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ROLE OF HERBAL MEDICINE IN THE TREATMENT OF NEURODEGENERATIVE DISEASE (ALZIEMER'S, PARKINSON'S)

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ABSTRACT

Neurodegenerative diseases, like Alzheimer's and Parkinson's, are becoming more common worldwide, affecting millions of people and leading to serious issues like memory loss, cognitive decline, and difficulty with movement. Unfortunately, current treatments mainly focus on managing symptoms rather than slowing or stopping the disease's progression. This has led many to look into alternative treatments, including herbal medicine, which has shown potential in supporting brain health. Herbal remedies are being studied for their ability to protect nerve cells, reduce inflammation, and improve brain function. Some plants, like Ginkgo biloba, Turmeric, Panax ginseng, Ashwagandha, and Centella asiatica, have been researched for their effects on Alzheimer's and Parkinson's diseases. These herbs have shown promise in boosting memory, protecting brain cells from damage, improving dopamine levels (which is crucial for Parkinson's), and reducing harmful brain inflammation. While the potential for herbal medicine is exciting, we still need more research, including clinical trials, to confirm how well these herbs work and determine the safest dosages. In summary, while herbal treatments might offer some hope as part of a larger strategy for managing these conditions, more rigorous studies are needed before they can be widely recommended as a standard treatment.

KEYWORDS: Alzheimer's, neurodegenerative, Aβ plaques, cognitive memory, medicinal herbs, neurofibrillary tangles.

INTRODUCTION

According to the WHO, Traditional medicine encompasses the entire body of knowledge, skills, and practices rooted in the theories, beliefs, and experiences native to various cultures, whether understood or not, employed in health maintenance and in the prevention, diagnosis, improvement, or treatment of both physical and mental health issues. These are medications or formulations derived from one or more plants and employed for any such purposes. Herbal medications represent the earliest type of health care recognized by humans. For thousands of years, traditional herbal remedies and their formulations have been extensively utilized in both developing and developed nations due to their natural origins and reduced adverse effects. Numerous herbal remedies are available that claim to alleviate symptoms of various issues, ranging from depression to colds and flu. The World Health Organization.[4] Herbal remedies play a crucial role in traditional medicine and are commonly found in ayurvedic, homeopathic, naturopathic, and other healthcare practices.[5] These alterations result in the development of Alzheimer's disease symptoms, which encompass increasing and significant cognitive decline and frequent behavioral issues such as depression, anxiety, aggression, and wandering [6] AD is marked by impairments in learning and memory, leading to significant cognitive decline accompanied by social and work-related issues. The gathering and collection of data from the environment is referred to as learning, whereas the established neural connections in the CNS responsible for encoding, storing, and retrieving information form memory. Both are linked to cognitive deficits observed in individuals with AD. The relationships among age, education, genetics, and environmental elements influence AD.[7, 8] AD is a complex disorder where over 200 proteins or enzymes linked to age-related biological mechanisms have been associated with the disease's development.[9,10] A significant positive association exists between aging and AD risk, which collectively influences the effects of diverse risks throughout an individual's life, encompassing biological factors, psychosocial influences, environmental exposures, and genetic predisposition. Table 1 summarizes the different etiological hypotheses linked to increased AD risk, including key protective and risk factors. The causes of Alzheimer's disease remain unclear, and the current treatment approach of one drug targeting one mechanism seems to lack clinical effectiveness. Despite various hypotheses being associated with AD up to now, the amyloid β (Aβ) hypothesis remains the most widely accepted explanation for the progression of AD.[11, 12, 13]

Herbal plants possess numerous phytochemically active substances, including Tannic acid, Quercetin, Kaempferol, Curcumin, Catechin, and Epicatechin. Many important natural compounds, including Triterpenes, Flavonoids, Sterols, Lignans, Tannins, Polyphenols, and Alkaloids, have been identified through phytochemical analyses of different plant parts, and they are recognized for demonstrating various pharmacological effects (such as anti-amyloidogenic, anti-inflammatory, antioxidant, and anti-cholinesterase activities). These compounds are known to inhibit the generation and lengthening of Amyloid-beta (Aβ) fibrils in a dose-dependent fashion.[14]

Table 1: List of various etiological hypotheses and their characteristic features related with Alzheimer's disease (AD) progression.

Etiological Hypothesis	Characteristic Features
Aβ cascade	Aβ peptides deposit as senile plaques, intraneuronal neurofibrillary tangles (NFTs), neurodegeneration
Tau hypothesis	Neurofibrillary tangles, impairment of axons of neurons
Inflammation hypothesis	Reactive gliosis and neuroinflammation
Cholinergic and oxidative stress hypothesis	Cholinergic neurons are damage, cellular oxidative stress

The clinical symptoms of AD are associated with the degeneration of cholinergic neurons in the hippocampus and cerebral cortex and with the heightened excitability of glutamatergic receptors.

Clinically, AD can be categorized into these stages:

a) Preclinical phase, marked by slight memory impairment with minimal neuropathological alterations affecting several cortical areas;

b) Mild initial stage, where symptoms manifest as difficulties in concentration or focus, memory disturbances, confusion, mood changes, and trouble with everyday problem-solving.

c) Moderate AD stage characterized by progressive spread of the disease to adjacent cortical regions, exacerbating memory and cognitive issues, and leading to challenging behaviors with loved ones.[15]

d) Advanced AD or late-stage illness that is identified throughout the entire cortical region with numerous neuritic plaques and NFTs. The last stage severely affects cognitive abilities and memory skills, as well as family interactions and behavioral coexistence.[16]

So far, only two categories of medications have been authorized for treating AD, and they function by modulating the brain's neurotransmitter system. One class increases the overall levels of acetylcholine (ACh) by inhibiting its breakdown through acetylcholinesterase/AChE

inhibitors, while the other class lowers glutamate levels using N-methyl D-aspartate receptor (NMDAr) antagonists. The drugs currently available (galantamine and memantine) merely alleviate symptoms in AD patients, without any prospects for a definitive cure or prevention.[17] The amyloid precursor protein (APP) undergoes processing by three distinct proteases through α and β-secretase pathways. Under typical physiological conditions, 90% of APP is cleaved via α and γ-secretase, resulting in soluble p3 and APP intracellular domain (AICD) fragments. When a minor fraction of APP molecules follows the β-secretase pathway, β-secretase cleaves APP. It leads to the creation of β-APPs and C99 peptides attached to the membrane. The γ-secretase cuts the C99 peptide, which is anchored in the membrane at its C-terminus, in the transmembrane region, yielding two main isoforms of Aβ consisting of 40 and 42 amino acids.[18, 19, 20, 21]

The Aβ 42 is non-polar and is the main factor behind plaque development linked to the early onset of Alzheimer's disease (EOAD). Given that the accumulation of Aβ is believed to be the underlying factor of the disorder, as illustrated in Fig. (1), no treatment has been confirmed to reverse, halt, or even lessen the advancement of the disease.[22]

