
184. Li C, *et al.* (2014) Melatonin lowers edema after spinal cord injury. *Neural Regen. Res.* **9** (24): 2205-2210.
185. Lee S & Notterpek L (2013) Dietary restriction supports peripheral nerve health by enhancing endogenous protein quality control mechanisms. *Exp. Gerontol.* **48** (10): 1085-1090.
186. Galán-Arriero I, *et al.* (2017) The role of Omega-3 and Omega-9 fatty acids for the treatment of neuropathic pain after neurotrauma. *Biochim. Biophys. Acta Biomembr.* **1859** (9 Pt B): 1629-1635.
187. Bouyer-Ferullo S (2013) Preventing perioperative peripheral nerve injuries. *AORN J.* **97** (1): 110-124.e119.
188. Klymenko A， Lutz D (2022) Melatonin signalling in Schwann cells during neuroregeneration. *Front. Cell Develo. Biol.* **10**: 999322.
189. Pan B, *et al.* (2021) Melatonin promotes Schwann cell proliferation and migration via the shh signalling pathway after peripheral nerve injury. *The Eur. J. Neurosci.* **53** (3): 720-731.
190. Özkan Y, *et al.* (2021) Comparison of the effects of electroacupuncture and melatonin on nerve regeneration in experimentally nerve-damaged rats. *J. Acupunct. Meridian Stud.* **14** (5): 176-182.
191. Yanilmaz M, *et al.* (2015) The effects of aminoguanidine, methylprednisolone, and melatonin on nerve recovery in peripheral facial nerve neurorrhaphy. *J. Craniofac. Surg.* **26** (3): 667-672.
192. Liu CH, *et al.* (2020) Melatonin promotes nerve regeneration following end-to-side neurorrhaphy by accelerating cytoskeletal remodeling via the melatonin receptor-dependent pathway. *Neuroscience* **429**: 282-292.
193. Lian L, *et al.* (2020) Neuroinflammation in ischemic stroke: Focus on microrna-mediated polarization of microglia. *Front. Mol. Neurosci.* **13**: 612439.
194. He B, *et al.* (2016) The nuclear melatonin receptor RORα is a novel endogenous defender against myocardial ischemia/reperfusion injury. *J. Pineal Res.* **60** (3): 313-326.
195. Li J, *et al.* (2022) Melatonin ameliorates Parkinson's disease via regulating microglia polarization in a RORα-dependent pathway. *NPJ Parkinson's Dis.* **8** (1):90.
196. Zhang Y, *et al.* (2019) Melatonin improves functional recovery in female rats after acute spinal cord injury by modulating polarization of spinal microglial/macrophages. *J. Neurosci. Res.* **97** (7): 733-743.
197. Liu ZJ, *et al.* (2019) Melatonin protects against ischemic stroke by modulating microglia/macrophage polarization toward anti-inflammatory phenotype through STAT3 pathway. *CNS Neurosci. Ther.* **25** (12): 1353-1362.
198. Lee MY, *et al.* (2007) Intravenous administration of melatonin reduces the intracerebral cellular inflammatory response following transient focal cerebral ischemia in rats. *J. Pineal Res.* **42** (3): 297-309.
199. Spagnuolo G, *et al.* (2018) Commitment of oral-derived stem cells in dental and maxillofacial applications. *Dent. J.* 6(4): 72.
200. Murphy MB, Moncivais K, Caplan AI (2013) Mesenchymal stem cells: environmentally responsive therapeutics for regenerative medicine. *Exp. Mol. Med.* **45** (11): e54.

201. Sipp D, Robey PG, Turner L (2018) Clear up this stem-cell mess. *Nature* **561** (7724): 455-457.
202. Rodríguez-Lozano FJ, *et al.* (2015) Cytoprotective effects of melatonin on zoledronic acid-treated human mesenchymal stem cells in vitro. *J. Craniomaxillofac. Surg.* **43** (6):855-862.
