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Review Article

Role of immune-pineal axis in neurodegenerative diseases, unraveling novel hybrid dark hormone therapies

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Abstract

The anti-oxidant effects of melatonin and the immune-pineal axis are well established. However, how they play a role in the pathogenesis of neurodegenerative diseases is not well elucidated. A better understanding of this neuro-immuno-endocrinological link can help in the development of novel therapies with higher efficacy to alleviate symptomatology, slow disease progression and improve the quality of life. Recent studies have shown that the immune-pineal axis acts as an immunological buffer, neurohormonal switch and it also intricately links the pathogenesis of neurodegenerative diseases (like Multiple sclerosis, Alzheimer's disease, Parkinson's disease) and inflammation at a molecular level. Furthermore, alteration in circadian melatonin production is seen in neurodegenerative diseases. This review will summarise the mechanics by which the immune-pineal axis and neuro-immuno-endocrinological disturbances affect the pathogenesis and progression of neurodegenerative diseases. It will also explore, how this understanding will help in the development of novel hybrid melatonin hormone therapies for the treatment of neurodegenerative diseases.

Keywords: Neuroscience, Physiology, Pharmaceutical science

1. Introduction

According to Rick Strassman, an eminent psychiatrist, “The pineal gland of evolutionarily older animals, such as lizards and amphibians, is also called the ‘third’ eye. Just like the two seeing eyes, the third eye possesses a lens, cornea, and retina. It is light-sensitive and helps regulate body temperature and skin coloration, two basic survival functions related to environmental light [1].” Several controversies and folklores in history surround the pineal gland. Be it theories on the psychedelic effect of N, N dimethyltryptamine secreted by the gland or Egyptian traditions considering it the eye of Horus, the third eye or the seat of the soul [2]. Clinical interaction with patients of Alzheimer’s disease generated our interest to explore the medical significance of the pineal gland. We became curious to know, if the pineal gland could be considered to be one of the central control centers of the body. The question is to explore the connections of the pineal gland and how those can be used to treat patients effectively and prevent disease progression.

1.1. The pineal gland and its current position in medicine

The pineal gland produces a large number of hormones. One of them, melatonin is recognized well for its circadian production and chronobiotic roles [3]. Others like N, N dimethyltryptamine, are under question for their psychedelic effects [2]. It is known well for its role as a potent endogenous hallucinogen, which is present in the brain of most mammals. Depression and stress are the psychological factors, which have been linked with the progress of cancer and inflammatory states [4]. The pineal gland is believed to house photosensitive cells similar to the eyes, as it is believed to have evolved from photoreceptors during the process of evolution. The environmental light/dark cycle adjusts its functioning. The retina detects light that activates the suprachiasmatic nucleus, which polysynaptically activates the pineal gland to cause nocturnal melatonin release. In inflammatory diseased states, it is established that melatonin secretion increases and its light/dark secretion cycle is also disrupted. Activation of the hypothalamic pituitary adrenal axis is also observed in association with it. Henceforth, currently we are aware that the pineal gland is affected by the state of the immune system and associated stressors [5].

1.2. Neurodegenerative diseases and their impact

Neurodegenerative diseases are a set of diseases that develop due to the progressive process of neuronal cell death, due to repeated insults by oxidants and stressors in the body. These diseases are progressive, and their clinical severity increases over time due to added loss of neurons. Different areas of the brain and different types of neurons whether inhibitory or excitatory can be affected in such diseases to result in a

permutation combination of symptomatology in each. Areas that mainly tend to be involved include memory, movement and speech. Some typical examples include Alzheimer's disease, multiple sclerosis, Huntington's disease, diabetic neuropathies, Parkinson's disease, Amyotrophic lateral sclerosis (A.L.S.), prion diseases and tauopathies. The underlying pathophysiology of all these diseases varies from demyelinating diseases, infectious diseases, age-associated diseases and other neurological pathologies.

However, the pathophysiological processes of these diseases lead to a common pathway which involves oxidative cell death [6]. They involve the accumulation of misfolded proteins in the form of intracellular inclusions within neurons. Some studies even show that some diseases like Alzheimer, Parkinson's and A.L.S. are bound to increase in the decades to come [7]. Taking the example of Alzheimer disease, according to Alzheimer's disease International (ADI) 2015 report, there are 46.8 million people with the disease worldwide. This is expected to double every 20 years, and the same is expected to increase up to 131.5 million people by 2050. With the increasing senile population and increasing upward trend of these diseases, it is essential to understand the way to prevent their onset and progression [8].

1.3. The potential links

Currently, we are aware of the antioxidant role of melatonin, the circadian rhythm and the effect of inflammatory states on the same. Direct antioxidant effects of melatonin at in-vivo and in-vitro levels are known [9]. However, a mechanism for how the pineal gland affects neurodegenerative diseases and other inflammatory diseases in the body needs to be clearly understood. The link between microglial signatures, sirtuins, and pathogenesis at the cellular level of such diseases and that of melatonin needs to be further cumulated and established. It is vital to find the links, as it will pave the way for better treatment methods that synchronize the circadian rhythm of this gland and its secretions to prove to be of therapeutic significance. This immuno-endocrinological link can help alleviate and slow down development of symptoms in patients with neurodegenerative diseases to improve the quality of life.

The paper will analyze both the physiological and pathological links between the immune-pineal axis, neurodegenerative diseases and inflammatory states. It will help us understand the physiological connections of the immune-pineal axis, the role of melatonin in both adaptive and innate immunity besides that on neuronal stem cells. Furthermore, it will explore the links that connect it to the pathophysiology of neurodegenerative diseases at an immunological level. Melatonin chronotherapy and development of melatonin hybrids are some of the new therapeutic approaches coming up to combat cognitive decline, neuropsychiatric complications and sleep disturbances associated with neurodegenerative diseases like Alzheimer's

disease. Our review will provide an insight into the novel experimental therapies that use these links and aim to control the spread of neurodegenerative diseases and prevent its progression.

2. Main text

2.1. Materials and methods

2.1.1. Data collection source

The research data was collected with an interest to explore new connections between the pineal gland and neurodegenerative diseases. It was with the primary motive to understand the working of the immune-pineal axis and how its mechanism is linked to the pathogenesis of various diseases. Relevant articles, abstracts and research papers were collected from reliable, and well-accepted web sources like PubMed and PMC.

2.1.2. Inclusion and exclusion criteria

To obtain relevant significant data strict inclusion criteria were applied while searching on the online databases. Reliable sources of data like PubMed and PMC were used for the study. For data extraction studies conducted within the last five years that is, human studies (including clinical trials and observational studies) and review articles were selected. However, cited articles found within full-length review articles and studies extracted from within the last five years, if found to be of relevance, were also included irrespective of the year of publication or having animal studies to present information in the correct perspective. Recent data was preferred to ensure proper significance of the same. All studies conducted globally were included with no specific localization to any particular region. PRISMA methodologies were used throughout the review.

2.1.3. Search content

Keywords were used and the following search results were obtained. Relevant studies were then selected based on their content and significance.

2.1.4. Ethical concerns

All data was obtained lawfully while ensuring accurate reporting of the same. Necessary citation and confidentiality were also maintained.

2.2. Results

Using our methodology, data collection yielded 224 non-duplicate articles. 174 of these were judged to be non-relevant upon screening their abstracts. Further, 7

articles were removed after full text screening of the papers while 3 were removed during data extraction due to lack of relevance and non adherence to the inclusion and exclusion criteria. Table 1 depicts the overview of data extracted. Fig. 1 outlines the process we used for section of studies for our review paper. PRISMA guidelines were followed in the paper. The review paper reviewed a total of 40 full-text articles. The review analyzed links of the immune pineal axis with respect to several neurodegenerative diseases. It found that melatonin (also known as the dark hormone) has

Table 1. Overview of data extraction, studies screened and included.