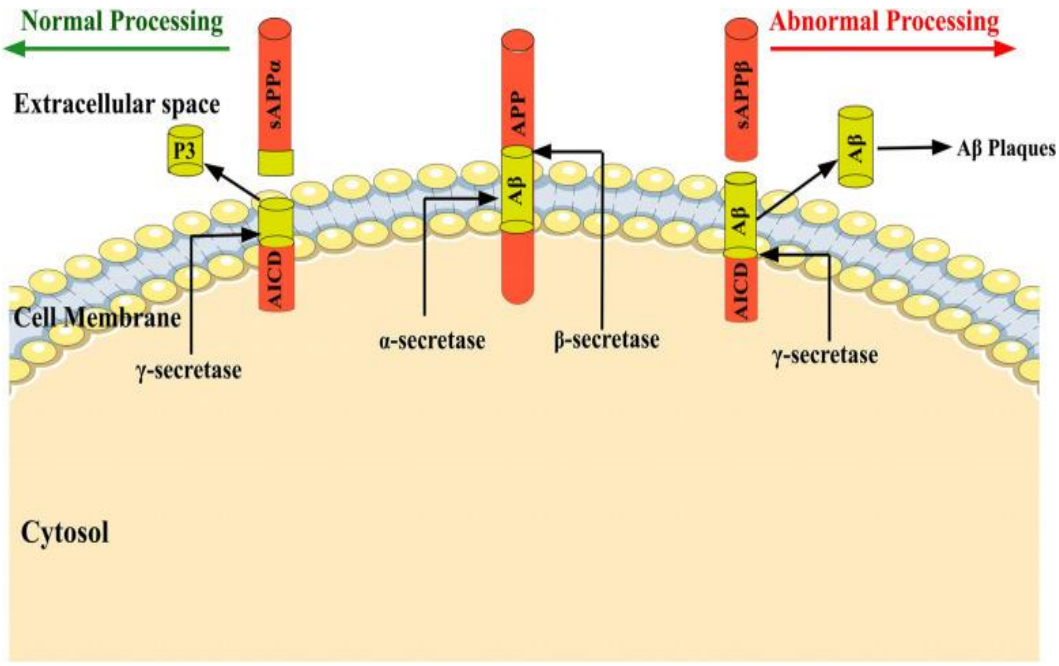


Fig. 1: No medicine even reduce the progression of the disease.[22]

The amyloid precursor protein (APP) is a membrane-spanning protein, and under normal physiological conditions, 90% of the APP undergoes cleavage by α and γ-secretase, resulting in soluble p3 and APP intracellular domain (AICD) fragments. When a minor fraction of APP molecules undergo the β-secretase pathway, β-secretase cleaves APP. This leads to the

production of β-APPs and membrane-associated C99 peptides. The γ-secretase cuts the C-terminal membrane-bound C99 peptide in the transmembrane domain, yielding two main isoforms of Aβ with lengths of 40 and 42 amino acids, which contribute to the formation of Aβ plaques.

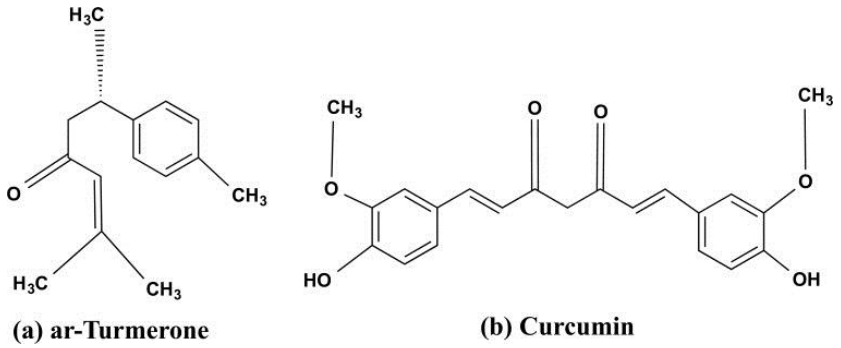
Herbal plants have various phytochemically active substances, including Tannic acid, Quercetin, Kaempferol, Curcumin, Catechin, and Epicatechin. Many important natural compounds, including Triterpenes, Flavonoids, Sterols, Lignans, Tannins, Polyphenols, and Alkaloids, have been identified through phytochemical analyses of different plant parts, and all are recognized for showcasing a diverse array of pharmacological effects (anti-amyloidogenic, anti-inflammatory, antioxidant, and anti-cholinesterase properties). These substances are recognized for inhibiting the formation and lengthening of Amyloid-beta (Aβ) fibrils in a dose-dependent way.[23]

2. HERBAL PLANTS OF INTEREST FOR THERAPEUTIC TREATMENT OF AD

Turmeric, particularly known as “Indian Saffron” in Europe, is a perennial rhizome and belongs to:

a) Curcuma longa (Turmeric)

Spice of Life Zingiberaceae family. Turmerone oil and water-soluble curcuminoids such as curcumin are the most important active ingredients of the turmeric plant as shown in Fig. (2a and b).[24] Despite being considered a common cooking spice turmeric exhibits healing, antioxidant, anti-inflammatory, anti-cancer, and anti-amyloid properties. However, since Vedic times, its medicinal properties have been documented to be used in the Ayurveda, Siddha, and Unani systems of medicine.[25, 26]



(a) ar-Turmerone (b) Curcumin

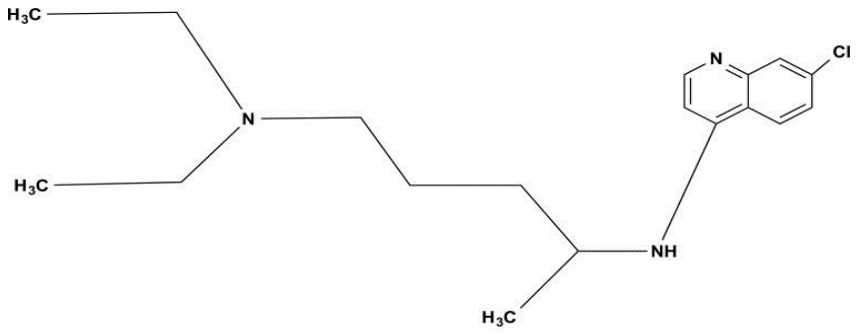
Fig. 2: Figure of ar-Turmeric and Curcumin.

The active phytochemical structures of (a) ar-Tumerone and (b) curcumin.

Curcuminoids (2-9% present) are the main active substances that contribute to turmeric's medicinal properties. Curcuminoids consist of curcumin (77%), demethoxycurcumin (17%), and bis-demethoxycurcumin (3%) as the primary active phytochemicals.[27] Curcumin operates through a pleiotropic mechanism. The buildup of Aβ is the main feature of Alzheimer's disease.[22] Curcumin targets the two histological markers of AD, specifically Tau and Aβ. Research indicates that curcumin doses between 0.1 and 1.0 M disassembled fibrillar Aβ40, impeded Aβ40 aggregation in the brain, and halted Aβ42 oligomer formation.[28, 29]

b) Ginkgo biloba

Ginkgo biloba, known as the Maidenhair tree, has been utilized for ages as a conventional remedy. E Gb 761 is a clearly defined extract derived from Ginkgo biloba leaves, comprising roughly 6% terpene lactones (2.8-3.4% ginkgolides A, B, and C, and 2.6-3.2% bilobalide) and 24% flavone glycosides (mainly Quercetin, Kaempferol, and Isorhamnetin) as illustrated in Fig. (3).[30] The EGb 761 extract from Ginkgo biloba leaves contributes to boosting the antioxidant function of brain cells (free-radical scavenging effect), playing a role in neuroprotection. It safeguards mitochondria via an anti-apoptotic function that preserves the mitochondrial membrane's integrity and stops the release of cytochrome c, ultimately hindering the development of the apoptosome and the apoptotic caspase cascade. The active phytochemical compounds present in *Ginkgo biloba* extracts prevent Aβ aggregation and amyloidogenesis as shown in Fig. (4).



