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Review

Melatonin hormone as a therapeutic weapon against neurodegenerative diseases

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Abstract: Brain disorders such as Alzheimer's and Parkinson's disease (PD) are irreversible conditions with several cognitive problems, including learning disabilities, memory loss, movement abnormalities, and speech problems. These disorders are caused by a variety of factors, mainly due to the toxic pollutants-induced biochemical changes in protein production, uncontrolled neuronal electrical activity, and altered neurotransmitter levels. Oxidative stress and toxicity associated with the increased glutamate levels decreased acetylcholine levels, and brain inflammation is the main contributing factor. Melatonin hormone is considered one of the potent treatment approaches for neurodegenerative disorders. Melatonin is released from the pineal gland and has a critical role in brain function regulation. Membrane receptors, binding sites, and chemical interaction mediate hormonal actions having multiple phenotypic expressions. It acts as a neurodegenerative agent against some neurological disorders such as Alzheimer's disease (AD), PD, depression, and migraines. Melatonin inhibits neurotoxic pollutants-induced Tau protein hyperphosphorylation, especially in AD. Other pivotal features of melatonin are its anti-inflammatory properties, which decrease pro-inflammatory cytokines expression and factors such as IL-8, IL-6, and TNF. Melatonin also reduces NO (an inflammation factor). In this review, we have highlighted the protective effects of melatonin, mainly spotlighting its neuroprotective mechanisms that will be beneficial to assess their effects in environmental pollution-induced neurodegenerative pathology.

Key words: Alzheimer's disease; Inflammation; Melatonin; Parkinson's disease; Neurodegenerative agent.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that affects 2% of the elderly populace worldwide (1). Amyloid plaques and filamentous sheaths with brain amyloid angiopathy are two major symptoms in AD patients. The imbalance between beta-amyloid (Aβ) synthesis from amyloid precursor protein and its brain clearance is the main cause of Aβ accumulation and its pathogenicity (2). Intracellular Aβ assemblages destroy the endolysosomal-autophagic system and subsequent synthesis of autophagic vacuole and malformed mitochondria in the neuron (3). There are significant interactions between Aβ and Tau proteins, which are the major microtubule-associated protein of a mature neuron that binds to microtubules and stabilizes the whole microtubule network (4). Beta-amyloid assemblages inside and outside the neurons. On the other hand, intra-neuronal hyperphosphorylated Tau, dendritic spines analysis, and synapse degradation may eventually lead to memory losses in AD-affected people. Amyloid plaques are identified in the early stage of AD in the cortex and hippocampus as they spread from pre-clinical stage to the clinical stage, propagated in the central nervous system or CNS (5). Glia-associated inflammations and neuronal deaths in AD decrease in neuronal functions and consequently cognitive impairments (6).

Parkinson's disease (PD) is another neurodegenerative disorder that affects about 1.8% of elderly people. It is caused by the progressive losses of dopaminergic neurons in the substantia nigra pars compacta (SNpc) in the mid-brain and a successive loss of dopamine and clinically manifested by defective motor functions, reduced cognitive functions, and depression. Biochemical analyses suggested that reactive oxygen species (ROS) or reactive nitrogen species (RNS) are pivotal mediators in PD. The disease occasionally has genetic links, the sign, and symptoms of PD likely develop, at least in part, after free radical damage to the SNpc. Additionally, the inflammation of neurons and malfunctioning of mitochondria contribute to the etiology of this disease and enhance the oxidative damages to the dopaminergic

neuronal population. Once a large percentage of these cells are lost, PD signs appear (7).

Melatonin (N-acetyl-5-methoxytryptamine) hormone is released from the midbrain pineal gland and some peripheral tissues. This hormone is one of the G-protein coupled receptors family, activating intracellular signaling pathways (8). Melatonin, a tryptophan metabolite, has several physiological roles such as circadian rhythms regulation, free radicals scavenging, immunity enhancement, and generally inhibiting biomolecules oxidation (9). This hormone has a protective effect on neurodegenerative disorders (10). Reduction in the melatonin serum level and cerebrospinal fluid (CSF), and decrease in daily melatonin are reported in AD patients. Further, melatonin levels in CSF decrease after developing AD neuron-based pathologies (11).

Melatonin content in CSF and human post-mortem glands is decreased with the first symptoms of AD neuropathology (12). There is a potent association between pineal content, CSF, and plasma melatonin levels, which may be an early marker in AD's early stages (13). Other features of AD can be characterized by synaptic degradation, neurites or neuronal degeneration, endosome aggregation, lysosomes, and abnormal mitochondria (such as extracorporeal aneurysms). Synapses deterioration and neuron apoptosis in the limbic system causes cognitive deficits in AD patients (Figure 1) (14).

