**Neuroprotective Potentials of Andrographolide (AG) and its structural analogues in Alzheimer’s Disease (AD)**

**Bhattacharya Vijeta\*1, M. Alagusundaram1, Mishra Namrata1, Goli Venketeshswarlu2, Chopra Neha1, Nem Kumar Jain3**

1- Department of Pharmaceutics School of Pharmacy ITM University, Gwalior, Madhya Pradesh, 474001.

2-Department of Biotechnology School of Pharmacy, ITM University, Gwalior, Madhya Pradesh, 474001.

3-Department of Pharmacology School of Pharmacy, ITM University, Gwalior, Madhya Pradesh, 474001.

**Abstract:**

The traditional herb Andrographis paniculata (A. paniculata) has a long history of use in eastern Asia and ancient China for the treatment of a number of illnesses, including laryngitis, rheumatoid arthritis, cancer, diarrhoea, and upper respiratory tract infections. Andrographolide is a compound derived from this herb. One or more of andrographolide's disease anticipation and/or healing strategies include anti-inflammation, anti-apoptosis, antioxidative stress and/or pro-apoptosis. Pharmacodynamic investigations have shown that andrographolide may cross the blood-brain barrier and distribute to numerous brain areas; as a result, its pharmacological effects on the central nervous system (CNS) have begun to be understood in recent years. For instance, andrographolide has been demonstrated in numerous models of cerebral ischemia to reduce the size of brain infarcts. These results suggest that andrographolide may be useful in the treatment of psychiatric disorders like anxiety and depression. Targeting treatments are part of the current AD treatment approach. The Food and Drug Administration has authorised the medication aducanumab, which is given intravenously and requires close patient monitoring because of a potentially harmful side effect known as amyloid-related imaging abnormalities (ARIA). There have been numerous scientific investigations on medicinal herbs. Due to their anti-inflammatory and antioxidant characteristics, herbs can be utilized to treat AD. Anti-inflammatory medications such as German chamomile, Ginseng, liquorice, turmeric, and white willow bark may decrease inflammation of the brain tissue in Alzheimer's. Researchers are working to create new medications with superior therapeutic efficacies. Andrographolide has been demonstrated to have therapeutic effects in a variety of AD models in several recent research. Inhibiting the neuroinflammatory response is thus a potential therapy option for AD. In this possible way, andrographolide and its derivative could offer a better choice to develop a novel therapeutic molecule to AD in near future.

**Key words:** andrographolide, Alzheimer’s disease, phytoconstituents, medicinal herbs, neuroprotective

**INTRODUCTION:**

With an estimated 30 million cases globally, Alzheimer's disease (AD) is the most prevalent cause of dementia. AD is a neurodegenerative disorder marked by gradual memory loss, diminished cognitive abilities, extensive neuronal death, and synaptic dysfunction[1].

Among the neuropathological indicators of AD amyloid precursor protein (APP), processing produces extracellular amyloid plaques and intracellular neurofibrillary tangles, which are primarily made of hyperphosphorylated tau protein[2,3]. The term "dementia" refers to a specific set of symptoms. Dementia is characterized by issues with memory, language, problem-solving, and other cognitive abilities. Dementia has numerous causes. [4-7] These reasons represent particular adjustments in the brain. One of the causes of dementia is Alzheimer's disease.**[8]** In addition to the loss of nerve cells, the aberrant proteins beta-amyloid and phosphorylated tau accumulate in the brains of people with Alzheimer's disease. The most frequent cause of dementia is the brain abnormalities brought on by Alzheimer's disease.[9]

By 2050, the number of people age 65 and older with Alzheimer's dementia is projected to reach 12.7 million. The incidence rate of Alzheimer's, or how many people per 100,000 are diagnosed with the disease for the first time each year, appears to be decreasing. [10] This trend has been attributed to reductions in risk factors for Alzheimer's disease over the course of the 20th century, like high blood pressure and illiteracy.[11] However, despite this possibly decreased incidence rate, it is anticipated that the number of persons with Alzheimer's will keep rising due to an increase in the population of adults 65 and older, who are at a higher risk of developing the disease.[12] It is unclear how COVID-19 will affect the amount and percentage of people who have Alzheimer's disease, including SARS-CoV-2 infection, COVID-19 mortality, and changes in healthcare access brought on by the COVID-19 pandemic.[13]Globally, over the course of the study, dementia incidence (147.95%),prevalence (160.84%), and death rate (189.29%) all increased significantly.

