

# Role of NMDA Receptors in Alzheimer's Disease Pathology and Potential NMDA Receptor Blockers from Medicinal Plants - A Review

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## Abstract

Alzheimer's disease is responsible for 60-70 percent of dementia cases worldwide. Globally, there are 24.3 million cases. Researchers have attempted to develop multi-target medications to suppress several mechanisms in Alzheimer's Disease, like protein mis-folding and related beta amyloid aggregation, oxidative stress, and decreasing Acetyl choline levels. NMDA-mediated neurotoxicity is often linked to cognitive impairment, as shown in Alzheimer's disease. NMDA receptors found to have to connection with beta amyloid peptide and tau protein deposition which are major characteristics of Alzheimer's disease. NMDA receptor antagonists are a viable therapy option for a many neurological disorders, as well as Alzheimer's disease. Currently, majority of the drugs used in the management of Alzheimer's disease are Acetyl choline Esterase inhibitors. Memantine is the only approved NMDA blocker, to be used in Alzheimer's disease, which is found to be effective only to a certain extend. There is a need for better therapeutic agents belonging to this class. This paper intends to provide a rapid reference about the involvement of NMDA receptors in the pathogenesis of Alzheimer's disease, as well as phyto constituents that have been identified to inhibit NMDA receptors.

**Keywords:** Alzheimer's Disease, Cognitive Functions, Dementia, Excitotoxicity, N-Methyl-D-Aspartate (NMDA) Receptor

## 1. Introduction

Dementia refers to a group of disorders that cause cognitive impairment. The most common form of dementia is Alzheimer's Disease (AD), which is a long-term condition that causes the central nervous system to deteriorate<sup>1</sup>. AD is responsible for nearly 60-70% of dementia, globally. It is estimated that, there are about 24.3 million AD patients in the world<sup>2</sup>. The rate of prevalence of dementia increases to double fold every six years in age groups of 65 and above, reaching 7% prevalence in age group of 75–79 years, 12% in 80–84 years, 20% in 85–89 years, and 40% in people with age 90 years or above<sup>1</sup>.

Through the years researchers have attempted to design and develop many drugs with multiple targets to interfere with various mechanisms involved in AD, such as beta amyloid aggregation, misfolding of protein, metal dys-homeostasis, decrease in the Acetyl choline levels, and oxidative stress, since AD is a multifactorial condition<sup>3,4</sup>. The NMDA receptor (NMDA-R), is a key molecular player in the CNS which controls a wide range of processes and its activation causes the formation of excitatory potentials at postsynaptic neuron at a slower rate, which in turn controls a range of brain functions, most notably long-term memory consolidation<sup>5</sup>. Memory and cognition problems, as in Alzheimer's disease, are often linked to

NMDA-mediated neurotoxicity. Excitotoxicity produced by the neurotransmitter Glutamate through the NMDA receptors is found to have a major role in the development of many disorders of CNS including Alzheimer's disease, Amyotrophic Lateral Sclerosis (ALS), and Huntington's disease<sup>6-8</sup>. Conditions such as major depression, epilepsy also have connection with abnormal functioning of NMDA receptor<sup>9,10</sup>. The balance of glutamate and inhibitory neurotransmitter Gamma Amino-Butyric Acid (GABA), has a very important role in the maintenance of CNS homeostasis<sup>11</sup>. Considering these aspects (NMDA) receptor antagonists appear to be a potential treatment method for various neurological diseases, including Alzheimer's disease, as indicated by the development of site-specific medicines throughout time<sup>12</sup>.

## 2. NMDA Receptor Mediated Excitotoxicity and AD

NMDA receptor activity has been associated to synaptic disruption in Alzheimer's disease<sup>13</sup>. Excitatory neurotransmission of glutamate through NMDA receptor is very much needed for by synaptic plasticity and neuron survival. Excessive NMDAR activity, on the other hand, can promote neuronal death by causing excitotoxicity. Protein kinase II dependent on  $Ca^{2+}$ /calmodulin (CaMKII)-mediated signaling mechanism is triggered by strong NMDA receptor activation, which leads to increased synaptic strength. But, a little rise in postsynaptic  $Ca^{2+}$  activates phosphates-mediated Long Term Depression (LTD) when NMDARs are activated. As a result, the balance of regionalized NMDA receptor signalling in synaptic and extra synaptic regions is skewed toward downstream signalling pathways, which eventually contribute to neuron death in Alzheimer's disease<sup>14,15</sup>.

