

NEUROPROTECTIVE POTENTIALS OF ANDROGRAPHOLIDE (AG) AND ITS STRUCTURAL ANALOGUES IN ALZHEIMER'S DISEASE (AD)

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

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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.

Keywords: andrographolide, Alzheimer's disease, phytoconstituents, medicinal herbs, neuroprotective

I. 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 US and 12 percent 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 percent 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

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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 the Alzheimer's.[18] A neurotransmitter which is very much 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 very early treatment of dementia and other disorders involving memory loss and Alzheimer's, herbs may hold promise. One of the most important 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 inspiration 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]

II. 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 of the risk factors that cannot be modified which including as age, family history, and inheritance, new research which 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 avert essential constituents 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 our healthy brain cells are harmed by different plaques and tangles. The brain shrinks as the injured cells perish. Alzheimer's symptoms including memory loss, difficulty in speech, disorientation, and mood swings are brought on by these alterations. This 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 themselves 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.

III. CURRENT TREATMENT STRATEGIES OF AD

Table 1: Current Treatment Strategies of Alzheimer Disease

Sl No	Treatment Strategies of Alzheimer's disease	Side effects	Reference	
1.	Cholinesterase - inhibitors	According to the cholinergic hypothesis of AD, cholinergic systems in the basal forebrain are damaged initial in the disease process, including the loss of acetylcholine neurons and enzyme function for acetylcholine synthesis and degradation. This principals to memory loss and fading of other cognitive and noncognitive functions, such as neuropsychiatric symptoms. By engaging CIs to postpone the failure of acetylcholine between synaptic clefts, cholinergic transmission may be enhanced. As of right now, three CIs—donepezil (Pfizer, New York, NY, USA), rivastigmine (Novartis, Basel, Switzerland), and galantamine (Janssen, Beerse, Belgium)—have been licenced for the treatment of mild to modest AD [Farlow, 2002]. These medications are assumed of as the gold standard and first treatment for AD.	nausea, diarrhoea, vomiting, low appetite, dyspepsia, anorexia, muscle cramps, fatigue, insomnia, dizziness, headache, and asthenia.	4,7,10,15, 31,33

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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 maximum commonly reported hostile events in memantine trials were dizziness, headache and confusion. A minor 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 surveys on corresponding clusters of patients with modest to severe	nausea, vomiting, appetite, anorexia, cramps, insomnia, headache diarrhoea, decreased dyspepsia, muscle fatigue, dizziness and confusion.	7.10,18,21,23

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		AD. However, patients with mild to moderate AD did not see this advantage.		
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 operative 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 A β 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	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	13,19,20,23

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		<p>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.</p>	<p>in the clinical syndrome of AD dementia.</p>	
7.	Disease-modifying treatments	<p>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</p>	<p>swelling and small hemorrhages in the brain.</p>	<p>14,29,35,38,44</p>

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		<p>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.</p>		
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IV. IMPORTANCE OF MEDICINAL PLANTS AND PHYTOCOMPOUNDS IN AD:

Different phytochemical constituents which found in medicinal plants can be extracted and used as fresh 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, WS is frequently used as a nerve tonic that helps our 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.
- 2. *Bacopa monnieri* (Brahmi):**The Scrophulariaceae family, which includes *Bacopa monnieri*, is found in wet and marshy environments. It is frequently used in Ayurvedic

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medicine and functions as a diuretic, a nerve tonic, a cardiogenic, 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, betulinic acid, sterols, alkaloids, polyphenols, and sulfhydryl compounds, have been linked to the plant's antioxidant activity. *B. 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.

- 3. 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 β -amyloid cell death in vitro, suggesting a potential role in treating Alzheimer's disease and preventing β -amyloid toxicity. The disease caused by β -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.
- 4. 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 the 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 achievement, 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.
- 5. 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-

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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%.

6. **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.
7. **Tinospora cordifolia (Giloy):** Tinospora cordifolia herb, a member of the Menispermaceae family, has the ability to progress recollection in both animals with normal memory and those lacking it. Choline supplementation advances intellectual 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.