203. Chen HH, *et al.* (2014) Additional benefit of combined therapy with melatonin and apoptotic adipose-derived mesenchymal stem cell against sepsis-induced kidney injury. *J. Pineal Res.* **57** (1): 16-32.
204. Kadry SM, El-Dakdoky MH, Haggag NZ, Rashed LA, Hassen MT (2018) Melatonin improves the therapeutic role of mesenchymal stem cells in diabetic rats. *Toxicol. Mech. Methods* **28** (7): 529-538.
205. Mortezaee K, *et al.* (2017) Preconditioning with melatonin improves therapeutic outcomes of bone marrow-derived mesenchymal stem cells in targeting liver fibrosis induced by CCl4. *Cell Tissue Res.* **369** (2): 303-312.
206. Lee SJ, Jung YH, Oh SY, Yun SP, Han HJ (2014) Melatonin enhances the human mesenchymal stem cells motility via melatonin receptor 2 coupling with Gαq in skin wound healing. *J. Pineal Res.* **57** (4): 393-407.
207. Danisovic L, *et al.* (2017) Effect of long-term culture on the biological and morphological characteristics of human adipose tissue-derived stem Cells. *J. Physiol. pharmacol.* **68** (1): 149-158.
208. Ma Y, *et al.* (2013) Melatonin ameliorates injury and specific responses of ischemic striatal neurons in rats. *J. Histochem. Cytochem.* **61** (8): 591-605.
209. Calvo JR, González-Yanes C, Maldonado MD (2013) The role of melatonin in the cells of the innate immunity: a review. *J. Pineal Res.* **55** (2): 103-120.
210. Zhang Z, *et al.* (2022) ADSCs Combined with Melatonin promote peripheral nerve regeneration through autophagy. *Int. J. Endocrinol.* **2022**: 5861553.
211. Liu W, *et al.* (2021) Extracellular vesicles derived from melatonin-preconditioned mesenchymal stem cells containing USP29 repair traumatic spinal cord injury by stabilizing NRF2. *J. Pineal Res.* **71** (4): e12769.
212. Ramezani M, *et al.* (2020) Therapeutic effects of melatonin-treated bone marrow mesenchymal stem cells (BMSC) in a rat model of Alzheimer's disease. *J. Chem. Neuroanat.* **108**: 101804.
213. Nasiri E, *et al.* (2019) Melatonin-pretreated adipose-derived mesenchymal stem cells efficeintly improved learning, memory, and cognition in an animal model of Alzheimer's disease. *Metab. Brain Dis.* **34** (4):1131-1143.
214. Tang Y, *et al.* (2014) Melatonin pretreatment improves the survival and function of transplanted mesenchymal stem cells after focal cerebral ischemia. *Cell Transplantat.***23** (10): 1279-1291.
215. Lu D, *et al.* (2022) Melatonin offers dual-phase protection to brain vessel endothelial cells in prolonged cerebral ischemia-recanalization through ameliorating ER stress and resolving refractory stress granule. *Transl. Stroke Res*. doi: 10.1007/s12975-022-01084-7.
216. Bseiso EA, AbdEl-Aal SA, Nasr M, Sammour OA, El Gawad NAA (2022) Nose to brain delivery of melatonin lipidic nanocapsules as a promising post-ischemic neuroprotective therapeutic modality. *Drug Deliv.* **29** (1): 2469-2480.
217. Bseiso EA, Abd El-Aal SA, Nasr M, Sammour OA, Abd El Gawad NA (2022) Intranasally administered melatonin core-shell polymeric nanocapsules: A promising treatment modality for cerebral ischemia. *Life Sci.* **306**: 120797.
218. Chen X, *et al.* (2022) Influence of melatonin on behavioral and neurological function of rats with focal cerebral ischemia-reperfusion injury via the JNK/FoxO3a/Bim pathway. *Comput. Math. Methods Med.* **2022**: 8202975.