Melatonin diversity functions can be recognized as the fact that melatonin receptors are located in numerous tissues (15). Brain melatonin receptors can be seen in the prefrontal cortex, cerebellum, hippocampus, basal nucleus, the substantia nigra, nucleus accumbens, retina, and also in various hypothalamus cells. Moreover, these receptors are revealed in peripheral tissues such as the gastrointestinal tract, adipose tissue, pancreas, ovary, skin, lung, heart, and lymphocytes (16).

Melatonin has two general class receptors, which include G-family receptors [(melatonin receptor 1 (MT1) and melatonin receptor 2 (MT2)] and quinone reductase [melatonin receptor 3 (MT3)] enzyme family. The MT1 and MT2 can initiate cell signaling pathways after binding to their ligand, each of which leads to a specific response (15, 16). Down-regulated immunity via MT2 and increased immunity via MT1 have been reported in the AD patients' hippocampus (17). MT1 and MT2 are unique receptors with distinguished pharmacological characteristics and chromosomal localization. MT1 and MT2 receptors are 350 and 362 amino acids in length, respectively, with molecular masses of 39–40 kDa (18). These receptors signal by coupling with heterotrimeric Gi protein which contains α, β, and γ subunits. Activation of these receptors promotes dissociation of G proteins into α, β, and γ dimers which interact with downstream cell signaling molecules (19). Downstream molecules in MT1 and MT2 receptors signaling by G-protein coupling involve adenylyl cyclase, phospholipase C, phospholipase A2, potassium channels, guanylyl cyclase, and calcium channels (20). Tissues enriched with MT1 and MT2 receptors include retina, brain, suprachiasmatic nucleus, pars tuberalis, ovaries, kidney, pancreas, adipocytes, and immune cells (21).

Figure 1. Melatonin protective effect on neurodegenerative diseases.

Other properties that consider melatonin as a protective factor against many diseases such as cancer or neurodegenerative diseases are its anti-apoptotic properties. Although melatonin anti-apoptotic signaling pathways have not yet been fully identified, it has been shown that melatonin can be activated by some protective pathways, such as increased Bcl-xL, Bcl-2, super oxidase dismutase, and glutathione peroxidase, or scavenging of free radicals (22). Inhibition of some factors involved in apoptosis such as caspase, decreased MAPK, and ERK activity prevented the increase of the Rip process in cells to comfort protection against apoptosis (23). Many studies have shown melatonin effects on AD, cerebrovascular diseases, Amyotrophic Lateral Sclerosis (ALS), and PD. Studies found that the occurrence of these diseases is usually accompanied by a loss of melatonin or its receptors (24).

Other melatonin functions comprise anti-inflammatory properties. Melatonin can affect many inflammatory factors such as NO and NOS (25). This hormone regulates cytokines synthesis such as IL-6, IL-8, and other inflammatory parameters. Melatonin slows down certain disease progression (26). El-Shenawy et al. (25) observed the anti-apoptotic effect of melatonin on neurodegenerative diseases. Melatonin can be used to reduce Huntington's symptoms (27). Moreover, *in vitro* melatonin has been unraveled to counteract ALS, Parkinson's, stroke, and AD pathways wherein melatonin prevents mitochondrial-dependent apoptotic pathways both *in vitro* and *in vivo* and interferes with cell survival (28).

Effect of environmental factors

Numerous environmental pollutants have been shown to mediate neurodegeneration through alterations in Tau phosphorylation, aggregation of proteins such as α-synuclein (α-syn), mitochondrial dysfunction, alterations in metal homeostasis (29). Studies have revealed that Aβ42 and cyclooxygenase 2 (neuroinflammation indicator) levels are higher in the hippocampus and frontal cortex of persons exposed to high air pollution (30). Air pollutants activate microglia and the generation of pro-inflammatory cytokines which led to ventriculomegaly (through toxicity to oligodendrocytes) and hypomyelination (30).

Previous *in vivo* studies on the Tg2576 mice showed that the acute subcutaneous administration of organo-

phosphate pesticide chlorpyrifos (50 mg/kg) increased memory loss and Aβ levels in the hippocampus and cortex and reduced motor activity after 6 months (31).