Keywords	Total citations extracted	Total Studies included	Studies included from PUBMED	Studies included from PMC
Immune-pineal axis	6	3	2	1
Melatonin AND neurodegenerative diseases	122	18	16	2
Pineal gland AND Immunity	8	5	4	1
Pineal gland AND neurodegenerative diseases	20	7	5	2
N,N Dimethyltryptamine AND pineal	7	1	1	0
pineal gland AND stress	50	4	2	2
pineal AND stress AND cancer	25	2	1	1

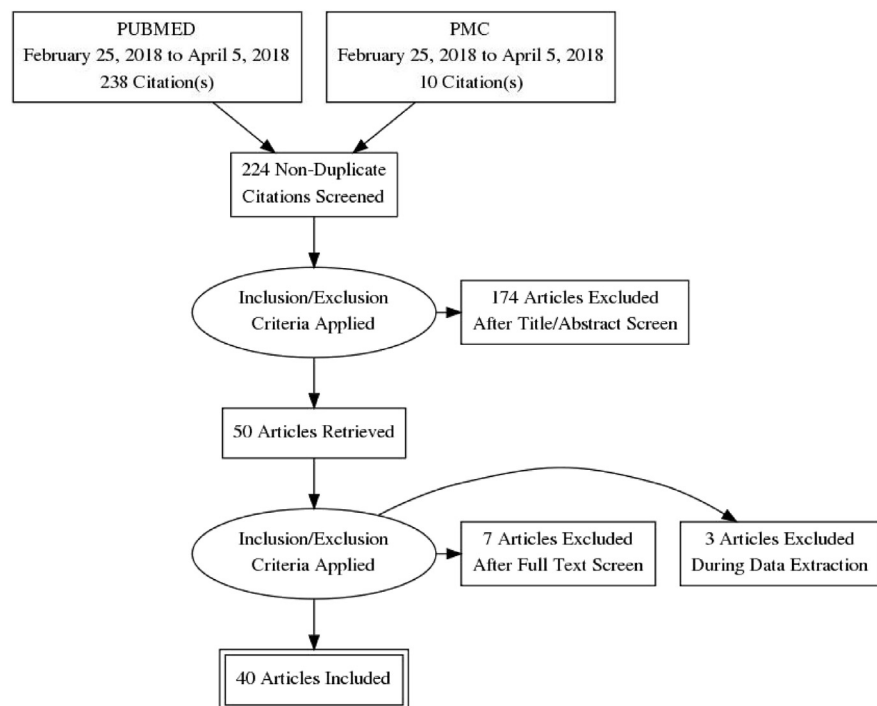


Fig. 1. PRISMA Flowchart depicting data extraction and analysis.

an important role in pathogenesis of neurodegenerative diseases. Furthermore, melatonin and its hybrids can be used as a part of novel therapeutic approaches to treat and prevent disease progression.

2.3. Discussion

The immune-pineal axis plays a crucial link and correlates with the pathophysiology of various neurodegenerative diseases. With advances in our knowledge about neuroimmunomodulation and its varied aspects, we can link endocrine mechanisms and chemical basis of these diseases. Inflammatory states can accelerate the response of NF- κ B (transcription nuclear factor kappa light chain enhancer of activated B cells) to cause microglia cells to produce melatonin rather than just pinealocytes causing dysregulation, which is central to inflammatory states and several neurodegenerative diseases [3]. It has also been correlated that levels of CSF melatonin are inversely linked to the oxidative damage acting as a promoting factor for neurodegenerative diseases.

Melatonin is an indole hormone produced by both neuronal and non-neuronal sources. Light regulates the release of the dark hormone from the pineal gland. Under normal physiological conditions it is chronobiotic in nature and is associated with nocturnal melatonin secretion. However, the release of melatonin by other sources like immune system cells and gastrointestinal tract is non-chronobiotic. The physiological variation of melatonin secretion by the pineal gland is complex and neuro-protective in action [10].

2.3.1. Pathophysiological basis: pineal gland and immunity in context of neurodegenerative diseases and inflammatory states

2.3.1.1. Melatonin and immunity

Melatonin is primarily produced by the pineal gland, while extra pineal sources mainly include the gastrointestinal tract and the retina. It is a versatile hormone with anti-oxidative and anti-apoptotic activity among several other pleiotropic effects. This hormone acts via endocrine, paracrine and autocrine modes of action [11]. It exerts an effect on the circadian rhythm, tumor suppression activity and immunity. Melatonin has held a controversial relationship with immunity since long, but recent research evidence establishes its role as an immunological buffer. Melatonin is seen to have both anti-inflammatory and immunostimulant role based on the immune status of the body. It exerts an anti-inflammatory effect in basal, immunosuppressed conditions, viral, parasitic infections, vaccination, and cancer states. However, it acts as an immuno-stimulant in exaggerated acute or chronic immune responses like septic shock, transplantation, experimental models of acute inflammation, type 1 diabetes mellitus and systemic lupus erythematosus. It also shows how

melatonin exerts a positive effect with negligible side effects, when in-vivo models of inflammation of above diseases were observed [12].

It exerts both suppression and stimulation action based on the inflammatory state of the body acting mainly via neutrophils and monocytes. It causes immune stimulation in immunosuppressed states and suppresses immunity in autoimmune and infectious diseases to prevent an immune override. It also exerts neurohormonal effects by its negative feedback mechanism in the immune-pineal axis. To elucidate the concept, on activation of NF- κ B pathway by PAMP's/DAMP's (pathogen associated molecular patterns/damage associated molecular patterns which are activated during inflammation) it reduces noradrenaline induced melatonin synthesis in pinealocytes. This is done via inhibition of transcription of the gene of AA-NAT enzyme by NF- κ B P50/P50 homodimers. AA-NAT enzyme is crucial in the pathway for synthesis of melatonin. Whereas, on the other side it increases melatonin production in macrophages and monocytes for initiating defense response to pathogens. This is done by AA-NAT enzyme gene activation by RelA/cRel heterodimers. Furthermore, melatonin exerts negative feedback by reducing NF- κ B production at both the sites. This hormone-mediated switch in the critical site of melatonin production from pinealocytes to immune-competent cells in coordination with the immune response of the body forms the basis for the immune-pineal axis [11, 13]. Fig. 2 depicts the mechanics of the immune pineal axis.

