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Natural substances with neuroprotective bioactive effects against Alzheimer's disease

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Memory problems are a hallmark of Alzheimer's disease, a neurodegenerative condition associated with aging. Numerous studies have been conducted to identify potential Alzheimer's disease treatments. The right course of treatment is still not readily available, though. Alzheimer's disease has no known cure; however, symptomatic treatment may help with memory loss and other issues associated with dementia. Since ancient times, traditional medicine has been used throughout the world to improve memory. Since a long time ago, natural therapy with herbs and medicinal plants has been utilized to treat memory problems caused by dementia, amnesia, and Alzheimer's disease. Different medical systems have employed medicinal plants, but the Unani School of Medicine in particular has demonstrated the potency of these plants in the treatment and management of memory impairments. The fundamental processes of activity are still being developed, though. The role of many medicinal plants in the conventional herbal therapy used to treat Alzheimer's disease and memory problems has been discussed in this research.

Keywords:Alzheimer's disease , Amyloid-beta ,Natural products

INTRODUCTION

Alzheimer's disease (AD) is a neurological condition that worsens with age and impairs memory and cognitive function. German neuropathologist and psychiatrist Alois Alzheimer made the discovery of AD in 1906. It is the fifth-greatest cause of death and accounts for 60 to 80 percent of all instances of dementia (Hung & Fu, 2017).

Globally, dementia will affect 65.7 million individuals in 2030 and 115.4 million in 2050, placing a tremendous strain on public health and social welfare. Although it can damage younger people as well, the condition is more common in people over 65. Age is one of the most important risk factors for AD. According to research, the number of people with Alzheimer's disease rises sharply with age, from 3% in those aged 65 to 74 to 17% in people between the ages of 75 and 84 to 32% in people over the age of 85 (Grodzicki & Dziendzikowska, 2020).

As a neurodegenerative disorder, AD gradually and permanently reduces memory and cognition, deteriorates behavior, slows thought, and eventually impairs the capacity to carry out daily activities, demanding full-time care. Severe depression can resemble the symptoms of AD. The disease's early stages are characterized by deficits in the capacity to encode and retain new memories; later stages are accompanied by progressive alterations in cognition and behavior (Wang et al. 2021).

The inability to recall memories is the most common and early sign of AD dementia. Short-term memory impairment is typically the initial clinical manifestation, but immediate memory impairment is commonly present as well. Later, distant memories are also affected. Conversely, the processing of memories that do not require hippocampal structures is not hampered by AD. People typically lose their ability to move and speak clearly in late-stage severe dementia caused by AD, which causes significant memory loss and the loss of their sense of time and location (Matziorinis & Koelsch, 2022). Its pathological and physiological mechanisms have been debatable because of AD's complicated etiology. Environmental and genetic factors both have an impact on the etiology of AD. Researchers have identified amyloid plaques, neurofibrillary tangles (NFTs), synapses, and/or neuronal loss as the primary pathogenic hallmarks (Akram & Nawaz, 2017).

Alzheimer's disease has been identified as a complex disease with multiple risk factors, including growing age, environmental exposures (heavy metals and trace metals), hereditary factors, vascular diseases, head injuries, and infections. The underlying cause of pathological alterations in Alzheimer's disease (Amyloid-beta (Aβ), NFTs, and synaptic loss) is yet unknown. Several hypotheses have been proposed as causes of AD, but two are thought to be the primary causes: some believe that cholinergic dysfunction is a critical risk factor for AD, while others believe that an alteration in amyloid-

protein production and processing is the primary initiating factor. However, there is currently no recognized explanation for describing the pathophysiology of AD (Armstrong, 2019).

The number of patients will probably decrease significantly if therapeutic intervention can stop the onset or progression of AD. Noncompetitive N-methyl-daspartate receptor (NMDA) antagonists (memantine) and cholinesterase inhibitors (rivastigmine, donepezil, and galantamine) are the primary pharmaceutical treatments for patients. It is legal to use cholinesterase inhibitors; NMDA antagonists are approved as a treatment for patients with moderate to severe AD, whereas medication for mild to moderate AD patients is available. Tramiprosate amyloid aggregators, lithium glycogen synthase kinase 3 (GSK3) inhibitors, methylthioninium chloride tau aggregation inhibitors, bapineuzumab immunotherapy, ginkgo biloba, omega-3 fatty acids, vitamin E, and docosahexaenoic acid are some further treatments (Islam et al. 2022).