In 2021, there were 325,000 nurse practitioners in the United States, and 12% of them had specialized expertise in gerontological care. Less than 1% of registered nurses, physician assistants, and pharmacists identify themselves as specializing in geriatrics. However, 73% of social workers reported having experience working with older adults Members of the skilled care workforce—licensed healthcare specialists who deliver medically necessary nursing or rehabilitation services as directed by a doctor—are among those offering therapy.[14] Physical therapy, occupational therapy, wound care, intravenous injections, and catheter care are all included in this form of care, which can be provided either at home or at a skilled nursing facility.

The medicine aducanumab, which is administered via intravenous infusion and necessitates close patient observation due to a potentially dangerous side effect known as amyloid-related imaging abnormalities (ARIA), was approved by the Food and Drug Administration (for more information about aducanumab. [15-16] Aducanumab is administered intravenously, therefore infusion nurses are becoming essential components of the dementia care profession. Neuropsychologists and other medical experts with expertise in conducting cognitive tests are also crucial to determining whether aducanumab is helping people with Alzheimer's. Physicians may advise patients to stop taking aducanumab if they do not experience an improvement in their ability to think clearly and carry out everyday tasks while taking the medication. It is also necessary to investigate whether there are enough of these workers in the dementia care field to meet demand.[17]

A number of antibodies that have gone to phase 3 studies in patients with symptomatic AD have not demonstrated efficacy in terms of a significant reduction in the PET ligand signal or any clinically significant effects (ponezumab, solanezumab, bapineuzumab [48], crenezumab)

Numerous scientific studies on medicinal herbs have been conducted. Herbs can be used to treat AD because of their anti-inflammatory and antioxidant properties. Patients with Alzheimer's disease are lacking in acetylcholine. German chamomile, Ginseng, licorice, turmeric, and white willow bark are anti-inflammatory medicines that may lessen inflammation of the brain tissue in Alzheimer's.[18] A neurotransmitter that is essential for thinking and reasoning is acetylcholine. Acetylcholine levels in the brains of people with mild-to-moderate Alzheimer's disease, a degenerative form of dementia, are unusually low. Therefore, any substance that improves the cholinergic system in the brain may be helpful in treating Alzheimer's disease and other brain disorders. Natural COX-2 inhibitors, which are often referred to as medicinal herbs for AD indication, are present in herbs that inhibit Acetylcholinesterase (AchE). Some ayurvedic herbs, including Guduchi, Yashtimadhuk, Padma (Nelumbo nucifera), Vacha, Convolvulus pluricaulis, Shankhpushpi, Pancha-Tikta-Ghruta Gugguli, Amalaki, Musta Arjun, Ashwagandha, Galo Satva, Kutaj, Green Chiretta (Andrographolide), and others When used regularly, they improve the brain's capacity for function and hence offer stability.[19] In the early treatment of dementia and other disorders involving memory loss and Alzheimer's, herbs may hold promise. One of the chief benefits is that they have low toxicity compared to pharmaceutical agents. They are less toxic than pharmaceutical agents, which is one of their main advantages.[20] Botanicals can be used in conjunction with medications or other complementary therapies including SAMe, fish oil, and antioxidant vitamins.

It is important to compare the present pharmacological treatment for AD with the usage of natural remedies. Identification of the active principle should be a part of such investigations in order to strengthen clinical trial validation. To ascertain the effectiveness of these drugs in reversing the cognitive decline associated with AD, additional large-scale, multicentre investigations are required.[21]

The medicinal plant Andrographis paniculate contains andrographolide, a bicyclic diterpenoid lactone that has been shown to have antiviral, anti-inflammatory, anti-tumor, and anti-cardiovascular activities in the treatment of several disorders. Andrographolide can enter the brain, according to pharmacokinetic research, and it has anti-disease Parkinson's and anti-ischemic-reperfusion actions in the brain.[22]

These findings offer strong encouragement for the potential use of andrographolide in the treatment of AD. In reality, a clinical trial to evaluate the effectiveness of andrographolide as a treatment for AD patients has been described as both continuing and completed.[23]

**POSSIBLE RISK FACTORS OF AD:**

Alzheimer's disease, according to researchers, has multiple causes. It most likely results from a combination of variables, including genetics, way of life, and environment. The danger of developing Alzheimer's has been established by scientists. While there are some risk factors that cannot be modified, including as age, family history, and inheritance, new research indicates that there may be additional aspects that we can control.