Although nanoparticles are promising therapeutically tools for neurodegenerative disease, some evidence associating them with alteration of the molecular mechanisms were involved in the pathogenesis of the neurodegenerative disease (32). Ze et al (33) showed that the nasal administration of 2.5–10 mg/kg TiO_2 nanoparticles for 90 days caused oxidative stress, cell death in the hippocampus, and a decline in cognition and memory-associated gene. Also, a reduction in electrophysiological endpoints and spatial cognition was found in another study on rats exposed to 0.5 mg/kg CuO-NPs (14 days, i.p.) that conformed by a high level of ROS formation and lipid peroxidation and decreased antioxidants enzymes level (34).

Numerous experimental and epidemiological studies emphasized the potential risk of exposure to environmental pollutants including nanoparticles, pesticides, metals, and the development of neurodegenerative diseases (35). Due to similar toxicity mechanisms based on the reduced levels of antioxidants enzymes and oxidative stress generation by these pollutants, natural antioxidants including melatonin, curcumin, resveratrol, etc, and their nanoformulations have gained more attention (35-37).

Melatonin induces improvement in neurodegenerative diseases

Numerous studies revealed the effect of melatonin on AD. Improved memory in Alzheimer's mice and *in vitro* reduction in beta-amyloid apoptosis by melatonin was studied (27). In another study, melatonin was able to prevent Tau protein hyperphosphorylation by inhibiting cAMP, reducing PKA activity, and reducing CREB phosphorylation *in vitro* (38).

Melatonin has strong anti-inflammatory properties, which suppresses pro-inflammatory cytokines and factors such as IL-8, IL-6, and TNF expression (39). Since melatonin is one of the best antioxidant agents as it directly scavenges free radicals, it is used in remarkably large numbers of experimental models in which the pathogenicity is thought to be mediated by free radicals in one way or another (7, 40). Also, melatonin reduces NO (an important factor involved in inflammation. Furthermore, according to Tan et al. (41) AFMK metabolism, which has melatonin-like abilities, was higher in meningitis patients than in normal individuals. Korkmaz et al. (42) also reported that melatonin inhibited inflammatory enzymes activation (Figure 2).

Melatonin decreases nitrate by reducing iNOS in PSLPS / IFN U by inhibiting NFkB activity. Melatonin can also show a protective effect in traumatic CNS defects (43). According to Hong et al. (44) in the chronic SCI (Spinal Cord Injury) model, melatonin reduced secondary injury and accelerated recovery by inhibiting lipid peroxidation which induced by neutrophils.

Effect of melatonin on Akt/ Protein Kinase (PKB) B Pathway

This pathway is cell survival key mediator and apoptotic stimuli factors. PI3K /Akt pathway has the main role in nerve cell survival (45). When PI3K is activated, membrane phospholipids produce phosphatidylinositol, which in turn induces Akt phosphorylation, succeeding that factors such as Bcl-2 are activated and inhibits apoptosis (46). These proteins are anti-apoptotic. Eliminating 2-Bcl endogenous nerve signals directly comforts neuron apoptosis in neurodegenerative diseases. JNK pathway prevents apoptosis in neurodegenerative disease (47). Melatonin suppresses apoptosis by affecting cellular signaling and downregulates the apoptosis process. During neurodegenerative disease progression, signaling cascades are mediated by neuronal protection factors including phospho-inositol 3 kinase activator pathway and N-kinase 3 protein kinase (48).

Effect of melatonin on decreasing Aβ toxicity

Aβ molecule (39−43 amino acids), a derivative form of amyloid precursor protein (APP), has a fundamental function in AD. APP is a member of the amyloid precursor protein family APLP1 and APLP2. All of these proteins pass through the membrane at one time and have a large outer membrane region. All members of this family can produce amyloid fragment and mRNA down-regulation levels by APP, leading to isoforms production, which are the most common forms in the nervous system (49, 50). The 695 amino acid variants of APP are predominantly in the CNS, but 751 and 770 amino acid variants are expressed elsewhere. Similar studies revealed potential properties for Aβ, which can be activated by kinetic enzymes in oxidative stress regulation (51).