Amnesia may be brought on by heavy drug use or psychological stress. In AD, many different allopathic medications are recommended; however, they have negative effects. A good source of medications for the treatment of AD and memory loss with few or no side effects could be herbal medicine (Guo et al. 2022).

The development of drugs for the treatment of AD has successfully and promisingly used natural products and their bioactive compounds as possible therapeutic leads. As a result, combinations or extracts of natural items may contain organic bioactive compounds that could be used as a therapeutic approach to treat or prevent AD (Bhat et al. 2022).

Mechanisms Underlying Alzheimer disease (AD)

Intracellular neurofibrillary tangles (NFTs) and extracellular amyloid deposition are two famous pathologic features of AD. Clinical dementia is brought on by amyloid buildup, which also causes cognitive deterioration. Amyloid-beta (Aβ) peptide synthesis and neuronal death are both affected by mutations in the amyloid precursor protein (APP) and presenilin, which are both involved in the development of AD (Giacobini & Gold, 2013).

According to recent research, neuroinflammation is an important pathogenic component of Alzheimer's. The extracellular protein A aggregates during AD pathogenesis, but intracellular NFTs show hyperphosphorylation of tau proteins in neurons. These neurons, which are mostly present in the cerebral cortex and hippocampus of the brain, cause neuronal cell death (Balgoon, 2023).

Inflammation and oxidative stress (OS) are brought on by the deposition of aggregated Aβ protein in the synapses of Alzheimer's patients. Oxidative stress on the brain's nucleic acids, proteins, and mitochondria leads to cognitive and neurological impairment. Depletion of cholinergic neurotransmission and excessive glutamatergic neurotransmission are further features of AD (Balgoon, 2023).

The brains of AD patients have two distinguishing characteristics. Extracellular deposits of Aβ, which are created when Aβ precursors are broken down, are found in senile plaques. Blood vessels can also have abnormal Aβ deposits. Patients with AD have NFTs, which are dense bundles of aberrant fibers made up of a different version of the microtubular-associated protein and located in the cytoplasm of neurons (Chen et al. 2021).

Extracellular Aβ pathology and neurofibrillary tau pathology (tangles and threads) are the two primary characteristics of AD. The Aβ hypothesis of AD pathogenesis and development has been the focus of the majority of studies for the past 25 years. But tau has reemerged as a potential therapeutic target in the treatment of Alzheimer's disease as a result of failure in clinical trials of Aβ-targeted therapy and the novel theory of prion-like replication of intracellular aberrant proteins (John et al. 2022).

Numerous neurodegenerative diseases have tau pathologies, but thorough examinations of pathological tau in diseased brains have shown that each disease's abnormal tau protein is structurally unique, supporting the theory that the diverse but recognizable tau pathologies progress through prion-like seed-dependent aggregation. Consequently, the development of disease-modifying therapies for AD and other memory disorders may depend on interventions in the conversion of normal tau to aberrant forms and in tau transmission from cell to cell (Kamran et al. 2020).

While several theories have been put forth to explain the pathophysiology of AD, the precise process is still unclear and complex. Some of the hypotheses that have been put forth include:

Hypothesis of amyloid:

Aβ precursor protein (APP) is a type I transmembranesialoglycoprotein that is encoded by a single gene on chromosome 21's 19 exons. The soluble version of APP has neurotrophic and neuroprotective properties. APP processing pathways can either be non-amyloidogenic or amyloidogenic. Multiple sites on the APP are broken down by the enzyme secretase, producing an Aβ monomer with amino acids in the range of 38–43. After then, Aβ monomers self-assemble into neurotoxic oligomers, which in turn lead to fibrillary aggregates that disrupt neurons and finally cause dementia (Chakraborty et al. 2022).

Neuroinflammation:

By releasing proinflammatory cytokines including interferon, interleukin, and tumor necrosis factor (TNF), which have been detected in AD patients and impact the brain, higher numbers of microglia and astrocytes produce persistent neuroinflammation. This is because

the action of β secretase, which cleaves APP to produce an Aβ peptide, is enhanced by reactive oxygen species (ROS) (Balgoon, 2023).

