Ashwagandha as a potential Anti-Alzheimer's Drug

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ABSTRACT

Alzheimer's Disease (AD), also called as just Alzheimer's is a progressive neurodegenerative disease that ischaracterized by memory loss, disorientation, mood disorders, and behavioural changes. It commonly occursin people above the age of 65, but early cases can start as early as mid-30s. The current medications forAlzheimer's are only palliative and include reversible cholinesterase inhibitors and Memantine, an NMDAantagonist. Various other drugs are also used to treat the behavioural and psychiatric changes that occur inthe later stages of the disease. Root extracts of *Withaniasomnifera*, commonly called as Ashwagandha, havebeen shown to have anti-Alzheimers activity, in silico, in-vitro and in-vivo. This activity of Ashwagandhais attributed mainly to 2 constituents; Withanosides and Withanolides. They are known to promote neurite outgrowth, reduce Aβ toxicity, improve cognitive functions and also reduce cholinergic activity in the CNS,by inhibiting the enzyme acetyl cholinesterase.

KEYWORDS: Alzheimer's, Ashwagandha, Withaniasomnifera, Withanoside, Withanolide

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INTRODUCTION

Alzheimers's disease was first described in 1906 by Alois Alzheimer, after whom the disease is named[1]. It is a neurodenegerative disease that primarily affects the hippocampus, the part of the brain associated with memory, which causes the classical symptom of Alzheimer's, which is memory impairment. The disease is idiopathic, i.e the cause is not definitively known, though risk factors have been identified. The disease is characterized by deposition of proteins in the brain, particularly two proteins called Aβ (Amyloid-β)[2] and tau protein[3]. The Aβ protein causes amyloid plaques and the tau protein causes neurofibrillary tangles. It is also seen as a loss of neurons and synapses in

certain regions of the bran like the cerebral cortex and some subcortical regions [4-5], leading to degeneration of the temporal and parietal lobes, as well as the frontal cortex. Chemically, Alzheimers's is a proteopathy, an irregularity in protein generation and folding, which causes the deposition of Aβ as amyloid plaques and tau protein as neurofibrillary tangles. The diagnostic tests for Alzheimer's are through cognitive tests to assess cognitive function and CT scans (Computed Topography) or MRI (Magnetic Resonance Imaging) or PET (Positron Emission Topography) with certain radio opaque dyes like florbetapir and flutemetamol can help in identifying the affected areas, andtheextentofdiseaseprogression[6].ThereareseveralriskfactorsindicatedinAlzheimer's,someofwhich are various forms of head injury, but the main risk factor is genetic[7]. Genetic causes account for less than 3% of the total Alzheimer's cases. This is called as early onset familial Alzheimer's[8]. Here, the disease is caused due to mutations in one of three genes that encode Aβ; APP (Amyloid-Beta precursor protein), and two presenilins PSEN 1 and 2 [9]. Mutations in these genes causes excess production of the Aβ protein that getsdepositedasamyloidplaques.Inthecaseofnon-familialAlzheimer's,manygeneshavebeenindicated asriskfactorsthatincreasethechancesofAlzheimer's,suchastheAPOE(ApolipoproteinE)alleles andthe alleles of the TREM 2 gene[10-11], but they are unconfirmed, due to variations between different populations. Though there are many hypotheses about the cause and progression of Alzheimers, the exact pathology that leads to the aggregation of the β protein is unknown. It has been indicated that various inflammatory pathways and multiple inflammatory mediators play an important role in the progression of Alzheimer's disease and therefore is a potential target for itstreatment.