In the review by Markus et al., an experimental trial by Ferreira et al. has been elucidated which has shown that corticosterone (in chronically inflamed rats) causes a reduction in NF- κ B. Chronic inflammatory states are associated with altered levels of Adrenal cortical hormones. Increased levels of these hormones flare up inflammation and cause nocturnal release of Melatonin which is involved in the diurnal variation phenomenon seen in chronic inflammation [11, 14]. However, the review also highlights that in acute inflammatory states like mastitis and caesarean section an inverse relation is seen and pro-inflammatory cytokines exert a negative feedback on the natural surge of nocturnal melatonin [15]. This explains how both the pathways as mentioned earlier involving pro and anti-inflammatory mediators act via the NF- κ B pathway. An interesting study analyzed the effect of melatonin on immunity as a whole via analyzing its therapeutic effect in experimental autoimmune encephalomyelitis (EAE), where it was found that it decreases the entry of Th 17 cells into the central nervous system of mice, inhibits antigen-specific T cell proliferation and decreases splenic IFN gamma, IL-17, IL6, CCL20 expression [16]. This signifies its role in adaptive immunity both at a central and peripheral level. Effect of melatonin has also been demonstrated to be present in cellular adaptive immunity. Experimental studies have shown that melatonin and zinc supplementation can stimulate proliferation of CD4+ and CD8+ in rats with Toxoplasmosis [97]. Whereas, pinealectomy and zinc deficient diet led to decline in cellular immunity levels in infected rats [98]. An experimental study on rats with Toxoplasma retinochoroiditis

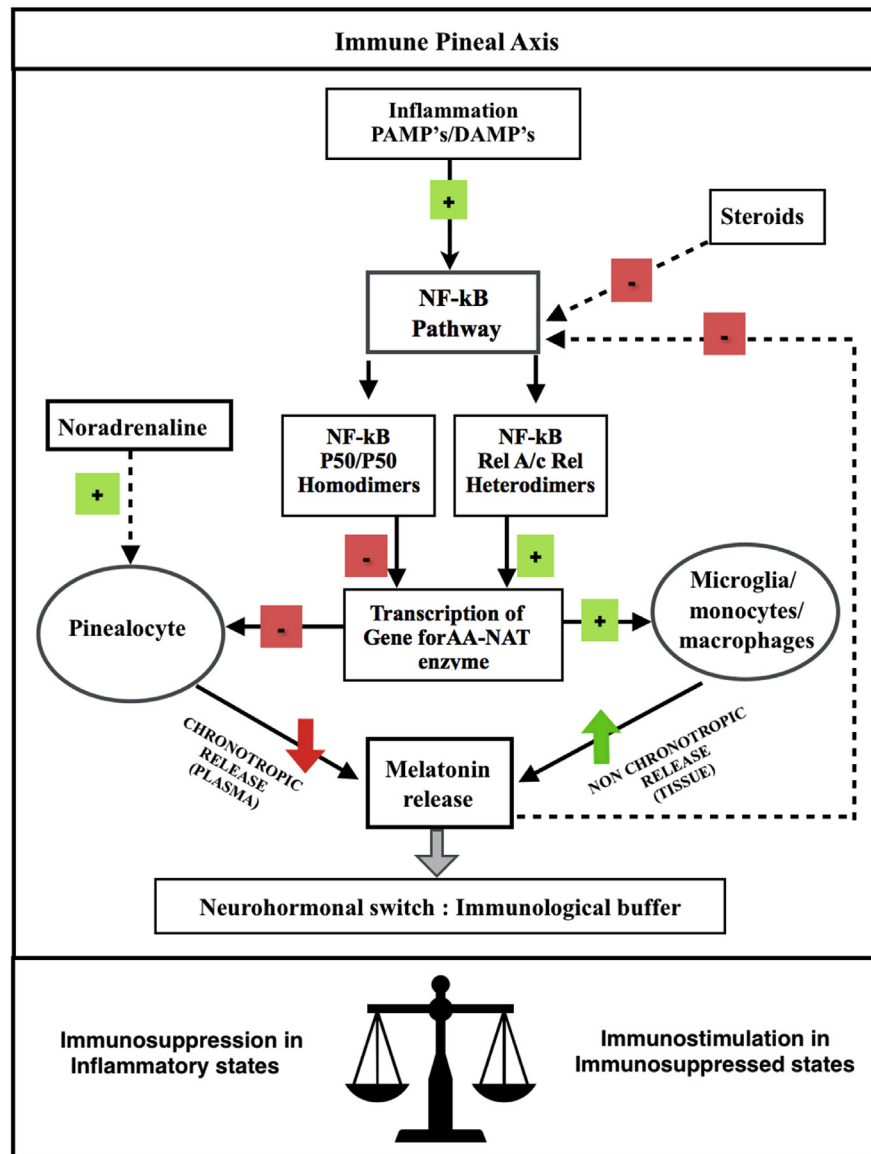


Fig. 2. The mechanics of the Immune-pineal axis.

demonstrated that melatonin and zinc supplementation was associated with increased permeability of lymphocytes, CD3+,CD4+ and CD8+ cells in the choroid and retina i.e. the main focus of infection [99]. Another study extended the perspective of immune modulatory effects of melatonin, by analyzing the neuro-immunomodulatory effect of melatonin on innate immunity which forms the first line of defence. In-vivo and in-vitro studies were performed to analyze the effect of melatonin on lymphocytes however, it is now further proposed that melatonin affects natural killer cells, monocytes-macrophages, dendritic cells and several other cells in the innate immune system too [17]. These mechanisms of the immune-pineal axis throws light on its role in the development of

neuroinflammatory states and neurodegenerative diseases, which are centred around the chronobiotic action of melatonin.

2.3.1.2. *Melatonin and stem cells*

Altered neurogenesis and neural stem cell (NSC) differentiation ability forms the underlying basis for several neurological diseases. The process of neurogenesis is under the influence of several hormonal, immunological and local factors, which affect stages of proliferation and differentiation. One crucial factor is melatonin, as several pieces of evidence suggest that it exerts protective influence in neurodegenerative diseases like Alzheimer's, Parkinson's and ischemic brain injury by influencing NSC's [18]. It affects the proliferation and differentiation of NSC's by affecting MAPK/ERK signaling pathways, transcription factors, apoptotic genes and histone acetylation. Melatonin along with stem cell transplantation in neurodegenerative diseases shows benefit due to its antioxidant, anti-inflammatory, anti-apoptotic and anti-free radical induced ageing properties [19, 20]. Some researches even suggest that adult-onset non-communicable diseases can be prevented by developmental reprogramming using melatonin in early life, which is associated with development origins of health and disease (DOHaD). Melatonin is shown to affect gene expression and produce long-term changes in organ transcriptome [21].

2.3.1.3. *Ageing, melatonin and neurodegenerative diseases*

Neurodegenerative diseases are intricately linked with the process of ageing. Some theories link decreased levels of melatonin with ageing and neurodegenerative diseases. In a study, low levels of melatonin have been linked to pineal calcification similar to bone formation that takes place with the course of ageing [22]. It can be further linked to neurodegenerative disease pathogenesis by for example, a study by Mahlberg et al. has shown that patients of Alzheimer's disease have a higher quantity of areas of the pineal gland which had undergone calcification as compared to other dementias [23]. Research evidence also suggests that reduction in pineal volume due to ageing and accelerated calcification showed a positive correlation with the cognitive decline seen in patients of Alzheimer's disease suggesting that altered hormonal activity plays a role in disease pathogenesis [24]. Some evidence suggests that the pineal thymus axis can play a role in neurodegenerative disease pathogenesis via command on the autoimmune process inside the body. As involution of thymus starts, mass production of auto-reactive cells occurs which act via autoimmune mechanisms coupled with the natural decline of melatonin with age. Henceforth, it causes the brain to have higher susceptibility to oxidative stress and also forms the basis for ageing, to eventually play a role in the neurodegenerative disease pathogenesis [25, 26]. To support this correlation between melatonin and ageing, a study by Hardeland et al. has shown that besides anti-oxidant action of melatonin which

protects against telomere attrition, melatonin also interacts with cellular oscillators and metabolic sensing to influence the action of SIRT1 which is akin to an accessory clock protein in the body. Henceforth, it may lead to a healthier ageing and hence a potential reduction in neurodegenerative diseases [27]. Besides acting on sirtuins, according to recent evidence it also attenuates the process of ‘inflammaging’, that is lowgrade inflammation which plays a role in the promotion of senescence. Melatonin and its kynuramine metabolites have been seen to prevent excitotoxicity, reduce the load of free radicals, and reduce the production of pro inflammatory cytokines. Inflammaging is speculated to have a role in initiation and progression of neurodegenerative diseases. Therefore, melatonin may play a role in preventing progression or severity of such diseases [28].

