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The Effect of Fulvic Acid on Alzheimer's Disease – A Systematic Review

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ABSTRACT

Introduction and aim of the study: Neurodegenerative diseases, including Alzheimer's disease, represent a significant health challenge. Therapies are being sought that could delay the development of these diseases and also mitigate their course. Fulvic acid, which is an organic humic compound with antioxidant and anti-inflammatory properties, has attracted increasing interest in the context of treating neurodegenerative diseases. Our study aims to evaluate the effects of fulvic acid on neurodegenerative diseases, mainly Alzheimer's disease, and to determine its therapeutic potential.

Materials and methods: The paper is based on an analysis of studies available in databases such as PubMed, Google Scholar, ResearchGate, and other scientific databases. Clinical trials, preclinical studies, and review papers on the use of fulvic acid in the context of Alzheimer's disease were searched.

Conclusions: Fulvic acid, due to its anti-inflammatory and neuroprotective abilities, shows promising potential in the treatment of Alzheimer's disease, especially in terms of slowing down the loss of cognitive function and protecting against neurodegeneration. It is advisable to conduct further studies aimed at a more thorough evaluation of the efficacy and safety of fulvic acid in the context of the treatment of Alzheimer's disease and other neurodegenerative diseases.

Keywords: fulvic acid, neurodegenerative diseases, Alzheimer's disease, shilajit, nutraceuticals

Introduction

Alzheimer's disease - pathogenesis and mechanisms

Alzheimer's disease (AD) is a chronic and slowly progressive primary degenerative brain disease belonging to the group of neurodegenerative diseases. It is recognized as the most common cause of dementia both in Poland and worldwide. Its etiology is still not fully understood. The primary pathogenetic mechanism leading to AD is the deposition of beta-amyloid, ALPHA-synuclein, and tau proteins in the brain. As a consequence, this leads to damage and atrophy of neurons and impaired neuronal conduction giving symptoms in the form of memory and behavioral disorders and impairment of normal functioning in daily life. [1] The excess of reactive oxygen species in AD patients and the elevated levels of inflammatory markers present also contribute to neuronal degeneration, indicating a link between dementia and inflammatory processes and oxidative stress. [2] Understanding the molecular mechanisms underlying this disease is crucial for the advancement of new therapies. The currently available treatments usually produce insufficiently satisfactory results. Drugs approved for the treatment of AD primarily slow down the process of cognitive loss but are not able to completely inhibit this process. Efficacy varies depending on the active substance used, the severity of the disease process, and the individual predisposition of the patient, such as age, comorbidities, or lifestyle. In addition to authorized medicinal products, various dietary supplements or nutraceuticals are used supportively. Some of these are already quite well known and researched, but further substances are constantly being discovered that may have a beneficial effect on neurodegenerative diseases. Among the relatively well-studied substances are ginkgo biloba [3], [4], [5]. [6], [7], omega 3 acids [8], vitamins: D, B9 and B12 [9], [10], [11] or NAD+ (nicotinamide adenine dinucleotide). [12], [13] A nutraceutical with broad applications, including potentially in neurodegenerative diseases such as AD, is fulvic acid.

Fulvic acid - chemical and biological properties

Fulvic acid (FA) is an organic substance classified as humic acid, naturally occurring mainly in soil, groundwater, and peat. A substance abundant in FA is also Shilajit - a blackish-brown powder or secretion derived from high mountain rocks. Most shilajit is obtained from the area between Nepal and India, although it is also found in Afghanistan, Russia, Tibet, and even Chile, where it is called Andean shilajit. This substance is known and used in Ayurvedic medicine. Interestingly, the health benefits of shilajit have been shown to vary depending on the region from which it was extracted. [14], [15] Fulvic acid, a constituent of shilajit, is soluble

in water under various pH conditions. It has a low molecular weight, so it is well absorbed from the gastrointestinal tract and takes only a few hours to be eliminated from the body. [15]

FA shows a multitude of applications. It is increasingly being investigated for its therapeutic potential in the treatment of neurodegenerative diseases, as it possesses several important biological properties that could be exploited, such as potent antioxidant oxidative stress-reducing, anti-inflammatory and chelating activities. This thesis aims to review the available studies on the effects of fulvic acid on Alzheimer's disease, with a particular focus on its impact on cognitive function, the importance of a therapy that could delay or halt the progression of this group of diseases, the comparison of efficacy with pharmacotherapy and the safety of use. It will also discuss the properties of fulvic acid.