Currently,thereisnocurativetherapyforAlzheimer'sdisease,andalltreatmentsaresymptomatic.Therearemainly 2 approaches that are used in the current therapy of Alzheimer's disease, one is the augmentationof cholinergic transmission[12]. This treatment mainly makes use of reversible AChE (Acetylcholine Esterase) inhibitorslikeDonepezil,Rivastigmine,andGalantamine. Whenthesedrugsareadministeredinearlycases of Alzheimer's disease, they show modest effect in reducing the cognitive impairment. This effect is however short-lived due to the down regulation of cholinergic receptors in the brain upon long term therapy[13]. Generally speaking anitcholinergic drugs only delay the onset of the disease by about half a year to one full year at the most, before the clinical progression of the disease begins again. The other approach is

relatively new;it involves the use of an NMDA- receptor antagonist called Memantine[14]. It is usually administered along with anticholinergic drugs, usually administered in the later stages of Alzheimers, asit has little to no effect in the early stages to treat dementia. Memantine is seen to delay the erosion of the mentalstatusofthepatients.Otherthanthese2approaches,theothertreatmentsusedinAlzheimer'sdisease are usually CNS drugs used to treat paranoia, depression andanxiety[15].

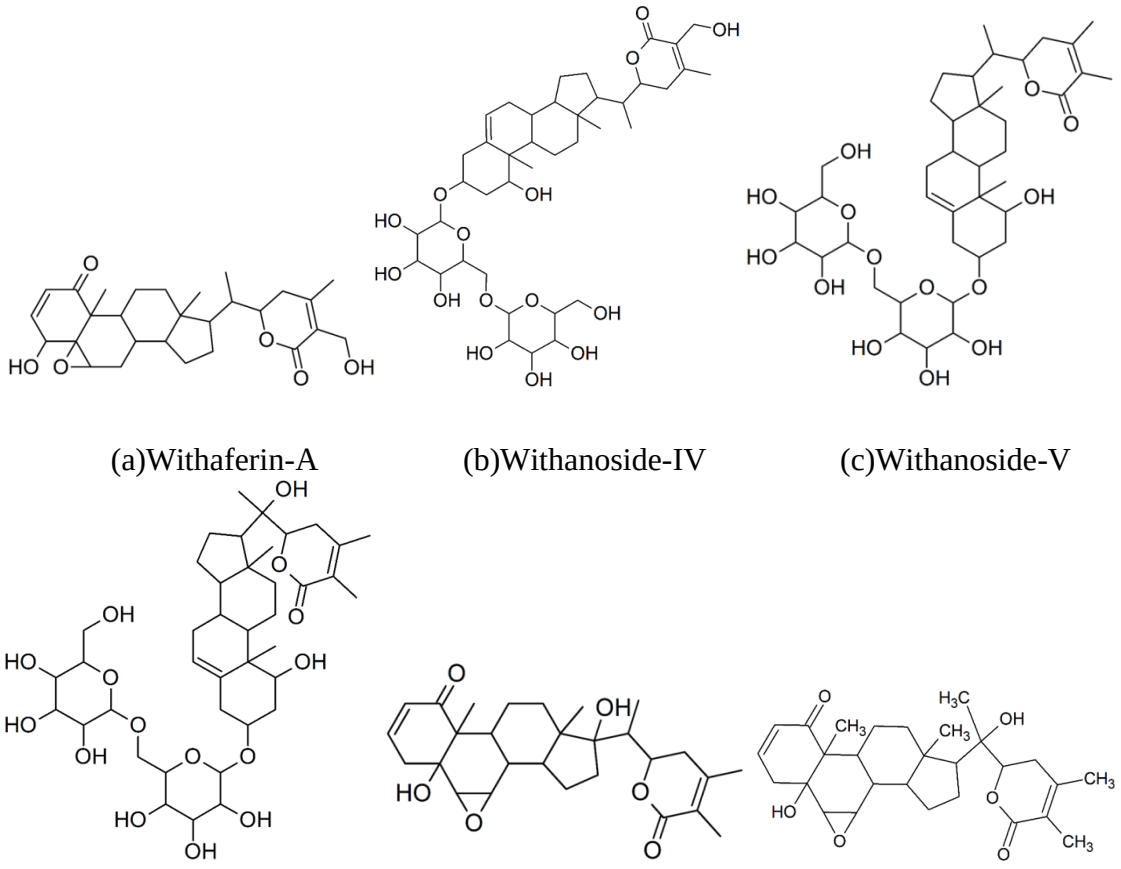
Ashwagandha: A Herbal Remedy

Ashwagandha is the common name for *Withania somnifera*, an evergreen shrub that belongs to the family Solanaceae.ItisalsocalledIndianGinsengandPoisonGooseberry[16].ItgrowslargelyintheNorth-Western areasofIndia.Ashwagandhahaslongbeenrecognizedasamedicinalplantin India.Itsmedicinal properties are well documented in the traditional systems of medicine like Ayurveda, Siddha and Unani-Tibb. It is has long been used as a tonic, which is prepared using the powder of the dried roots of the plant. The plant is known to contain several classes of phytoconstituents, such as alkaloids, glycosides and saponins amongothers[17].ThevariousphytoconstituentsofAshwagandhahasbeenidentifiedtohavemanybiological activities, of which the anti-inflammatory, antineoplastic, neuroprotective and hepatoprotective properties are of specialinterest[18-19].

Neuroprotective Effect

SincetheexactaetiologyofAlzheimer'sdiseaseisnotknown,thegeneralneuroprotectiveeffectsproduced by the constituents of Ashwagandha bear some importance. Multiple aqueous and alcoholic extracts of the plant were seen to protect nerves from oxidative stress by limiting the formation of free radical species and alsominimizetheDNAdamage[20].ThisactivityoftheplantismainlyattributedtotheWithanolides,aclass of steroidal lactones[21]. They have been known to promote the reconstruction of neuronal networks, both in-vivo and in-vitro simulations, particularly they are known to decrease the time required for axonal regeneration and synaptic reconstruction[22]. They are also shown to improve object location memory in rats, indicating cognitive improvement. The aqueous extract was also seen to increase