Cholinergic Hypothesis:

Mental state, brain adaptation, sleep-wake cycle regulation, cerebral blood flow control, and neuronal function are affected by cholinergic neurotransmission. The cholinergic system is also essential for cognitive performance. And so, impairment could result in memory loss. The hydrolysis of acetylcholine (Ach), which results in signal termination, is carried out by acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). AD patients showed unaltered or enhanced BuChE activity. AChE is also linked to the development of neurotoxic Aβ fibrils, implying that AChE-induced Aβ aggregation contributes to the advancement of AD (Hampel et al. 2018).

Oxidative Stress (OS):

ROS such as hydroxyl radicals, hydrogen peroxide, peroxide, and superoxide anion radicals are produced by oxygen consumption and cellular signaling. In typical circumstances, the intrinsic antioxidant system controls the balance of ROS. Any issue with the clearing of ROS after its production in pathological circumstances. The danger of ROS exposure is higher in the brain because it uses the most energy, consumes the most oxygen compared to other organs, and performs mitochondrial respiration. Brain OS may be a precursor to AD and may influence the course of the illness. Additionally, the formation and deposition of Aβ in AD are influenced by lipid peroxidation and protein oxidation (Sharma & Kim, 2021).

Hypothesis of Tau:

Tau protein is a phosphoprotein with six isoforms that range in length from 352 to 441 amino acids and 38 phosphorylation sites. Based on their interactions with the microtubule and the nature of their amino acids, the tau domains are identified. By interacting with tubulin, phosphorylated tau protein contributes to intracellular trafficking and aids in stabilizing axonal microtubule assembly. Normal tau is transferred to NFTs and paired helical filament tau (PHF-tau) as a result of aberrant tau phosphorylation. Microtubules are made unstable by hyperphosphorylated tau, which kills nerve cells. According to research, hyperphosphorylated tau is three to four times more prevalent in the brains of AD patients than it is in healthy individuals (Wegmann et al. 2021).

Other theories that help to explain the pathophysiology of AD include those involving homocysteine, insulin-degrading enzymes, biometaldyshomeostasis, and phosphodiesterase (Pirolla et al. 2021).

Classification of natural products has effect against Alzheimer

The available treatments for AD are insufficient and have significant negative side effects. As interest in herbal therapy has grown recently, so has scientific curiosity about how plants might be used medicinally to cure illness and enhance health, frequently without causing any noticeable adverse effects. The treatment of Alzheimer's disease and memory loss involves the substantial use of medicinal herbs (Schultz et al. 2018).

Ancient societies, including Egyptian, Indian, and Chinese ones, are where herbal remedies first appeared. Medicinal herbs are used in Chinese and Ayurvedic medicine to treat Alzheimer's disease, neurodegenerative disorders, and cognitive disorders (Chakraborty et al. 2022). Many of the western medications for memory loss come from plants. It improves overall health and wellbeing and uses medicinal herbs to treat AD. The treatment of Alzheimer's disease and memory loss involves the substantial use of medicinal herbs (Jadhavet al. 2019).

Researchers studied the action of plant bioactive compounds in AD treatment, and the results detected that specific dietary components reduce the prevalence of AD. Fundamentally, the traditional medical system is preventive, protective, nourishing, and curative. Traditional medicines treat patients safely and effectively while having little to no negative effects (Gorjiet al. 2018) (Grodzicki & Dziendzikowska, 2020).

In addition, "secondary metabolites" of plants are considered to be naturally occurring bioactive compounds. In this regard, it has been demonstrated that a variety of compounds isolated from a variety of plants, including rhizomes, roots, seeds, and leaves, can suppress the formation of damaging plaque and enhance cholinergic signaling (Singh et al. 2022).

Neuroprotective Activity Targeting Tau Protein from Natural Products for AD

The tau protein is 3–4 times more phosphorylated in the AD brain than in a healthy brain. Tau hyperphosphorylation encourages tau detachment from microtubules and causes aberrant tau aggregation, which happens before AD manifests itself. Protein phosphatase 2A (PP2A), which has decreased activity in the AD brain and cannot be effectively addressed by medications, is primarily responsible for tau dephosphorylation (Wegmann et al. 2021).