V. ANDROGRAPHOLIDE AND ITS ANALOGUES IN AD:

1. **Varella Nallar et al (2014) 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 APP^{swe}/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.
2. **Felipe G Serrano et al (2014) ⁶⁰:** Amyloid (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. 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

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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.

- 3. Rivera DS et al (2020) 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.

VI. 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. 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.

REFERENCES

- [1] Y. Dai, S.R. Chen, L. Chai, J. Zhao, Y. Wang, Y. Wang, Overview of pharmacological activities of *Andrographis paniculata* and its major compound andrographolide, *Crit. Rev. Food Sci. Nutr.* 10 (2018) 1–13.
- [2] U. Rasool, P.S.A. Parveen, S.K. Sah, H. S, Efficacy of *Andrographis paniculata* against extended-spectrum β -lactamase (ESBL) producing *E. coli*, *BMC Complement. Altern. Med.* 18 (2018) 244.
- [3] L.S. Chua, Review on liver inflammation and anti-inflammatory activity of *Andrographis paniculata* for hepatoprotection, *Phytother. Res.* 28 (2014) 1589–1598.
- [4] T. Suriyo, N. Pholphana, N. Rangkadilok, A. Thiantanawat, P. Watcharasit, J. Satayavivad, *Andrographis paniculata* extracts and major constituent diterpenoids inhibit growth of intraheptic cholangiocarcinoma cells by inducing cell cycle arrest and apoptosis, *Planta Med.* 80 (2014) 533–543.
- [5] R.C. Saxena, R. Singh, P. Kumar, S.C. Yadav, M.P. Negi, V.S. Saxena, A.J. Joshua, V. Vijayabalaji, K.S. Goudar, K. Venkateshwarlu, A. Amit, A randomized double blind placebo controlled clinical evaluation of extract of *Andrographispaniculata* (KalmCold) in patients with uncomplicated upper respiratory tract infection, *Phytomedicine* 17 (2010) 178–185.
- [6] R.A. Burgos, J.L. Hancke, J.C. Bertoglio, V. Aguirre, S. Arriagada, M. Calvo, D.D. Cáceres, Efficacy of an *Andrographis paniculata* composition for the relief of rheumatoid arthritis symptoms: a prospective randomized placebo-controlled trial, *Clin. Rheumatol.* 28 (2009) 931–946.
- [7] K. Bensch, J. Tiralongo, K. Schmidt, A. Matthias, K.M. Bone, R. Lehmann, E. Tiralongo, Investigations into the antiadhesive activity of herbal extracts against *Campylobacter jejuni*, *Phytother. Res.* 25 (2011) 1125–1132.
- [8] W.S.D. Tan, W. Liao, S. Zhou, W.S.F. Wong, Is there a future for andrographolide to be an anti-inflammatory drug? Deciphering its major mechanisms of action, *Biochem. Pharmacol.* 139 (2017) 71–81.
- [9] M.T. Islam, Andrographolide, a new hope in the prevention and treatment of metabolic syndrome, *Front. Pharmacol.* 8 (2017) 571.