Methodology

The paper is based on an analysis of studies available in databases such as PubMed, Google Scholar, ResearchGate, and other scientific databases. Clinical trials, preclinical studies, and review papers on the use of fulvic acid in the context of Alzheimer's disease were searched. Particular attention was paid to improvements in cognitive test scores, comparisons of the efficacy of fulvic acid with pharmacotherapy (e.g. memantine, rivastigmine), and the relationship of the efficacy of fulvic acid use to the age of patients.

Effects of fulvic acid on cognitive function and improvement of quality of life

As the population ages, the number of people with cognitive impairment increases. Dementia encompasses a range of neurological disorders characterized by memory loss and cognitive impairment that impair daily functioning and lead to a progressive loss of independence. [16], [17] Alzheimer's disease is the most common form of dementia, accounting for 60-80% of patients with the condition. [18]

As we age, certain cognitive domains such as memory or speed of information processing become impaired. [19] Some of these domains decline gradually throughout life, some deteriorate at later ages and others remain virtually unchanged. [20] For example, the decline in episodic memory usually begins around 70 years of age. Information processing speed shows a gradual decline and slower reaction times can be observed in people aged 50-60 years. Short-term memory and general knowledge tasks show a slight decline until later in life. Emotional processing remains well preserved in older age. [21] The rate and degree of cognitive impairment varies between individuals. This is influenced by genetic factors, lifestyle (including physical activity levels), and education, among others. [22]

Studies on the effects of fulvic acid on cognitive function in Alzheimer's disease have shown rather inconclusive results. Data on the efficacy of FA are limited, as the results are mainly from in vitro and preclinical studies. This is related to the fact that nutraceuticals, which are classified as dietary supplements in most countries, are not as strictly and rigorously regulated as drugs. Based on research, fulvic acid has been attributed to a wide variety of properties, including antioxidant, immunomodulatory, anti-inflammatory, analgesic, anti-anxiety, and anti-diabetic properties. [23]

The most relevant properties of FA in terms of AD treatment are its anti-inflammatory and antioxidant properties, as well as its specific ability to bind to the tau protein and prevent pathological self-association of its molecules. In a study by Alberto Cornejo et al. (2011) showed that fulvic acid promotes the breakdown of preformed fibrils of the tau 4RMBD fragment, and data suggest that it also affects the aggregation process of the full-length tau protein. [24] This is of particular relevance in Alzheimer's disease, as the disease is closely associated with tau protein accumulation and inflammation. [25], [26], [27], [28]

Some studies suggest that fulvic acid can help improve performance in cognitive tests such as working memory tests and executive function tests. One study found that Andean shilajit in combination with folic acid administered to healthy subjects significantly improved not only cognitive function and memory but also mood. The subjects also declared a significant increase in energy and attention levels and support in daily activities. [23]

Carrasco-Gallardo et al. (2012) conducted morphometric studies on primary cultured rat hippocampal cells, which showed that both shilajit alone and a formulation consisting of shilajit, vitamin B6, B9, and B12 promoted neuritogenesis in hippocampal cells in primary cultures, although the compound formulation had better effects. [29]

Jomehpour et al. (2024) investigated the effect of fulvic acid-coated iron oxide nanoparticles on an in vitro model for studying amyloid aggregation - egg white lysozyme. Properties such as the anti-inflammatory and anti-amyloidogenic effects of fulvic acid and the ability of iron oxide nanoparticles to reduce/eliminate amyloid aggregation were considered. The results indicate effective inhibition of amyloid aggregate formation while showing no in vitro toxicity. [30]

In a rat study, Ghosal et al. (1993) showed that shilajit and its active constituents, including fulvic acid, significantly increased learning and also produced a significant anti-anxiety effect. [31]

Comparison of the efficacy of fulvic acid with pharmacotherapy

Currently, an estimated 24 million people worldwide suffer from Alzheimer's disease, but to date, only two classes of drugs have been approved for its treatment. [32]

There are four drugs on the market (donepezil, memantine, galantamine, rivastigmine), which belong to two groups: acetylcholinesterase inhibitors and antiglutaminergic drugs. Acetylcholinesterase inhibitors help correct the acetylcholine deficiency observed in people with Alzheimer's disease (AD), while antiglutamatergic drugs regulate glutamate levels through antagonism towards N-methyl-D-aspartate (NMDA) receptors.