The NMDA receptor has multiple modulator sites. Antibodies to receptors bind to these locations. The NMDA receptor's agonist-binding domain is found in tetramer, composed of two NR2 and two NR1 subunits. The channel pore and the NR2 subunit, which possesses a glutamate-binding site, have been studied. D-Amino Phosphono-Valeric acid (APV), one of the earliest NMDA-R antagonists, functions as a competitive antagonist at the glutamate-binding site. Recently studies have been directed towards the development of receptor antagonist at the N-terminal regions of the NR2 and NR1

subunits, due to substantial adverse effects following non-selective, competitive NMDA receptor antagonism<sup>16,17</sup>.

### 2.1 NMDA Receptors and Tau Protein

Tau is a key component of the Neurofibrillary Tangles, which are a pathological characteristic of Alzheimer's disease. Tau is a protein present only in the axon of neurons, in the healthy brain. It is involved in the construction and stability of microtubules. It is hyper phosphorylated in Alzheimer's disease brains. Tau is involved in the formation of fibrils which are present as threads in dendrites and neurofibrillary tangles in the axons and somato-dendritic portion. In familial autosomal dominant AD, amyloid deposition in cerebrum leads to cerebral tau disease. In sporadic AD, NFTs occur before AD pathology in the majority of afflicted locations<sup>18,19</sup>.

### 2.2 $\beta$ amyloid Peptide and NMDA Receptors

N-methyl-D-aspartate receptors are receptors for the amino acid N-methyl-D-aspartate. The breakdown of  $Ca^{2+}$  homeostasis induced by  $\beta$  amyloid peptide ( $A\beta$ ) is hypothesised to be linked to the early cognitive abnormalities seen in Alzheimer's disease<sup>20</sup>. Glutamate-induced stimulation of NMDA receptors, followed by synaptic NMDA receptor desensitisation, NMDA receptor internalisation, and activation of extra synaptic or perisynaptic NMDA receptors cause long-term depression induction and Synaptic depression<sup>21</sup>.  $A\beta$  causes neurotoxicity or neuroprotection by down regulating the synaptic NMDAR response by increasing NMDAR endocytosis.  $A\beta$  decreases neuronal glutamate absorption and increasing extra synaptic NMDA receptor activity thereby producing neurotoxicity<sup>14</sup>. Increased levels of  $A\beta$  oligomers are linked to early synaptic failure in Alzheimer's disease, resulting in fast NMDA receptor dependent synaptic depression<sup>22</sup>.

## 3. NMDAR Antagonists in the Management of AD

CNS illness in which neuronal death linked to excitotoxicity produced by glutamate could be managed by blocking NMDARs. NMDAR-blocking drugs include memantine, phencyclidine, ketamine, and dizocilpine. However, practical application of phencyclidine,

ketamine, and dizocilpine is hampered by severe side effects such as increased affinity and prolonged duration on the receptor<sup>23</sup>. The affinity on Memantine, on the receptor site is comparatively less and is well tolerated. Hence, it is effective to manage mild to severe Alzheimer's disease<sup>24,25</sup>. Memantine inhibits NMDAR-mediated excitotoxicity, has high voltage dependence, and has a fast unblocking kinetic property<sup>26</sup>. Memantine inhibits the NMDAR, just like  $Mg^{2+}$ . It is active during over-activation of the receptor in pathological conditions, while enabling the transmission of transitory impulses required for memory and learning<sup>27</sup>. Memantine has been shown to promote astroglial release of neurotrophic factors<sup>28</sup>. FDA has approved the combination of memantine and donepezil to be used in moderate to severe Alzheimer's Disease<sup>23</sup>.

#### 4. Herbs in Modulating NMDA-R Activity

NMDA-R activity has been linked to numerous herbs and their constituents that have been shown to improve memory, cognition, and protect the nervous system<sup>29</sup>.

