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PHARMACOLOGICAL EFFECTS OF ASHWAGANDHA ON NEURODEGENERATIVE DISEASES: AN OVERVIEW

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ABSTRACT

Neurodegenerative diseases affect various activities of your body, such as balance, movement, talking, breathing, and heart functions which may leads a serious problem for your health. There are some of these diseases are genetic and sometimes caused by a medical condition such as alcoholism, a tumor, or a stroke, toxins, chemicals, and viruses. Sometimes unknown causes may lead neurodegenerative diseases. Alzheimer's disease (AD) is an irreversible neurodegenerative disorder which can produce various neurological symptoms like mental confusion, loss of memory, and mood swings resulting in permanent functional impairments. Withania somnifera which is also known as 'Ashwagandha' and 'Indian Winter Cherry', is an important medicinal herb in India which is widely used in Indian systems of medicine as an, nerve tonic, anti-stress, memory enhancer and against cognitive deficits and other neurological disorders. In this review, we focused on the various effects of Withania extracts and other withania related compounds on in vitro and in vivo models of neurodegenerative diseases such as Alzheimer's disease.

KEYWORDS: Neurodegenerative, alcoholism, tumor, toxins, Alzheimer's disease (AD), impairments, Withania somnifera.

INTRODUCTION

Neurodegenerative disease is the progressive structural and functional loss of neurons which may cause serious defects in the body, sometimes death may also occur. Many neurodegenerative diseases including amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, Alzheimer's disease, Huntington's disease, and prion diseases occur during the process of neurodegeneration. In Alzheimer's disease, spinal cord injury, Parkinson's disease, and Huntington's disease, there are disturbance of neuronal networks are occurred which cause of the functional impairment.[1,2] Alzheimer's disease (AD) is the most common progressive format of dementia which effects the middle age, elderly men and women which leads malfunctioning of various biochemical pathways, generally the hyper activation of acetylcholine esterase (AChE).[3] In Alzheimer's disease, Aβ deposits in the brain which leads axonal atrophy, plaques, neurofibrillary tangles, synaptic degeneration and degeneration of cholinergic neurons on different parts of the brain are responsible for the pathogenesis of AD.[4] The etiology of disease is not well defined. There is a number of attempts have been done to identify the major pathologies of Alzheimer's disease.[5] Indian traditional medicinal systems and Ayurvedic formulations are very favorable for life-threatening disease such as cancer, neurodegenerative disorder and bacterial infections like tuberculosis and cholera. There are many plant materials and their chemical constituents have been found to have a direct action against various such types of neurological disorders.[6,7] Withania somnifera (WS) is also referred as Medhya Rasayana (nootropic or rejuvenating), that has traditionally been defined for different neurological disorder, including dementia.[8] Madhya Ras Ayana can retard brain aging disorder and help in different types of other central nervous system (CNS) disorders.[9]

ALZHEIMER'S DISEASE

Alzheimer's disease is a pathological condition which affects the brain and neurons.[10] In starting the symptoms of Alzheimer's disease are less but become more severe over time.[11] This disease was discovered by Dr. Alois Alzheimer. He first described this pathological condition in 1906. Generally Alzheimer's disease produces common symptoms like loss of memory, problems in language, and impulsive behavior.[12] This disease condition is also occurred due to presence of plaques and tangles in the brain and due to loss of connection between the nerve cells, or neurons in the brain.[13] By this way informations cannot distributed between different regions in the brain or between the brain and the muscles or organs.[14]

First symptoms

The first symptoms are often aging, stress and difficulties in cognition short term memory loss above sixty aged. These primary symptoms may affect various different complex activities of daily living routine.[15]

STAGES OF ALZHEIMER'S DISEASE

Early stage

In earlier stage there are difficulties with language, perception, problems with the executive functions of attentiveness, problems in planning, flexibility, and thinking. [16] Apathy and depression may be also seen in this stage, with apathy remaining as the most persistent symptom throughout the course of the disease.[17] Language problems are also a major problem that is characterized by a vocabulary shrinking and decreased word frequency and fluency, leading to difficulties in oral and written language. With the progressing of this disease, people cannot continue to perform many tasks independently and need assistance or supervision.[18]

Middle stage

In this stage the patients being unable to perform general daily living activities. Speech difficulties are major problems arises in this stage due to an inability to recall vocabulary that leads to frequent incorrect word during speaking. Reading and writing frequencies are also progressively lost.[19] With time increases and AD progresses, the complex motor sequences become less coordinated respectively so there are chances of unbalancing of body or falling is increased. In this phase, memory problems become more worsen, and the person may fail to recognize close relatives.[20] Behavioral and neuropsychological alteration become more worsens.[21] The AD patients can also develop urinary incontinence.[22]

