A Systematic Review of Natural Products for the Alzheimer's Disease

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Review Article

ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by the accumulation of tau tangles and amyloid plaques, which results in cognitive decline. Natural substances and phytomedicines with antioxidant, anti-inflammatory, anti-amyloidogenic, and neuroprotective properties offer promising therapeutic modalities for AD. The investigation of these plant-based remedies is in line with the goal of developing safe, effective, multimodal, and culturally sensitive therapies that can be used to manage or cure a variety of illnesses while minimizing side effects and enhancing general health. The antioxidant effectiveness of these treatments is demonstrated by a number of patents, with the inhibition of tau hyperphosphorylation among the suggested mechanisms. In addition, a few natural extracts show promise in crossing the blood-brain barrier, and some have anti-inflammatory qualities as well.

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Keywords: Alzheimer's disease; cognitive impairment; health disorders; phytomedicines.

1. INTRODUCTION

Alzheimer's disease (AD) is a neurological illness that worsens with time and is identified by behavioural and personality changes, memory loss [1], and cognitive impairment. It is linked to the build-up of aberrant protein deposits, such as tau tangles and amyloid plaques, in the brain and is the most prevalent cause of dementia [2]. AD primarily affects older persons and significantly impairs quality of life and day-to-day functioning. Since there is no known cure for AD, the main goals of current therapies are to control symptoms and prevent the disease's progression [3].

An estimated 50 million people worldwide suffered from dementia in 2017, according to Alzheimer's Disease International (ADI), and by 2050, this number is expected to triple.

In addition to the potential to lessen the side effects and restrictions associated with existing treatments, finding alternative treatments for diseases like Alzheimer' [4] is important because it will help patients live longer and with a higher quality of life.

The prospect of natural products to offer safe, multimodal, and culturally relevant therapeutic options with a focus on preventing, managing, or treating a wide variety of health disorders while minimizing side effects and enhancing general well-being is the foundation for the justification for investigating their use in healthcare [5].

Alzheimer's Disease: Pathogenesis and current treatment: The cumulative accumulation of tau tangles and amyloid plaques in the brain causes neuronal damage and cognitive impairment, which is the hallmark of Alzheimer's disease (AD), a neurodegenerative condition [6]. Genetic, environmental, and lifestyle variables are implicated in AD development, however its exact cause is yet unknown. NMDA receptor antagonists and cholinesterase inhibitors are two common treatment approaches that are mostly focused on managing symptoms [7]. There are currently studies investigating natural therapies that may be able to alleviate symptoms with fewer side effects as part of scientific efforts to address the underlying diseases caused by tau and amyloid [8]. AD is a complex problem that motivates academics to work together to develop new treatment approaches [9].

Pathological features of AD: Alzheimer's disease is an illness of the brain [10]. Cholinergic neurotransmitter levels in the brain, intracellular Tau (τ) microtubule protein and extracellular beta-amyloid (Aβ) plaque accumulation, neuroinflammation, oxidative stress [11], calcium homeostasis disturbance, and bio-metal ions (copper, iron, and zinc) Unbalanced state are some significant biological pathways involved in the pathogenesis of AD. This disrupts communication between brain cells, leading to memory problems and difficulty thinking [12].

The two most notable histopathological features of AD are the accumulation of extracellular plaques and intracellular fibrillary tangles (NFTs) of the Aβ peptide [13]. Aβ is a membrane protein that is generated by the cleavage of amyloid precursor protein (APP) [14], and it is a membrane receptor with common properties that is broken down by proteases like β- and γ-secretase. The process of Aβ accumulation leads to the formation of oligomers and fibrils that are stored in the senile plaques. The accumulation of tau protein in the cytoplasm of neurons impairs axonal transmission because it causes microtubule structure to be disturbed [15]. These two pretinopathies have the potential to cause vascular dysfunction, oxidative stress (OS), and disruption of the blood-brain barrier (BBB).

