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COMMENTARY

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: *Withinia 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 (Aβ) 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 potential for AD treatment through multiple mechanisms. It reduces Aβ aggregation, suppresses NF-κB and Hsp90, and inhibits iNOS, thereby decreasing Aβ-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]. Aβ deposition is a hallmark of AD,

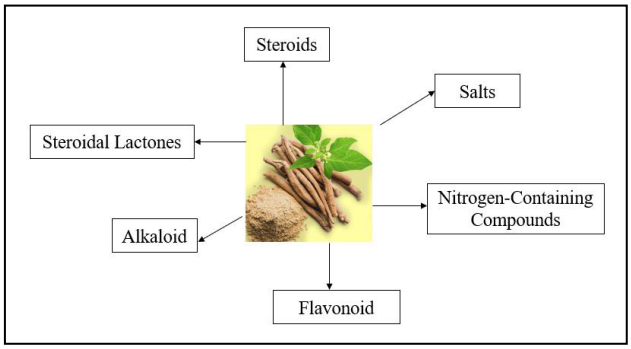

Figure 1. Phytoconstituents from *Withania somnifera*.

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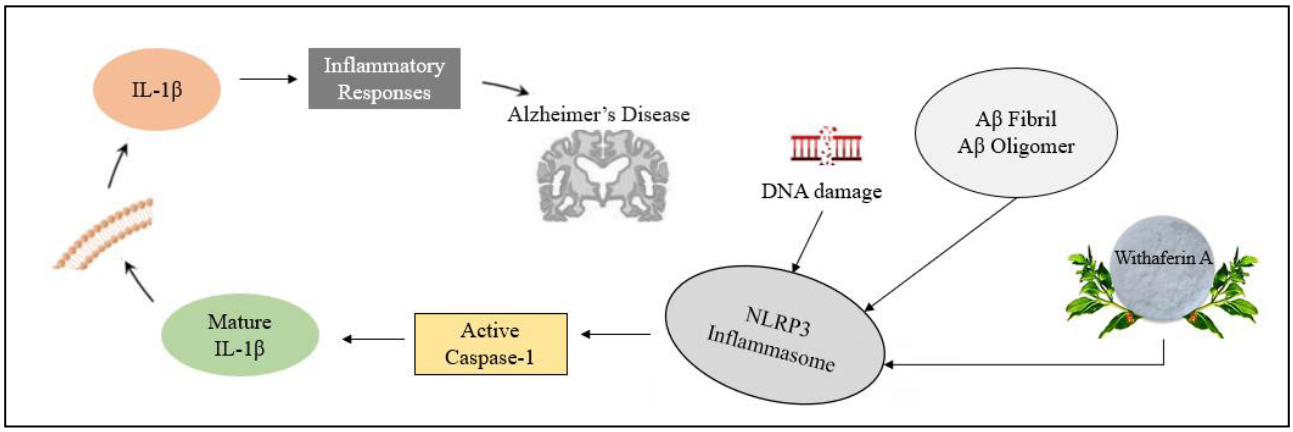

Figure 2. Overview of inflammatory signaling pathways altered by withaferin A.

and withanolide A from *Withania somnifera* demonstrates therapeutic potential by reducing Aβ secretion, aggregation, and neurotoxicity in APP-transfected cells. WA also increases α-secretase and insulin-degrading enzyme (IDE) activity, thereby promoting Aβ breakdown [6]. Withanamide binds specifically to Aβ (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, Aβ fibrils activate microglia, triggering NF-κB and the NLRP3 inflammasome, which release pro-inflammatory cytokines (Figure 2) [9]. WA effectively inhibits NF-κB by targeting IKKβ, 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 Aβ 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 H_2O_2- 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 Aβ clearance [13]. Further large-scale trials are needed to confirm Ashwagandha's therapeutic potential in AD.

Declarations

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Conflict of interest statement: All authors declare that they have no competing interests.

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