

Withania somnifera: a promising neuroprotective ally against Alzheimer's disease

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Abstract

Withania somnifera, or Ashwagandha, shows promise as a neuroprotective agent in Alzheimer's disease (AD), a neurodegenerative disorder characterized by cognitive decline. Bioactive compounds in Ashwagandha, particularly withanolides, exhibit antioxidant, anti-inflammatory, and anti-amyloidogenic properties, positioning it as a potential therapeutic for AD. These compounds target key AD pathologies by modulating amyloid-beta plaque formation and reducing oxidative stress. Preclinical studies reveal that Ashwagandha extracts enhance cognitive function, inhibit amyloid-beta aggregation and decrease neuroinflammation, potentially slowing AD progression. Furthermore, its neurorestorative effects, such as promoting neuronal regeneration and improving synaptic plasticity, contribute to cognitive health. Animal studies demonstrate improved cognitive and behavioral outcomes following ashwagandha administration, while *in vitro* research corroborates its role in minimizing neurotoxicity. Although clinical studies are sparse, Ashwagandha's multi-targeted approach makes it a promising candidate for AD management.

Keywords: *Withania somnifera*, neuroprotective, medicinal plant, Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and memory loss, impacting millions of people globally [1]. Despite advances in the understanding of AD pathology—including amyloid-beta (A β) plaques, tau hyperphosphorylation, and neuroinflammation—effective therapies are urgently needed [2]. *Withania somnifera* (Ashwagandha), a traditional Ayurvedic herb, shows promise in AD management due to its antioxidant, anti-inflammatory, and neuroprotective properties. Key bioactive compounds (Figure 1), such as withanolides and withaferin A, help reduce oxidative stress, inhibit plaque formation, and modulate inflammation [3].

Withaferin A (WA) from *Withania somnifera* shows po-

tential for AD treatment through multiple mechanisms. It reduces A β aggregation, suppresses NF- κ B and Hsp90, and inhibits iNOS, thereby decreasing A β -induced neurotoxicity. WA enhances cognitive function by boosting neuroprotective proteins (Hsp27, Hsp70), lowering tau aggregation, and modulating microglial activity [4]. Berghe *et al.* demonstrated that WA alleviates TAR DNA-binding protein-43, a pathological hallmark of AD, while boosting the autophagic marker LC3BII and its activation of Nrf2, which enhances antioxidant defenses and preserves synaptic function [5]. A β deposition is a hallmark of AD,

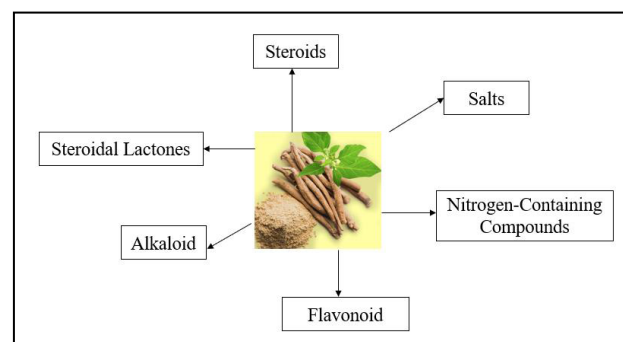


Figure 1. Phytoconstituents from *Withania somnifera*.

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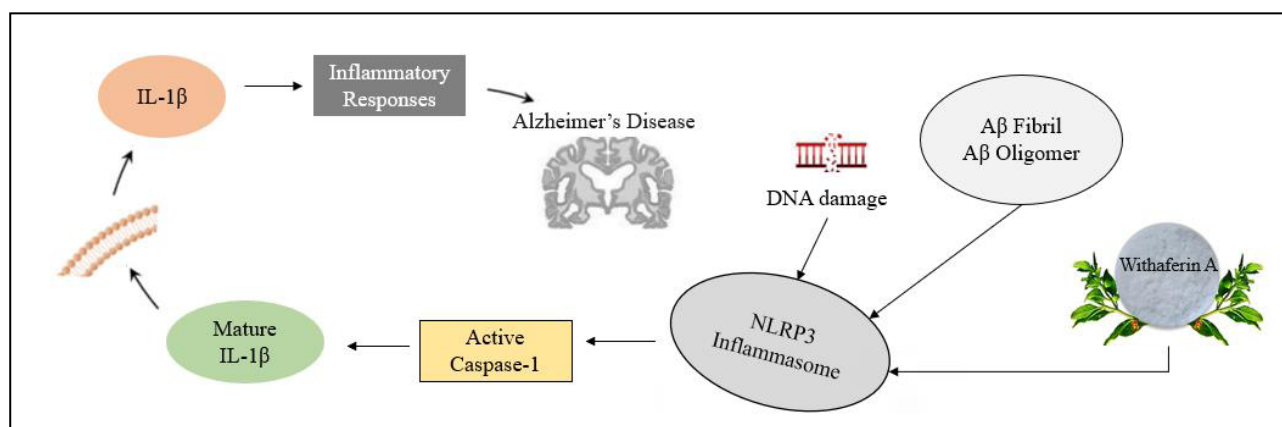


Figure 2. Overview of inflammatory signaling pathways altered by withaferin A.

and withanolide A from *Withania somnifera* demonstrates therapeutic potential by reducing A β secretion, aggregation, and neurotoxicity in APP-transfected cells. WA also increases α -secretase and insulin-degrading enzyme (IDE) activity, thereby promoting A β breakdown [6]. Withanamide binds specifically to A β (25-35), limiting fibril formation and neuronal death [7]. Additionally, withanolide A and withanamides enhance antioxidant enzymes, reducing oxidative stress and mitochondrial dysfunction, positioning them as promising AD treatments [7].