There's also chronic brain inflammation, which further damages cells. As AD progresses, brain atrophy results from the loss of neurons in the cerebral cortex [16,17], which causes the link between the temporal lobe and the hippocampus to break. The connections between neuron cells, called synapses, get disrupted too, making it hard for them to communicate [18]. These issues profoundly impact people's ability to recall and think, talk and decide.

Some people with AD also have problems with blood vessels in their brains. Changes in brain metabolism and substances in the fluid around the brain can help diagnose AD [19]. Understanding these issues is important for diagnosing and finding treatments for this serious brain disease.

Current pharmacological treatments and their limitations: Current pharmacological treatments for Alzheimer's disease (AD) primarily include two types of medications [20]:

1. Cholinesterase Inhibitors (e.g., Donepezil, Rivastigmine, Galantamine): These drugs enhance the levels of acetylcholine, a neurotransmitter important for memory and cognitive function [21]. However, their effectiveness is often limited to improving symptoms temporarily, and they may not slow the underlying disease progression. Common side effects include nausea and vomiting [22].

2. NMDA Receptor Antagonist (e.g., Memantine): Memantine regulates glutamate, another neurotransmitter, to help manage symptoms [23]. It may be used in moderate to severe AD. Like cholinesterase inhibitors, memantine mainly addresses symptoms without altering the course of the disease. Side effects can include dizziness and confusion [24].

Limitations of these medications include their inability to stop or reverse the neurodegenerative process, and their effectiveness tends to decline over time. They may provide temporary relief but do not represent a cure for AD. Additionally, they can have side effects that can be challenging for some patients to tolerate. Hence, the search for more effective treatments and potential disease-modifying agents continues.

Natural products as potential therapeutics: Certain natural substances from plants, fungi, or microorganisms have properties that can be used for making medicines. These substances are being studied to see if they can help treat different diseases. Scientists are looking into their potential to create new treatments and therapies because they come from nature and have different useful qualities.

Natural products that promise to prevent Alzheimer's disease: In the past few decades, there has been a surge in demand for plant-derived herbal medicines that are either approved or in various stages of clinical trials for various diseases. This is due to the side effects and toxicity displayed by synthetic drugs and other therapeutic strategies. Even though synthetic chemistry currently rules the field of drug discovery and production, plant-derived compounds have a significant role to play in the treatment and prevention of a wide range of diseases.

Nowadays, one of the best interventions available for treating and slowing the progression of many illnesses, including diabetes, cancer, and neurological conditions like AD, is herbal medicine.

Because they work well and have fewer negative effects than synthetic medications, natural products have gained a lot of popularity as supplements recently.

More than 80 percent of medications were created either explicity or implicity from natural compounds prior to the development of post-genomic high-efficiency screening technologies. Based on natural materials, reports state that over half of the treatments developed later 1994.

Several Herbal products and phytochemicals possess protective of neurons, anti-allergic, anti-cholinesterase, and free radical scavenger benefits. that offer promise for the treatment of neurological disorders.

Advantages of natural products in AD treatment: Natural products offer potential advantages in Alzheimer's disease (AD) treatment [25], such as their multifaceted actions targeting various aspects of the disease, lower risk of side effects, neuroprotective properties, antioxidant and anti-inflammatory effects, cognitive enhancement, potential disease modification, and cultural acceptance [26].

Mechanisms of action: Various mechanisms by which natural products may affect AD pathology Because natural products contain a wide range of bioactive chemicals, they have drawn attention for their potential to impact the pathophysiology of Alzheimer's disease (AD) through multiple methods [27]. These systems consist of:

1. **Antioxidant properties**: Packed with polyphenols and flavonoids, many natural products serve as antioxidants, preventing oxidative stress in the brain, which is related to the pathology of AD [28]. These substances lessen cell damage by scavenging dangerous free radicals.

2. **Inflammatory-reduction benefits:** Chronic neuroinflammation is one of AD's main characteristics. Natural substances with anti-inflammatory qualities, such resveratrol and curcumin, can lessen neuroinflammation and the resulting neuronal damage [29].