A person with Alzheimer's experiences brain alterations. It has fewer healthy cells, and as time passes, it gets smaller. The brain cells frequently have two different kinds of defects as well:

• **Neurofibril tangles.** Inside brain cells, there are twisted fibers that prevent essential substances from flowing from one area of the cell to another.

* **Beta-amyloid plaques**. In contrast to how proteins degrade between nerve cells in a healthy brain, these protein clumps cling together and accumulate between nerve cells.
* The surrounding healthy brain cells are harmed by plaques and tangles. The brain shrinks as the injured cells perish. Alzheimer's symptoms including memory loss, speech difficulties, disorientation, and mood swings are brought on by these alterations. The condition also causes brain cells to produce less of the neurotransmitters, which nerves need to communicate with one another.[51,52]
* A few factors may increase a person's risk of developing Alzheimer's. Research has so far connected the illness with:
* **Age**: As you age, you become more susceptible to Alzheimer's. After age 65, it begins to rise for the majority of individuals.
* **Gender**: More women than males get the illness.
* **Ancestral history**: A person is more likely to get Alzheimer's disease themself if a parent or sibling has the disease.
* **Down syndrome (DS)**. People with this illness often get Alzheimer's disease in their 30s and 40s, while the cause of this is unknown.
* **Head trauma**. A significant head injury and Alzheimer's disease have been linked in several research.
* **Other elements**. Your risk may be increased by having high blood pressure and high cholesterol.