2.3.1.4. Other effects of melatonin in the pathophysiology of neurological diseases

Release of melatonin hormone by the pineal gland peaks during the night. It follows the circadian rhythm of the body. Levels during the day are as low as 10–20 pg/ml while those at night can increase up to 80–120 pg/ml. Levels can though be suppressed by intense light stimuli. Melatonin acts on cells via melatonin receptors (MT1 and MT2). MT1 is primarily found in the hippocampus, retina, thalamus, vestibular nuclei, cerebrum and cerebellum. Whereas, MT2 is found in the hippocampus, cerebrum, cerebellum, reticular thalamus, substantia nigra (pars reticulata), supraoptic nucleus, and the red nucleus [29, 30]. In the central nervous system besides immunity and antioxidant role, the dark hormone is also linked to neuronal development, growth, and neuronal circuit formation [11]. Melatonin also shows neuroprotective effect by acting on these receptors to regulate levels of neurotrophic peptides like brain-derived neurotrophic factor which play an essential role in the central nervous system for neuronal health [31, 32].

Melatonin exerts its antioxidant property by increasing activity of antioxidant enzymes and increasing glutathione content [33]. It acts via RZR/ROS receptors and MT1/MT2 receptors to increase synthesis of antioxidant enzymes like glutathione peroxidase, glutathione reductase and superoxide dismutase. It also acts as a free radical scavenger and protects against free radical-induced damage at the level of lipid membranes, which leads to lipid peroxidation, and at the level of DNA by decreasing protein damage which is seen in traumatic injury of the brain and spinal cord [32, 34]. It can also bind to metals, which helps in metal-induced toxicity by forming chelating complexes to decrease hydroxyl radical-induced damage. It has anti-nitrosative action and also inhibits activation of NF- κ B pathway by preventing DNA binding. Hence, it has anti-inflammatory effect at the level of the CNS by affecting the secondary injury pathway [32]. It also has anti-apoptotic property in healthy cells [35, 36, 37]. Whereas in cancer cells, it induces apoptosis via RZR/

ROS receptors [38, 39]. This anti-apoptotic activity via inactivation of intrinsic apoptotic pathways plays a crucial role in patients of several neurodegenerative diseases [40]. Due to its anti-estrogen action via estrogen receptor alpha it also exerts oncostatic properties [41]. It also affects sirtuins, which is a subtype of histone deacetylase enzyme and plays an essential role in cell cycle, DNA repair mechanisms, and apoptosis. They play an essential role in pathogenesis and are a significant target in cancer and neurodegenerative diseases. Melatonin is seen to increase the activity of SIRT1 (sirtuin) in healthy cells, which provides a protective action. However, the opposite is seen in the case of cancer cells which reflects its oncostatic property [42]. Furthermore, experimental research findings show that supplementation of melatonin and zinc can lead to improved immunity in rat models of breast cancer [96].

Evidence shows that melatonin also acts as a mitochondrial protector and helps in preventing neurodegenerative diseases since mitochondrial dysfunction is considered a primary event in the initiation of their pathogenesis. Therefore, melatonin has higher neuroprotective value in earlier stages of neurodegenerative diseases [43]. Some studies also suggest that decreased production of melatonin and N-acetyl serotonin can serve as a basis for genetic association with several diseases. This makes glial melatonin and N-acetyl serotonin crucial in the treatment of neurodegenerative diseases and psychiatric disorders, as they are vital for regulation of local inflammation at the interface between glial cells and neurons [44]. The antioxidant, anti-inflammatory and neuroprotective action of melatonin seems to play a role in improving prognosis of neurodegenerative diseases and a neuro-inflammatory state like traumatic brain injury and is a potential therapeutic strategy in these diseases.

2.3.2. Evidence for the role of melatonin in neurodegenerative diseases

Neurodegenerative diseases are associated with a disruption of the circadian rhythm, which is central to the pathogenesis of these disorders. Altered melatonin synthesis and secretion are associated with higher oxidative and inflammatory stress, which can precipitate such states. Diseases like multiple sclerosis, ischaemic stroke and Huntington's disease are associated with altered levels of melatonin [45]. Its role in various neurodegenerative diseases is elucidated further in the article. Table 2 depicts the overview of the studies included. Fig. 3 depicts an outline of the mechanisms involved.

Furthermore, immunity and inflammation play their own role in neurodegenerative disease pathogenesis through cytokines and chemokines, which alter the permeability of the blood brain barrier affecting innate immunity cells in the C.N.S. (microglia and astrocytes). The role of immune pineal axis as an immunological buffer is evident as immunotherapies stimulating the immune response may improve the outcome whereas, it has been seen that anti-inflammatory drugs have a protective

Table 2. Overview of studies: Immune pineal axis and specific neurodegenerative diseases.

Study Type	Case Reports	Observational studies	Experimental studies	Clinical trials	Review articles
Multiple Sclerosis	Lopez-Gonzalez et al. [55] Sandyk R [49]	Sandyk R et al. [50] Gholipour T et al. [51] Adamczyk-Sowa M et al. [52, 53] Alvarez- Sanchez N et al. [54]			
Parkinson's disease		Breen DP et al. [57]	Singhal N.K. et al. [58]	Ortiz GG et al. [59]	Shen Y et al. [56] Naseem M et al. [32] Mack JM et al. [60]
Alzheimer's disease		Liu RY et al. [69] Cardinali DP et al. [72] Zhou JK et al. [70]	Pappolla M et al. [63] Deng YQ et al. [64] Wang XC et al. [67] Li XC et al. [65]	Asayama K et al. [74] Wade AG et al. [75]	Lahiri DK et al. [71] Tan DX et al. [61] Lahiri DK et al. [62] Saeed Y et al. [73] Lin L et al. [66] Maes M et al. [68]
Huntington's disease		Kalliolia et al. [77]	Wang X et al. [78] Chakraborty J et al. [79]		Bartlett DM et al. [76]
Amyotrophic lateral sclerosis				Weishaupt JH et al. [83]	
Ischaemic Stroke		Fiorina P et al. [80] Carvalho LA et al. [81]	Chern et al. [82]		
Other neuropsychiatric diseases					
Spinal cord injury/ Traumatic brain injury		Seifman MA et al. [86]	Kabadi SV et al. [31]		Naseem M et al. [32]
Delirium				Al-Aama T et al. [85]	
Epilepsy					Vishnoi S et al. [84]

role in neurodegenerative diseases [46]. In several neurodegenerative diseases chiefly Alzheimer's, multiple sclerosis and Parkinson's disease, the peripheral immune cells (T cells) and immune competent cells in the C.N.S. (microglia, astrocytes, oligodendrocytes) have been seen to release inflammatory mediators to recruit lymphocytes to play a role in C.N.S. inflammation [47]. Inflammation has been seen to be an important in the pathophysiology of neurodegenerative diseases and associated depression. Molecular mechanisms of neuro-inflammation are consistent across ageing, dementia, diabetes, hypertension and depression. Low-grade inflammation leads to micro vascular changes, hypo-perfusion, loss of oligodendrocytes and increased risk of stroke. Neuro-inflammation was also seen to be linked with increased risk of dementia. Ageing which is a major factor for development of neurodegenerative diseases is also intricately linked with inflammation. Systemic inflammatory factors increase in the body with the process of ageing which lead to chronic activation of microglia and parenchymal macrophages in the C.N.S. with increased number of astrocytes. This chronic pro-inflammatory state