3. **Amyloid-resistant activity:** Certain natural compounds may prevent the development of

harmful amyloid plaques by preventing the aggregation of amyloid-beta peptides [30]. Curcumin and epigallocatechin gallate (EGCG) are examples of compounds that can prevent or enhance amyloid-beta aggregation [31].

4.Tau stabilization: Neurofibrillary tangles in AD are caused by abnormal tau protein [32].

Methylene blue and other natural compounds showed efficacy in stabilizing tau proteins and lowering the production of tangles.

5. Neuroprotection: A number of natural supplements, including ginkgo biloba [33], improve cerebral blood flow and supply essential nutrients to neurons, protecting them from further harm [34].

Table 1. Specific natural product examples along with their mechanisms of action

Natural Products	Mechanism of Action
Curcumin [from turmeric]	One polyphenolic compound that has strong anti-inflammatory and antioxidant qualities is curcumin. Curcumin can inhibit the aggregation of amyloid beta peptides and reduce inflammation and oxidative stress in the brain, which may slow the progression of AD [40].
Green Tea Polyphenols [Epigallocatechin]	Green tea contains EGCG, a potent antioxidant and anti-inflammatory compound that may inhibit the production of amyloid-beta aggregation, lessen brain inflammation, and shield neurons from oxidative stress [41].
Resveratrol [From Red Grapes and berries]	The anti-inflammatory and antioxidant properties of resveratrol are well-known. It might increase the activity of brain-related proteins and decrease the accumulation of amyloid beta plaques [42].
Ashwagandha [Withania somnifera]	An adaptogen with possible neuroprotective qualities is ashwagandha. It can prevent damage to nerve cells and lower stress, both of which are linked to cognitive decline [43].
Bacopa Monnieri	Bacosides found in bacopa have the potential to improve synaptic communication and stimulate the growth of new neurons. By promoting healthy brain function, bacopa can also improve memory and cognitive function [44].
Omega -3 Fatty Acids s [from fish oil]	Omega-3 fatty acids, especially EPA and DHA, have anti-inflammatory and neuroprotective properties [45]. They can strengthen neural structure, lessen inflammation, and enhance cognitive performance.
Saffron [Crocus Sativus]	Safranal and crocin, two substances found in saffron, are anti-inflammatory and antioxidants. For those with AD, saffron may enhance mood and memory [46].
Ginkgo Biloba	Flavonoids and terpenoids found in ginkgo biloba extract increase cerebral blood flow, which in turn improves the delivery of nutrients and oxygen to brain cells. For AD patients, this improved circulation can help with memory and cognitive function [47].
Berberine	Because of its small size and ability to cross the blood-brain barrier, BBR has the potential to function as an anti-neurodegenerative drug by targeting specific molecular targets, such as AD. It has been demonstrated that BBR inhibits a number of pathogenic enzymes, including as [AchE]butyrylcholinesterase (BchE), (MAOA), and MAOB in AD. BBR limits intracellular fibrous nerve nodes and amyloid extracellular plaques. through lowering oxidative stress, inflammation, blocking AchE activity, and having anti-amyloid properties, enhanced memory function [48].
Huperzine A [From Huperzia serrata]	As an acetylcholinesterase inhibitor, huperzine A stops acetylcholine, a neurotransmitter crucial to memory and cognition, from being broken down. Huperzine A may increase cognitive function in AD by raising acetylcholine levels [49]. In addition to inhibiting Ache, Hupa affects mitochondria and activates the cholinergic system, both of which have neuroprotective effects. Hupa is known to improve mitochondrial function, prevent acetylcholinesterase activity, and lessen the buildup of Aβ plaque.

6. Neurogenesis: A number of natural ingredients, such as berries' flavonoids and resveratrol, can promote the growth of new neurons in the brain, especially in areas that are important for memory and learning [35].

7. Cholinergic enhancement: AD can be linked with acetylcholine insufficiency, a neurotransmitter that is essential for memory. The enzyme acetylcholinesterase is inhibited by natural compounds such as huperzine A [36], which increases acetylcholine levels and enhances cognitive performance.