**CURRENT TREATMENT STRATEGIES OF AD:**

 **Table-1 Current treatment strategies of Alzheimer disease**

|  |  |  |  |
| --- | --- | --- | --- |
| **Sr.no** | **Treatment Strategies of Alzheimer’s disease** | **Side effects** | **Reference** |
| 1. | **Cholinesterase- inhibitors** | The cholinergic hypothesis of AD proposes that cholinergic systems in the basal forebrain are damaged early in the disease process, which including loss of acetylcholine neurons and loss of enzyme function for acetylcholine synthesis and degradation, which results in memory loss and deterioration of other cognitive and noncognitive functions, such as neuropsychiatric symptoms. Cholinergic transmission may be enhanced by using CIs to delay the breakdown of acetylcholine between synaptic clefts. Three CIs are now approved for the treatment of mild to moderate AD: donepezil (Pfizer, New York, NY, USA), rivastigmine (Novartis, Basel, Switzerland), and galantamine (Janssen, Beerse, Belgium) [Farlow, 2002]. These drugs are regarded as the gold standard and first line of therapy for AD. | nausea, diarrhoea, vomiting, decreased appetite, dyspepsia, anorexia, muscle cramps, fatigue, insomnia, dizziness, headache, and asthenia. | 4,7,10,15,31,33 |
| 2. | **N-methyl-D-aspartate antagonist** | An additional treatment option for moderate-to-severe AD is memantine. This drug is a moderate-affinity, non-competitive NMDA antagonist that protects neurons from excitotoxicity. Memantine showed improvement in cognition, ADL, and behaviours in patients with moderate to severe AD after 6 months of administration, based on a holistic review of RCTs with parallel groups and double-blinding. Another comprehensive review that included six RCT trials found memantine to be potentially beneficial for reducing the behavioural and psychological signs and symptoms of dementia. | The most frequently reported adverse events in memantine trials were dizziness, headache and confusion. A small group of patients might develop agitation | 5,6,9,11,16 |
| **3.** | **Combination Therapy** | The combined therapy of memantine and donepezil compared to the placebo group significantly improved cognitive function, language, ADL, behavioral, and overall state in RCT investigations on corresponding clusters of patients with modest to severe AD. However, patients with mild to moderate AD did not see this advantage. | nausea, diarrhoea, vomiting, decreased appetite, dyspepsia, anorexia, muscle cramps, fatigue, insomnia, dizziness, headache and confusion. | 7.10,18,21,23 |
| 4. | **Serotonin reuptake inhibitors** | For treating comorbid depression in AD dementia, fluoxetine, sertraline, paroxetine, citalopram, and fluvoxamine are generally regarded as some of the utmost effective antidepressants. | Side effects of SSRIs include Nausea, vomiting, or diarrhoea Headache Drowsiness Dry Mouth Insomnia Restlessness, restlessness, or restlessness. Sexual problems, such as depression, depressed sex, or weak sex., Weight loss or gain due to appetite. | 14,17,19,22,25 |
| 5. | **Antipsychotics** | Atypical agents’ olanzapine, risperidone, quetiapine, ziprasidone and aripiprazole | Due to an increase in cerebrovascular disease and deaths among dementia patients on antipsychotics, antipsychotic usage is debatable. In addition, antipsychotic usage raises the risk of lung illness, brain damage, and osteoporosis. | 52,53,54 |
| 6. | **The amyloid hypothesis** | The Aβ is created by the successive proteolysis of the amyloid precursor protein (APP) by the enzymes secretase (BACE1) in the extracellular domain and secretase in the transmembrane region. Secretase (nonamyloidogenic pathway) or secretase (amyloidogenic pathway) first cleaves it within the luminal domain, almost completely shedding the ectodomain and producing C-terminal fragments (CTFs). A transmembrane aspartyl protease known as BACE1 (-site APP cleaving enzyme) is the principal neuronal secretase that cleaves APP within the ectodomain to produce the N-terminus of A. The intramembranous cleavage of and CTFs by secretase constitutes the second proteolytic step in APP processing. Positions 40 and 42 of A correspond to the primary sites of -secretase cleavage. | In the field of research on Alzheimer's disease (AD), a conflict has existed for many years. On the one hand, proponents of the amyloid hypothesis contend that abnormal accumulation and aggregation of the -amyloid (A) peptides, which make up amyloid plaques, are a significant factor in setting off a series of pathological occurrences that result in the clinical syndrome of AD dementia. | 13,19,20,23 |
| 7. | **Disease-modifying treatments** | A critical phase in the pathophysiology of AD, the synthesis of A, is caused by the cleavage of the overexpressed APP [Griffin, 2006]. A creates senile plaques, which are very insoluble and proteolysis-resistant fibrils (SPs). The tau protein makes up NFTs. The internal support structures for the movement of nutrients, vesicles, mitochondria, and chromosomes within the cell are called microtubules, and tau is a part of these structures in healthy individuals. As a result, in AD, both A and tau are important targets for disease-modifying treatments. In the field of research on Alzheimer's disease (AD), a conflict has existed for many years. On the one hand, proponents of the amyloid hypothesis contend that abnormal accumulation and aggregation of the -amyloid (A) peptides, which make up amyloid plaques, are a significant factor in setting off a series of pathological occurrences that result in the clinical syndrome of AD dementia. | swelling and small hemorrhages in the brain. | 14,29,35,38,44 |

**IMPORTANCE OF MEDICINAL PLANTS AND PHYTOCOMPOUNDS IN AD:**

Different phytochemical constituents found in medicinal plants can be extracted and used as raw materials for various scientific studies. Pharmaceutical enterprises use a variety of secondary metabolites from plants that are both commercially necessary and useful. Because they have fewer adverse effects than synthetic drugs and are necessary to address the growing demand for treatment, medicinal plants have recently acquired widespread popularity. According to several studies, medicinal plants like Centella Asiatica, Ginkgo biloba, Withania somnifera, Bacopa monnieri, Salvia officinalis, Melissa officinalis, Tinospora cordifolia, Glycyrrhiza glabra, etc. are used in the treatment of Alzheimer's disease. **[53-58]**

1. **Withania somnifera (Ashwagandha):**

In Ayurveda, Withania somnifera is frequently used as a nerve tonic that helps the body adjust to stress. W. The root of somnifera, a member of the Solanaceae family, is widely used. It has antioxidant and immune system-enhancing properties as well as free radical scavenging properties.8 W. Since somnifera has a soothing effect while other adaptogens tend to stimulate, it is effective in treating Alzheimer's disease in people.