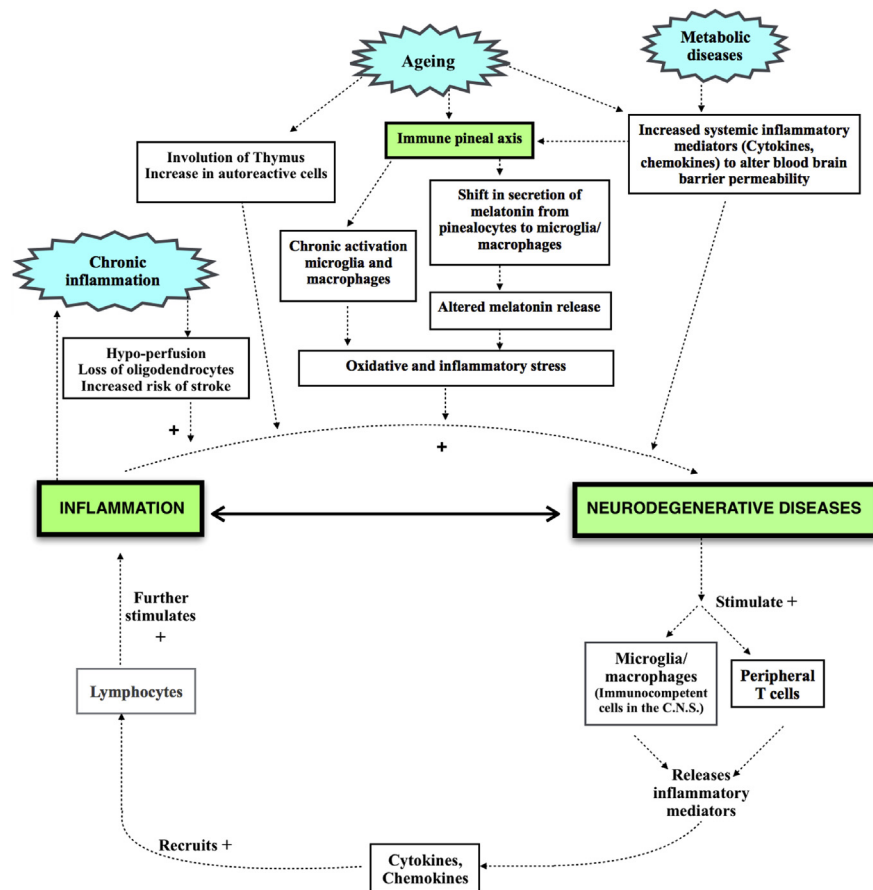


Fig. 3. Role of the immune-pineal axis in the pathophysiology of neurodegenerative diseases.

has been positively correlated with the development of neuropsychiatric disorders [48].

2.3.2.1. Multiple sclerosis

Multiple sclerosis is a neurodegenerative disease characterized by multiple exacerbation and remissions, which can be related to the cyclic variation of melatonin hormone [49]. It is a non-traumatic cause of disability in the younger population. Inflammation, oxidative stress and neuron demyelination lies central to its pathogenesis. A study showed that progressive decline of melatonin levels over the span of time could be correlated with the remitting relapsing course of the illness [50]. This is in sync with a case-control study by Gholipour T et al. which enrolled 28 patients diagnosed with relapsing-remitting multiple sclerosis using revised McDonald criteria with ten age and sex-matched healthy controls. On analyzing the relation between reduced urinary levels of melatonin and cognitive scores in patients of multiple sclerosis. Melatonin levels in urine were significantly lower in patients with respect to controls and had a positive correlation with functional composite scoring

in case of patients. However, its relation with the expanded disability severity score was not significant, and levels of 25-hydroxyvitamin D were not analyzed which has a negative association with the levels of melatonin hormone [51]. These studies suggest a potential role of melatonin supplementation in these patients.

Furthermore, a case-control study by Adamczyk-Sowa M et al. which enrolled 102 patients with multiple sclerosis showed that melatonin supplementation reduced plasma homocysteine concentration to levels similar to that in healthy controls. This shows that it plays a beneficial role due to its antioxidant action [52]. This is further supported by another case-control study which analyzed multiple sclerosis impact scale 29 (MSIS 29) between 102 patients and 20 matched controls to show its potential role in improving the quality of life of patients as it decreased the mean MSIS-29 score as compared to groups treated with interferon beta [53]. It is also seen to decrease inflammation by regulating T helper lymphocytes activity in patients of a relapsing remitting type of multiple sclerosis [54]. These studies on the potential role of melatonin and its effect on the pathophysiology of multiple sclerosis are further supported by a case report where a patient with primary progressive multiple sclerosis improved on melatonin therapy. The causality behind the resolution of symptoms and melatonin drug therapy is suggested based on the temporal association of treatment and its prolonged course [55].

2.3.2.2. *Parkinson's disease*

Parkinson's disease characteristically has motor and non-motor disease complexes; with underlying pathology pointing at nigro-striatal dopamine (DA) depletion along with neuroimmunoendocrinal (NIE) disturbances associated with pineal gland and melatonin levels. NIE is chiefly associated with non-motor symptoms. Whereas classical motor symptoms are associated with the dopamine-melatonin imbalance in the mesencephalic pineal axis. This neuroimmunoendocrinal network is associated with altered chronobiotic production of melatonin and hence causes sleep disturbances, neuropsychiatric manifestations and gastrointestinal problems associated with the disease [56]. A case-control study by Breen DP et al. enrolling 12 patients and 12 matched controls has demonstrated that reduced melatonin levels are seen in patients with Parkinson's disease, and they are associated with reduction of hypothalamic volume especially the suprachiasmatic nucleus of anterior hypothalamus which controls the function of pineal gland and hence secretion of melatonin [57]. Some researches have also shown that melatonin supplementation improved semi Parkinsonism like diseases which were simulated using 6-OHDA (6-hydroxydopamine) [32].

An experimental study shows the neuroprotective action of melatonin in Parkinson's disease. In the experimental study of in-vivo models having manganese ethylene bis-dithiocarbamate and 1,1-dimethyl-4, 4-bipyridinium (paraquat) induced Parkinson's

disease showed that melatonin had a protective effect when it was given in combination with silymarin [58]. Another study which was a double-blinded randomized control trial enrolling 13 patients has found that melatonin supplementation is associated with predominantly reduced cyclooxygenase 2 activity, and also that of nitrates and lipoperoxides in patients of Parkinson's. However, no change was observed concerning glutathione peroxidase activity [59]. These signal at the possible mechanism (antioxidant role) by which melatonin is seen to improve disease prognosis. A review by Mack JM et al. reports that melatonin can improve not only the motor symptoms associated with the disease but also has neuroprotective role due to its antioxidant ability, blockage of NF- κ B pathway, and improvement of α 7nAChR-dependent cholinergic activities. It also helps to improve non-motor symptoms like sleep disturbances, memory disorders, and psychic involvement like depression and anxiety [60].