In order to alleviate the symptoms of AD, some natural medications have been demonstrated to suppress tau hyperphosphorylation in animal models of AD by modifying the activity of CDK5, GSK3, or PP2A. In the hippocampus of model rats, TongmaiYizhi Decoction, which contains huperzine A and six raw ingredients, drastically lowers CDK5 and CDK5 expression (Basheer et al. 2023).

Safflower yellow from Carthamus tinctorius (Asteraceae) reduces tau hyperphosphorylation by A1-42 and enhances learning and memory in AD model rats via inhibiting the GSK-3 activation and GSK-5 signaling

pathways. In both in vitro and in vivo settings, ginsenoside Rd from Panax ginseng improves PP2A activity and reduces okadaic acid-induced neurotoxicity as well as tau hyperphosphorylation (Chen et al. 2021).

Many of the substances that prevent tau aggregation are natural products with antioxidant capabilities. In vitro, tau protein nucleation and tau protein filament formation can be inhibited by crocin from the Iridaceae plant Crocus sativus. The expansion of the repeat domain and axons in mutant tau protein can be enhanced in vitro by extracts of Glycyrrhizainflata (Fabaceae) and P. ginseng (Araliaceae), which can stop tau aggregation (Wegmannet al. 2021).

Purpurin, which inhibits tau fibrillization and breaks down the pre-formed fibrils; resveratrol, which inhibits the aggregation of the repeat domain of tau along with many other neuroprotective mechanisms; curcumin, which inhibits tau aggregation by stabilizing its native state; folic acid; and the root extract are additional examples of natural products that can inhibit tau protein aggregation (Viswanathan et al. 2020).

Natural products with Anti-Oxidative

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are thought to be essential for a variety of physiological processes occurring inside the human body, including the control of the cell cycle, activation of enzymes and receptors, and the monitoring of inflammation, phagocytosis, gene expression, and signal transduction. These oxidative species can be neutralized and eliminated by the human body, ensuring that their concentrations stay within the normal range (Sharma & Kim, 2021).

Overly high concentrations of ROS and RNS can cause OS with significant pathological damage when there is an imbalance between the production or accumulation of these oxidative species and their neutralization or elimination. In comparison to other regions of the body, the brain is more sensitive to the effects of OS due to greater metabolic activity and limited cellular regeneration (Chen et al. 2021).

The nuclear factor E2-related factor 2 (Nrf2) pathways are one of the key strategies. In response to OS , Nrf2 is a transcription factor that promotes the production of antioxidant genes. Antioxidant response element (ARE), which plays a significant role in lowering OS , inflammation, and the buildup of toxic metabolites, is a common response element of all these antioxidant genes. Due to OS in AD, Nrf2 expression is reported to be increased in the neurons. At the same time, some ARE-containing gene products have lower levels, indicating this pathway has been disrupted. As a result, it is generally acknowledged that OS plays a significant role in gradually degrading neuron structure and affecting neuron function, which is thought to be one of the main reasons for the emergence of severe neurodegenerative illnesses, including AD. The development of antioxidant treatments as neuroprotective agents for the treatment of AD has received significant research attention (Liang et al. 2019).

Compounds known as antioxidants have the ability to interact with free radicals and change them into harmless forms. A major contributing element in the onset and course of AD, according to extensive studies, is OS. Antioxidants can mitigate the harmful effects of oxidation. Antioxidants are divided into two categories based on how frequently they occur in nature: natural antioxidants and synthetic antioxidants, with the majority of synthetic antioxidants coming from natural sources. The most well-known natural antioxidants include carotenoids, ascorbic acid, α tocopherol, flavonoids, and vitamin A (carotenoid). These compounds all protect an organism from ROS-caused damage (Sharifi-Rad et al. 2020).

Several of the plant-based natural antioxidants, including carotenoids, antioxidant vitamins, and the phenolic and polyphenolic chemical groups, are acquired from plants. Because of their ability to scavenge free radicals, donate hydrogen atoms and electrons, and chelate with metal cations, phenolics and polyphenolics, which have one or more hydroxyl groups on their aromatic ring(s), have a well-established reputation for having strong antioxidant capacity (Shah & Gupta, 2020).