1. **Bacopa monnieri (Brahmi):**

. The Scrophulariaceae family, which includes Bacopa monnieri, is found in wet and marshy environments. It is frequently used in Ayurvedic medicine and functions as a diuretic, a nerve tonic, a cardiotonic, and a treatment for asthma, insomnia, epilepsy, and rheumatism. Numerous phytochemicals found in this plant, including bacosides A and B, bacopasides III to V, and bacosaponins A, B, and C, as well as jujubogenin bisdesmosides bacopa saponins D, E, and F, betulic acid, sterols, alkaloids, polyphenols, and sulfhydryl compounds, have been linked to the plant's antioxidant activity. monnieri was used to improve memory and cognitive abilities. excerpts from B. monnieri's neuropharmacological effects and nootropic effects have been thoroughly studied. In the hippocampus, B. monnieri enhance protein kinase activity, which may explain how it improves memory. B. Monnieri likewise prevented monnieri also inhibited cholinergic degeneration and shows enhanced cognition effect in Alzheimer model of rat.

1. **Centella asiatica (Gotu Kola):**

The Apiaceae family includes Centella Asiatica, which may be found not only in Bangladesh and Sri Lanka but also throughout all of India. Triterpenes, asiatic acid, asiaticoside, adecassoside, sapogenins, glycosides, madecassic acid, vellarin, and centelloside are only a few of the bioactive substances it contains. Asiatic acid and asiaticoside reduced hydrogen peroxide-induced cell death, decreased free radical concentration, and inhibited -amyloid cell death in vitro, suggesting a potential role in treating Alzheimer's disease and preventing -amyloid toxicity. The disease caused by -amyloid in mice's brains was reversed, and elements of the oxidative stress response were altered, by extracts of Centella asiatica. It is a crucial plant for nerve and brain tissue and is said to be able to improve intelligence, memory, and lifespan.

1. **Ginkgo biloba:**

The Ginkgo biloba plant is native to China and a member of the Ginkgoaceae family. excerpt from G. Biloba was used to cure headaches, depression, problems with insufficient blood circulation, and awareness loss. This extract was estimated to have about 24% flavonoids and 6% terpene lactones. There is substantial proof that standardized ginkgo extract exhibits a number of molecular and cellular neuroprotective processes, including the reduction of apoptosis, suppression of membrane lipid peroxidation, anti-inflammatory properties, and inhibition of amyloid aggregation formation. Regarding its potential significance in cognitive disorders, there have been numerous clinical investigations. Chronic treatment on learning and memory in mice revealed that G. Biloba improved two-response sequence acquisition, storage, and retrieval for food reward G. Biloba affects cognitive function in an animal model of Alzheimer's disease without changing the histopathological effects of the overexpressed amyloid precursor protein. G. Acetylcholinesterase activity is greatly reduced by ginkgo Biloba extract, and improvement in scopolamine-induced deficiencies in passive avoidance was observed when AChE activity was inhibited. Increased baseline levels of acetylcholine are indicated by decreased acetylcholinesterase activity.

1. **Curcuma longa (Turmeric):**

The Zingiberaceae family member Curcuma longa has anti-inflammatory properties that are also linked to a lower risk of Alzheimer's disease. Curcumin also slows the build-up of plaque in the brain. It reduces oxidative stress and amyloid pathology. Epidemiologic studies revealed that the prevalence of Alzheimer's disease is 4.4 times lower in Southeast Asian nations where turmeric is commonly consumed in food. One study found that low doses of curcumin reduced A levels in mice with Alzheimer's disease by up to 40% when compared to control drug. Curcumin's anti-inflammatory properties have been linked to a lower risk of Alzheimer's disease, according to another study. At a lesser dose, curcumin reduced the amount of A plaques that these mice with Alzheimer's disease have on their brains by 43%.

1. **Glycyrrhiza glabra:**

Glycyrrhiza glabra is a member of the Fabaceae family and contains a number of bioactive substances, such as linalool oxide, geraniol, benzoic acid, terpinen, tetramethyl pyrazine, propionic acid, ethyl linolenate, butanediol, feuferaldehyde, methyl ethyl ketone This might be advantageous for the treatment of AD.

1. **Lepidium meyenii:**

It is a member of the Brassicaceae family and is renowned for promoting memory and learning functions It has been shown to improve memory in Alzheimer's sufferers. It improves memory impairment brought on by ovariectomy, in part because of its antioxidant and acetylcholinesterase inhibitory effects. It increases the amount of acetylcholine.