It should be noted that the available drug therapies have their limitations. Current treatments focus on alleviating symptoms rather than completely curing the disease. These medications are used to slow down the course of the disease, improve cognitive abilities in the short term, and alleviate behavioral problems. While they do not eradicate the disease, they do promote patient independence and contribute to an improved quality of life for both sufferers and their carers.

There are currently no drugs on the market that can stop, let alone reverse, the neurodegenerative process in the brain.

Another reason that contributes to the low efficacy of the listed drugs is their limited passage from the circulation to the central nervous system across the blood-brain barrier. This requires an increase in dosage, which may result in secondary side effects. [33]

Cholinesterase inhibitors are used to treat the early and moderate stages of Alzheimer's disease. We initially use 5 mg of Donepezil in the evening, which is gradually increased to a dose of 10 mg per day. We test the effectiveness of the response to the drug by determining improved memory, behavior, and functioning in the subject. If, after 3 months, there are no satisfactory treatment effects, termination of therapy should be considered. The results collected suggest that approximately ⅕ of the subjects indicate benefit from the therapy, with ⅓ of the patients having no benefit. In addition, little improvement in cognitive and functional function is indicated and response rates are variable. [34]

Studies conducted on groups of patients taking donepezil at doses of 5 mg and 10 mg daily showed significant differences compared to the placebo group. After 12 weeks of therapy, improvement in cognitive function, as assessed by the Mini-Mental State Examination (MMSE) test, was observed. In the group of patients taking 5 mg donepezil daily, the weighted mean difference (WMD) was 1.08, falling within the confidence interval of 0.61-1.54. In contrast, in the group receiving the 10 mg daily dose, the score was slightly higher at 1.27 (95% CI: 0.88-1.66). Both results were statistically significant ($p < 0.00001$). After 24 weeks of treatment, the

therapeutic effects persisted. The WMD in the group of patients taking 5 mg donepezil daily was 1.44 (95% CI: 0.64-2.24, $p = 0.0004$), while the WMD in the group taking 10 mg daily was 1.50 (95% CI: 0.97-2.04, $p < 0.00001$). This indicates that extended use of the drug continued to provide cognitive benefits, with the higher dose being associated with a slightly better effect. In addition, there was a beneficial effect of treatment on behavioral disorders after 24 weeks of treatment, which was not observed after 12 weeks. The mean difference (MD) was -4.42 (95% CI: -7.93 to -0.91, $p = 0.01$), indicating a significant alleviation of behavioral symptoms. However, despite the positive effects on cognitive and behavioral function, taking donepezil at both 5 mg and 10 mg daily did not translate into improvements in the patient's quality of life, regardless of the length of therapy. [35]

Memantine (NMDA receptor antagonist) is a drug used to treat moderate to severe forms of Alzheimer's disease. Initially a dose of 5 mg per day is used, gradually increasing the dose by 5 mg to reach a maximum dose of 20 mg per day. It shows little benefit in moderate to severe forms of Alzheimer's disease. In the moderate form of the disease, we see improved effects when Memantine and Donepezil are used concurrently. Both Donepezil and Memantine are not effective in mild cognitive impairment.

Studies on patient groups taking memantine showed several crucial observations. Caregivers of patients taking memantine spent an average of 48.5 hours less per month on care compared to the placebo group. Analysis of the Mini-Mental State Examination (MMSE) test results showed that patients in the placebo group performed worse compared to those taking memantine, but this difference was not statistically significant. Furthermore, a similar degree of impairment in the performance of daily activities was observed in both groups. In addition, data analysis showed a difference of 0.3 points between the placebo group and the group taking memantine, with a p-value of 0.06. When analysed considering only observed cases, the p-value was slightly higher at 0.03. [36].