8. Mitochondrial support: Alzheimer's disease (AD) is linked to mitochondrial malfunction [37]. Coenzyme Q10 and alpha-lipoic acid are examples of organic substances that can improve mitochondrial function and support the metabolism of neural energy.

9. Metal chelation: AD is due to the brain's excess iron and copper. These metals may be chelated by natural compounds like curcumin and green tea polyphenols, reducing their neurotoxic effects [38].

10. Apoptosis inhibition: By blocking apoptotic pathways, several natural compounds might lessen the death of neurons [39]. In the impacted regions of the brain, this might aid in protecting the current neurons.

Safe and side effects of natural products: Even though they are usually thought to be safer than their synthetic counterparts, natural products can still have unintended side effects. Allergic reactions, gastrointestinal issues, or drug interactions with other medications are examples of adverse reactions.

 Notably, bleeding episodes have been linked to herbal supplements like ginkgo biloba. Although they are generally safe, caution is advised, especially for those who are taking medications at the same time or have a history of medical issues [50].

The safety profile of natural products varies, which emphasizes the need to consult medical professionals for advice. Sufficient research and adherence to recommended dosages are essential for the safe integration of natural products into healthcare procedures.

An assessment of natural products' safety profiles: Because natural products may have side effects, it is important to evaluate their safety profiles. Adverse reactions, such as gastrointestinal problems or allergic reactions, can happen even with products that are thought to be safe.

Products differ in terms of safety, which highlights the need for customized assessment and advice from medical experts. Thorough investigation and compliance with suggested dosages are essential to guarantee the safe integration of natural products into medical protocols.

The informed and cautious use of these compounds for therapeutic purposes is facilitated by an awareness of potential risks and the communication of such risks.

Possibility of integrating herbal items with current AD medications: Natural products and currently available Alzheimer's disease medications may work synergistically to boost therapeutic outcomes and reduce side effects. In order to assess the safety, effectiveness, and mechanisms underlying these combinatory approaches in the therapy of Alzheimer's disease, a systematic investigation and distant validation are essential.

However, present chEI`s are commonly associated with side effects. Anorexia and weight loss are two of the most underreported and unacknowledged side effects of ChEIs. which, especially in the elderly population, are linked to mortality. In addition to gastrointestinal (GI) symptoms, bradycardia is often experienced by patients. Thus, the search for novel and safer ChEIs is imperative. Many phytocompounds have a great deal of promise to develop into the next generation of ChEIs. The following section provides a summary of the research that report cholinesterase inhibitory action from plant sources.

The medications used to treat AD are AchE inhibitors, such as the naturally occurring alkaloids galanthamine, donepezil, tacrine, and rivastigmine. The US FDA has approved tacrine and donnezepil, both of which were created synthetically. The natural alkaloid physostigmine served as the model for rivastigmine. Huperzine A, another naturally occurring alkaloid, also known as AChEI, is a nutritional product that promotes memory. memory.

Acanthaceae: The AChE inhibitory activity of a methanolic extract made from Adhatoda vasica's

leaves, roots, and seeds was studied. It was thought that different phytocompounds from the alkaloid and β-carboline groups that the plant has previously been found to contain were responsible for mediating this activity [51].

Brusqueraceae: Reports state that the Boswellia socotran plant extracts, in both chloroform and methanolic form, exhibited strong inhibitory effects against AChE when tested in vitro utilising the Ellman method. Chloroform extract at a 200 µg dosage demonstrated more than 50% inhibitory activity against AchE [52].

Cortinariaceae: AChE and BChE inhibition was examined in two alkaloids that were isolated from Cortinarius infractus: infractopicrin and 10-hydroxy-infractopicrin [53]. Higher selectivity for AChE inhibition was shown by both alkaloids; this selectivity was greater than that of the conventional AChEI-galantamine. It was proposed, using docking studies, that their selectivity was related to BChE's absence of pi-pi interaction.