2.3.2.3. *Alzheimer's disease*

Alzheimer's is a form of irreversible dementia that is associated with altered sleep pattern, which is among the few circadian disturbances which are attributed with the pineal gland and suprachiasmatic center in the brain. It is associated with classical symptoms of cognitive dysfunction, psychiatric and behavioral disturbances affecting memory, language and intellect. There are several proposed mechanisms through which melatonin supplementation can improve prognosis in Alzheimer's disease some of which include antioxidant action [61], inhibition of deposition of beta-amyloid protein [62, 63], suppressing the development of neurofibrillary tangles inside neurons. Studies propose that it decreases tau hyper phosphorylation and also influences protein kinases and phosphates [64, 65, 66, 67]. These all play a vital role in the pathogenesis of the disease entity. A study by Maes M et al. has found that oxidative stress and pro-inflammatory cytokines lead to the production of neuroregulatory tryptophan catabolites such as kynurenic acid and quinolinic acid which further decrease the availability of tryptophan required for the synthesis of serotonin which is involved in further synthesis of N-acetyl serotonin and melatonin. Hence, oxidative stress leads to decrease in melatonin that has been related to the development of Alzheimer's disease besides concomitant depression and altered immunity [68]. It can be hypothesized that melatonin decreases oxidative stress and also plays a vital role by acting at the pathophysiological level to prevent progression of this neurodegenerative disease. This is further supported by a case-control study by Liu RY et al. in which postmortem ventricular CSF analysis was done in 85 patients of Alzheimer's disease in respect to 82 matched healthy controls. The study explained that the melatonin levels in CSF were seen to decline in old controls as well as in patients of Alzheimer's disease. However, the values of melatonin in patients were 1/5th to those seen in controls. Besides this, there was no difference in the levels when the presenile and senile population of

Alzheimer's disease were considered. Furthermore, patients expressing apolipoprotein E epsilon 3/4 had higher melatonin levels than those expressing apolipoprotein E epsilon 4/4 and hence a better prognosis. They suggested that melatonin supplementation could improve the quality of life associated with the disease. However, its effect on behavioral changes needs an extensive study [69]. Similar results are seen in a study by Zhou et al., which has also studied the neuropathological association between lower CSF melatonin levels and changes of Alzheimer's disease [70].

2.3.2.3.1. Evidence of therapeutic potential of melatonin in Alzheimer's disease

A review by Lahiri et al. highlights and adds evidence to show how melatonin is neuroprotective, neutralizes metal-induced toxicity and also causes a reduction in levels of A-beta peptides (based on few animal studies mentioned in the review) that pathologically precipitate the disease along with other factors like ageing, metal toxicities, gene expression variants in neurons and altered cholinergic activity. They suggested that it should be a part of drug therapy in combination with other FDA approved drugs like Memantine and cholinesterase inhibitors. They also suggested walnut intake in patients with Alzheimer's as it is rich in melatonin [71]. This is supported further by a retrospective cohort study on patients of mild cognitive impairment (MCI) wherein 96 patients were enrolled. It shows that melatonin showed potential as an add-on drug in MCI patients, which includes those with Alzheimer's disease who have developed cognitive impairment in advance of dementia. The results showed that patients on melatonin performed better in the Alzheimer's disease assessment scale specifically the cognitive component and also the mini mental status examination. Besides this, their Beck depression inventory scales decreased and only 9.8% in their group required benzodiazepine support as compared to 62.8% in the subset not receiving melatonin to help improve their sleep quality [72]. This is supported by another review by Saeed et al. which comments that melatonin therapy and bright light therapy can help in improving circadian rhythm, sleep quality and prevent disease progression in patients of Alzheimer's disease [73]. In a double blinded randomized control trial by Asayama K et al. on patients of Alzheimer's which included 20 patients (out of which 9 were given placebo and 11 were given melatonin), shows that melatonin improved cognitive and non-cognitive functions like sleep time and night activity in patients diagnosed with Alzheimer's type of dementia [74]. Wade et al. also obtained similar results in their randomized control trial of six months duration, which enrolled 80 patients wherein, the effect of 'prolonged release melatonin' was analyzed with respect to placebo [75]. These studies not only complements other studies but also shows that besides neuropsychiatric symptoms, improvement in cognition is also seen. Studies show that it can improve sleep,

improve cognition, prevent or decrease disease progression and reduce sundowning phenomenon seen in patients [66].

2.3.2.4. *Huntington's disease*

Huntington's disease (an autosomal dominant disorder) presents usually in the younger population chiefly in the second and third decade (similar to multiple sclerosis). Altered melatonin synthesis is central to its pathogenesis. Some studies discuss that Huntington's is associated with hypothalamic atrophy with loss of orexin releasing neurons present in the suprachiasmatic nucleus that controls the pineal gland and microglial activation. Loss of these neurons firstly leads to circadian rhythm disturbances, as mean and peak levels are decreased with late morning rise of melatonin. It also causes HPA (hypothalamic-pituitary-adrenal) axis dysfunction, which leads to comorbid depression seen in neurodegenerative diseases [76]. This is supported by an observational study by Kalliolia et al. where melatonin level reduction was significantly associated with the diseases state. Furthermore, in this study, it seemed to explain the disrupted sleep-wake cycle and circadian behavior changes were seen in patients with this disease state [77]. In the study by Tan DX et al., the possible neuroprotective role of melatonin has been suggested [22]. These all studies seem to signify role of melatonin in patients of Huntington's disease. To support this, an experimental study by Wang X et al. has shown that melatonin inhibits mutant huntingtin (htt) mediated toxicity in the cells via activation of caspases and also preserves the function of MT1 receptors. Hence, it shows how it has a potential protective role in the probable pathway that accelerates the neurodegenerative changes seen in the disease [78]. Also, another experimental study by Chakraborty J et al. shows that melatonin improves learned fine motor skills associated with the disease. However, it does not help in improving behaviors that are not associated with learning [79].

2.3.2.5. *Ischemic stroke*

A case-control study by Fiorina et al. assessed 13 ischemic stroke patients and 5 healthy controls to study the effect of nocturnal melatonin rhythm (via nocturnal melatonin urinary excretion) and associated immunological involvement in them. It was found that decreased nocturnal melatonin excretion was associated with lowered cell-mediated immunity levels and a decrease in CD3 lymphocyte subsets in patients with ischemic stroke. Furthermore, when the cortisol/melatonin ratio was measured, it was impaired which is a marker of depression and can be linked to psychiatric problems associated with the disease [80]. However, it is in discord with a case-control study by Carvalho et al. which studied 32 depressed drug-free patients diagnosed as per DSM IV (Diagnostic and statistical manual of mental disorders) criteria and matched 32 healthy controls who have demonstrated that nocturnal melatonin levels are not much different from that found in patients with depression.

However, the same can occur in severe depression [81]. The association of nocturnal melatonin reduction in patients with ischemic stroke, the degree of its association with depression and the level of melatonin reduction (which leads to psychiatric involvement) needs further study. These results in patient-centric case-control studies are further supported by an experimental study by Chern et al., where they found that melatonin supplementation helped in healing the blood-brain barrier's integrity, and also played a role in gp91phox cell infiltration which improved the survival rate seen in models of stroke [32, 82].

2.3.2.6. *Amyotrophic lateral sclerosis (A.L.S.)*

A.L.S. is a motor neuron disease that affects voluntary muscle movement. It is a fatal disease with poor prognosis. Only few treatment options are available to improve the quality of life of patients afflicted with the disease. A randomized control trial by Weishaupt JH et al. that enrolled 31 patients with sporadic A.L.S. showed that circulating serum carbonyl levels were normalized by melatonin supplementation in patients. This suggests that melatonin can play a neuroprotective role due to its antioxidant action in patients of A.L.S [83].