There are studies demonstrating the potential protective effect of fulvic acid in neurodegenerative diseases, particularly in the context of Alzheimer's disease (AD) and Parkinson's disease (PD), by modulating the aggregation of pathological proteins. In studies, fulvic acid has been shown to significantly reduce the aggregation of the tau protein, which plays a key role in the pathogenesis of AD. In cellular models, a reduction in tau aggregation to $89.73 \pm 5.43\%$ ($p = 0.032$) and $74.14 \pm 15.01\%$ ($p = 0.041$) was observed under different experimental conditions, suggesting its potential protective effect. Furthermore, fulvic acid did not affect tau protein levels, indicating that its mechanism of action is based on inhibition of aggregation rather than degradation of protein. Similarly, in Parkinson's disease, fulvic acid was

shown to reduce aggregation of alpha-synuclein (aSyn), a protein key to the formation of Lewy bodies. The study showed a significant reduction in the number of cells with aSyn aggregates to 88.9 ± 7.8% ($p = 0.006$), and analysis with proteinase K confirmed a reduction in the protein's resistance to degradation. However, the ability of fulvic acid to degrade already existing aSyn aggregates was not observed, suggesting that it mainly acts by inhibiting the aggregation process rather than reversing it. Additional studies indicate a possible synergistic effect of fulvic acid in combination with B vitamins, which may stabilize cognitive function in AD patients. Furthermore, it has been shown that fulvic acid can increase neurite growth, potentially supporting a neuroprotective effect in neurodegenerative disorders.

A study in a group of 16 patients with dementia possibly due to Alzheimer's disease showed less progression of cognitive decline, reduced neuropsychological symptoms, and caregiver stress compared to the placebo group. Furthermore, the complex has been shown to control the formation of the oligomeric marker tau in the blood of patients with Alzheimer's disease. [37]

In summary, pharmacological treatment of neurodegenerative diseases, such as Alzheimer's disease, focuses on slowing the progression of the disease and alleviating symptoms through acetylcholinesterase inhibitors and antiglutaminergic drugs. While these drugs can improve cognitive function and quality of life, they do not stop the neurodegenerative process and are associated with side effects.

Fulvic acid, on the other hand, which shows promising potential in studies, mainly acts at the level of aggregation of pathological proteins such as tau and alpha-synuclein, which may have beneficial effects on neuroprotection. Despite the promising results, its efficacy has not yet been fully confirmed clinically.

Comparing the two approaches, pharmacological drugs are proven to treat symptoms but do not stop the disease, while fulvic acid may have potential as an adjunctive therapy, but needs further research to confirm its role in neurodegenerative treatment.

Influence of age on the effect of fulvic acid

The relationship between age and the effectiveness of fulvic acid treatment in Alzheimer's disease can be quite complex. In general, age can affect the effectiveness of therapy for many reasons, such as metabolic changes, the severity of the disease, and the body's tolerance and response to treatment.

Previous research suggests that older people may have different outcomes in response to therapies, including fulvic acid. However, several factors may also influence these outcomes, such as the patient's general health and other comorbidities. [23]

The relationship between age and the efficacy of fulvic acid in the treatment of Alzheimer's disease is still poorly studied. Preliminary studies suggest that elderly patients may benefit more from the neuroprotective properties of fulvic acid, particularly in the context of preventing further neuronal damage and not necessarily improving cognitive function. In younger age groups, where neurodegenerative processes are not yet as advanced, fulvic acid may act more as a supportive agent and its effects are less noticeable in cognitive tests.

Fulvic acid supplementation improves cognitive function in patients with mild cognitive impairment: a randomized, double-blind, placebo-controlled clinical trial. This clinical trial evaluated the effect of fulvic acid supplementation on cognitive function in patients with mild cognitive impairment that may precede Alzheimer's disease. The results show an improvement in cognitive function after fulvic acid supplementation. [38[

However, it should be emphasized that further clinical trials are needed to fully assess the efficacy and safety of fulvic acid in the treatment of Alzheimer's disease, especially in the context of different age groups.

Comparison of the safety profile of fulvic acid and pharmacotherapy

Alzheimer's disease is clinically manifested by cognitive impairment, and various types of pro-cognitive substances, i.e. those with beneficial effects on memory or attention, are used to improve these. [39] Fulvic acid is being investigated as a potential therapeutic agent for the treatment of dementia in Alzheimer's disease. Compared to currently approved drugs such as donepezil, rivastigmine, galantamine (acetylcholinesterase inhibitors, IAChE) memantine (NMDA receptor antagonist), and aducanumab (monoclonal antibody), fulvic acid may show different safety and efficacy profiles. [39], [40]

Cholinesterase inhibitors for the treatment of cognitive impairment include donepezil, rivastigmine, and galantamine. [39] In an analysis of 13 studies [41] involving 3,518 patients, the risk of adverse effects during donepezil use was higher than in the placebo group (OR: 1.53, 95% CI: 1.30-1.80, $p < 0.00001$). In seven studies involving 3,210 patients, the risk of adverse effects while taking rivastigmine was even higher than for donepezil (OR: 1.87, 95% CI: 1.12-3.12, $p = 0.02$). In another analysis involving 3,587 patients, the risk was OR: 2.47 (95% CI: 1.73-3.53, $p < 0.00001$).