The hydroxyl groups replaced on the aromatic rings of these phenolic and polyphenolic compounds, in particular, give them the ability to carry out their anti-oxidative action. Flavonoids, the most prevalent class of polyphenolic chemicals, have a wide spectrum of antioxidative effects against tumors, inflammation, and cell signaling caused by free radicals. It is not unexpected that several natural flavonoids, derivatives of flavonoids, and naturally occurring sources high in flavonoids are being thoroughly studied for the treatment of AD, given that AD may be caused by this defective cell signaling (Minochaet al. 2022).

Flavonoids' ability to suppress the generation of free radicals by regulating the cell signaling pathways involved in the expression of antioxidative proteins and glutathione synthesis, as well as cell proliferation and survival, is one explanation for their neuroprotective effects (Minochaet al. 2022).

The other class of phenolic chemicals, known as non-flavonoids, has slightly more varied structures than flavonoids. In particular, phenolic acids and other non-flavonoids with significant antioxidant activity include lignans, coumarins, stilbenes, quinones, curcuminoids, and tannins. A key strategy for lowering OS associated with the beginning and progression of AD is the attenuation of ROS levels, which dietary polyphenols have been shown to do in vitro and in vivo (Zhor et al. 2023).

Phenolic compounds are naturally occurring

molecules that are included in essential food items for humans, such as nuts, fruit, seeds, various herbal beverages, flowers, and vegetables. It has been demonstrated that consuming phenolic compounds can reduce the prevalence of chronic degenerative disorders, such as AD (Issaoui et al. 2020).

Some phenolic acid compounds isolated from wine have demonstrated neuroprotective activity in vitro, in part through the prevention of RNS-induced stress injury. Phenolic acids isolated from the medicinal plant Rosmarinus officinalis have demonstrated neuroprotective activity in vitro through silencing Nrf2 expression and decreasing ROS and RNS levels (Chen et al. 2021).

Another class of natural substances with the ability to interact with free radicals and display antioxidant characteristics is called carotenoids. Carotenoids are primarily found in microorganisms such as yeasts, algae, plants, fungi, archaea, and eubacteria. They are lipophilic pigmented compounds with an isoprenoid skeleton that can be folded and connected in a variety of ways to form a variety of structures with a variety of physicochemical and biological properties. When taken in sufficient amounts, carotenoids have been shown to have a variety of positive health effects on people, most notably the prevention of AD symptoms, in part due to the lowering of ROS and RNS (Thakur & Modi, 2022).

Together with other antioxidants like retinol and α-tocopherol, AD patients' serum levels of six tested carotenoids are significantly reduced. Numerous epidemiological studies have also linked eating a diet high in carotenes to a lower incidence of neurodegenerative illnesses like AD. (Grodzicki & Dziendzikowska, 2020).

Anti-Aβ Aggregation from Natural Sources for AD

The Aβ hypothesis, the most common mechanism in AD pathogenesis, claims that extracellular deposits of Aβ cause NFTs, which cause neuronal loss and vascular damage. It is believed that Aβ is the primary reason for AD. Its buildup in the brain is thought to constitute an early damaging event in the pathogenesis of AD, which over time may result in personality changes and cognitive impairment in addition to memory loss. The small, soluble aggregates known as oligomers, which are crucial in cell and tissue toxicity, especially in neurodegenerative illnesses like AD, are thought to be the most dangerous species of Aβ aggregates (Pirollaet al. 2021).

According to the genetic, biochemical, and histological evidence supporting the amyloid cascade hypothesis of AD, the deposition of Aβ in the brain as a result of a discrepancy between its production and clearance starts a chain of events that eventually results in AD dementia. According to the amyloid cascade hypothesis of AD, tau aggregation, inflammation, and other alterations that are seen in AD brains are a result of Aβ aggregation, which is the initial event. In the therapy of AD, preventing the formation of Aβ aggregates as well as lowering or eliminating them should be therapeutically beneficial (Hung & Fu, 2017).

The development of therapeutic candidates to control aberrant Aβ aggregation has been one of the main areas of emphasis for drug discovery efforts in the AD field. Clinical trials have looked at a number of synthetic medications, such as verubecestat, LY288672, and AN1792, as well as monoclonal antibody-based medicines like donanemab, which targets $A\beta_{3\text{-}42}$, and aducanumab, which targets an Aβ conformational epitope. All of them, though, have failed to effectively treat AD (Jadhav et al. 2019).