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- [10] L. Wang, F. Cao, L.L. Zhu, P. Liu, Y.R. Shang, W.H. Liu, X. Dong, H.D. Bao, P. Gong,
- [11] Z.Y. Wang, Andrographolide impairs alpha-naphthylisothiocyanate-induced cholestatic liver injury in vivo, *J. Nat. Med.* 73 (2019) 388–396.
- [12] Y. Zhao, M. Wang, Y. Li, W. Dong, Andrographolide attenuates viral myocarditis through interactions with the IL-10/STAT3 and P13K/AKT/NF- κ B signalling pathways, *Exp. Ther. Med.* 16 (2018) 2138–2143.
- [13] R. Al Batran, F. Al-Bayaty, M.M. Al-Obaidi, M.A. Abdulla, Acute toxicity and the effect of andrographolide on *Porphyromonas gingivalis*-induced hyperlipidemia in rats, *Biomed Res. Int.* 2013 (2013) 594012.
- [14] S. Eugene Leo Prakash, R. Manavalan, Acute toxicity studies of andrographolide. *Research journal of pharmaceutical, Biol. Chem. Sci.* 2 (2011) 547.
- [15] J.T. Coon, E. Ernst, Andrographis paniculata in the treatment of upper respiratory tract infections: a systematic review of safety and efficacy, *Planta Med.* 70 (2004) 293–298.
- [16] A. Panossian, A. Hovhannisyanyan, G. Mamikonyan, H. Abrahamian, E. Hambardzumyan, E. Gabrielian, G. Goukasova, G. Wikman, H. Wagner, Pharmacokinetic and oral bioavailability of andrographolide from *Andrographis paniculata* fixed combination Kan Jang in rats and human, *Phytomedicine* 7(2000) 351–364.
- [17] R. Bera, S.K. Ahmed, L. Sarkar, T. Sen, S. Karmakar, Pharmacokinetic analysis and tissue distribution of andrographolide in rat by a validated LC-MS/MS method, *Pharm. Biol.* 52 (2014) 321–329.
- [18] X.B. Suo, H. Zhang, Y.Q. Wang, HPLC determination of andrographolide in rat whole blood: study on the pharmacokinetics of andrographolide incorporated in liposomes and tablets, *Biomed. Chromatogr.* 21 (2007) 730–734.
- [19] M. Li, H. Li, F. Fang, X. Deng, S. Ma, Astragaloside IV attenuates cognitive impairments induced by transient cerebral ischemia and reperfusion in mice via anti-inflammatory mechanisms, *Neurosci. Lett.* 639 (2017) 114–119.
- [20] R. Yang, S. Liu, J. Zhou, S. Bu, J. Zhang, Andrographolide attenuates microgliamediated A β neurotoxicity partially through inhibiting NF- κ B and JNK/MAPK signaling pathway, *Immunopharmacol. Immunotoxicol.* 39 (2017) 276–284.
- [21] D.S. Rivera, C. Lindsay, J.F. Codocedo, I. Morel, C. Pinto, P. Cisternas, F. Bozinovic, N.C. Inestrosa, Andrographolide recovers cognitive impairment in a natural model of Alzheimer's disease (*Octodon degus*), *Neurobiol. Aging* 46 (2016) 204–220.
- [22] F.G. Serrano, C. Tapia-Rojas, F.J. Carvajal, J. Hancke, W. Cerpa, N.C. Inestrosa, Andrographolide reduces cognitive impairment in young and mature APP^{swe}/PS- mice, *Mol. Neurodegener.* 9 (2014) 61.
- [23] T. Wang, B. Liu, W. Zhang, B. Wilson, J.S. Hong, Andrographolide reduces inflammation-mediated dopaminergic neurodegeneration in mesencephalic neuroglia cultures by inhibiting microglial activation, *J. Pharmacol. Exp. Ther.* 308 (2004) 975–983.
- [24] Z. Zhang, D. Lai, L. Wang, P. Yu, L. Zhu, B. Guo, L. Xu, L. Zhou, Y. Sun, S.M. Lee, Y. Wang, Neuroprotective effects of the andrographolide analogue AL-1 in the MPP⁺/MPTP-induced Parkinson's disease model in vitro and in mice, *Pharmacol. Biochem. Behav.* 122 (2014) 191–202.
- [25] M.I. Iruretagoyena, J.A. Tobar, P.A. González, S.E. Sepúlveda, C.A. Figueroa, a. R.A. Burgos, J.K. Hancke, A.M. Kalergis, Andrographolide interferes with T cell b. activation and reduces experimental autoimmune encephalomyelitis in the mouse, c. *J. Pharmacol. Exp. Ther.* 312 (2005) 366–372.
- [26] L.M. Lien, C.C. Su, W.H. Hsu, W.J. Lu, C.L. Chung, T.L. Yen, H.C. Chiu, J.R. Sheu, K.H. Lin, Mechanisms of andrographolide-induced platelet apoptosis in human platelets: regulatory roles of the extrinsic apoptotic pathway, *Phytother. Res.* 27 (2013) 1671–1677.
- [27] Y.Y. Chen, M.J. Hsu, C.Y. Hsieh, L.W. Lee, Z.C. Chen, J.R. Sheu, Andrographolide inhibits nuclear factor- κ B activation through JNK-Akt-p65 signaling cascade in tumor necrosis factor- α -stimulated vascular smooth muscle cells, *Transfus. Apher. Sci.* 2014 (2014) 1–10.
- [28] W.J. Lu, K.H. Lin, M.J. Hsu, D.S. Chou, G. Hsiao, J.R. Sheu, Suppression of NF- κ B signaling by andrographolide with a novel mechanism in human platelets: regulatory roles of the p38MAPK-hydroxyl radical-ERK2 cascade, *Biochem. Pharmacol.* 84 (2012) 914–924.
- [29] Y. Ding, C. Shi, L. Chen, P. Ma, K. Li, J. Jin, Q. Zhang, A. Li, Effects of andrographolide on postoperative cognitive dysfunction and the association with NF- κ B/MAPK pathway, *Oncol. Lett.* 14 (2017) 7367–7373.
- [30] L.J. Estcourt, P.M. Fortin, S. Hopewell, M. Trivella, C. Doree, M.R. Abboud, Interventions for