Donepezil is an acetylcholinesterase inhibitor that shows neuroprotective effects by increasing nicotinic receptor activity in cortical neurons. [39] Clinical trials conducted in 2018 confirmed the efficacy of this drug in the treatment of dementia in Alzheimer's disease, showing positive

effects on cognitive function, social functioning, overall quality of life, and the ability to care for oneself. [35]

The dosage of donepezil can be adjusted according to the severity of the disease symptoms. For mild to moderate stage, the recommended dose is 5 mg or 10 mg per day, while for moderate to severe stage, extended-release tablets are available. In addition, the drug can be administered in the form of a transdermal system, applied once a week. Donepezil can be taken independently of meals, which facilitates its use in clinical practice. [39]

In terms of metabolism, donepezil is mainly excreted via the kidneys, indicating the need for special caution in patients with renal insufficiency. The drug interacts with substances metabolized by cytochrome P450 enzymes (CYP3A4 and CYP2D6), such as fluoxetine, ketoconazole, and quinidine. In addition, it may interact with cholinolytics, cholinomimetics, muscle relaxants and drugs affecting neuromuscular conduction, requiring caution in concomitant use. [39]

The most common side effects are related to the gastrointestinal tract (nausea, vomiting, diarrhea). [39] Research studies have also shown the effect of the drug on heart rhythm. Findings indicate a frequent occurrence of bradycardia in patients taking donepezil, as well as atrioventricular conduction disturbances, QT interval prolongation, AV blocks, and torsade de pointes which may increase the risk of cardiovascular problems. Side effects such as insomnia, muscle cramps, and fatigue are also observed. Despite these potential side effects, donepezil is generally well tolerated at recommended therapeutic doses. [42], [43], [44]

Rivastigmine is an acetylcholinesterase and butyrylcholinesterase inhibitor used in the symptomatic treatment of dementia in Alzheimer's disease. [39] A 2015 clinical trial showed its beneficial effects on cognitive function, ability to function daily, and behavioral symptoms in patients with Alzheimer's disease. [45] The drug is available in various forms, including orally disintegrating tablets, oral solutions, and a transdermal system, allowing the optimal route of administration to be selected for the patient. The transdermal system further improves the tolerability of the drug and facilitates its use. [39], [46]

Rivastigmine is administered twice daily, which increases the risk of missing a dose. It is recommended to take it with a meal to minimize the risk of gastrointestinal side effects, which, of all cholinesterase inhibitors, it predisposes to most frequently. It causes nausea, vomiting, and diarrhea much more often than donepezil, as well as loss of appetite and weight loss. Common side effects include extrapyramidal symptoms, sleep disturbances, muscle spasms, and weakness. In patients with Parkinson's disease, it may exacerbate tremors and other extrapyramidal symptoms. CNS effects are more commonly observed with long-term oral