In-depth research has recently been concentrated on examining natural items for cheaper and safer treatments, which can offer a better answer for managing AD. The development of such natural product-based AD therapeutics uses two main strategies: targeting the secretases to prevent the production of Aβ and directly interfering with Aβ aggregates (Gorji et al. 2018).

After secretases cleave APPs, Aβ peptides are produced. The specialized endoproteolytic cleavage of APPs by α, β, and γ secretases occurs at the plasma membrane after they have been produced in the brain by either non-amyloidogenic or amyloidogenic routes (Sharifulinaet al. 2022).

Because α and β secretases must compete for the cleavage of APP, as well as because secretase's cleavage of APP prevents the formation of Aβ, two approaches to developing drugs that target these two secretases have emerged as highly promising ways to reverse the neuropathological changes associated with the majority of AD symptoms: raising secretase activity or lowering β secretase activity (Hung & Fu, 2017).

By modifying the activity of α or β secretase, a number of natural substances have shown their ability to control the generation of Aβ in AD. Ginsenoside Rg1 is a triterpene saponin (glycoside) component found in the Panax ginseng root that has the ability to both raise α secretase and reduce β secretase levels in vitro. Additionally, it can considerably enhance the mice's cognitive deficiency and lower the Aβ level in the transgenic AD mice's cerebra. Trihydroxychalcone (TDC), a phenolic molecule derived from Glycyrrhiza glabra, exhibits neuroprotective properties both in vitro and in vivo by lowering beta-site amyloid precursor protein cleaving enzyme (BACE1) levels while having no impact on levels of α or γ secretase (Hampelet al. 2021).

In vitro studies have shown that the polyphenol EGCG, which is primarily obtained from green tea, increases α secretase secretion and inhibits the development of aberrant Aβ aggregates. It can block the amyloidogenic pathway and lessen the activity of β secretase at the same time. Polymethoxyflavones, which are derived from citrus peels or black ginger and

are frequently used to treat viral infections and allergies, have the ability to inhibit BACE1-related amyloidogenesis in vitro without impairing the activities of α secretase (Pirollaet al. 2021).

Berberine, an isoquinoline alkaloid derived from Berberis vulgaris and Coptidis rhizome, could lessen BACE1 activity, lower Aβ levels, and lessen behavioral symptoms in AD animal models by decreasing α / γ secretases activity and boosting α secretases. In vitro and in vivo, liggustilide, produced from liggusticum chuanxiong, was able to facilitate the non-amyloidogenic pathway of APP cleavage by upregulating α secretase activity (Chakraborty et al. 2022).

Neuroprotective Activity Targeting Cholinergic Neurotransmission from Natural Sources for AD

In reality, the enzyme acetylcholinesterase (AChE), which is primarily in charge of metabolizing Ach and has been identified as the most efficient therapeutic target for creating AD medicines, is inhibited by three out of the four recognized single medications, extending the lifespan of ACh. Boosting the expression of choline acetyltransferase (ChAT), a crucial enzyme in the acetylcholine biosynthetic pathway, and protecting cholinergic neurons by promoting the expression of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and their receptors are other approaches that target cholinergic neurons and acetylcholine to protect from AD-related neurotoxicity (Ahmad et al. 2017).

Rutaceae, Berberidaceae, and Ranunculaceae, all of which contain significant levels of isoquinoline alkaloids, were demonstrated to successfully inhibit AChE function in vitro in a study using aqueous extracts from 80 traditional Chinese medicinal herbs. The alkaloid mixtures palmatine, coptisine, and berberine have been shown to have synergistically enhanced inhibitory action (Smaranda et al. n.d.).

Huperziaserrata (Lycopodiaceae) extracts reduced the cognitive impairment in AD mice by inhibiting AChE activity. Many lycopodium alkaloids have been synthesized and identified as powerful AChE inhibitors. Iridaceae extracts had a modest amount of AChE-inhibitory action. To enhance spatial memory in AD mice, orchidaceae might significantly raise ChAT expression in the medial septum and hippocampus (Taqui et al. 2022).