EGb761

Fig. 3: The bioactive chemical structure of Gingko biloba extract Egb761.

Other potential pathways for EGb761's neuroprotective effects on AD include ion homeostasis, stimulation of growth factor production, and modulation of tau protein phosphorylation. It was hypothesized that *Ginkgo biloba* extracts exhibit promising efficacy against AD by inhibiting amyloid-beta aggregation.[31, 32]

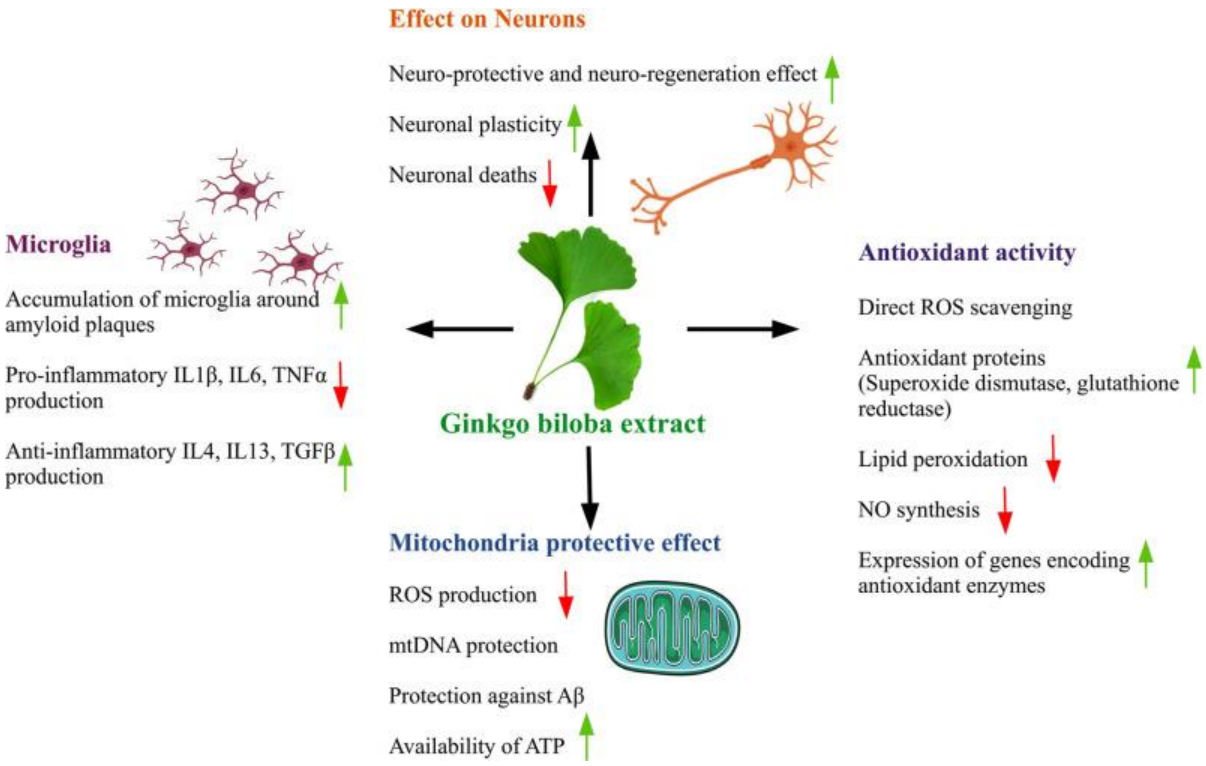


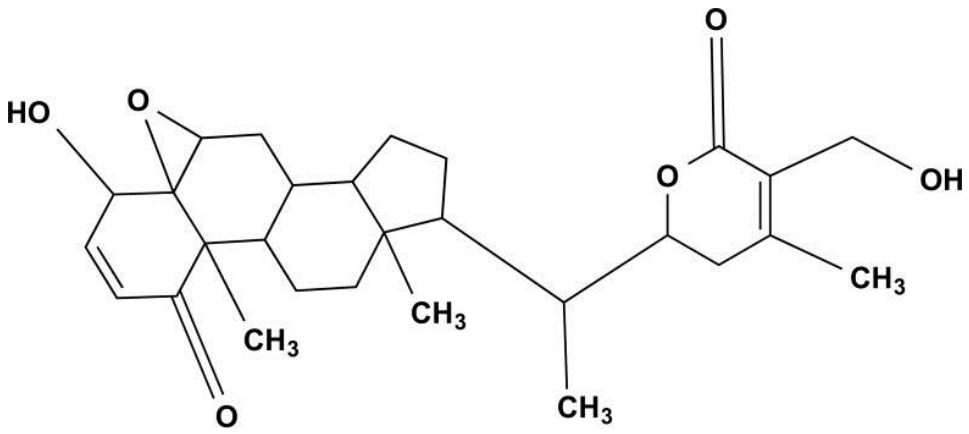
Fig. 4: The several mechanisms by which Ginkgo extract provides neuroprotection in Alzheimer's disease.

c) Withania somnifera (Ashwagandha)

Withania somnifera (WS) belongs to the Solanaceae family. The alkaloid extract from WS roots is used for its soothing effects on the central nervous system and has antioxidant properties as well as the ability to scavenge free radicals. The extracts of WS can help sustain a healthy immune system.[33]

The ergostane-type steroidal lactones, Withasomniferin A, Dehydrowithanolide R, Withasomidienone, withaferin A depicted in Fig. (5), Withasomniferols A to C, phytosterols Sitoindosides VII to X, and beta-sitosterol are some of the steroidal compounds identified in WS extracts. Withasomniferols A is a Withanolide derived from the roots of WS. It has been shown to alleviate the toxicity induced by amyloid β-42 in human neurons.[35, 36]

In Alzheimer's disease, the accumulation of Aβ plaques leads to the death of neuronal cells. The Withanamides found in WS prevent this neuronal cell death. Molecular modeling and simulation research has demonstrated that the interaction of Withanamides A and C with the active motif of Aβ (25-35) inhibits fibril formation.[37]



Withaferin

Fig. 5: Structure of Withferin.

The chemical structure of Withaferin A. It is a lactone produced from *Withania somnifera* with anti-inflammatory, immunomodulatory, anti-metastasis, and anti-carcinogenic activities.

It was found that axons and dendrites of neurons were greatly regenerated after continuous treatment with a methanol extract of Ashwagandha. In addition to cellular regeneration, Ashwagandha improved mice's memory by reversing amyloid peptide-induced memory loss. Studies have proven that oral administration of Withania Somnifera extract containing withanolides and Withanosides have halted the progression of AD. It also recovers plaque pathology and the development of Aβ peptides and oligomers in the brains of middle-aged and old-aged APP/PS1 AD transgenic mice [38]. These above-mentioned studies have proved that Withanolides and Withanosides can act as potential therapeutic active compounds against AD.