219. Yawoot N, *et al.* (2022) Melatonin attenuates reactive astrogliosis and glial scar formation following cerebral ischemia and reperfusion injury mediated by GSK-3β and RIP1K. *J. Cell. Physiol.* **237** (3): 1818-1832.
220. Liu L, *et al.* (2021) Melatonin ameliorates cerebral ischemia-reperfusion injury in diabetic mice by enhancing autophagy via the SIRT1-BMAL1 pathway. *FASEB J.* **35** (12): e22040.
221. Chen S, *et al.* (2022) Modulation of α7nAchR by Melatonin Alleviates Ischemia and Reperfusion-Compromised Integrity of Blood-Brain Barrier Through Inhibiting HMGB1-Mediated Microglia Activation and CRTC1-Mediated Neuronal Loss. *Cell. Mol. Neurobiol.* **42** (7): 2407-2422.
222. Liu L, *et al.* (2021) Melatonin protects against focal cerebral ischemia-reperfusion injury in diabetic mice by ameliorating mitochondrial impairments: involvement of the Akt-SIRT3-SOD2 signaling pathway. *Aging* **13** (12): 16105-16123.
223. Tuncer M, Pehlivanoglu B, Sürücü SH, Isbir T (2021) Melatonin improves reduced activities of membrane ATPases and preserves ultrastructure of gray and white matter in the rat brain ischemia/reperfusion model. *Biochemistry* **86** (5): 540-550.
224. Fenton-Navarro B, Garduño Ríos D, Torner L, Letechipía-Vallejo G, Cervantes M (2021) Melatonin decreases circulating levels of galectin-3 and cytokines, motor activity, and anxiety following acute global cerebral ischemia in male rats. *Arch. Med. Res.* **52** (5): 505-513.
225. Chen KH, *et al.* (2021) Synergic effect of combined cyclosporin and melatonin protects the brain against acute ischemic reperfusion injury. *Biomed. Pharmacother.***136**: 111266.
226. Liu L, *et al.* (2019) Melatonin ameliorates cerebral ischemia/reperfusion injury through SIRT3 activation. *Life Sci.* **239**: 117036.
227. Zang M, *et al.* (2020) The circadian nuclear receptor RORα negatively regulates cerebral ischemia-reperfusion injury and mediates the neuroprotective effects of melatonin. *Biochim. Biophys. Acta Mol. Basis. Dis.* **1866** (11): 165890.
228. Chern CM, Liao JF, Wang YH, Shen YC (2012) Melatonin ameliorates neural function by promoting endogenous neurogenesis through the MT2 melatonin receptor in ischemic-stroke mice. *Free Radic. Bio. Med.* **52** (9): 1634-1647.
229. Lee S, *et al.* (2012) Beneficial effects of melatonin on stroke-induced muscle atrophy in focal cerebral ischemic rats. *Lab. Anim. Res.* **28** (1): 47-54.
230. Yang Y, *et al.* (2015) Melatonin prevents cell death and mitochondrial dysfunction via a SIRT1-dependent mechanism during ischemic-stroke in mice. *J. Pineal Res.* **58** (1): 61-70.
231. Jang JW, *et al.* (2012) Melatonin reduced the elevated matrix metalloproteinase-9 level in a rat photothrombotic stroke model. *J. Neurol. Sci.* **323** (1-2): 221-227.
232. Jallouli S, *et al.* (2022) Effect of melatonin intake on postural balance, functional mobility and fall risk in persons with multiple sclerosis: a pilot study. *Int. J. Neurosci.***1**:11.
233. Escribano BM, *et al.* (2022) Protective effects of melatonin on changes occurring in the experimental autoimmune encephalomyelitis model of multiple sclerosis. *Mult. Scler. Relat. Disord.* **58**: 103520.
234. Yosefifard M, Vaezi G, Malekirad AA, Faraji F, Hojati V (2019) A randomized control trial study to determine the effect of melatonin on serum levels of IL-1β and TNF-α in patients with multiple sclerosis. *Iran. J. Allergy Asthma Immunol.* **18** (6): 649-654.