2.3.2.7. *Other neurological conditions*

Some studies indicate that neurological diseases like epilepsy are due to oxidative stress due to glutamate excitotoxicity, which leads to the production of nitrosamines. These studies suggest that melatonin, which acts as a free radical scavenger is shown to be effective in experimental models, and patients who have epilepsy, as it protects the brain from degeneration and stress susceptibility due to its low antioxidant levels. It is also shown that melatonin plays a protective role during seizures [84]. A randomized control trial (double blind) by Al-Aama T et al. have studied 145 patients over the age of 65 years and used confusion assessment method (C.A.M.) to measure the level of delirium in these patients. The patients were given 0.5 mg melatonin or placebo treatment at night for 14 days, and they were randomized by a double-blind approach. Their study concluded that exogenous melatonin supplementation in elderly patients admitted in acute care settings has a potentially protective role to protect against the development of delirium [85].

Spinal cord injury with emphasis on traumatic brain injury leads to initiation of primary, followed by secondary injury cascades, which leads to free radical generation and oxidative damage. Some studies have shown that melatonin due to its antioxidant and neuroprotective action can be of therapeutic value, even in such injuries that tend to have a poor prognosis and devastating neurological deficit as it crosses the blood-brain barrier readily. In traumatic brain injury according to Naseem et al., it exerts neuroprotective action via inhibiting release of proinflammatory cytokines, provides an anti-oxidant effect, and reduces cerebral edema. It also leads to blockage

of activation of NF- κ B, especially late phase activation (which plays a vital role in traumatic brain injury). It also helps in restoring the integrity of the blood brain barrier [32]. An experimental study by Kabadi et al. showed that melatonin both individually or when combined with uridine was found to be successful in reducing posttraumatic brain edema in models replicating the disease state [31]. This is supported by the clinical observational study of Seifman M.A. et al., which clearly indicates that natural healing process in the body showed a similar response. They have shown that endogenous melatonin levels increase in the C.S.F. of patients after traumatic brain injury and that it has a significant association with increase in oxidative damage [86]. Table 3 depicts the summary of important studies highlighting the position of melatonin in neurodegenerative diseases.

2.3.3. Immune-pineal axis paving the way for promising novel therapies

Progressive weakening of the immune-pineal axis with age and decline in levels of melatonin makes the brain susceptible to oxidative stress and neurodegeneration. Studies mentioned above proposed that melatonin due to its pleiotropic effects can be used in the treatment of neurodegenerative diseases. Melatonin is observed to control adaptive immunity centrally and peripherally, which signifies its role in treating CNS autoimmune diseases like multiple sclerosis [16]. The neuroprotective action, antioxidant, anti-apoptotic, mitochondrial protection ability and anti-inflammatory properties makes melatonin of therapeutic importance in improving the quality of life and disease progression in neurodegenerative diseases. The anti-apoptotic action is characteristically vital as often these diseases are associated with impaired mitochondrial activity followed by apoptotic cell death [87]. Furthermore, specific targets have also been identified for example in Alzheimer's disease studies have found that MT2 receptor immunoreactivity is reduced whereas, that of MT1 is increased in the hippocampus. This suggests a future therapeutic potential of specific melatonin receptor MT1/MT2 regulators and hybrid melatonin derivatives, which should be looked into [66].

2.3.3.1. Newer molecules

A study by Ramos E et al. proposes the development of melatonin multi target hybrids by its combination with tacrine, berberine, tamoxifen, and curcumin to act against neurodegenerative diseases [26]. In support of this research, an experimental study by Chojnacki JE et al. who developed curcumin and melatonin hybrids, showed its neuroprotective ability on MC65 cells, along with antioxidant action, and high blood-brain barrier permeability. Therefore, it poses an example of improvement in the potency of melatonin through techniques of hybridization [88]. A study by Buendia et al. who developed compound 5h (a multi-target hybrid derived from melatonin and ethyl cinnamate), which acts on Nrf2 factor and

Table 3. Summary of important studies highlighting the position of melatonin in neurodegenerative diseases.

Study	Study type	Year of publication	Conclusion
Multiple sclerosis			
López-González et al. [55]	Case-report	2015	Symptom relief in patient of primary progressive multiple sclerosis on melatonin therapy.
Gholipour et al. [51]	Case control study	2015	The diseased state led to reduced urinary melatonin levels which were further positively associated with cognitive scores.
Adamczyk-Sowa et al. [52]	Case control study	2016	Melatonin supplementation has anti-oxidant action in multiple sclerosis as led to reduced plasma homocysteine levels.
Adamczyk-Sowa et al. [53]	Case control study	2014	Melatonin therapy improved quality of life measured by higher reduction in MSIS 29 score in multiple sclerosis patients as compared to those treated with interferon beta.
Álvarez-Sánchez et al. [54]	Case control study	2017	Melatonin therapy decreased Th1 and Th2 responses and created a protective cytokine microenvironment in patients if relapsing remitting multiple sclerosis as compared to controls.
Parkinson's disease			
Breen et al. [57]	Case control study	2016	In patients with Parkinson's disease, reduced melatonin levels were seen to be positively associated with reduction of volume of mainly the suprachiasmatic nucleus of anterior hypothalamus that controls pituitary function.
Ortiz et al. [59]	Review article	2017	Patients with Parkinson's disease on melatonin therapy showed reduced cyclo oxygenase 2, lipoperoxide and nitrate activity. This anti-oxidant activity of melatonin is seen to play a therapeutic role in these patients.
Sheen et al. [56]	Review article	2016	This highlights how the NIE network in Parkinson's disease is affect to lead to disturbances in cyclic melatonin production and plays an integral role in disease presentation. This affects sleep wake cycle, gastrointestinal system and mental status of patients to produce symptomatology.
Mack et al. [60]	Case control study	2016	Melatonin supplementation is seen to improve motor symptoms, non motor symptoms besides having neuroprotective action in patients with Parkinson's disease.
Alzheimer's disease			
Cardinali et al. [72]	Retrospective cohort study	2012	Melatonin supplementation in patients with Alzheimer's disease was associated with improved mini mental status examination scores, cognition and sleep quality.
Zhou et al. [70]	Observational study	2003	Post mortem ventricular CSF examination of 121 subjects showed positive association between melatonin levels and modified Braak staging for cortex. This signified that decrease in CSF melatonin levels might be an early event in Alzheimer's disease.
Asayama et al. [74]	Clinical trial	2003	Melatonin is seen to improve both cognitive and non-cognitive functions in patients with Alzheimer's disease.
Wade et al. [75]	Clinical trial	2014	Prolonged release melatonin therapy is seen to be associated with improved cognition and sleep quality in patients of Alzheimer's disease, particularly those with comorbid insomnia.
Saeed and Abbott [73]	Review article	2017	In patients with Alzheimer's disease, melatonin therapy is seen to improve sleep quality, circadian rhythm and decreases disease progression.