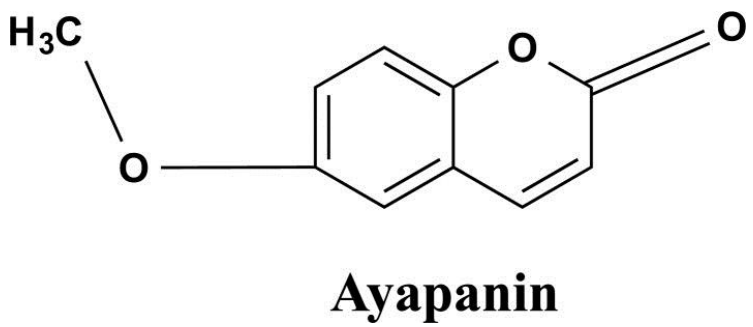
d) Convolvulus pluricaulis (Shankhpushpi)

The methanolic extracts from all four varieties, specifically Convolvulus pluricaulis Choisy and Clitorea ternatea Linn. (CT), Canscora decussata Schult. (CD) and Evolvulus alsinoides L. (EA) are regarded as sources for Shankhpushpi by Indian practitioners. Shankhpushpi has served as a nerve tonic to enhance cognitive abilities and memory performance.[39]

Different secondary metabolites such as flavanol glycosides, triterpenoids, steroids, and anthocyanins have been recognized as the main bioactive compounds present in the isolated extract of Shankhpushpi, as illustrated in Fig. (6). These substances may lead to multiple pharmacological effects besides improving cognitive function.

The ethanolic extract of Shankhpushpi significantly boosts antioxidant activity within brain cells during in-vitro testing. It operates by neutralizing free radicals and serving as an antioxidant. A recent study indicates that it reduces - Aβ buildup in the brain, which safeguards against memory decline in AD.[40, 41]

The neuropharmacological activity suggests that E. alsinoides is the most potent among the four types of Shankhpushpi. It enhances the activity of antioxidant enzymes and regulates tau-induced oxidative stress by reestablishing acetylcholinesterase activity.[42] A significant enhancement in passive avoidance learning and retention was noted in young adult rats that had been treated with CT aqueous root extract.[43] Age-matched saline controls and CT-treated rats displayed a notable rise in dendritic branching points, intersections, and dendritic processes extending from neuron soma in the Amygdala region, suggesting that CT enhances memory by fostering neuronal growth.[44]



Ayapanin

Fig. 6: The chemical structure of Ayapanin isolated from the sources of Shankhpushpi. It improves scopolamine-induced spatial memory impairment.

e) Tinospora cordifolia (Giloy)

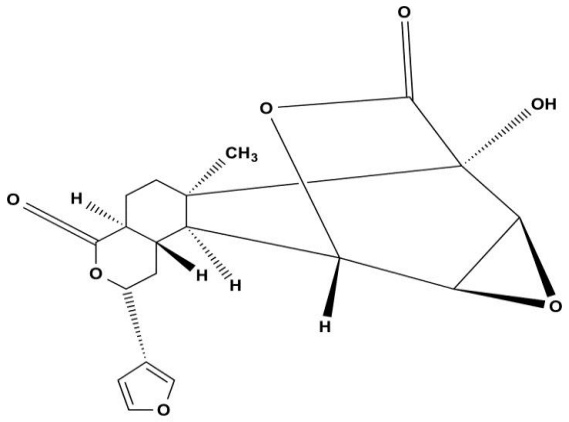
Tinospora cordifolia (TC), commonly called Giloy, belongs to the Menispermaceae family and has been traditionally employed in Ayurvedic medicine, recognized as an adaptogen or restorative agent. It has antioxidant, immunomodulatory, anti-inflammatory, antihyperglycemic, antispasmodic, antiulcer, and numerous additional properties. Recent studies involving both humans and animals have highlighted the presumed antistress advantages of Tinospora cordifolia.[45] TC roots water extract aids in enhancing verbal learning and logical memory.[46, 47]

The most likely mechanisms of antidepressants involve preventing the reabsorption of amines in the brain. Histological examination of the hippocampus in rats treated with cyclosporine showed that T. cordifolia provides protection against neurodegenerative changes.[48, 49]

In mice, TC extracts have demonstrated comparable anti-stress effects. Certain research indicates that when combined with other plants, it enhances memory and spatial learning in rats.[50]

Various research teams are focusing on safeguarding against neuroinflammation and oxidative damage. Various antioxidant substances have been researched to assess their capability to shield against neuroinflammation and oxidative stress, which contribute to changes in mitochondrial function and the generation of free radicals.[51]

A recent investigation has shown that T. cordifolia leaf extract has antioxidant and anti-inflammatory properties. The research indicated a reduction in NF-κB nuclear translocation and an increase in antioxidant enzymes in activated human monocytic (THP-1) cells.[52] In RAW264.7 cells activated by LPS, the aqueous extract of T. cordifolia significantly reduced the expression of inflammatory cytokine genes such as IL-1β and TNF-α, hepcidin, and NO production. Tinosporaside (illustrated in Fig.7) was identified through HPLC analysis, which probably played a role in T. cordifolia's capacity to alleviate inflammation.[53]



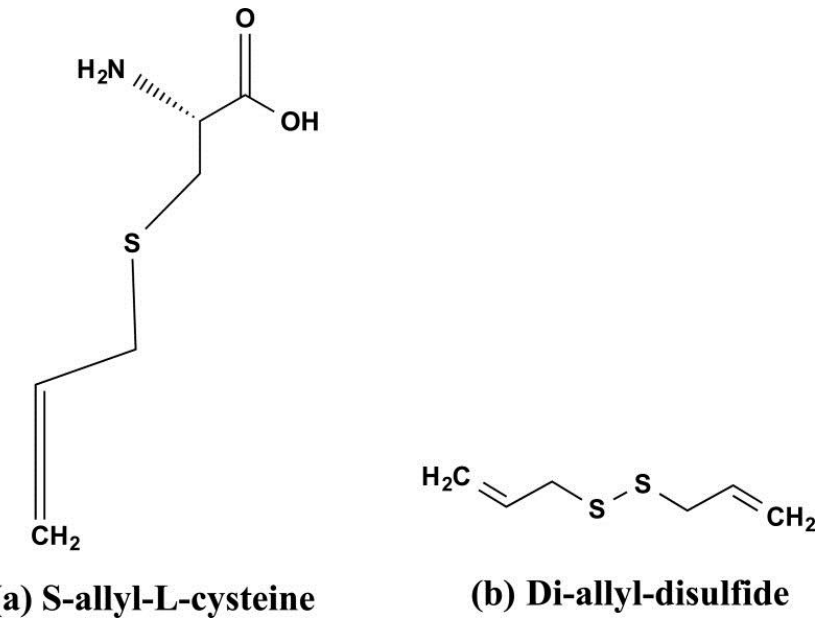
Tinosporide

Fig. 7: The chemical structure of Tinosporide extracted from the stem of *T. Cordifolia*.

f) Allium sativum Linn. (Garlic).

Allium sativum belonging to the Amaryllidaceae family has been utilized as a herbal medicine since ancient times. Aged garlic extract (AGE) is a non-toxic solvent extract of garlic powder. It is derived from an extended extraction period of ≥ 15 months at room temperature.

The aging process converts allicin, an unstable compound is transformed into a stable substance. It contains two key compounds Di-allyl-disulfide (DAD) and S-allylcysteine (SAC) as shown in Figs. (8a and b).[54, 55]



(a) S-allyl-L-cysteine (b) Di-allyl-disulfide

Fig. 8: The bioactive chemical structures isolated from *Allium sativum*. (a) S-allyl-L-cysteine (SAC), and (b) di-allyl-disulfide (DAD).