235. Abo Taleb HA, Alghamdi BS (2020) Neuroprotective effects of melatonin during demyelination and remyelination stages in a mouse model of multiple sclerosis. *J. Mol. Neurosci.* **70** (3):386-402.

236. Ghareghani M, *et al.* (2019) Melatonin therapy modulates cerebral metabolism and enhances remyelination by increasing PDK4 in a mouse model of multiple sclerosis. *Front. Pharmacol.* **10**: 147.
237. Emamgholipour S, Hossein-Nezhad A, Sahraian MA, Askarisadr F, Ansari M (2016) Evidence for possible role of melatonin in reducing oxidative stress in multiple sclerosis through its effect on SIRT1 and antioxidant enzymes. *Life Sci.* **145**: 34-41.
238. Álvarez-Sánchez N, *et al.* (2017) Melatonin reduces inflammatory response in peripheral T helper lymphocytes from relapsing-remitting multiple sclerosis patients. *J. Pineal Res.* 63(4): e12442.
239. Khyati, Malik I, Agrawal N, Kumar V (2021) Melatonin and curcumin reestablish disturbed circadian gene expressions and restore locomotion ability and eclosion behavior in Drosophila model of Huntington's disease. *Chronobiol. Int.* **38** (1): 61-78.
240. Gupta S, Sharma B (2014) Pharmacological benefits of agomelatine and vanillin in experimental model of Huntington's disease. *Pharmacol. Biochem. Behav.* **122**: 122-135.
241. Chakraborty J, Nthenge-Ngumbau DN, Rajamma U, Mohanakumar KP (2014) Melatonin protects against behavioural dysfunctions and dendritic spine damage in 3-nitropropionic acid-induced rat model of Huntington's disease. *Behav. Brain Res.* **264**: 91-104.
242. Antunes Wilhelm E, Ricardo Jesse C, Folharini Bortolatto C, Wayne Nogueira C (2013) Correlations between behavioural and oxidative parameters in a rat quinolinic acid model of Huntington's disease: protective effect of melatonin. *Eur. J. Pharmacol.* **701** (1-3): 65-72.
243. Shen X, Tang C, Wei C, Zhu Y, Xu R (2022) Melatonin induces autophagy in amyotrophic lateral sclerosis mice via upregulation of SIRT1. *Mol. Neurobiol.* **59** (8): 4747-4760.
244. Zhang Y, *et al.* (2013) Melatonin inhibits the caspase-1/cytochrome c/caspase-3 cell death pathway, inhibits MT1 receptor loss and delays disease progression in a mouse model of amyotrophic lateral sclerosis. *Neurobiol. Dis.* **55**: 26-35.
245. Weishaupt JH, *et al.* (2006) Reduced oxidative damage in ALS by high-dose enteral melatonin treatment. J. *Pineal Res.* **41** (4):313-323.
246. Kabadi SV, Maher TJ (2010) Posttreatment with uridine and melatonin following traumatic brain injury reduces edema in various brain regions in rats. *Ann. N. Y. Acad. Sci.* **1199**: 105-113.
247. Campolo M, *et al.* (2013) Combination therapy with melatonin and dexamethasone in a mouse model of traumatic brain injury. *J. Endocrinol.* **217** (3): 291-301.
248. Dehghan F, Khaksari Hadad M, Asadikram G, Najafipour H, Shahrokhi N (2013) Effect of melatonin on intracranial pressure and brain edema following traumatic brain injury: role of oxidative stresses. *Arch. Med. Re.* **44** (4): 251-258.
249. Ding K, *et al.* (2014) Melatonin stimulates antioxidant enzymes and reduces oxidative stress in experimental traumatic brain injury: the Nrf2-ARE signaling pathway as a potential mechanism. *Free Radic. Biol. Med.* **73**: 1-11.
