

NATURAL PRODUCT FOR THE PREVENTION AND TREATMENT OF ALZHEIMER'S DISEASE

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Abstract:

The discovery of natural product with therapeutics effect is widely growing interest, especially for the treatment of neurodegenerative diseases such as dementia or alzheimer's disease (AD). As there are no effective treatment is available to prevent the development of these disease, dietary intake of foods or plant-based extracts with antioxidant properties might have beneficial effects on human health and improve brain functions. AD or dementia is a neurodegenerative disease that causes neuron cell death, brain to shrink impaired cognitive function and leads to memory loss. It induces alterations in the central nervous system with psychological and physiological negative effects. In the present commentary we discuss whether natural product could be a novel treatment for AD on the basis current clinical trials conducted, there is evidence to suggest that single herbal drugs formulations may offer certain benefits to the approved drugs. In the last decades, attention to herbal or natural drugs increased, they have become a major focus in the quest for AD remedies and may represent a real promise for curing the disease.

Keywords: Natural Product, Neurodegenerative, Alzheimer's Disease, Curcuma Longa, Centella Asiatica, Galanthamine.

1. Introduction

The Alzheimer's disease (AD) is a problem of modern society. It is a progressive neurologic disorder that destroys memory and other important mental functions, destroy brain cell connections and the cells themselves degenerate and die [1,2]. Alzheimer's disease (AD), the most common type of dementia [3] It is also called senile dementia. It is becoming an epidemic as well as an economic burden worldwide [4-6], as per WHO 47.5 million people around the world are living with dementia. and about 60% to 70% of this population has AD [7,8] in other report AD has been reported to affect about 44 million people worldwide, and it is predicted to triple by 2050 [9].

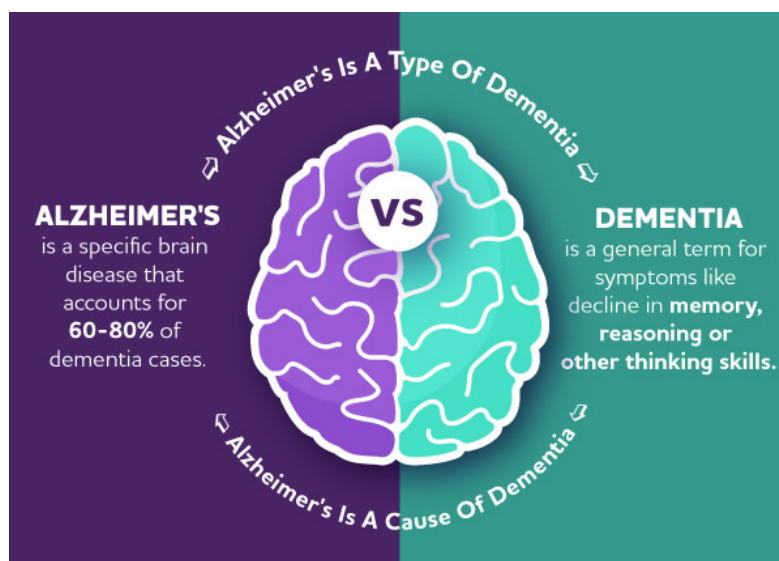


Figure 1: Corelation between Alzheimer's and Dementia

In early-stage AD effected person may have difficulty remembering things but over time, symptoms get worse. People have difficulty to recognize family members, speaking, reading or writing and they may become anxious or aggressive. Medications may temporarily improve or slow progression of symptoms. But there is no treatment that cures AD or alters the disease process in the brain. In advanced stages of the disease, complications from severe loss of brain function, such as dehydration, malnutrition or infection, and finally result in death [10]. it has been a clinical challenge to treat AD, although considerable efforts have been made to develop effective therapeutic agents for AD, but neither a consensus concerning the pathogenesis of the disease nor a successful therapy is yet available. The natural product chemistry brings tremendous diversity and abundant resource for medical needs[11]. The ultimate aim of Alzheimer's disease (AD) therapy is to stop or slow down the disease progression. Cholinesterase inhibitors have a modest clinical effect on the symptoms, [12-14], Drugs such as Curcumin, galantamine, Isothiocyanates, *Bacopa monnieri*, *Centella asiatica*, donepezil, or rivastigmine inhibit Acetylcholinesterase (AChE), and improves cholinergic transmission. These drugs have been used to alleviate the symptoms of AD, which are caused by the degeneration of cholinergic neurons and injured transmission. However, the inhibition of Acetylcholinesterase has not been very effective in the treatment of Alzheimer.

1.2 Natural Products

The discovery of new natural compounds with new therapeutic effect is an interested & widely growing field, especially for the treatment of neurodegenerative diseases. As there are no pharmacological treatment is available to effectively prevent the development of these diseases. Dietary intake of foods or plant-based extracts with antioxidant properties might have beneficial effects on human health and improve brain functions.