The most well-known ones are the Bushen-Yizhi formula, which could control nerve growth factor (NGF) signal transduction and the anti-apoptotic cholinergic pathway to improve ibotenic acid (IBO)-induced memory impairment in an AD rat model, as well as a bioactive component of ginger called 6-shogaol, which could boost NGF levels and treat Aβ or scopolamine-induced memory impairment in animal models of dementia(Chen et al. 2021)**.**

Anti-Neuroinflammatory from Natural Products for AD

An important characteristic of AD disease that has been linked to neuroinflammation is the deposit of Aβ in the brain. Natural items with anti-inflammatory qualities could be used as a potential treatment to lessen the symptoms of AD, not only in the early preventive stage but also in the disease management stage, as inflammation can also contribute to neurodegeneration and speed up the progression of AD. γ, IL-1β, and TNF-α (Daily et al. 2021).

High levels of ROS, enhanced microglial activation, cytokine production, and activated nuclear factor kappa B (NF-KB) all contribute to the neuroinflammatory process in AD. Pro-inflammatory cytokines, such as IFN-γ, lL-1β, and TNF-α, were detected in high concentrations in the cerebrospinal fluid, serum, and brains of AD patients. Numerous investigations have established a direct link between elevated cytokine levels at all stages of the disease and cognitive deterioration in AD patients. NF-κB is best described as a transcription factor that is ubiquitously expressed to control the expression of several genes. It also regulates the encoding of proteins involved in the immune and inflammatory processes (Jadhavet al. 2019).

Since NF-κB is a well-known negative regulator of Nrf2, the neuroprotective mechanism brought on by the activation of the Nrf2 pathway has also been linked to the anti-inflammatory effects involving NF-κB. In the brains of people with AD, its activation has been demonstrated to be associated with Aβ induced neurotoxicity. Anti-inflammatory medicine use for a prolonged period of time can slow the development and progression of AD, with NF-κB being a significant mediator of brain inflammation in AD (Boza-Serrano et al. 2022).

Natural products' ability to reduce neuroinflammation makes them capable of producing anti-amyloid effects, which is advantageous for the treatment of AD. It is thought that these natural compounds' anti-inflammatory properties interact with a variety of targets and influence a number of signaling pathways in a synergistic manner (Martins et al. 2020).

Through their anti-inflammatory properties, some natural compounds made from plants and animals, such as omega-3 fatty acids, have demonstrated neuroprotective efficacy. Many different mechanisms, including the suppression of microglia activation, the reduction of pro-inflammatory cytokine production from activated microglia, the inhibition of NF-κB, and the activation of p38 MAPK, have been described for the anti-neuroinflammatory activity of various natural compounds. The anti-neuroinflammatory activity of such natural compounds is also at least partially responsible for their ability to activate Nrf2 and have antioxidant characteristics (Chitreet al. 2019).

Polyphenols, carotenoids, terpenes, alkaloids, and

marine natural products are only a few of the key structural categories of natural products that have anti-neuroinflammatory activity. Cryptolepine, an alkaloid derived from the plant Cryptolepissanguinolenta, is one example of an alkaloid with anti-neuroinflammatory properties. According to studies, cryptolepine inhibits the activation of NF-κB and p38 MAPK in the microglia, lowering levels of PGE2, IL-6, IL-1β and TNF-α in rat microglia (Hu et al. 2023).

Tetrandrine, another alkaloid derived from Radix Stephaniatetrandra, exhibits encouraging anti-neuroinflammatory effects by inhibiting NF-κB activation in a rat model of AD. It has been well shown that flavonoids and other polyphenolic chemicals have anti-inflammatory properties. Tiliroside, kaempferol, quercetin, epigallocatechin-3-gallate (EGCG), apigenin, resveratrol, punicalagin, mangiferin, curcumin, and urolithin A are examples of this structural category (Mir et al. 2021).

Because of their fundamentally suppressive effects on pro-inflammatory transcription factors and their capacity to activate antioxidant and anti-inflammatory transcription factors, flavonoids are regarded as the most significant subclass for preventing neuro inflammation in AD (Henriques et al. 2020).