(continued on next page)

Table 3. (Continued)

Study	Study type	Year of publication	Conclusion
Lin et al. [66]	Review article	2013	Melatonin in Alzheimer's disease is seen to improve cognition besides non-cognitive activities like sleep and reduces disease progression.
Maes and Anderson [68]	Review article	2016	Oxidative stress is seen to decrease melatonin levels, which is associated with development of Alzheimer's disease, depression and changes in the immunity.
Huntington's disease			
Kalliolia et al. [77]	Observational study	2014	Reduced melatonin levels were positively associated with the diseased state and associated symptomatology in patients with Huntington's disease.
Bartlett et al. [76]	Review article	2016	Huntington's disease is associated with neuronal loss in the suprachiasmatic nucleus is associated with decreased mean melatonin levels, sleep disturbances and comorbid depression.
Amyotrophic lateral sclerosis			
Weishaupt et al. [83]	Clinical trial	2006	Melatonin supplementation in patients with A.L.S. was seen to have a neuroprotective anti-oxidant role by reduction in serum carbonyl levels.
Other neuropsychiatric diseases			
Seifman et al. [86]	Observational study	2008	During healing phase of traumatic brain injury, an increase in melatonin levels was seen in the C.S.F. of patients in order to combat oxidative damage.
Al-Aama et al. [85]	Clinical trial	2011	Melatonin supplementation in elderly patients is seen have protective role against the development of delirium.
Naseem and Parvez [32]	Review article	2014	Melatonin is seen to have a neuroprotective action in spinal cord injury and traumatic brain injury via modulating immune pathways and restoring the integrity of the blood brain barrier.
Vishnoi et al. [84]	Review article	2016	Melatonin due to its anti-oxidant action has neuroprotective role in epilepsy.

regulates free radical homeostasis to act as an intrinsic protector in the cells. The hybrid induces Nrf2 to exert neuroprotective action, which is especially marked in models of Alzheimer's and brain ischemia [89].

Another study by Benchekroun et al. has developed an antioxidant additive approach. Herein, they have combined melatonin and other molecules like isocyanide, lipoic acid, formaldehyde and tacrine derivatives via Ugi reaction to develop compound 5c. This compound 5c activates Nrf2 pathway to offer neuroprotection besides its antioxidant action [90]. The review by Herrera et al. highlights drugs centred around melatonin, which has a varied effect on MT1/MT2 receptors. It provides evidence that drugs like Agomelatine, which are used in the psychiatric management of major depressive disorder (due to its 5hydroxytryptamine 2C receptor antagonistic action) have an agonistic action on MT1/MT2 receptors through which they increases the levels of brain-derived neurotrophic factor (which increases proliferation of NSC's and neurogenesis especially marked in the hippocampus). Other compounds like N-acetyl bio esterases of melatonin and melatonin pinoline hybrids

(partial agonist with a preference for MT 2 receptor subtype were also shown to influence neurogenesis primarily due to agonistic action at the receptor level. They also promoted early maturation and differentiation of neural stem cells, which is typically associated with an agonistic effect on MT2 receptor subtype [91].

2.3.3.2. Potential futuristic melatonin drug therapy in Alzheimer's disease

An experimental study by Lopez et al. developed melatonin N, N dibenzyl N methylamine derivative hybrid molecules. This hybrid molecule has more potent action

Table 4. Summary of relevant studies showing novel molecules of melatonin for treatment of neurodegenerative diseases.

Author/Publication year	Country of research	Combinations proposed	Main findings
Ramos E et al. 2017 [26]	Spain	Melatonin with tacrine, berberine, tamoxifen, curcumin, N,N-dibenzylamine	Potential therapeutic effects of melatonin hybrids to potentiate the pleiotropic actions of melatonin.
Chojnacki JE et al. 2014 [88]	U.S.A.	Melatonin with curcumin	Hybrids with neuroprotective ability for MC65 cells, besides strong blood brain barrier permeability and anti-oxidant action.
Buendia I et al. 2015 [89]	Spain	Melatonin with Ethyl cinnamate	Developed compound 5h, which induces Nrf2 intrinsic pathway of cell protection to play neuroprotective role in diseases, like Alzheimer's and brain ischaemia.
Bencheikroun et al. 2016 [90]	France, Spain	Melatonin with tacrines, lipoic acid and other compounds.	Developed compound 5c, which activates Nrf2 pathway and has antioxidant action.
Author/Publication year	Country of research	Combinations proposed	Main findings
Herrera-Arozamena C et al. 2016 [91]	Spain	Focusses on drugs like Agomelatine, and hybrids of N-acetyl bioesterases and Pinoline compounds with melatonin.	Focusses on drugs that have an agonistic effect on MT1/MT2 receptors and also stimulate neurogenesis via NSC's.
Lopez-Iglesias B et al. 2014 [92]	Spain	Hybrids of melatonin with N, N dibenzylamine	Developed potent hybrid molecule with special ability to displace propidium from peripheral sites of AchE to prevent beta amyloid aggregation seen in Alzheimer's disease.
Wang J et al. 2016 [93]	People's Republic of China	Melatonin and Donezepil hybrids	Developed compound 4u as multi target hybrid ligands against Alzheimer's disease. Prevent beta amyloid aggregation besides inhibiting acetylcholinesterase activity.
Luo XT et al. 2015 [94]	People's Republic of China	Melatonin and benzylpyridinium bromides	Developed potent AchE inhibitor action at both active and peripheral sites for Alzheimer's disease. Developed compound also has neuroprotective effects in SH-SY5Y neuroblastoma cells.
Daulatzai MA 2016 [95]	Australia	Combination drugs approach consisting of melatonin, minocycline, modafinil and memantine.	Comprehensive multi target therapy to improve cognition in Alzheimer's disease.

than melatonin alone, low toxicity, penetrates the blood-brain barrier and has better neuroprotective capabilities even at low micromolar concentrations. Besides actions of melatonin like anti-oxidant, anti-inflammatory, NSC's promotion and inhibition of acetyl cholinesterase (AChE) activity they have a unique ability to displace the molecule propidium from the site of AChE (acetyl-cholinesterase) to prevent beta-amyloid aggregation which is the hallmark in the pathogenesis of Alzheimer's disease [92]. A study by Wang J et al. has developed a series of hybrid compounds by fusing Donepezil and melatonin which has higher efficacy as it quickly penetrates the blood-brain barrier, inhibits both catalytic anionic and peripheral anionic sites of AChE, reduces cell death induced by free radical stress and chelates metal ions [93]. Similar to this study, an experimental study by Luo XT et al. has developed melatonin derived benzylpyridinium bromides which exert multiple actions like that in the study before, but with a characteristically high anti-acetyl cholinesterase activity at both active and peripheral sites [94]. Due to the multitude of mechanisms in the pathogenesis of Alzheimer's disease, Daulatzai et al. has proposed the 'four M drug' approach consisting of melatonin (neuroprotective and antioxidant), minocycline (anti-inflammatory), modafinil (sleep quality, improves wakefulness), and memantine (non-competitive NMDA receptor blocker) which is comprehensive to improve prognosis and cognition in patients afflicted with the disease [95].

Therefore, further clinical trials must be warranted to test and establish protocols for incorporation of melatonin as a supplemental therapy in treating patients with neurodegenerative diseases. Table 4 shows the summary of studies on hybrid dark hormone molecules for treatment of neurodegenerative diseases.

3. Conclusion

Our research was focused on exploring links of the immune-pineal axis with the pathogenesis of neurodegenerative diseases. An extensive review of the literature and its analysis has helped us realize that it not only can act as the inciting factor but also plays a vital role in the progression and course of these diseases. The studies helped to analyze the molecular basis of diseases like multiple sclerosis, Alzheimer's disease, Parkinson's disease, and how they are linked to the circadian melatonin rhythm in the body. This understanding opens new portals for treatment and prevention by conducting melatonin level screening strategies in high-risk groups. Analysis of a considerable number of studies focusing on all aspects of the natural pathogenesis of neurodegenerative diseases and novel treatment strategies enhance the strength of this paper, although the paper primarily focused on studies based on the last five years. Experimental novel therapies have also started exploring this arena. Further, studies to explore the therapeutic effects of such melatonin based novel molecules should be warranted in order to provide significant clinical application and practical value.

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Author contribution statement

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