Melatonin anti-fibrillogenic effects have been unraveled by various microscopic and spectroscopic techniques (52). Further, the reaction between melatonin and Aβ has been assumed to be associated with structure and melatonin properties (53). Studies from spectrometric techniques have identified that melatonin interacts with about 40 amino acid residues of Aβ, especially aspartate and histidine, which are favorable to form β-sheet. Breaking these bonds results in the Aβ molecule's dissolution. Melatonin interaction with succinate imidazole-carboxylate bridges led to β-sheet structure conversion into random coils. Thus melatonin not only prevents the β-sheet formation and reduces neurotoxicity but also reduces Aβ peptide secretion through increased proteolytic degradation (54). Aβ molecule's over-expression led to cellular damage including lipid peroxidation, increased intracellular free calcium concentration, mitochondrial DNA oxidative damage, and released apoptosis indicators. Studies have shown that melatonin regulates mitochondrial internal membrane fluidity and

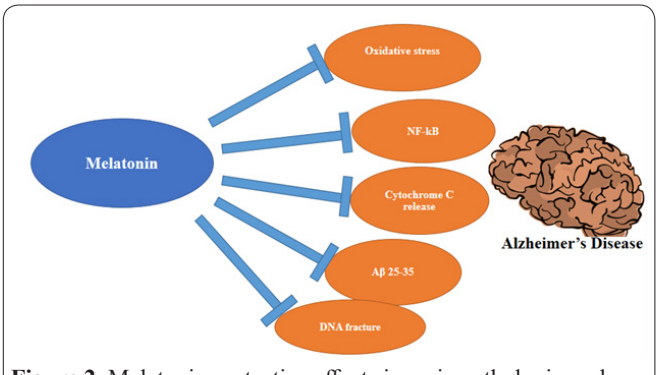

Figure 2. Melatonin protective effects in main pathologic molecular pathways.

binds to the mitochondrial membrane. Suppression of Aβ aggregation is considered as the main factor in AD treatment. Recently, various researches have shown that melatonin can react with Aβ40 and Aβ42 molecules to prevent their gradual progression to β-sheet or amyloid fiber (Table 1) (54, 55).

Table 1. Molecular targets and pathways involved in neurodegenerative diseases ameliorated by melatonin.

Target	Melatonin effect
Cytochrome C	Reduce Cytochrome C release
NF-κB	Reduce Aβ25-35 apoptosis
Bax	Reduce Aβ25-35 apoptosis
Caspase 3	Reduce Aβ25-35 apoptosis
DNA Fracture	Reduce Aβ25-35 apoptosis
AICD	Reduce α-secretase
β-Secretase	Reduce β-APP
μ-Secretase	Reduce β-APP
Insulin receptor	Reduce IRS-1
Par-4	Reduce Par-4 regulation
Akt	Reduce GSK-3β
Tau	Reduce neurofibrillary tangles
GSK-3β	Reduce c99
mTOR	Decreased central nervous system
BMAL-1	Suppress central nervous system
IDE	Decrease senile production
Insulin signaling	Decreased GLUT-1 and -3 GLUT-3
Fasl/ TNFR	Supress caspase 8 and 10
caspase 8 and 10	Decreased apoptosis
ROS	Decreased Jnk/p38 phosphorylation
ROS	Decreased glutamate excitotoxicity
Calmodulin	Decreased caMKII

Melatonin suppresses Tau proteins synthesis

Tau is the leading protein found in the axon which stabilizes neural pathways, microtubules, and neural transmission. This gene is located on chromosome 17 long arm and contains 16 exons (56). Tau is present not only in neuron axons but also in oligodendrocytes. Tau hyperphosphorylated form is not soluble, in which its propensity to microtubules is reduced and spontaneously forms complex interconnected structures (57). Tau proteins accumulate outside of AD and other CNS diseases (39). These types of disorders are known as Tauopathy. The amount of neurofibrillary strings is one of the AD prognosis markers (58).

The main components of these coils are hyperphosphorylated and accumulated Tau protein forms. Like Aβ oligomers, abnormal Tau protein intermediate aggregates also have deleterious effects on cells and cause cognitive impairment. Insoluble complex strands may have no adverse effect but decrease synaptic transmission and neuron numbers are due to neurofibrillary coils' detrimental effects. Parkinson's disease has identified more than 30 mutations in the *tau* gene on chromosome 17 (59). In contrast, there is no mutation in Tau protein in AD, and neurofibrillary coil formation is not a result of Tau protein mutation. However, an increase in the amount of Tau phosphorylation in cerebrospinal fluid is directly related to a decrease in cognitive tests score. Increased levels of Tau phosphorylated in cerebrospinal fluid can be administrated as a proper biomarker in predicting and diagnosing AD early stages in cognitive impairment patients. Melatonin synthesis inhibition caused spatial memory impairments in mice and elevated Tau phosphorylation via PP-2A activity suppression (60). Melatonin supplementation with 5-hydroxyindole-O-methyltransferase significantly increased memory retention arrested Tau, and reduced hyperphosphorylation, oxidative stresses, and PP-2A activities (60).