pharmacotherapy and are among the rare complications of rivastigmine. In contrast, it occurs more frequently when taking its counterpart, donepezil. During the use of the transdermal system, there is a possibility of skin reactions at the site of application, the most common of which include contact dermatitis, also allergic reactions to the transdermal patch may manifest as blistering and swelling outside the borders of the patch., less commonly, angioedema has been observed. [39], [46] Studies have shown that the use of this form of the drug is associated with fewer reports of nausea and vomiting and other gastrointestinal-related side effects. [47]
The drug is mainly metabolized in the liver and excreted by the kidneys, so particular caution is required in patients with renal and hepatic insufficiency. In addition to the indicated side effects, rivastigmine may interact with cholinomimetics and anticholinergic drugs, which may potentiate or attenuate its pharmacological effects. In addition, long-term use of rivastigmine was associated with an increased risk of death compared with patients treated with donepezil. [46]
Another drug used in the treatment of Alzheimer's dementia is galantamine for mild to moderate Alzheimer's disease. [39] In clinical trials, it has been shown to improve cognitive function, patients' general functioning, and ability to perform daily activities, while delaying the onset of behavioral disturbances [48] In addition, galantamine has vasodilator properties - an effect that may be beneficial in patients with coexisting hypertension. However, galantamine may cause some adverse effects, including an increase in skeletal muscle tone and effects on smooth muscle, which may lead to increased intestinal peristalsis, bladder muscular contraction, and pupillary constriction. Therefore, caution is required in its use, especially in patients with gastrointestinal or urinary tract disease. The safety profile for this substance for gastrointestinal symptoms is comparable to other cholinesterase inhibitors. [39]
Memantine is used as an add-on therapy to cholinesterase inhibitors in patients with moderate to severe Alzheimer's disease [49] Its use as monotherapy is considered when the patient cannot tolerate cholinesterase inhibitors, has contraindications to other therapies or when the disease is at a very advanced stage and expectations of cholinesterase inhibitor efficacy are limited.
The benefits of memantine include its antiparkinsonian effects, which have been confirmed in animal model studies [50] It also shows positive effects in patients with dementia progressing to parkinsonism or vascular dementia. [39]
Memantine is generally well tolerated, but elimination is prolonged in patients with moderate to severe renal impairment, increasing the risk of overdose. The drug is excreted mainly via the kidneys, leading to potential interactions with pharmaceuticals, such as cimetidine, ranitidine, procainamide, nicotine, quinidine, and quinine. In addition, memantine is contraindicated in

patients with severe hepatic impairment, as part of the drug is metabolized in this organ. Co-administration of memantine with amantadine, ketamine, or dextromethorphan may lead to pharmacological psychosis. Rare side effects include dizziness, constipation, increased blood pressure, and epileptic seizures, especially in the advanced stages of the disease. [39]

Aducanumab is a drug registered in the United States for the treatment of early-onset Alzheimer's disease. [39] Data from the EMERGE study showed a statistically significant benefit with high doses of the human monoclonal antibody compared to placebo, while the ENGAGE study did not confirm this relationship. Dose- and time-dependent reductions in pathophysiological markers of Alzheimer's disease were observed in both studies. The most common side effect of the drug during both trials was imaging abnormalities associated with amyloid edema. [51]

Side effects associated with aducanumab include damage to small blood vessels, leading to microhemorrhages, and spontaneously resolving cerebral edema. Regular MRI follow-up is needed to detect any abnormalities related to amyloid accumulation (ARIA). Other side effects include nausea, headache, dizziness, and neurological symptoms. [39], [51]

Fulvic acid

Potential benefits of fulvic acid in the treatment of neurodegenerative diseases include delaying the progression of Alzheimer's disease and improving cognitive function by reducing inflammation and oxidative stress. Fulvic acid can also be used as an adjunct to other drug therapy in the treatment of neurodegeneration.

Several animal toxicological studies have been conducted using Sprague-Dawley (SD) rats or ICR mice. Genotoxicity and toxicity of multiple doses of fulvic acid were considered. Compared to the control group, no significant changes (all $p > 0.05$) were found in all FA-treated groups in the in vitro mammalian chromosome aberration test, the in vivo sperm shape abnormality test, and the in vivo mouse micronucleus test.

An acute toxicity test showed the absence of mortality and toxic effects after oral administration of a maximum dose of 5000 mg/kg bw/day to mice and rats. In a 60-day subchronic study conducted at doses of 0 (control), 200, 1000, and 5000 mg/kg/day, there were no significant changes (all $p > 0.05$) in body weight, feed intake, clinical signs, hematological and biochemical parameters, organ weights or histopathological findings.

Based on these results, the no observed adverse effect level (NOAEL) for FA supplementation was set at 5000 mg/kg bw/day, which was the highest dose tested. These findings suggest that oral administration of FA has a high level of safety. [40]

In addition, the clinical trial confirmed the safety of fulvic acid (FA) in humans at a daily dose of 1.8 g. No adverse effects or side effects were observed. [52] Unfortunately, contemporary research on the safety of fulvic acid in the treatment of neurodegenerative diseases is limited. Although fulvic acid has shown low toxicity levels, further research into its long-term safety is needed.