Current AD treatments, such as acetylcholinesterase (AChE) inhibitors and NMDA receptor antagonists, offer only temporary cognitive relief. WA from *Withania somnifera* shows promise as an AD therapy by restoring cholinergic markers, inhibiting AChE and butyrylcholinesterase (BuChE), and enhancing acetylcholine levels. Studies show that WA boosts cholinergic neurotransmission and improves cognitive function without affecting other receptors. At 50 mg/kg, WA provides neuroprotection by increasing dopamine levels, potentially reducing motor deficits [8]. In AD, A β fibrils activate microglia, triggering NF- κ B and the NLRP3 inflammasome, which release pro-inflammatory cytokines (Figure 2) [9]. WA effectively inhibits NF- κ B by targeting IKK β , thereby reducing pro-inflammatory mediators such as TNF- α and IL-1. WA also modulates nitric oxide and COX-2 levels, inhibits iNOS, and decreases VCAM-1 and ICAM-1 expression, thus curbing microglial inflammation and potentially reducing A β accumulation and neurodegeneration. WA disrupts the CDC37-HSP90 complex and influences AD-related proteins such as AKT and IKK, underscoring its therapeutic potential in AD treatment [10].

Nanoparticle-based drug delivery holds promise for AD treatment by enabling targeted transport across the blood-brain barrier (BBB). *Withania somnifera* extracts rich in withanolides were shown by Sehgal *et al.* to reduce H₂O₂- and amyloid-induced cytotoxicity in AD mouse models, enhancing lipoprotein kinase levels [11]. Withaferin A-loaded nanoparticles by Madhu *et al.* provided sustained neuroprotection with efficient release [12]. Mancini *et al.* developed mApoE-PA-LIP nanoparticles that act as amyloid-beta “sinks”, and enhance A β clearance [13]. Further large-scale trials are needed to confirm Ashwagandha’s therapeutic potential in AD.

Declarations

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References

1. Niu S, Zhang LK, Zhang L, Zhuang S, Zhan X, Chen WY, *et al.* Inhibition by multifunctional magnetic nanoparticles loaded with alpha-synuclein RNAi plasmid in a Parkinson’s disease model. *Theranostics*, 2017, 7(2): 344-356. [Crossref]
2. Notter T, Aengenheister L, Weber-Stadlbauer U, Naegeli H, Wick P, Meyer U, *et al.* Prenatal exposure to TiO₂ nanoparticles in mice causes behavioral deficits with relevance to autism spectrum disorder and beyond. *Transl Psychiatry*, 2018, 8(1): 193-204. [Crossref]
3. Vaidya VG, Naik NN, Ganu G, Parmar V, Jagtap S, Saste G, *et al.* Clinical pharmacokinetic evaluation of *Withania somnifera* (L.) dunal root extract in healthy human volunteers: a non-randomized, single dose study utilizing UHPLC-MS/MS analysis. *J Ethnopharmacol*, 2024, 322: 117603. [Crossref]
4. Barua N, Ibn Aziz MA, Tareq AM, Sayeed MA, Alam N, Alam NU, *et al.* *In vivo* and *in vitro* evaluation of pharmacological activities of *Adenia trilobata* (Roxb.). *Biochem Biophys Rep*, 2020, 23: 100772. [Crossref]
5. Vanden Berghe W, Sabbe L, Kaileh M, Haegeman G, & Heynink K. Molecular insight in the multifunctional activities of withaferin A. *Biochem Pharmacol*, 2012, 84(10): 1282-1291. [Crossref]
6. Tiwari S, Atluri VSR, Yndart Arias A, Jayant RD, Kaushik A, Geiger J, *et al.* Withaferin A suppresses beta amyloid in APP expressing cells: studies for Tat and cocaine associated neurological dysfunctions. *Front Aging Neurosci*, 2018, 10: 291-305. [Crossref]
7. Roy A. Role of medicinal plants against Alzheimer’s disease. 2018, 11: 205-208. [Crossref]
8. Bhattacharya SK, Kumar A, & Ghosal S. Effects of glycowithanolides from *Withania somnifera* on an animal model

- of Alzheimer's disease and perturbed central cholinergic markers of cognition in rats. *Phytotherapy Research*, 1995, 9.
9. Howes MJ, Perry NS, & Houghton PJ. Plants with traditional uses and activities, relevant to the management of Alzheimer's disease and other cognitive disorders. *Phytother Res*, 2003, 17(1): 1-18. [[Crossref](#)]
 10. Purushotham PM, Kim JM, Jo EK, & Senthil K. Withanolides against TLR4-activated innate inflammatory signalling pathways: a comparative computational and experimental study. *Phytother Res*, 2017, 31(1): 152-163. [[Crossref](#)]
 11. Sehgal N, Gupta A, Valli RK, Joshi SD, Mills JT, Hamel E, *et al.* *Withania somnifera* reverses Alzheimer's disease pathology by enhancing low-density lipoprotein receptor-related protein in liver. *Proc Natl Acad Sci USA*, 2012, 109(9): 3510-3515. [[Crossref](#)]
 12. Madhu S, Komala M, & Pandian P. Formulation development and characterization of withaferin-A loaded polymeric nanoparticles for Alzheimer's disease. *BioNanoScience*, 2021, 11(2): 559-566. [[Crossref](#)]
 13. Mancini S, Minniti S, Gregori M, Sancini G, Cagnotto A, Couraud PO, *et al.* The hunt for brain A β oligomers by peripherally circulating multi-functional nanoparticles: potential therapeutic approach for Alzheimer disease. *Nanomedicine*, 2016, 12(1): 43-52. [[Crossref](#)]

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