Protective effect of melatonin in neuroinflammation

In some species, pinealectomy and other experimental processes which inhibit the melatonin secretions stimulate the immunosuppression stage which is further reversed by administrating the melatonin (61). In various *in vivo* experimental models and *in vitro* studies, melatonin induces inflammatory cytokines and nitric oxide synthesis. Melatonin induces T-lymphocytes, monocytes, natural killer cells, granulocytes, cell-dependent cytotoxicities, and antibodies-dependent response (62). In addition, NF-κB DNA binding inhibition by melatonin significantly reduces pro-inflammatory response and leads to a 50% reduction of Aβ-induced pro-inflammatory cytokines. However, T-lymphocyte and NK-cells are of immense interest in neural inflammation. Melatonin has an anti-inflammatory effect via targeting IL-6, IL-2, IL-1b, IL-12, IL-1, TNF-α, and IFN-β cytokines (63).

Melatonin in monocytes increases ROS formation and cellular toxicity, indicating dual effects of melatonin on inflammation (64). Although, its effect on the synthesis of monocytes and microglial cells has not been reported. Melatonin has significant effects on lymphocytes number alteration and other leukocytes in peripheral immune system tissues. However, these changes in the immune system during adolescence may have an adverse health effect and indirectly affect CNS. Further, melatonin directs inhibition of prostaglandin E2 (PGE2) on IL-2 synthesis. It upregulates anti-inflammatory factors L-10 and IL-2 (65). These two anti-inflammatory effects of melatonin in macrophages are mediated by the kB-NF pathway, which involves cyclooxidase 2 (COX 2) expression through iOS activation. Reports have revealed that melatonin inhibits apical apoptosis and DNA fragmentation by inhibiting caspase-1 activity and IL-1β secretion in brain cells. It also prevents inflammation through Akt / K-PI3, JNK, and Akt phosphorylation pathways. Melatonin regulates apoptotic signals by downregulating phosphorylation / MEK1, 1-Raf, and ERK1, thereby preventing cellular damages (66).

Melatonin as free radicals scavenger

ATP is produced in the mitochondrial electron transfer chain during cellular respiration. In normal conditions, 5.5% of oxygen is changed into approximately one species of oxygen (67). The maximum amount of ROS radicals is superoxide anion (O_2) which is composed of an electron origin of oxygen (O_2) molecule. Other low-cost ROS compounds containing anion nitrite peroxide are hydroxyl radicals, carbonate radicals, and nitrogen dioxide (NO_2) which are synthesized by defective cellular components and have deleterious effects on protein synthesis (67). Henceforth, free radical

scavenging has a key role in many neurological, immune disorders, inflammatory, and mitochondrial diseases. Incomplete mitochondrial function is one of the most effective causes of free-radicals species in diseases such as neurodegenerative diseases, ischemia, and the aging process. Hence, increased free radicals, respiratory activity and mitochondrial production activity, and defects in the electron transport chain are causing mitochondrial dysfunction and cellular death. Melatonin induces glutathione synthesis, another antioxidant that decreases mitochondrial electron chain electron emission (68).

Melatonin is selectively absorbed by mitochondria and acts as a potent antioxidative agent and regulates mitochondria bioenergetic functions (69). It increases mitochondrial membrane permeability and stimulates disparate antioxidant enzymes. Hence, melatonin can resist oxidative damage by repairing microsomal membranes. Melatonin reduces free radicals production. It prevents electron emission over the long term and thus improves mitochondrial function by inhibiting electron charging. The highest level of melatonin is found in mitochondria (70).

Protective effects of melatonin in the cholinergic system

The cholinergic system association in Aβ has been demonstrated which indicated that acetylcholine level alteration can reverse the long-term potentiation inhibition by Aβ. Long-term amplification is a phenomenon in which response amplitude increases with the application of high excitation frequencies in a neuronal circuit, a possible memory, and a learning mechanism. Hence, acetylcholine increment can be considered as the main therapeutic agent in AD (51). Another study revealed that melatonin prevented peroxynitrite from blocking the transfer of acetylcholine from synaptic vesicles. Aβ has the main role in stimulating glutamate release by microglial cells and preventing neurons from accumulating excess glutamate. So, Aβ inhibits glutamate uptake. In another study, the administration of kinetic acid led to glutamate release and brain impairment via NMDA. As a result, glutamate receptor activation led to a Ca^{++} influx which increased through the NMDA-controlled channels over NO synthesis by activating NOS (71). The effect of abnormal glutamate secretion is due to increased glutamate levels and its toxic effect on neurons in AD by NMDA receptors. This is due to glutamate receptors' destruction or an increase in glutamate secretion. Melatonin downregulates glutamate synthesis and NMDA induction. Apoptosis induced by glutamate in hippocampal regions of the brain is reduced by melatonin administration (72). Hippocampal MT2 receptors in combination with melatonin can prevent the development of learning disorders in mice. Some studies in rats revealed that melatonin administration reduced glutamate levels and axons, dendrites, and neuron structural deficits due to hypoxia in the brain (73).