Fabuceae: It was determined how well Albizia adianthifolia extracts and fractions worked against AChE. Strong inhibitory effects were observed for the methanolic extract, n-hexane fraction, ethyl acetate fraction, and chloroform fraction. For these fractions and extracts, the IC50 values were 11.80 ± 0.88 [54].

Iridaceae: Extract from the stigmas of crocus satives and its components were analysed to evaluate their potential use against AD. Our research indicates that saffron extract exhibits AchE inhibiting action. Safranol, crocetin, dimethyl crocetin has low micromolecular range [55].

2. EUPHORBIACEAE

An analysis of the Euphorbiaceae family plant Jatropha Gossypyfolia revealed inhibitory action against BchE and achE. Different plant parts, such as the leaves, stembark, and root utilized to produce dichloromethane, methanol, and ethyl acetate, exhibit inhibitory effect on achE and BchE. The greatest inhibition of achE and bchE is shown with ethyl acetate [56].

Lycopodiaceae: Hyperzine A is a Chinese medicinal plant and used for treatment of AD. To study , alternative source on Hyperzine A, Three species of Huperzia (H. cuernavacensis, H. dichotoma, and H. linifolia) were tested using an

In vitro anticholinesterase activity assay. Significant inhibition of AChE was demonstrated by methanolic and alkaloidal extracts of all three plants [57].

Malvaceae: In order to prepare the extract and test for cholinesterase inhibition, gossypium herbaceam flowers were utilized. The extract has a cytotoxicity-preventive effect and inhibits achE in PC12 cells. In a different investigation, the plant Sida rhombitolia linn showed the strongest inhibitory effect on achE when it was extracted using methonal, ethyl acetate, and n-hexane [58].

Verbenace: As part of a research on the possible therapeutic benefits of Avicennia officinalis for AD, the plant was analyzed for the presence of cholinesterase inhibitory components. At doses less than 2 mg/ml, Avicennia officinalis leaf extract inhibited 50% of the activity of TchE and BchE [59].

3. FUTURE DIRECTION

It is necessary to conduct thorough clinical trials to further investigate the potential efficacy of compounds and foods in Alzheimer's disease (AD). It is also critical to investigate combinations of these drugs for therapeutic and preventive uses [60].

Researching plant-derived extracts to find strong and safer compounds while taking traditional and ethnobotanical evidence into account is a prudent approach.

The remedies proposed in the reviewed patents cover a broad range of activities, including several therapeutic targets. The most frequently proposed mechanism of action includes decreased amyloid fibril deposition in the brain, inhibition of beta-amyloid peptide aggregation, and inhibition of AChE.

Numerous patents mention the suggested remedies' antioxidant properties. One of the proposed mechanisms of action is the reduction of tau hyperphosphorylatio61. Some of the activities of the natural extracts include facilitated blood-brain barrier crossing. Additionally, a few of the suggested extracts have anti-inflammatory properties.

Treatments in combination may reduce the amount of tau hyperphosphorylation and aggregation, oxidativestress, neuroinflammation, Aβ levels, and Aβ plaque load [61].

These results highlight the need for more research in this area and provide insightful information about potential complementary medicine approaches for treating and preventing AD.

4. CONCLUSION

The neurodegenerative illness AD progresses over time and lacks a viable cure. Several factors contribute to the ineffectiveness of current treatments: challenges in figuring out the disease's etiology, creating medications that target particular therapeutic targets, and creating subsequent clinical trial designs. A cutting-edge therapy approach to the condition of AD is the use of natural ingredients. Additionally, it has been demonstrated that these substances are useful in the treatment of several illnesses and conditions that coexist with aging and AD. Traditional medicine has long employed the synergism found in herbal extracts and fractions to great effect in treating AD and related illnesses. Phytomedicines and natural substances with antioxidant, anti-inflammatory, anti-amyloidogenic, and neuroprotective properties may serve as therapeutic agents. The role of secondary metabolites produced from plants, specifically alkaloids, terpenoids, and flavonoids, as therapeutic agents against AD has also been considered in light of the anticipated benefits of therapeutic chemicals derived from medicinal plants. These properties are covered in this review.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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