Discovery of natural products is a challenging task for designing new leads. Bioactive compounds derived from natural resources. New natural compound discovers by its phytochemical analysis,

characterization and pharmacological investigation. It focuses on the success of these resources to finding and discovering an effective drug compounds that can be useful for human resources. Only natural product drug discovery plays an important role to develop the scientific evidence of these natural resources. From a decade, natural drug has been acting as a source of therapeutic agents and have shown beneficial uses in several disease [15].

Herbal drug has long been used in china as therapy for dementia. *The Complete Work of Jingyue* published in 1624 contains the earliest known description in the world of an herbal therapeutic strategy for dementia [14]. A number of scientific researchers have been carried out on herbal compounds. They have anti-inflammatory and antioxidant activities that may be used in the treatment of AD. Alzheimer's patients have deficiency of neurotransmitter acetylcholine, that plays a key role in cognitive function and reasoning. The brains of those with mild-to-moderate Alzheimer's disease have abnormally low acetylcholine concentrations. This means that any compound that enhances the cholinergic system in the brain may be useful in treating Alzheimer's disease and similar brain malfunctions.

Although considerable efforts have been made to develop effective therapeutic agents for AD therapy, but still there is no significant clinical success in the drug development. Considerable research is underway to develop newer agents for the management of AD. A hope and promise are expected to herbal drugs they will cure AD or prevent the loss of mental abilities at some time in the future. There are various herbal drugs that can be useful in treatment of neurodegenerative disease or alzheimer some discussed below or listed in Table 1.

Galanthamine: Galanthamin is a bioactive compound that was discovered accidentally in the early 1950s, and the plant extracts were initially used to treat nerve pain and poliomyelitis [16]. Galanthamin is an alkaloid that has been isolated from the bulbs and flowers of *Galanthus nivalis*, *Galanthus caucasicus*, *Galanthus woronowii*, and some other members of the Amaryllidaceae family. It can also be produced synthetically. Galantamine is a specific, competitive, and reversible acetylcholinesterase inhibitor that has been recently approved for the symptomatic treatment of Alzheimer's disease [17]. It may improve the ability to think and remember or slow the loss of these abilities in people who have AD. Galantamine works by increasing the amount of a certain natural substance in the brain that is needed for memory and thought. Currently Galantamine available in market in an extended-release tablet, capsule, and a solution to take by mouth, but they cause side effects such as nausea, vomiting, diarrhoea, loss of appetite, stomach pain, heartburn, weight loss etc.

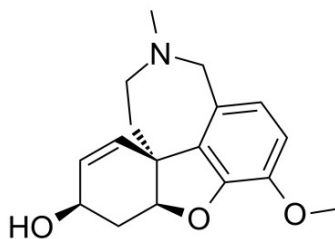


Figure 2: Chemical structures of galanthamine

1.2.1. Curcumin

Turmeric of *Curcuma longa* is a rhizomatous plant of the ginger family, Zingiberaceae. The active compounds are water-insoluble curcuminoids, including curcumin, demethoxycurcumin, and bis-demethoxycurcumin [18]. Curcumin is the main curcuminoid and it is responsible for the yellow colour of the turmeric root [19]. Curcumin has antitumor, anti-inflammatory, antioxidant, antibacterial activities, among others. Curcumin can decrease oxidative damage status in the brain. Some symptoms of AD were also reduced by curcumin's antioxidant and anti-inflammatory properties. In a clinical trial, curcumin has shown several beneficial effects on healthy middle-aged people, including lowering the plasma β -amyloid protein concentrations [20]. More experiments are needed to evaluate the exact mechanism of *C. longa*.

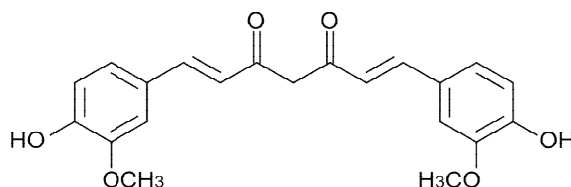


Figure 3: Chemical structures of Curcumin

1.2.2. Centella asiatica:

Centella asiatica is a traditional medicinal herb with high antioxidant activity, which decreases amyloid- β ($A\beta$) deposition in the brain. At the same time, aggregated $A\beta$ -induced oxidative stress is the trigger in the pathogenesis of AD [21].