In mice with cognitive impairment, carotenoids from Crocus sativus are thought to have an anti-neuroinflammatory effect through a mechanism involving NF-κB. Thymoquinone, the bioactive component of Nigella sativa, carnosic acid, and carnosol, natural diterpenes found in Rosmarinus officinalis, and Ginkgo biloba extract, which is rich in polyphenolic compounds and terpene lactones, have all been shown to inhibit neuroinflammation by lowering levels of inflammatory mediators (Scuto et al. 2022).

Side effects and problems associated

Although the effectiveness of natural products and their isolated natural constituents as neuroprotective agents and valuable sources for investigating cutting-edge treatments for AD is well known, many of them are still untested, and their clinical use is difficult to monitor for a variety of reasons (S. K. Singh et al. 2019).

It is challenging to perform quality control on the raw materials because the quality of the natural source materials for natural products depends on genetic factors as well as other extrinsic factors like environmental conditions, harvest time, and agricultural and collection practices. Even more complicated are the basic specifications and procedures for quality control of the final blend of natural products that incorporate hundreds of natural elements (Novoveská et al. 2019).

Their physicochemical instability, limited water solubility, rapid metabolism, low bioavailability, and distribution to the CNS are some specific restrictions and difficulties related to plant-based substances and their isolated compounds from nature that may impact their clinical efficacy in treating AD. These issues have been adequately covered in a number of reviews (Shabbir et al. 2020).

Because they are chemically unstable, polyphenols like resveratrol and curcumin are easily broken down or transformed into inactive compounds. Because of the blood-brain barrier, some neuroprotective natural products, such as polyphenols and polysaccharides, may face additional challenges that limit their therapeutic usefulness. The blood-brain barrier demands sufficient lipophilicity from natural products in order to be able to penetrate the CNS (Akbari et al. 2022).

On the other hand, while carotenoids and alkaloids are lipophilic enough to pass the blood-brain barrier, their poor solubility in water causes additional issues that result in low bioavailability. The transition of the neuroprotective natural compounds' fascinating preclinical outcomes to clinical applications has also proven to be exceedingly difficult. Despite the fact that various natural treatments, including ginger extracts, have been tested on AD patients, no definitively encouraging outcomes have been found (Marino et al. 2022).

If natural substances show therapeutic promise for AD, more investigation is required. Numerous studies have shown that anti-inflammatory natural substances have the potential to cure AD (Kamran et al. 2020),(Daily et al. 2021); nevertheless, more studies are needed to assess their clinical use in carefully monitored human studies. According to several studies, the results of in vitro efficacy trials may not always translate into advantages in vivo (Jadhavet al. 2019). Due to significant species differences, it is also not practical to extrapolate outcomes from animal models to people looking for new Alzheimer's treatments (Taqui et al. 2022). Preclinical research on natural anti-inflammatory substances must prioritize the application of cutting-edge technologies in addition to conventional methods to address this problem.

People all over the world increasingly favor using medicine-food homology (MFH) in their everyday diets to prevent AD from developing and occurring. The quick advancement of contemporary science and technology ought to offer a more sophisticated theory and a broader perspective for illuminating the benefits of conventional MFH theory in AD (Yan et al. 2022). More basic and clinical research is necessary to create new medications in order to treat chronic diseases, especially in recent years. MFH should be used as a resource to develop and generate novel anti-AD medications or healthcare goods because it is a renewable and promising resource.

CONCLUSIONS

The most common neurodegenerative disease in the world is AD, which currently has no effective therapies or medications to combat the symptoms. With a rich supply

of pharmacological principles and a wide variety, medicinal plants can play a key role in the development of new chemical entities. Alkaloids, flavonoids, and phenolic acids, among other secondary metabolites of plants, are essential for promoting regeneration and/or preventing neurodegeneration. Different herbal treatments and isolated plant components have demonstrated substantial promise in the management and treatment of AD. Diversified medicinal plants with the same taxonomic ancestry have certain pharmacological characteristics in common. By screening unknown species from the already reported beneficial families, this review will provide a foundation for future research into anti-AD medications.

Supplementary materials
The supplementary material / supporting for this article can be found online and downloaded at: https://www.isisn.org/article/10.3390/antiox12081524/s1,

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Conflict of interest
The authors declared that present study was performed in absence of any conflict of interest.

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