Other phytochemicals present in AGE comprise Allixin, Ajoene, Polyphenols, Thiosulfinates, and Flavonoids. Lately, there has been increasing interest in AGE's potential to enhance cognitive function.[56, 57]

In AD, Aβ triggers the expression of GRP-78, thereby enhancing neuronal death caused by ER stress. The SAC element of AGE demonstrated a significant neuroprotective effect against neuronal death caused by ER stress.[58, 59]

AGE was discovered to have inhibited the ongoing decline of hippocampal-related cognitive functions by diminishing the buildup of cerebral Aβ.[60]

Cognitive impairment is a common condition in AD, and AGE has significantly diminished cognitive impairment in rats by improving working memory and reference memory.[61]

Raw garlic extract can disrupt Aβ fibrils. The peak defibrillation was observed after 2-3 days of incubation. The boiled aqueous extract of garlic maintained its anti-amyloidogenic properties, suggesting that this activity is non-enzymatic in nature.[62]

Consequently, Allium sativum may serve as a beneficial agent for treating AD, as illustrated in Fig. (9). Consuming garlic every day might also inhibit the buildup of Aβ in the human brain.

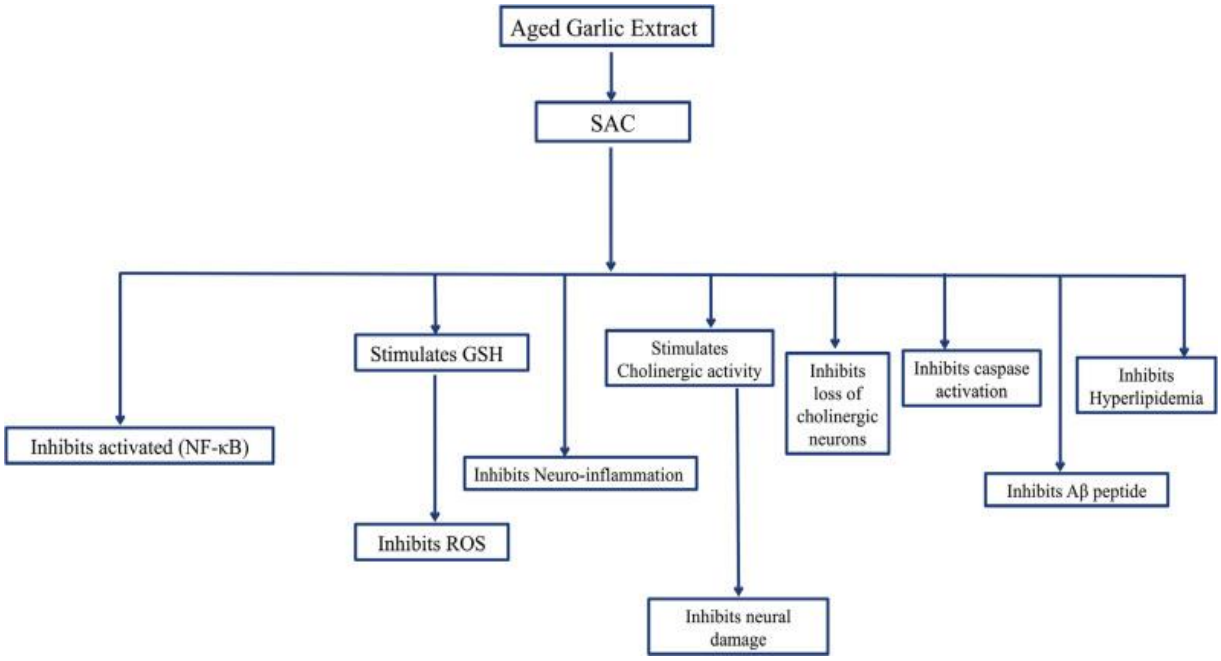


Fig. 9: There are several mechanisms by which S-allyl-cysteine (SAC) provides neuroprotection against Alzheimer's disease.

g) Ocimum sanctum (Tulsi)

Ocimum sanctum is a member of the Lamiaceae family and has been employed in Ayurveda for centuries owing to its various therapeutic benefits. O. sanctum is known as the 'Incomparable one' herb in India and is valued for its medicinal properties. The chemical makeup of O. sanctum is complex and contains a variety of nutrients and biologically active substances.

Holy basil's stem and leaves contain many biologically active phytochemicals, such as Triterpenoids, Saponins, Tannins, and Flavonoids. The phenolic group, which includes active compounds, demonstrates anti-inflammatory and antioxidant properties such as apigenin Fig. (10a), rosmarinic acid Fig. (10b), Isothymusin, Isothymonin, and Cirsimaritin. In male albino rabbits, the lipid peroxidation activity of erythrocytes induced by hypercholesterolemia was inhibited in a dose-dependent manner following treatment with an aqueous extract of O. Sanctum.[47]

Moreover, oral feeding notably decreases the peroxidative harm caused by Hypercholesterolemia to the liver and aortic tissues. The compounds isolated from the aqueous extract of O. sanctum include Civsimavatine, Eugenol, Civsilineol, and Apigenin, which have been examined for their cyclooxygenase inhibitory or anti-inflammatory effects.

A study found that linoleic acid, found in different concentrations in the fixed oil of various O. sanctum species, can inhibit both the lipoxygenase and cyclooxygenase pathways of arachidonate metabolism, potentially aiding in inflammation reduction.[48]

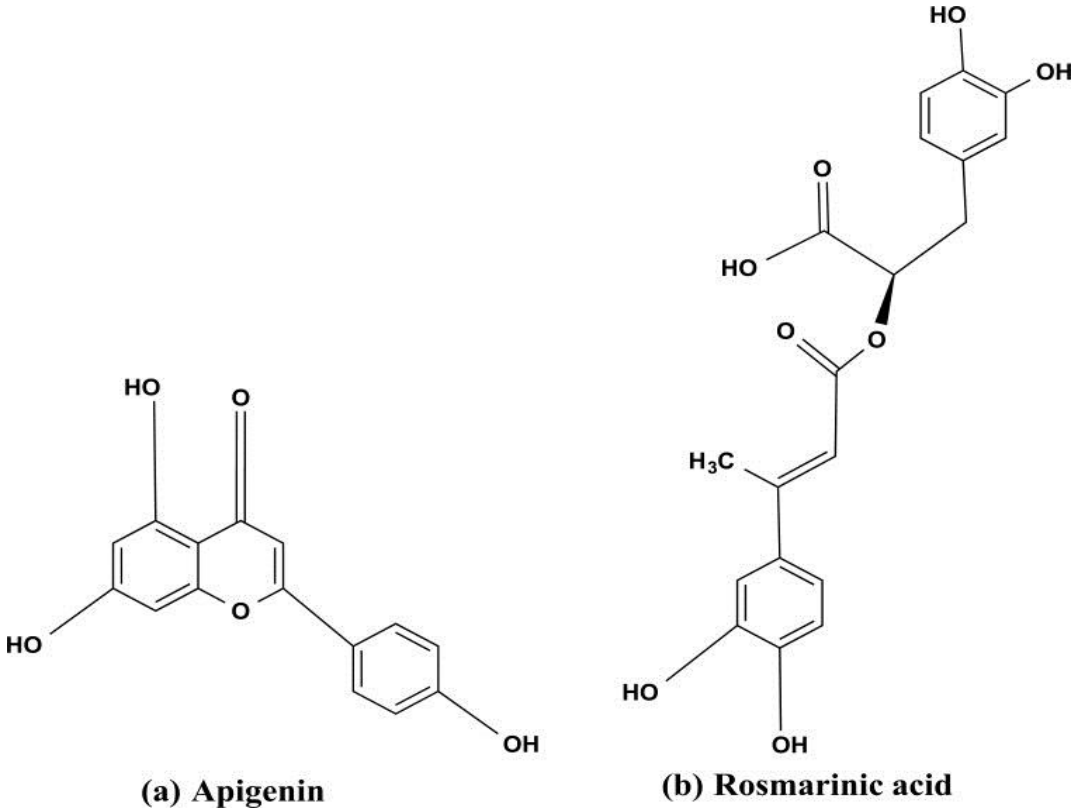


Fig. 10: The bioactive chemical structures isolated from *Ocimum sanctum*. (a) Apigenin, and (b) Rosmarinic acid.