Curcumin extracted from *Curcuma longa* L. showed inhibitory properties against NMDA activation in rat retinal neurons. NMDA-induced necrotic and apoptotic cell death were both reduced<sup>30</sup>.

Polypeptides from *Achyranthes bidentatae* have been shown to have neuroprotective properties. Pretreatment with these polypeptides increased the viability of rat hippocampus neurons challenged with NMDA. The rise in intracellular  $Ca^{2+}$  caused by NMDA was also reduced<sup>31,32</sup>.

In rat hippocampus cells, saponins extracted from *Panax ginseng* reduced NMDA-induced current and  $Ca^{2+}$  response<sup>33</sup>.

The efficacy of *Ginkgo biloba* L to treat Alzheimer's disease and vascular disorders has been reported<sup>34-36</sup>. Suppression of  $A\beta$  formation is thought to be the fundamental mechanism<sup>37</sup>. In rat hippocampus cells, bilobalide, a phytoconstituent of *Ginkgo biloba*, has been demonstrated to block downstream NMDA signalling<sup>38</sup>.

*Scrophularia ningpoensis* is a *Scrophularia* species. Glutamate-stimulated rat cortical neurons were discovered to be protected by Hems<sup>39</sup>. 8-O-E-p-methoxycinnamoyl harpagide, iridoids identified from *Scrophularia ningpoensis*, appears to be the culprit. Hems works by blocking the NMDA receptors<sup>40</sup>.

The ginsenoside, Protopanaxadiol ginsenoside-Rd (Rd), is a constituent of the plants *Panax notoginseng* and *Panax ginseng*. Recent studies revealed that neuroprotection was exhibited by Protopanaxadiol ginsenoside-Rd in cultured neurons. The mechanism was found to be prevention of excessive  $Ca^{2+}$  influx, associate with NMDA, glutamate excitotoxicity. This suggests that Rd may have blocking action on NMDA receptor<sup>41</sup>.

Currents produced by the NMDA receptors in neurons were found to be inhibited by aqueous extracts of certain Chinese stroke medicine plants - *Salvia miltiorrhiza*, *Scutellaria baicalensis* and *Stephania tetrandra*. The action was similar to that of  $Mg^{2+}$ . Aqueous extract of the plant *Uncaria rhynchophylla* decreased neuronal death caused by NMDA associated excitotoxicity by  $59.13 \pm 3.52\%$ <sup>42</sup>.

Ethanollic extract of root of the herb *Radix Polygalae*, which is a commonly used plant in traditional system of medicine in Asia, found to have protective effect against NMDA mediated neurotoxicity, and also found to induce BDNF (brain-derived neurotrophic factor) expression<sup>43</sup>.

Isoliquiritigenin from the plant *Uncaria thorn* exhibited NMDA receptor binding and inhibition of the glutamate-induced elevation in influx of  $Ca^{2+}$ <sup>44</sup>.

#### 5. Conclusion

Dementia associated with AD is a major health problem globally, that especially affects the elderly. With the increasing life expectancy, India has a very large geriatric population, second only to China, and hence Alzheimer's dementia is of great concern in the coming decades. AD is as a degenerative disease affecting the neurons. Considerable decline in the cholinergic effects in the brain is believed to be one of the major contributors of cognitive decline in AD. The major class of drugs that are used to manage AD are AChEi (Acetyl Choline Esterase Inhibitors). They increase the level of ACh in brain and provide improvement of cognitive functions. Memantine is a NMDA receptor blocker that prevents excitotoxicity and eventual damage of neurons. It is the only approved drug of its class. All the drugs that are currently used in the management of AD, has limited efficacy, hence this is an area of active research for the development of better therapeutic agents. Large numbers of articles related with evaluation of AChE inhibitory action of phytochemical constituents has been published. But relatively few works have been done to explore NMDA blocking potential

of plants. This article aimed to review the publications related with the topics such as, involvement of NMDA receptor in the pathogenesis of AD, and NMDA blocking potency of constituents of medicinal plants. The authors are hopeful that this work would provide a ready reference in this regard.

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