1. **Tinospora cordifolia (Giloy):**

Tinospora cordifolia, a member of the Menispermaceae family, has the ability to improve memory in both animals with normal memory and those lacking it. Choline supplementation improves cognitive performance by immune-stimulating the body and enhancing acetylcholine production. Tinospora cordifolia is regarded as a memory and learning enhancer in Ayurveda. Tinospora cordifolia root aqueous extract improved verbal learning and logical memory.

**ANDROGRAPHOLIDE AND ITS ANALOGUES IN AD:**

**Varella Nallar et al 59:** Hippocampal neurogenesis declines in Alzheimer's disease (AD), and this has been linked to cognitive difficulties. We have previously demonstrated that the primary bioactive ingredient of Andrographis paniculate, andrographolide (ANDRO), stimulates proliferation in the hippocampus of the APPswe/PSEN1E9 (APP/PS1) mice model of AD. This proliferation was determined by labelling with the mitotic marker Ki67. Here, we expanded on how ANDRO affected hippocampus neurogenesis in APP/PS1 mice and assessed how much this process contributed to ANDRO's cognitive effects. Incorporating BrdU showed that 8-month-old APP/PS1 mice treated with ANDRO for 4 weeks had enhanced proliferation in the dentate gyrus. Neonatal immature neurons, neural progenitors, and neuroblasts were all cell types that were decreased in APP/PS1 animals compared to age-matched wild-type mice, despite ANDRO having no influence on neuronal differentiation of new-born cells. Immature neurons' migration, total dendritic length, arborization, and orientation were unaffected by ANDRO, indicating that it had no impact on the early morphological development of developing neurons. The performance of APP/PS1 mice in the object location memory task was also improved by ANDRO therapy. Co-treatment with the anti-mitotic medication TMZ did not completely reverse this impact, indicating that other. The observed improvement in cognition could be explained by the effects of ANDRO in addition to the rise in neurogenesis. Overall, our results show that ANDRO promotes proliferation in the hippocampus of APP/PS1 mice, which accelerates neurogenesis.

**Felipe G Serrano et al: Amyloid 60: (A)** oligomers play a major role in synaptic dysfunction and the loss of spatial memory that is linked to neuronal dysfunction in Alzheimer's disease (AD), a neurodegenerative condition. This impairment involves synaptic dysfunction brought on by the loss of synaptic proteins, which aids in the course of AD. It's interesting to note that the usage of natural substances is an emerging conceptual approach in the hunt for medications with therapeutic potentials for treating neurodegenerative diseases. In this study, we show that andrographolide (ANDRO), a labdane diterpene extracted from Andrographis paniculata, rises the gradient of field excitatory postsynaptic potentials (fEPSP) in the CA1 region of hippocampal slices, inhibits long-term depression (LTD), and shields long-term potentiation (LTP) against damage caused by A oligomers in vitro, most likely by inhibiting glutamate Additionally, ANDRO suppresses changes in neuropathology in two distinct age groups of mice (7- and 12-month-old mice) employed in an A-PPswe/PS-1 Alzheimer's model. Androgen deficiency reduces A levels, affecting the ontogeny of amyloid plaques, and reduces tau phosphorylation surrounding the A oligomeric species in the hippocampi and cortices of 7-month-old mice. Furthermore, we found that ANDRO restores spatial memory abilities in two separate age groups, protecting synaptic plasticity and synaptic proteins in the process. Our findings imply that ANDRO may be employed as a viable preventive treatment for AD development.