250. Ding K, *et al.* (2014) Melatonin reduced microglial activation and alleviated neuroinflammation induced neuron degeneration in experimental traumatic brain injury: Possible involvement of mTOR pathway. *Neurochem. Int.* **76**: 23-31.
251. Senol N & Nazıroğlu M (2014) Melatonin reduces traumatic brain injury-induced oxidative stress in the cerebral cortex and blood of rats. *Neural Regen. Res.* **9** (11): 1112-1116.
252. Yürüker V, Nazıroğlu M, Şenol N (2015) Reduction in traumatic brain injury-induced oxidative stress, apoptosis, and calcium entry in rat hippocampus by melatonin: Possible involvement of TRPM2 channels. *Metab. Brain Dis.* **30** (1): 223-231.

253. Babaee A, *et al.* (2015) Melatonin treatment reduces astrogliosis and apoptosis in rats with traumatic brain injury. *Iran. J. Basic Med. Sci.* **18** (9): 867-872.
254. Ding K, *et al.* (2015) Melatonin protects the brain from apoptosis by enhancement of autophagy after traumatic brain injury in mice. *Neurochem. Int.* **91**:.46-54.
255. Kelestemur T, *et al.* (2016) Targeting different pathophysiological events after traumatic brain injury in mice: Role of melatonin and memantine. *Neurosci.Lett.* **612**: 92-97.
256. Lin C, *et al.* (2016) Melatonin attenuates traumatic brain injury-induced inflammation: a possible role for mitophagy. *J. Pineal Res.* **61** (2): 177-186.
257. Wu H, *et al.* (2016) Melatonin attenuates neuronal apoptosis through up-regulation of K(+) -Cl(-) cotransporter KCC2 expression following traumatic brain injury in rats. *J. Pineal Res.* **61** (2): 241-250.
258. Dehghan F, *et al.* (2018) Does the administration of melatonin during post-traumatic brain injury affect cytokine levels? *Inflammopharmacology* **26** (4): 1017-1023.
259. Grima NA, *et al.* (2018) Efficacy of melatonin for sleep disturbance following traumatic brain injury: a randomised controlled trial. *BMC Med.* **16** (1): 8.
260. Rehman SU, *et al.* (2019) Neurological enhancement effects of melatonin against brain injury-induced oxidative stress, neuroinflammation, and neurodegeneration via AMPK/CREB signaling. *Cells* **8** (7): 760
261. Salman M, Kaushik P, Tabassum H, Parvez S (2021) Melatonin provides neuroprotection following traumatic brain injury-promoted mitochondrial perturbation in Wistar rat. *Cell. Mol. Neurobiol.* **41** (4): 765-781.
262. Rui T, *et al.* (2021) Deletion of ferritin H in neurons counteracts the protective effect of melatonin against traumatic brain injury-induced ferroptosis. *J. Pineal Res.* **70** (2):e12704.
263. Ge J, *et al.* (2020) Effect of melatonin on regeneration of cortical neurons in rats with traumatic brain injury. *Clinical and investigative medicine. Med. Clin. Exp.* **43** (4): E8-16.
264. Li SS, *et al.* (2021) Androgen is responsible for enhanced susceptibility of melatonin against traumatic brain injury in females. *Neurosci. Lett.* **752**: 135842.
265. Cao R, *et al.* (2021) Melatonin attenuates repeated mild traumatic brain injury-induced cognitive deficits by inhibiting astrocyte reactivation. *Biochemical and biophysical research communications Biochem. Biophys. Res. Commun.* **580**: 20-27.
266. Wu C, *et al.* (2022) A novel mechanism linking ferroptosis and endoplasmic reticulum stress via the circPtpn14/miR-351-5p/5-LOX signaling in melatonin-mediated treatment of traumatic brain injury. *Free Radic. Biol. Med.* **178**: 271-294.