Centella asiatica are commonly known as Gotu Kola, brahmi and it is listed in ancient Indian Ayurvedic medical text Caraka Susmita as Mandukaparni for the treatment of dementia. It has also been used for increasing intelligence, memory and longevity [22]. The dried herb has growing popularity in the USA and other Western countries, where it is sold as the dietary supplement "gotu kola" [23]. Asiatic acid and asiaticoside have been isolated from *C. asiatica*, and these compounds have shown the ability to reduce H_2O_2 -induced cell cytotoxicity, Specific This approach has been continued over the centuries to the modern day as the ingestion of powdered dry leaves of *Centella asiatica* mixed with milk is used in some parts of India as a treatment to improve memory. Extracts of this herb are well tolerated and may have pro-cognitive effects in

asiatica decreased beta-amyloid levels and oxidative stress, prevented the shrinkage of neuronal processes, and protected against beta-amyloid-associated toxicity and behavioural abnormalities but these effect not have been confirmed in human, but it is expected *Centella asiatica* is considered to be safe with mild side effects, although a few cases of liver toxicity have been reported [25].

1.2.3. Caffeine

Caffeine has well-known short-term stimulating effects on central nervous system, but the long-term impacts have been less clear. Dementia and Alzheimer's disease are rapidly increasing public health problems in ageing populations but the curative treatment is lacking. Thus, the protective effects of caffeine against dementia/AD are of great interest [26]. A number of meta-analyses and reviews reported that the regular consumption of caffeine reduces the risk of developing AD, particularly in the elderly people[27]. In 2007 a study reported that consumption of caffeine reduced the risk of AD by approximately by 30% [27]. In the CAIDE (Cardiovascular Risk Factors, Aging and Dementia) study, coffee drinking of 3-5 cups per day at midlife was associated with a decreased risk of dementia/AD by about 65% at late-life [26].

however, some studies reported different results they observe consumption caffeine may be particularly beneficial before the Alzheimer disease occur i.e., during the pre-morbid phase. Overall, the results suggested a protective effect of coffee consumption, however, there was a large heterogeneity across the studies.[17]

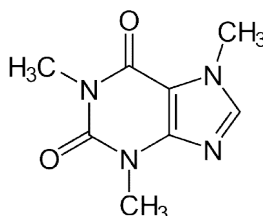


Figure:4 Chemical structures of caffeine

1.2.4. Isothiocyanates(ITCs):

Now researcher focus to finding a new type of cholinesterase inhibitor that would overcome the brain availability and hepatotoxic liability. Isothiocyanates investigated as potential cholinesterase inhibitors which help to dealing with the treatment of Alzheimer's disease [28].

Isothiocyanates derived from the hydrolysis of the corresponding glucosinolates (GLs), found in *Brassica vegetables* (Family: *Brassicaceae*) and small amount present in *Moringaceae* plants. It has demonstrated isothiocyanates exert neuroprotective properties. Specifically, strong evidences suggest that antioxidant effects may be ascribed. It is reported in vitro and in vivo models isothiocyanates have neuroprotective effects, it is effective in counteracting oxidative stress, inflammatory and apoptotic mechanisms.

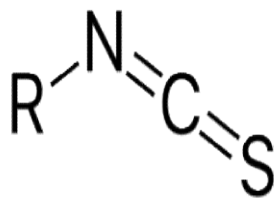


Figure 5: General structure of an isothiocyanate

Table 1. Herbal drug that can be useful in the treatment of Alzheimer's disease.

No.	Medicinal Plants, <i>Name</i> and (Family)	Mechanism of Action
1.	<i>Abies koreana</i> E.H. Wilson (Pinaceae)	Improves the memory in scopolamine model of AD in mice model.
2.	<i>Acorus gramineu</i> Sol. (Acoraceae)	Exerts AChE inhibitory and antioxidant activity. Increases the learning and memory ability in rat model of AD.
3.	<i>Avicennia officinalis</i> L. (Acanthaceae)	Exerts AChE inhibitory activity <i>in vitro</i>
4.	<i>Bacopa monnieri</i> (L.) Pennel (Plantaginaceae)	Improved cognitive function and reduced loss of neurons in animal model of AD. Enhances learning and memory in randomized double-blind placebo-controlled trial.
5.	<i>Berberis darwinii</i> Hook (Berberidaceae)	Exerts AChE inhibitory activity <i>in vitro</i> .
6.	<i>Caulis spatholobi</i> (L.) (Fabaceae)	Exerts AChE inhibitory activity
7.	<i>Centella asiatica</i> (L.), Urb. (Apiaceae)	Reduces apoptosis and hippocampal A β levels <i>in vitro</i> and <i>in vivo</i> . Enhances learning and memory function in mice models of AD. Potential use in the prevention and treatment of beta-amyloid toxicity and AD.
8.	<i>Cinnamomum zeylanicum</i> , Blume (Lauraceae)	Inhibits the formation of A β oligomers. Reduces A β toxicity in neuronal PC12 cells. Reduces A β oligomer and improves cognition in mice model of AD.
9.	<i>Citrus medica</i> (L.) (Rutaceae)	Elicits anti-cholinesterase activity.
10.	<i>Cocus nucifera</i> (L.) (Arecaceae)	Protect from amyloidosis and taupathy (neurofibrillary targets in brain of ovariectomized rats Reduces deposition of A β in cerebral cortex and tau-1 expression in hippocampus