Research was performed to evaluate the efficacy of O. sanctum extract as a nootropic and anti-amnesic substance in mice. The amnesic reaction of mice to scopolamine (0.04 mg/kg), diazepam (1 mg/kg), and aging was diminished by an aqueous extract of the whole O. sanctum plant.[49] The analysis of control (piracetam-treated), scopolamine, and aged mouse groups revealed a notable decrease in transfer latency and an elevation in step-down latency when administered O. sanctum extract. Consequently, the preparation of O. Sanctum could be beneficial for addressing cognitive disorders, such as AD and dementia. Choline acetyltransferase (ChAT) production can be induced and sustained in human Cerebral Microvascular Endothelial Cells (HCMECs) by an ethanol extract from O. sanctum.[50]

Consequently, it could be a potential neuroprotective agent, but extensive in vitro studies are still necessary. In human cerebral microvascular endothelial cells (HCMECs), an ethanolic extract of O. sanctum can stimulate and maintain the production of Choline Acetyltransferase

(ChAT). Therefore, it may serve as a potential neuroprotective agent, although additional in vitro research is required.[51]

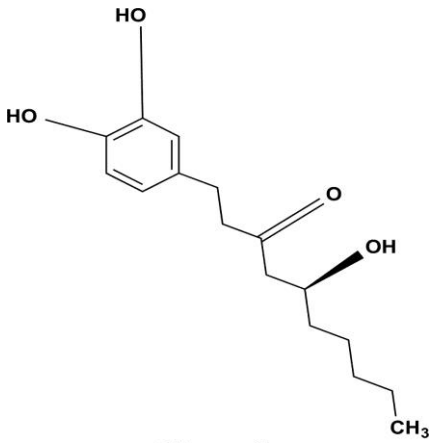
h) Zingiber officinale (Ginger)

i) For centuries, ginger (Zingiber officinale Roscoe) has been used in Indian cuisine and for a range of medicinal purposes. Ginger extracts (GE) possess anti-inflammatory properties. Inflammation is crucial in the cause of AD, leading scientists to explore anti-inflammatory medications for managing the condition.

ii) A recent investigation found that a combination of ginger extracts from Zingiber officinale Roscoe and Alpinia galanga can inhibit the activation of THP-1 cells by TNF, IL-1, LPS, and Aβ.[53] In a study based on molecular dynamics simulations of ginger, its two constituents, named Mol1 and Mol2, were recognized as possible natural inhibitors of HssAChE (acetylcholinesterase), demonstrating effectiveness comparable to the preferred drug (donepezil) for Alzheimer's disease treatment.[54] The reduction of numerous inflammatory response indicators by GE indicates that this herbal formulation may be a potential treatment for AD. Numerous compelling pharmacological and physiological roles of gingerols (structure illustrated in Fig.11) and shogaols have been reported, encompassing antipyretic, cardiotonic, chemopreventive, anti-inflammatory, and antioxidant properties[55]

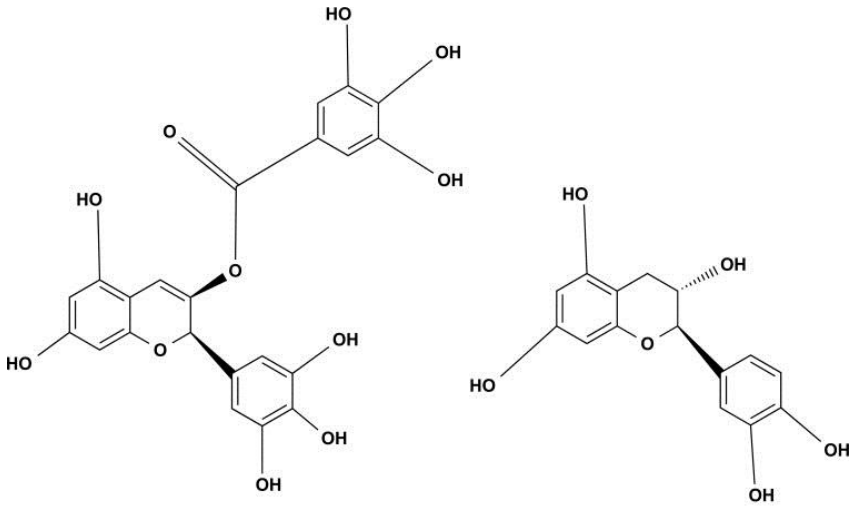
iii) Cinnamon zeylanicum (Cinnamon)

Cinnamon belongs to the Lauraceae family and its important active compounds are made up of cinnamaldehyde and a flavonoid. So far, the main phenolic chemicals isolated from *Cinnamon* have been catechin and epigallocatechin gallate (EGCG) as shown in Figs. (12a and b) that can cross the bloodbrain barrier and can target all the three AD hallmarks *i.e.*, inhibition of the aggregation of Aβ, inhibition of tau hyperphosphorylation and degradation of plaques. *Cinnamon* reduces the production, accumulation, and toxicity of Aβ plaques in PC12 neuronal cells. In AD fly models, the inhibitory effects are similar. It also aids in tau phosphorylation inhibition and acetylcholinesterase activity suppression. It inhibits the generation of intracellular ROS and the expression of pro-inflammatory cytokines such as NF-kB, IL-6, and TNF.[56]



Gingerol

Fig. 1: The bioactive chemical compound gingerol is isolated from ginger.



(a) Epigallocatechin gallate (b) Catechin

Fig. 12: The phytochemically active chemical structure of (a) epigallocatechin gallate, and (b) Catechin isolated from *Cinnamon.*

j) Centella asiatica (Gotu kola)

In Asia, *Centella asiatica*, a plant belonging to the Apiaceae (Umbelliferae) family, has been utilized as a traditional medicine for more than 2000 years. The whole plant and its extract, including the ethanolic and aqueous extracts, of *C. asiatica* have both been discovered to possess a multitude of therapeutic properties and biological activities. Triterpenoids, such as Asiatic acid and Asiaticoside as shown in Fig. (13), make up the majority of the active compounds of *C. asiatica* ethanol extract (CAE).[57]

It possesses excellent antioxidant capabilities for activating the antioxidative defence system inside the brain, reducing Fe^{3+}, and scavenging 2,2-diphenyl-1-picrylhydrazyl (DPPH). It also reduces lipid peroxidation and protects against DNA damage.[58]