**Rivera DS et al 61:** Dementia of the most frequent type is Alzheimer's disease (AD). A number of alterations in the brain, counting the development of extracellular amyloid-beta (Ab) peptide aggregates and the intracellular buildup of hyperphosphorylated tau protein, are associated with the beginning and progression of this condition. Also mentioned are dysregulated neuroplasticity, synapse loss, and a decrease in cellular energy metabolism. The downregulation of canonical Wnt signalling in AD has also been demonstrated. Surprisingly, we previously demonstrated that in transgenic (Tg) and wild-type (WT) mice, the in vivo suppression of Wnt signalling promotes the emergence of AD markers. Furthermore, we discovered that Wnt signalling increases energy metabolism, which is essential for Wnt's capacity to support the restoration of cognitive function in AD. Therefore, we predicted that several symptoms in a presymptomatic transgenic animal model of AD would be alleviated by activating canonical Wnt signalling. To investigate the latter, we employed the J20 Tg transgenic mice model to examine the impact of andrographolide (ANDRO), a canonical Wnt signalling activator, on the mild AD phenotypic expression (high amounts of amyloid aggregates). In J20 Tg mice, we discovered that presymptomatic ANDRO treatment reduced the decline in cellular energy metabolism indicators. Moreover, the cognitive performance of the treated animals improved. Electrophysiological parameters demonstrated substantial abnormalities in presynaptic function in J20 Tg animals at the synaptic level, which were all fully recovered by ANDRO treatment. Finally, electron microscope study of hippocampus synaptosomes showed that ANDRO therapy restored the length of synapses. Together, these findings lend credence to the hypothesis that canonical Wnt signalling stimulation during presymptomatic stages may be a novel pharmaceutical approach to postpone the beginning of AD.

**CONCLUSION:**

The pharmacological effects of andrographolide on Alzheimer's disease are outlined in this review. Andrographolide is a compound derived from the traditional herb Andrographis paniculata (A. paniculata), which has a very long history of use in eastern Asia and ancient China for the treatment of a variety of diseases, including laryngitis, rheumatoid arthritis, cancer, diarrhoea, and upper respiratory tract infections. Anti-inflammation, antioxidative stress, anti-apoptosis, and/or pro-apoptosis are some of the andrographolide's disease prevention and/or treatment methods. Andrographolide can pass the blood–brain barrier and distribute to various brain regions, according to pharmacodynamic studies, and as a result, its pharmacological effects on the central nervous system (CNS) have started to be understood in recent years. For instance, andrographolide has been shown to decrease the size of brain infarcts in many models of cerebral ischemia. Andrographolide inhibits neuroinflammatory response and synaptic dysfunction in models of Alzheimer's disease (AD), which may be demonstrated by reversing reductions in synaptic proteins such as postsynaptic membrane dense substance-95 and pro-inflammatory cytokine production brought on by AD. Additionally, andrographolide may slow the start and/or progression of Parkinson's disease, multiple sclerosis, and cognitive impairment brought on by diabetes or surgery. Andrographolide has also been demonstrated to inhibit changes in hippocampal neurogenesis, mood-associated behavior, and abnormalities in serum corticosterone levels caused by chronic stress. These findings imply that andrographolide may have the probable to treat psychiatric conditions like anxiety and depression. In the early treatment of dementia and other disorders involving memory loss and Alzheimer's, herbs may hold promise. They are less toxic than pharmaceutical agents, which is one of their main advantages. Botanicals can be used in conjunction with medications or other complementary therapies including SAMe, fish oil, and antioxidant vitamins. The preferably treatment is started, the better the prognosis, according to a review of the research. In order to delay or potentially prevent the emergence of symptoms, clients who have family members with a history of Alzheimer's disease or other conditions affecting poor memory may start taking these therapies before symptoms appear.

Millions of individuals worldwide are afflicted by AD, a neurodegenerative condition. Families and societies may experience tremendous economic hardships as a result. The symptoms of AD cannot be effectively treated by medicine at this time. Researchers are working to create new medications with superior therapeutic efficacies. Andrographolide has been demonstrated to offer therapeutic effects in certain recent investigations effects in a variety of AD models. For instance, long-term andrographolide therapy (4 mg/kg, 3 months) has been demonstrated to prevent the decline in spatial learning and memory function in the South American rodent species Octodon degus. Pathology is similar to Alzheimer's in elderly people [27]. The field excitatory postsynaptic potential (fEPSP) in the CA1 stratum radiatum of the hippocampus was improved by andrographolide, and the decline in the protein levels of AD markers like synaptophysin (SYP), vesicular glutamate transporter 1 (vGluT1), and the GluN2A subunit of the NMDA receptor was reversed. These findings are consistent with those made in vitro, where it was discovered that andrographolide (10 M) treatment increased the slope of fEPSP in the CA1 of the hippocampus in normal wild-type mice, which then resulted in inhibition of glycogen synthase kinase-3 (GSK-3) activity, reversal of GluA2, GluN2B, and PSD-95 decrease, and enhancement of long-term potentiation (LTP) in hippocampal slices-incubated with A oligomers.

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