267. Xie LL, Li SS, Fan YJ, Qi MM, Li ZZ (2022) Melatonin alleviates traumatic brain injury-induced anxiety-like behaviors in rats: Roles of the protein kinase A/cAMP-response element binding signaling pathway. *Exp.Ther. Med.* **23** (4): 248.
268. Xie LL, *et al.* (2022) Melatonin mitigates traumatic brain injury-induced depression-like behaviors through HO-1/CREB signal in rats. *Neurosci. Lett.* **784**: 136754.
269. Fu J, *et al.* (2022) Protective effects and regulatory pathways of melatonin in traumatic brain injury mice model: Transcriptomics and bioinformatics analysis. *Front. Mol. Neurosci.***15**: 974060.
270. Paul R, *et al.* (2018) Melatonin protects against behavioral deficits, dopamine loss and oxidative stress in homocysteine model of Parkinson's disease. *Life Sci.* **192**: 238-245.
271. Rasheed MZ, *et al.* (2018) Melatonin improves behavioral and biochemical outcomes in a rotenone-induced rat model of Parkinson's disease. *J. Environ. Pathol. Toxicol. Oncol.* **37** (2): 139-150.
272. Ran D, *et al.* (2018) Melatonin attenuates hLRRK2-induced long-term memory deficit in a Drosophila model of Parkinson's disease. *Biomedical reports* 9(3):221-226.

273. Daneshvar Kakhaki R, *et al.* (2020) Melatonin supplementation and the effects on clinical and metabolic status in Parkinson's disease: A randomized, double-blind, placebo-controlled trial. *Clin. Neurol. Neurosurg.* **195:** 105878.
274. Delgado-Lara DL, *et al.* (2020) Effect of melatonin administration on the PER1 and BMAL1 clock genes in patients with Parkinson's disease. *Biomed. Pharmacother.* **129**: 110485.
275. Zheng R, *et al.* (2021) Melatonin attenuates neuroinflammation by down-regulating NLRP3 inflammasome via a SIRT1-dependent pathway in MPTP-induced models of Parkinson's disease. *J. Inflamm. Res.* **14**: 3063-3075.
276. Jiménez-Delgado A, *et al.* (2021) Effect of melatonin administration on mitochondrial activity and oxidative stress markers in patients with Parkinson's disease. *Oxid. Med. Cell. Longev.* **2021**: 5577541.
277. Jung YJ, Choi H, & Oh E (2022) Melatonin attenuates MPP(+)-induced apoptosis via heat shock protein in a Parkinson's disease model. *Biochem. Biophys. Res. Commun.* **621**: 59-66.
278. Asemi-Rad A, *et al.* (2022) The effect of dopaminergic neuron transplantation and melatonin co-administration on oxidative stress-induced cell death in Parkinson's disease. *Metab. Brain Dis.* **37** (8): 2677-2685.
279. Luengo E, *et al.* (2019) Pharmacological doses of melatonin impede cognitive decline in tau-related Alzheimer models, once tauopathy is initiated, by restoring the autophagic flux. *J.Pineal Res.* **67** (1): e12578.
280. Chen D, *et al.* (2020) Melatonin directly binds and inhibits death-associated protein kinase 1 function in Alzheimer's disease. *J. Pineal Res.* **69** (2): e12665.
281. Wang P, *et al.* (2021) Melatonin ameliorates microvessel abnormalities in the cerebral cortex and hippocampus in a rat model of Alzheimer's disease. *Neural Regen. Res.* **16** (4): 757-764.
282. Labban S, Alshehri FS, Kurdi M, Alatawi Y, Alghamdi BS (2021) Melatonin improves short-term spatial memory in a mouse model of alzheimer's disease. *Degener. Neurol. Neuromuscul. Dis.* **11**: 15-27.
283. Chen D, *et al.* (2022) Melatonin ameliorates tau-related pathology via the miR-504-3p and CDK5 axis in Alzheimer's disease. *Transl. Neurodegener.* **11** (1): 27.