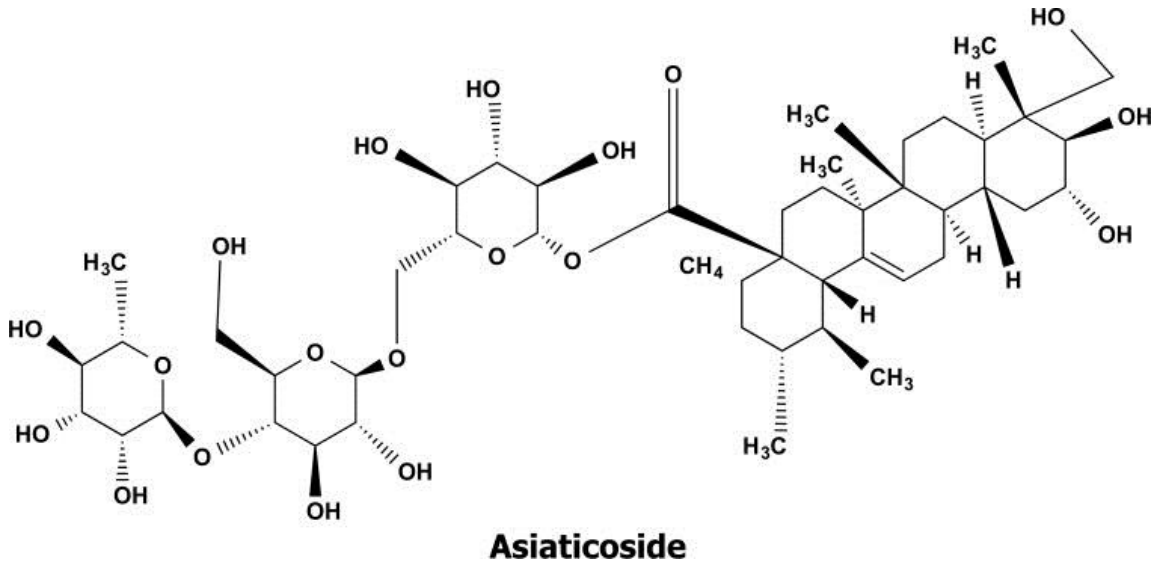


Fig. The bioactive chemical structure of Asiaticoside isolated from *Centella asiatica* extract.

According to Ayurveda, *C. asiatica* is a renewing plant for neurons and other brain cells that can boost intelligence and memory. Its compounds were discovered to have a protective effect against Aβ-induced neurotoxicity, which is linked to AD dementia.[59] The antioxidative defence system in cells, including the activities of Catalase, Superoxide Dismutase, Glutathione Reductase, Glutathione Peroxidase, and levels of Glutathione Disulphide, and glutathione is modulated by CAE. It aids in the death of Aβ cells *in vitro*, making it a promising medicine for the treatment and prevention of AD. Studies have shown that *C. asiatica* can treat AD-like diseases in rats by inhibiting hyperphosphorylated tau (P-tau) bio-synthetic and anti-apoptosis proteins.[60]

3. Nanoformulation of natural compounds

The nanotechnology approach of disease treatment has gained a lot of interest over the past few decades. One of the greatest advantages of nanodrug delivery is to increase in the bioavailability and thereby maximizing the therapeutic index of the drug by specifically targeting particular cells or tissues. This helps to reduce the overall side effect of the drug.[61]

The use of nanotechnology for treating diseases has attracted significant attention in recent decades. A major benefit of nanodrug delivery is the enhancement of bioavailability, which in turn optimizes the therapeutic index of the drug by selectively targeting specific cells or tissues. This contributes to minimizing the total side effects of the medication.[61]

The tiny drug molecules are enclosed within nanoparticles that carry them to the target site. While there are numerous benefits in addressing neurodegenerative diseases, the treatment approaches offer only short-term relief because administering the drug to the brain remains difficult.[62] Recent progress in nanotechnology involves utilizing nanoparticles for neurodegenerative disorders.

The size range of nanoparticles enables them to traverse different biological barriers in the body, particularly the blood-brain barrier, which poses a significant challenge.[63]

Numerous studies have been conducted to create nanoformulations of natural compounds, yet it remains uncertain if the nano-encapsulated compound retains the same activity as the raw version. Numerous studies have addressed the types of nanoformulations for herbal medicine and natural compounds. Curcumin, a traditional Ayurvedic remedy sourced from the turmeric plant, has been recognized for its healing attributes for centuries. Certain drawbacks of curcumin include its limited solubility in water and low bioavailability; therefore, curcumin nanoparticles are employed to address this problem. A widely used approach for preparing Curcumin nanoparticles is the wet-milling technique, where Curcumin is sprayed into boiling water while being sonicated and stirred.[64] Research indicates that nano Curcumin exhibited enhanced solubility, antibacterial, and antifungal properties in comparison to raw Curcumin. Additional techniques are likewise employed to create nano Curcumin particles. Shaikh et al. and Duan et al. synthesized nanoparticles via the emulsion-diffusion evaporation technique, resulting in stable, spherical nanoparticles.[65] The molecule's bioavailability significantly rises (ninefold increase) when the nanoparticles are taken orally. A different method involves nanoprecipitation, which is utilized for encapsulating Curcumin in the polymer (PLGA-PEG).[66]

Like curcumin, various research approaches have been suggested to enhance the bioavailability of Resveratrol. Research indicates that the nanoscale size of Resveratrol enhances its solubility and transport through the plasma membrane.[67] Some drawbacks of Resveratrol include its limited bioavailability, low solubility, and the compound's quick metabolism. The nano approach addresses these drawbacks effectively. A typical approach for preparing Resveratrol nanoparticles involves using the high shear homogenization technique to create microparticles, followed by the ultrasound method to generate nanoparticles. The concentration of tissue in the brain, liver, and kidney increases when

Resveratrol is incorporated into lipid core nanoparticles. Resveratrol encapsulated in a biodegradable nanoparticle has been noted for its effectiveness against glioma.[68]

Polymeric nano-micelles serve as innovative delivery colloid systems that can be utilized for the nano-encapsulation of phenolics that are poorly water soluble and amphiphilic. They possess a diblock copolymer configuration featuring a hydrophilic outer layer and a hydrophobic inner core. The formation of micelles is driven by two forces. The appealing force causes molecules to associate while the repulsive force stops micelles from growing indefinitely into a separate macroscopic phase.

- The formation of micelles from amphiphilic block copolymers occurs alongside the reduction of free energy, with entropy change typically viewed as the key factor in forming stable polymeric micelles. The level of polymers in solutions is the key factor in the entropy-driven process of micelle formation. At extremely low concentrations, the polymers exist solely as individual chains.
- As the concentration rises to a certain level known as critical micelle concentration (CMC), polymer chains begin to aggregate, creating micelles that enable the hydrophobic portion of the copolymer to stay away from the aqueous medium in which the polymer is dispersed. Song et al. effectively incorporated the anti-cancer drug curcumin into MPEG-P (CL-co-PDO) micelles utilizing a solid dispersion approach, achieving a high encapsulation efficiency (>95%). The micelles containing curcumin were monodisperse, exhibiting a PDI under 0.15 and small particle sizes around 30 nm. Lu et al. created polymeric micelles loaded with Resveratrol, utilizing an amphiphilic block copolymer. The impact of polymeric micelles containing Resveratrol was examined on the survival and Aβ safeguarding of PC12 cells. The research indicates that nanoparticles loaded with Resveratrol exhibited no toxicity to cells and safeguarded PC12 cells from Aβ-induced harm in a dose-dependent fashion (1–10 μM) by reducing intracellular oxidative stress and caspase-3 activity.
- Plants remain a consistently plentiful source of therapeutic medications for AD therapy due to their AChE inhibitory properties. Numerous plant extracts from different solvents have been noted to exhibit anticholinesterase activity. Root extracts of Acacia nilotica and Withania somnifera, both aqueous and methanolic, exhibited moderate anticholinesterase activity (IC50 values of 0.079 and 33.38 μg/ml, respectively).[69]

➢ **γ- and β-secretase inhibitors**

Much lesser inhibitory activity was observed in hydroethanolic seed extracts of *Myristica fragrans*, which showed 50% enzyme inhibition at a concentration range between 100 and 150 µg/mL. Also, *Pinus nigra* was used to extracting essential oils possessing 94.4 µg/mL activity. Similarly, different extracts of plants belonging to varied plant families have shown considerable cholinesterase inhibitory activity.[70]