Late stage

The final stage is also called as the late stage or severe stage. In this stage the patient is totally dependents upon caretakers. The language of patients is constricted to a simple phrases or even single word and sometimes leading with a complete loss of speech. [23] Subjects with Alzheimer's disease can ultimately not be able to perform even the simplest tasks independently due to muscle mass and mobility deteriorates. The peoples with Alzheimer's disease can not be able to feed themselves. Sometime the death may be caused.[24]

ASHWAGANDHA

Although various types of drugs are clinically utilized for the treatment of neurodegenerative disease, some of these drugs are natural (herbals and minerals) and some are synthetic and semisynthetic yet for fundamental treatment of neurodegenerative diseases there are lack of drugs and greatly needed.[25] Ashwagandha (Common Names: Withania, winter.

Cherry, Indian Winter Cherry, Indian Ginseng) which botanical name is *Withania somnifera* belonging with family Solanaceae is one of the most valuable herbal drugs which is widely used in Indian traditional medicine (Ayurveda) as a *Rasayana* drug as well as in other medicine system.[26] These plants grow mostly in tropical regions of the Canary Islands, India and Sri Lanka, China and Africa. It is also cultivated in warmer areas of Europe.[27] In India ashwagandha is widely cultivated Uttar Pradesh, Punjab, Gujarat, Haryana, Rajasthan, Madhya Pradesh and Maharashtra.[28] *Withania somnifera* (Ashwagandha) is clinically used for the treatment of various neurological symptoms like mental confusion, loss of memory, mood swings, insomnia, loss of memory, amyotrophic lateral sclerosis. From the traditional use of Ashwagandha proves that it may possibly useful to improve the neurodegenerative diseases.[29] Ashwagandha also has been reported to include various pharmacological effects such as antiinflammatory, anti-tumor, anti-oxidant, immunomodulatory, and anti-neuropsychiatric disease effects.[30] Ashwagandha contains bioactive compounds including withanolides and withanamides which are responsible for showing anti-Alzheimer's activities.[31]

Major bioactive chemical constituents of Ashwagandha.

S. No.	Name of chemical constituents	Pharmacological role
1	Withanolide A	Reduction of cerebral infraction, restore blood brain barrier disruption and cerebral edema[32]
2	Withanolide D	Neurons growth and Memory improvement[33]
3	3-β-hydroxy-2, 3- dihydro-withanolide F	Synaptic reconstruction and Memory improvement[34]
4	Withaferin A	Cognitive and memory enhancement, anti-tumor, anti- inflammatory, and immunomodulatory activities[35]
5	Isopelletierine	Anti Anthelmintic activities[36]
6	Anaferine	Anti inflammatory and anti-stress activities[37]
7	Cuseohygrine	Anti-diabetics, anti-hypertension and anti-cancer[38]
8	Anahygrine	
9	Withanoside I	Enhance the production of acetylcholine by enhancing M_1 and M_2 receptor binding capacity[39 & 40]
10	Withanoside II	Enhance the production of acetylcholine by enhancing M_1 and M_2 receptor binding capacity[39 & 40]
11	Withanoside III	Enhance the production of acetylcholine by enhancing M_1 and M_2

		receptor binding capacity[39 & 40]
12	Withanoside IV	Axonal growth and functional recovery of brain and Neurite growth[41]
13	Withaperuvin D	Memory enhancer [42]
14	Solasodines	Immunomodulatory by suppreing mitogeninduced splenocyte activation[43]
15	Withasomniferin-A	Anti-cancer[44]

The cholinesterase inhibitory activity of Ashwagandha occurred due to presence Withanolide A, withaferin-A, 2, 3 dihydrowithaferin-A, withanoside IV and VI, Withaperuvin D and Withanolide D. These chemical constituents are isolated from Withania somnifera root extract. Withanolide A, are responsible to regeneration and reconstruction of presynaptic and postsynaptic neurons. From the fruit extracts of ashwagandha Withanamides are isolated.[32-42]

CONCLUSION

Ashwagandha (*Withania somnifera)* and its related constituents are showing various activities against Alzheimer's disease. Ashwagandha extracts also showing positive effects to reduce neurodegenerative diseases effects such as Parkinson's disease and Huntington's disease. In latest, novel drug substituents was synthesized as a derivative of constituents of Ashwagandha for the treatment of spinal cord injury. From these results, it is suggested that Ashwagandha is a potential basis drugs showing positive action against neurodegenerative diseases. In addition, it is find out that the modulation of astrocyte properties of ashwagandha can lead to recovery of spinal cord injury and treat it by the destruction of A*β* in the brain. Further studies of Ashwagandha will be probably continued to resolving neurodegenerative disease as more effective.

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