NEUROPROTECTIVE POTENTIALS OF
ANDROGRAPHOLIDE (AG) AND ITS STRUCTURAL ANALOGUES IN ALZHEIMER'S DISEASE (AD)

- preventing silent cerebral infarcts in people with sickle cell disease, *Cochrane Database Syst. Rev.* 5 (2017) CD012389.
- [32] S. Bhaskar, P. Stanwell, D. Cordato, J. Attia, C. Levi, Reperfusion therapy in acute ischemic stroke: dawn of a new era? *BMC Neurol.* 18 (2018) 8.
- [33] P. Surinkaew, P. Sawaddiruk, N. Apaijai, N. Chattipakorn, S.C. Chattipakorn, Role of microglia under cardiac and cerebral ischemia/reperfusion (I/R) injury, *Metab. Brain Dis.* 33 (2018) 1019–1030.
- [34] G. Hsiao, M.Y. Shen, K.H. Lin, C.Y. Chou, N.H. Tzu, C.H. Lin, D.S. Chou, T.F. Chen,
- [35] J.R. Sheu, Inhibitory activity of kienin on free radical formation of activated platelets
- [36] in vitro and on thrombus formation in vivo, *Eur. J. Pharmacol.* 465 (2003) 281–287.
- [37] K. Grundler, R. Rotter, S. Tilley, J. Pircher, T. Czermak, M. Yakac, E. Gaitzsch, S. Massberg, F. Krötz, H.Y. Sohn, U. Pohl, H. Mannell, B.F. Kraemer, The proteasome regulates collagen-induced platelet aggregation via nuclear-factor-kappa-B (NFκB) activation, *Thromb. Res.* 148 (2016) 15–22.
- [38] C. Huang, L. Tong, X. Lu, J. Wang, W. Yao, B. Jiang, W. Zhang, Methylene blue
- [39] attenuates iNOS induction through suppression of transcriptional factor binding amid
- [40] iNOS mRNA transcription, *J. Cell. Biochem.* 116 (2015) 1730–1740.
- [41] 36 E. Pineda-Molina, S. Lamas, Nitric oxide as a regulator of gene expression: studies
- [42] with the transcription factor proteins c-Jun and p50, *Biofactors* 15 (2001) 113–115.
- [43] 37 J.R. Matthews, C.H. Botting, M. Panico, H.R. Morris, R.T. Hay, Inhibition of
- [44] NFκB DNA binding by nitric oxide, *Nucleic Acids Res.* 24 (1996) 2236–2242.
- [45] 38 D.V. Krysko, T. Vanden Berghe, K. D'Herde, P. Vandenabeele, Apoptosis and
- [46] necrosis: detection, discrimination and phagocytosis, *Methods* 44 (2008) 205–221.
- [47] 39 N. Plesnila, Role of mitochondrial proteins for neuronal cell death after focal cerebral
- [48] ischemia, *Acta Neurochir. Suppl. (Wien)* 89 (2004) 15–19.
- [49] 40 T. Engel, N. Plesnila, J.H. Prehn, D.C. Henshall, In vivo contributions of BH3-only
- [50] proteins to neuronal death following seizures, ischemia, and traumatic brain injury,
- [51] *J.Cereb. Blood Flow Metab.* 31 (2011) 1196–1210.
- [52] 41 P. Thisoda, N. Rangkadilok, N. Pholphana, L. Worasuttayangkurn, S. Ruchirawat,