Role of melatonin in PD treatment

PD is a neurological disorder in which dopaminergic cells damage substantia nigra and striatum. Several research reports emphasized mutation, oxidative stresses, and free radical-induced increment in mitochondrial and dopamine-metabolizing enzymes (74). Therefore, antioxidants administration has been recommended as a promising therapy for PD (75). Singhal et al. (76) used neurotoxin (MPTP) in the rat PD model and found a melatonin-induced reduction in MPTP-mediated lipid peroxidation and hypertriglyceridemia. Within the last decade, hundreds of reports present scientific data for the therapeutic roles of melatonin in several OS-related disorders with the protective actions being attributed towards the direct and indirect antioxidant traits of indole. Melatonin is being used in several experimental models in which the pathogeny is thought to be mediated by free radicals in one way or another. The primary proof of a special relevance between melatonin and PD came from findings of decreased pineal activities and successive reductions in circulating melatonin concentrations in PD-affected people (40).

Melatonin also increases antioxidant enzyme levels, besides prevention of apoptosis in the hippocampus. This preventive mechanism of melatonin involves inhibition of extracellular calcium exchange through mitochondrial membrane, stimulating mtPTP pathway, avoiding ROS formation, and cytochrome C secretion reducing. Another study in the mice animal model indicated that melatonin inhibited caspase-3 activity. MPTP exerts its neurodegenerative effects by increasing NO synthesis, which led to dopaminergic fiber impairment in the striatum nerve end. Melatonin acts through the JNK pathway to prevent dopaminergic apoptosis in substantia nigra and striatum and thus, it downregulates iNOS and NO levels in nerve cells and influences this process (77).

Melatonin also stimulates Mn-SOD, antioxidant, and GPx antioxidants in dopaminergic cells (78, 79). Further, melatonin increases mitochondrial complexes 1 and 3 activity and has beneficial effects. It preserves mitochondrial homeostasis, reduces free radicals synthesis, and improves ATP synthesis. Therefore, melatonin may prevent apoptotic cascade and dedopaminergic neuron apoptosis (80).

In contrary to the above, a few studies have been revealed that abnormal aggregation of cytoskeleton affects neurodegenerative disease pathogenesis. Levi's bodies, which are cytopathological markers of PD, are abnormal structures of tubulin, ubiquitin, and microtubule proteins 1 and 2. Melatonin is very effective in the formation and regeneration of cytoskeleton formation and hence, it is possible to be one of the potential therapeutic molecules in neurodegenerative diseases. Various studies have revealed that melatonin has a potent curative significance as a neuroprotective agent in PD, ALS, and brain trauma. Moreover, melatonin clinical trials established its neuroprotective effects (81). Recent studies showed improved therapeutic potential of melatonin using biological origin nanocarriers for drug delivery (82). These nanoformulations could provide high effectiveness in crossing the blood-brain barriers and extending the melatonin release (82, 83). The distinguishing features enable melatonin to protect neurodegeneration by targeting mitochondrial-related pathways (84). Of course, it should be noted that attention to other factors such as genetic issues, gene therapy and genetic diversity in this regard is very important (85-87).

Conclusion

Melatonin is an endogenous, non-toxic, and antioxidative agent. It is considered a beneficial agent in different neurodegenerative disorders including AD and PD as a co-treatment with conventional therapeutic methods. Various studies on melatonin suggest that it can be used as a supplement in neurodegenerative disorders through its multiple effects, especially anti-apoptotic and anti-inflammatory properties. The experimental data collectively suggested that melatonin use would reduce their disease burden. Because neural diseases are generally caused by oxidative damages, melatonin has been investigated in varied experimental models. Melatonin-based therapy seems to be an ideal approach to reduce cognitive impairments in AD and PD-affected elderly people.

Conflict of interest

None.

Acknowledgments

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