Many plant extracts and their derived compounds are found to influence the Aβ production pathways, mainly by interacting with brain enzymes like β- and γ-secretases. As explained earlier, both β- and γ-secretases are involved in the synthesis of Aβ. β-secretase cleaves the APP to form a transmembrane C-99 fragment with the N-terminus of the Aβ peptide (Figure 2) followed by the action of γ-secretase, which cleaves C-99 fragment in the transmembrane domain to make the C-terminus of Aβ.[71]

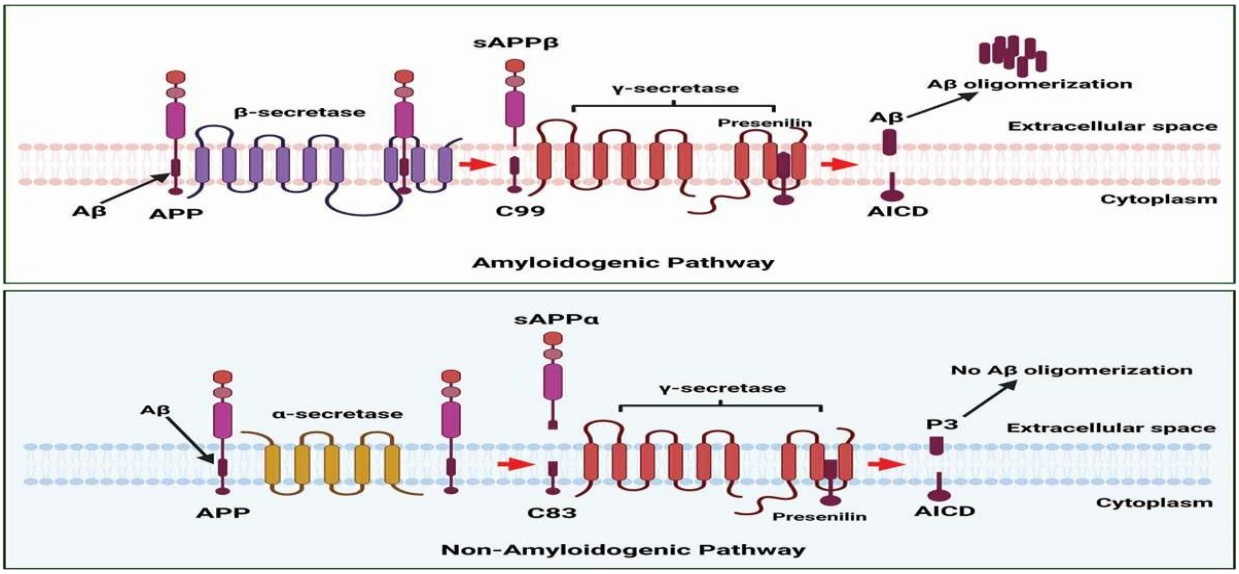


Fig. β- and γ-secretases are involved in the synthesis of Aβ. β-secretase cleaves the APP to form transmembrane C-99 fragment with the N-terminus of the Aβ peptide. This is followed by the action of γ-secretase, which cleaves C-99 fragment in the transmembrane domain to make the C-terminus of Aβ.

Besides processing β-APP, γ-secretase is crucial for the cleavage of the Notch family of cell-surface receptors, proteins essential for transcriptional regulation in neuronal development.[72] Consequently, the application of γ-secretase inhibitors has offered understanding into proteolytic function and implies that this type of inhibition could serve as a beneficial approach for Alzheimer's disease treatments.[73]

A triterpene extracted from Actaea racemosa decreased Aβ toxicity formation by modulating γ-secretase activity. Therefore, it indicates that the isolated compound could associate with the γ-secretase APP complex, influencing the cleavage of APP and subsequently reducing the production of Aβ peptides. It was shown that green tea polyphenol epigallocatechin-3-gallate (EGCG) reduced LPS-induced Aβ elevation levels by inhibiting the activities of LPS-induced β- and γ-secretase.

Nonetheless, the inhibition of Notch protein by γ-Secretase inhibitors influences neuronal development since Notch interacts with various substrates crucial for neuronal development. Therefore, β-secretase, known as β-site APP cleaving enzyme 1 (BACE-1), is a transmembrane aspartic protease found in nearly all tissues but in greater concentrations in brain neurons, making it a highly promising target for pharmaceutical research on AD in contrast to γ-secretase.[75]

- **α- secretase activators**
- The α-secretase enzyme proteolytically cuts the APP through the non-amyloidogenic route at the L688 residue within the Aβ sequence, thus inhibiting the generation of Aβ (Figure 2). In 1998, the initial enzyme for α-secretase was suggested, as ADAM17, referred to as tumor necrosis factor-converting enzyme (TACE), was identified to exhibit α-secretase activity. Subsequently, ADAM9 and ADAM10 were also demonstrated to possess α secretase activity. These three proteins are part of the ADAM (a disintegrin and metalloprotease) family. Mutations in ADAM10 are said to change the processing of APP, resulting in AD by elevating Aβ levels. Therefore, a potentially valuable but overlooked strategy for addressing AD could be to stimulate α-secretase processing of βAPP.[76] Moderate overexpression of ADAM10 in an APP mouse model demonstrated a reduction in Aβ levels, inhibiting its buildup. Reduced levels of Aβ are shown to improve cognitive deficiencies. Numerous investigations have confirmed that multiple medications presently utilized in AD therapy enhance α-secretase activity by stimulating related signaling pathways. Therefore, it is regarded as one of the most effective treatment options in AD. I'm sorry, but it appears that the text you want me to paraphrase is missing. Could you please provide the text again?

- **Aβ inhibitors**

Isolation guided by bioactivity has resulted in the identification of new bioactive compounds from plants that are effective in protecting neuronal cells from Aβ-induced damage. In vitro tests were commonly utilized to evaluate the effectiveness of isolated substances. It is noted

that phenolic compounds, alkaloids, and glycosides make up the main portion of the isolated compounds exhibiting Aβ inhibitory activity. Their ability to act as antioxidants and their lipophilic nature allow them to easily pass through the blood-brain barrier.

FUTURE PROSPECTS

Hypertension, depression, and neurodegenerative disorders are escalating at a remarkable and concerning pace, while their treatments tend to be costly, produce side effects, and are largely ineffective. It is essential to explore our traditional herbs to develop effective disease-fighting remedies. The phytochemicals discussed in this review may serve as a potential treatment for AD, as several of these compounds have demonstrated clinically favorable outcomes in reducing AD. Due to the involvement of various factors in the development and progression of AD, a significant transition from a single-target drug development strategy to a multi-target approach would lead to a more effective drug development strategy, making herbal compounds particularly suitable for these conditions. In such a scenario, herbal plants are sure to yield positive outcomes since they have been used for centuries, are less likely to cause side effects, and are also economical. The new functional identification for AD may prove advantageous in the future.[78]

CONCLUSION

Alzheimer's disease (AD) is a global health concern due to its rising cases. It causes cognitive impairment and neurodegeneration. A number of evidence collected through clinical, animal, and *in vitro* studies indicates that the herbal plants reviewed in this research article help in neurogenesis and have many other therapeutic benefits. Traditional medicines with a strong knowledge base combined with modern science and techniques, help in improving the formulations that may be employed in drug development against AD and other neurogenerative diseases.

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