- [53] J. Satayavivad, Inhibitory effect of *Andrographis paniculata* extract and its active
- [54] diterpenoids on platelet aggregation, *Eur. J. Pharmacol.* 553 (2006) 39–45.
- [55] 42 Y.D. Li, B.Q. Ye, S.X. Zheng, J.T. Wang, J.G. Wang, M. Chen, J.G. Liu, X.H. Pei,
- [56] L.J. Wang, Z.X. Lin, K. Gupta, N. Mackman, A. Slungaard, N.S. Key, J.G. Geng, NF-
- [57] κB transcription factor p50 critically regulates tissue factor in deep vein thrombosis,
- [58] *J. Biol. Chem.* 284 (2009) 4473–4483.
- [59] 43 M. Li, H. Li, F. Fang, X. Deng, S. Ma, Astragaloside IV attenuates cognitive
- [60] impairments induced by transient cerebral ischemia and reperfusion in mice via anti-
- [61] inflammatory mechanisms, *Neurosci. Lett.* 639 (2017) 114–119.
- [62] 44 M. Poittevin, P. Lozeron, R. Hilal, B.I. Levy, T. Merkulova-Rainon, N. Kubis,
- [63] Smooth muscle cell phenotypic switching in stroke, *Transl. Stroke Res.* 5 (2014)
- [64] 377–384.
- [65] 45 W. Yao, Q. Sun, L. Huang, G. Meng, H. Wang, X. Jing, W. Zhang,
- [66] Tetrahydroxystilbene glucoside inhibits TNF-α-induced migration of vascular
- [67] smooth muscle cells via suppression of vimentin, *Can. J. Physiol. Pharmacol.* 294
- [68] (2016) 155–160.
- [69] 46 C.C. Chang, Y.F. Duann, T.L. Yen, Y.Y. Chen, T. Jayakumar, E.T. Ong, J.R. Sheu,
- [70] Andrographolide, a novel NF-κB inhibitor, inhibits vascular smooth muscle cell
- [71] proliferation and cerebral endothelial cell inflammation, *Acta Cardiol. Sin.* 30
- [72] (2014) 308–315.
- [73] 47 C Li, J. He, X. Zhong, H. Gan, Y. Xia, CX3CL1/CX3CR1 axis contributes to
- [74] angiotensin II-induced vascular smooth muscle cell proliferation and inflammatory
- [75] cytokine production, *Inflammation* 41 (2018) 824–834.
- [76] 48 H. Jing, S. Wang, M. Wang, W. Fu, C. Zhang, D. Xu, Isobavachalcone attenuates
- [77] MPTP-induced Parkinson's disease in mice by inhibition of microglial activation
- [78] through NF-κB pathway, *PLoS One* 12 (2017) e0169560.
- [79] 49 Q. Wang, Q. He, Y. Chen, W. Shao, C. Yuan, Y. Wang, JNK-mediated microglial
- [80] DICER degradation potentiates inflammatory responses to induce dopaminergic
- [81] neuron loss, *J. Neuroinflamm.* 15 (2018) 184.
- [82] 50 I.U. Song, J.S. Kim, S.W. Chung, K.S. Lee, Is there an association between the level

ANDROGRAPHOLIDE (AG) AND ITS STRUCTURAL ANALOGUES IN ALZHEIMER'S DISEASE (AD)