neurotransmitter levels, and lower oxidative stress in various animalmodels[23].



(a)Withaferin-A (b)Withanoside-IV (c)Withanoside-V

(d)Withanoside-VI (e)Withanone (f)Withanolide-A

Figure 1: Structures of some phytoconstituents of *Withania somnifera*

Anti-Alzheimer's Effect

The constituents of *W. somniera*, along with their general neuroprotective effects, also show activity as potential drugs in the treatment of Alzheimer's disease [24]. It is important to note that the anti-Alzeihmer's property of *W. somnifera* cannot be attributed to a single constituent alone. Most of the properties, occur as a result of synergistic action of multiple constituents working through various different mechanisms, that produce the final desirable effect. The aqueous extract of the root, showed improved cognitive and psychomotorabilitiesinhealthyindividuals[25].Itwasalsoseentoimprovetheclearanceof Aβ(Amyloid-β) bytheactivationofalipoproteinlikeproteinintheliver.In-

silicostudieshavealsoshownthat2constituents,Withanamide A and C bind to Aβ[26-27], which is indicative of fibril formation inhibition in the neurons and therefore in the long term, reduce the Aβ toxicity in the cells. Withanolides are also known to activate P-glycoprotein, thereby increasing the efflux of the amyloid protein[28]. There is also potential disease modifying properties in constituents like Withanosides, which are known to possess neuro-regenerative properties, by promoting regeneration of axons and dendrites. Along with these activities, the Withanolides havesomeanticholineseraseactivitywhichalsohelpsinimprovingtheconditionofdementiain Alzherimer'spatients[29].Sinceneuroinflammmationalsoplaysaroleintheprogressionofthe disease,theantiinflammatory properties of the constituents become useful in this regard. Withaferin-A is known to inhibit the migration of cytokines like TNF-α and Interleukin-1β (IL-1β), and therefore can help in the reduction of long-term Aβ toxicity in thecells[30-31].

CONCLUSION

The phytoconstituents of *Withania somnifera* have proven to have very beneficial effects in slowing the progression of Alzheimer's disease and in some cases, has also shown very promising activity in reversing the physiological damage caused by Alzheimer's disease through its neuro-regenerative properties, which helps in axonal and synaptic reconstruction. The lack of drugs to satisfactorily treat Alzheimer's disease makes Ashwagandha an ideal starting point to identify a new therapeutic compound.

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CONFLICT OF INTEREST:

No conflict of interest.

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