In conclusion, compared to drugs used to treat Alzheimer's disease, such as memantine, donepezil, rivastigmine, galantamine, or aducanumab, fulvic acid has a favorable safety profile. These drugs, especially rivastigmine, can cause side effects such as gastrointestinal disorders, dizziness or sleep disturbances, and extrapyramidal symptoms. In contrast, fulvic acid, being a natural compound, shows relatively low toxicity and is well tolerated by patients, with minimal side effects such as mild allergic reactions or skin irritation when applied externally. It also appears to be better tolerated, especially in terms of cardiovascular side effects, than acetylcholinesterase inhibitors. Preliminary studies indicate a lack of serious side effects, making it potentially safer for long-term therapy. In the future, it may represent a promising alternative in AD therapy, especially for patients who tolerate standard treatment poorly.

However, it is worth noting that fulvic acid has not been as extensively studied for long-term use as pharmacological drugs, so further research in this area is needed.

Table 1: Comparative table of safety profile

Drug	Side effects	Risk of adverse effects on the cardiovascular system
Fulvic acid	Nausea, diarrhoea, mild allergic reactions	No significant action
Donepezil (IAChE)	Nausea, vomiting, bradycardia, dizziness	Increased risk

Rivastigmine (IAChE)	Nausea, diarrhoea, bradycardia, sleep disturbance	Increased risk
Galantamine (IAChE)	Nausea, headaches, stomach problems	Increased risk
Memantine	Agitation, hallucinations, hypertension, headaches	Moderate risk

Table 2: A comparison table summarises the main benefits and risks of treating Alzheimer's disease with each drug.

Medicines	Benefits	Risks/adverse effects
Donepezil	- It improves cognitive function, social functioning and quality of life (Birks and Harvey, 2018). - Neuroprotective effects.	- Gastrointestinal side effects: nausea, vomiting, diarrhoea. - Bradycardia, atrioventricular conduction disturbances. - Interactions with drugs metabolised by CYP3A4 and CYP2D6.

Rivastigmine	- Beneficial effects on cognitive function and behavioural symptoms (Birks and Grimley Evans, 2015). - Available in various forms (tablets, transdermal system).	- Skin reactions when using the transdermal system. - Gastrointestinal side effects. - Interactions with cholinomimetics and anticholinergic drugs.
Galantamine	- It improves cognitive function, functioning and delays the onset of behavioural disorders (Loy and Schneider, 2006). - It dilates blood vessels, lowering blood pressure.	- Increase in skeletal muscle tone. - Bowel motility disorders, bladder spasm, pupil constriction.
Memantine	- Antiparkinsonian effects (Rogawski and Wenk, 2015). - Beneficial in the treatment of dementia with parkinsonism and vascularisation.	- Prolonged elimination in renal disorders. - Risk of drug interactions (cimetidine, ranitidine, procainamide, nicotine, quinidine). - Risk of pharmacological psychosis when used with amantadine, ketamine.
Aducanumab	- Registered for the treatment of early-onset AD. - The EMERGE study showed significant benefits compared to placebo.	- Damage to small blood vessels (microinfarcts). - Oedema of the brain (ARIA). - Nausea, headaches, dizziness and neurological symptoms.

Fulvic acid	- Potential delay in AD disease progression. - Improving cognitive function by reducing inflammation and oxidative stress.	- Low level of toxicity. - Further studies on long-term safety needed. - Possibility of slight allergic reactions or skin irritation with external use.

[35]. [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50], [51], [52]

Conclusions

To summarise the current findings, fulvic acid, thanks to its anti-inflammatory and neuroprotective abilities, shows promising potential in the treatment of Alzheimer's disease, especially in terms of slowing down the loss of cognitive function and protecting against neurodegeneration. Although studies show mixed results in improving cognitive function, there is evidence that fulvic acid can form as an adjunct treatment, especially when combined with pharmacotherapy. Its favorable safety profile makes it a promising alternative, especially among the elderly, where long-term use of traditional drugs can be associated with serious side effects. However, it requires further large-scale studies to confirm the efficacy and safety of fulvic acid in the long-term treatment of Alzheimer's disease. Studies involving a larger group of patients are needed,

Further clinical studies aimed at a more thorough evaluation of the efficacy and safety of fulvic acid in the treatment of Alzheimer's disease and other neurodegenerative diseases are advisable. It is also worth investigating the molecular mechanisms by which fulvic acid shows its protective properties in the nervous system.

Declaration of generative AI and AI-assisted technologies in the writing process.

Authors used AI-assisted technology: Deepl and Grammarly to improve the grammatical and linguistic correctness of the manuscript.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Disclosure

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