- [83] of high-sensitivity C-reactive protein and idiopathic Parkinson's disease? A comparison
[84] of Parkinson's disease patients, disease controls and healthy individuals,
[85] *Eur. Neurol.* 62 (2009) 99–104.
[86] 51 S. Iannaccone, C. Cerami, M. Alessio, V. Garibotto, A. Panzacchi, S. Olivieri,
[87] G. Gelsomino, R.M. Moresco, D. Perani, In vivo microglia activation in very early
[88] dementia with Lewy bodies, comparison with Parkinson's disease, *Parkinsonism*
[89] *Relat. Disord.* 19 (2013) 47–52.
[90] 52 G. Xu, Y. Li, K. Yoshimoto, G. Chen, C. Wan, T. Iwata, N. Mizusawa, Z. Duan,
[91] J. Liu, J. Jiang, 2,3,7,8-Tetrachlorodibenzo-p-dioxin-induced inflammatory activation
[92] is mediated by intracellular free calcium in microglial cells, *Toxicology* 308
[93] (2013) 158–167.
[94] 53 G. Xu, Y. Li, K. Yoshimoto, Q. Wu, G. Chen, T. Iwata, N. Mizusawa, C. Wan, X. Nie,
[95] 2,3,7,8-Tetrachlorodibenzo-p-dioxin stimulates proliferation of HAPI microglia by
[96] affecting the Akt/GSK-3 β /cyclin D1 signaling pathway, *Toxicol. Lett.* 224 (2014)
[97] (2014) 362–370.
[98] 54 W.F. Chiou, C.F. Chen, J.J. Lin, Mechanisms of suppression of inducible nitric
[99] oxide synthase (iNOS) expression in RAW 264.7 cells by andrographolide, *Br. J.*
[100] *Pharmacol.* 129 (2000) 1553–1560.
[101] 55 S.Y. Yu, L.J. Zuo, F. Wang, Z.J. Chen, Y. Hu, Y.J. Wang, X.M. Wang, W. Zhang,
[102] Potential biomarkers relating pathological proteins, neuroinflammatory factors
[103] and free radicals in PD patients with cognitive impairment: a cross-sectional study,
[104] *BMC Neurol.* 14 (2014) 113.
[105] 56 M. Greter, F.L. Heppner, M.P. Lemos, B.M. Odermatt, N. Goebels, T. Laufer,
[106] R.J. Noelle, B. Becher, Dendritic cells permit immune invasion of the CNS in an
[107] animal model of multiple sclerosis, *Nat. Med.* 11 (2005) 328–334.
[108] 57 C. Sie, T. Korn, Dendritic cells in central nervous system autoimmunity, *Semin.*
[109] *Immunopathol.* 39 (2017) 99–111.
[110] 58 Y. Dou, N. van Montfoort, A. van den Bosch, R.A. de Man, G.G. Zom, W.J. Krebber,
[111] C.J.M. Melief, S.I. Buschow, A.M. Woltman, HBV-derived synthetic long peptide
[112] can boost CD4+ and CD8+T-cell responses in chronic HBV patient's ex vivo, *J.*
[113] *Infect. Dis.* 217 (2018) 827–839.
[114] 59 Varela-Nallar L, Arredondo SB, Tapia-Rojas C, Hancke J, Inestrosa NC.
[115] Andrographolide Stimulates Neurogenesis in the Adult Hippocampus. *Neural Plast.*
[116] 2015; 2015:935403. doi: 10.1155/2015/935403. Epub 2015 Dec 22. PMID: 26798521;
[117] PMID: PMC4700200.
[118] 60 Serrano FG, Tapia-Rojas C, Carvajal FJ, Hancke J, Cerpa W, Inestrosa NC.
[119] Andrographolide reduces cognitive impairment in young and mature A β PPswe/PS-1
[120] mice. *Mol Neurodegener.* 2014 Dec 18; 9:61. doi: 10.1186/1750-1326-9-61. PMID:
[121] 25524173; PMID: PMC4414355.
[122] 61 Rivera DS, Lindsay C, Codocedo JF, Morel I, Pinto C, Cisternas P, Bozinovic F, Inestrosa
[123] NC. Andrographolide recovers cognitive impairment in a natural model of Alzheimer's
[124] disease (*Octodon degus*). *Neurobiol Aging.* 2016 Oct; 46:204-20. doi:
[125] 10.1016/j.neurobiolaging.2016.06.021. Epub 2016 Jul 5. PMID: 27505720.