284. Fan L, *et al.* (2022) Melatonin ameliorates the progression of alzheimer's disease by inducing TFEB nuclear translocation, promoting mitophagy, and regulating NLRP3 inflammasome activity. *Biomed. Res. Int.* **2022**: 8099459.
285. Chen C, *et al.* (2021) Melatonin ameliorates cognitive deficits through improving mitophagy in a mouse model of Alzheimer's disease. *J. Pineal Res.* **71** (4): e12774.
286. Li LB, *et al.* (2022) Novel melatonin-trientine conjugate as potential therapeutic agents for Alzheimer's disease. *Bioorg. Chem.* **128**: 106100.
287. Özşimşek A, Övey İ S (2022) Potential effects of melatonin on trpa1 channels in the prevention and treatment of alzheimer's disease. *Noro Psikiyatr. Ars.* **59** (3):188-192.
288. Rudnitskaya EA, *et al.* (2015) Melatonin Attenuates Memory Impairment, Amyloid-β Accumulation, and Neurodegeneration in a Rat Model of Sporadic Alzheimer's Disease. *J. Alzheimers Dis.* **47** (1): 103-116.
289. Li Y, *et al.* (2019) Melatonin enhances autophagy and reduces apoptosis to promote locomotor recovery in spinal cord injury via the PI3K/AKT/mTOR signaling pathway. *Neurochem. Res.* **44** (8):2007-2019.
290. Jing Y, *et al.* (2019) Melatonin treatment alleviates spinal cord injury-induced gut dysbiosis in mice. *J. Neurotrauma* 36(18):2646-2664.

291. Xu G, Shi D, Zhi Z, Ao R, Yu B (2019) Melatonin ameliorates spinal cord injury by suppressing the activation of inflammasomes in rats. *J. Cell. Biochem.* **120** (4):5183-5192.
292. Shen Z, *et al.* (2017) Melatonin inhibits neural cell apoptosis and promotes locomotor recovery via activation of the Wnt/β-catenin signaling pathway after spinal cord injury. *Neurochem. Res.* **42** (8):2336-2343.
293. Jing Y, Bai F, Chen H, Dong H (2016) Meliorating microcirculatory with melatonin in rat model of spinal cord injury using laser Doppler flowmetry. *Neuroreport* **27** (17):1248-1255.
294. Krityakiarana W, *et al.* (2016) Effects of melatonin on severe crush spinal cord injury-induced reactive astrocyte and scar formation. *J. Neurosci. Res.* **94** (12): 1451-1459.
295. Jing Y, Bai F, Chen H, Dong H (2017) Melatonin prevents blood vessel loss and neurological impairment induced by spinal cord injury in rats. *J. Spinal Cord Med.* **40** (2):222-229.
296. Paterniti I, *et al.* (2017) PPAR-α modulates the anti-inflammatory effect of melatonin in the secondary events of spinal cord injury. *Mol. Neurobiol.* **54** (8): 5973-5987.
297. Yuan XC, *et al.* (2017) Effects of melatonin on spinal cord injury-induced oxidative damage in mice testis. *Andrologia* **49** (7): e12692.
298. Wang H, *et al.* (2022) Melatonin attenuates spinal cord injury in mice by activating the Nrf2/ARE signaling pathway to inhibit the NLRP3 inflammasome. *Cells* **11** (18).
299. Bi J, *et al.* (2021) Melatonin synergizes with methylprednisolone to ameliorate acute spinal cord injury. *Front. Pharmacol.* **12**: 723913.
300. Gao K, Niu J, Dang X (2020) Neuroprotection of melatonin on spinal cord injury by activating autophagy and inhibiting apoptosis via SIRT1/AMPK signaling pathway. *Biotechnol. Lett.* **42** (10): 2059-2069.
301. Yang Z, Bao Y, Chen W, He Y (2020) Melatonin exerts neuroprotective effects by attenuating astro- and microgliosis and suppressing inflammatory response following spinal cord injury. *Neuropeptides* **79**: 102002.

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