11.	<i>Collinsonia candadensis</i> (L.) (Lamiaceae)	Called horsebalm. Major constituents are carvacol and thymol that crosses blood- brain barrier which are used for AD,
12.	<i>Convolvulus pluricaulis</i> Choisy (Convolvulaceae)	Dose-dependent enhancement of memory was found in mice.
13.	<i>Curcuma longa</i> (L.) (Zingiberaceae)	Statistics indicate definitely (4.4-fold) lower incidence of AD in countries where Curcuma longa is part of daily diet.
14.	<i>Danggui-Shaoyao-San</i> (Apiaceae)	Improve cognitive function in age related memory dysfunction, reduces A β 25-35 induced neuronal cell death and antiapoptotic effect in PC12 cells, ameliorate A β 25-35 induced impairment of spatial learning and memory in mice
15.	<i>Desmodium gangeticum</i> (L.) (Fabaceae)	Elicits AChE inhibitory activity. Improves learning and memory in scopolamine and ageing models of AD in mice
16.	<i>Epimedium koreanum</i> (L.) (Berberidaceae)	Exerts AChE inhibitory activity <i>in vitro</i>
17.	<i>Galanthus nivalis</i> (Amaryllidaceae)	acetylcholinesterase inhibitors Used to treat mild to moderate vascular dementia and Alzheimer's
18.	<i>Malus domestica</i> Borkh. (Rosaceae)	Improves learning and memory in and process organized synaptic signaling in open label trial Exerts antioxidant activity in mice model of AD
19.	<i>Morus alba</i> L. syn.: <i>Morus atropurpurea</i> Roxb. (Moraceae)	Augments the antioxidant defense system Improves learning and memory in mice model of AD
20.	<i>Murraya koenigii</i> Sprangel (Rutaceae)	Improves memory and learning in mice models of AD
21.	<i>Oldenlandia affinis</i> Roem. & Schult. (Rubiaceae)	Inhibits β -secretase activity and decreases A β production
22.	<i>Phagnalon saxatile</i> (L.) Cass. (Asteraceae)	Exhibits antioxidant and acetyl cholinesterase inhibitory activity.
23.	<i>Physostigma venenosa</i> (L.) Balf. (Labiatae)	Its physostigmine content has relevance to cholinergic therapy in Alzheimer's disease
24.	<i>Pinus nigra</i> J.F. Arnold, Syn.: <i>Pinus heldreichii</i> H. Christ (Pinaceae)	Exerts AChE inhibitory activity <i>in vitro</i>
25.	<i>Prosopis Africana</i> (Guill. & Perr) Taub. (Fabaceae)	Inhibits β -secretase activity and decreases A β production

26.	<i>Pterocarpus erinaceus</i> Poir. (Fabaceae)	Inhibits β -secretase activity and decreases A β production
27.	<i>Paeoniae alba</i> Pall. (Paeoniaceae)	Exerts AChE inhibitory activity
28.	<i>Salvia miltiorrhizae</i> Bunge (Labiatae)	Exerts AChE inhibitory activity
29.	<i>Rhizophora x lamarckii</i> (Hybrid of <i>Rhizophora apiculata</i> & <i>R. Stylosa</i> (Rhizophoraceae)	Exerts AChE inhibitory activity <i>in vitro</i>
30.	<i>Salvia leriifolia</i> Benth. (Lamiaceae)	Exerts antioxidant, anti-inflammatory and cholinesterase inhibitory activity.
31.	<i>Salvia officinalis</i> , (L) (Lamiaceae)	Improves learning and memory in patients of moderate AD in a double blind randomized placebo controlled multicenter trial.
32.	<i>Salvia sclareoides</i> Brot. (Lamiaceae)	Exerts AChE inhibitory activity <i>in vitro</i>
33.	<i>Sesuvium portulacastrum</i> (L) (Aizoaceae)	Exerts AChE inhibitory activity <i>in vitro</i>
34.	<i>Suaeda monica</i> Forsk. Ex J.F. Gmel. (Chenopodiaceae)	Exerts AChE inhibitory activity <i>in vitro</i>
35.	<i>Tabernaemontana divaricata</i> (L) R.Br. ex Roem. & Schult. (Apocynaceae)	Inhibits cortical AChE activity and enhances cortical neuronal activity
36.	<i>Thespesia populnea</i> (L) (Malvaceae)	Exerts inhibition of AChE activity. Improves learning and memory in diazepam and scopolamine models of AD in mice.
37.	<i>Trichilia emetic</i> Vahl. (Meliaceae)	Inhibits β -secretase activity and decreases A β production
38.	<i>Valeriana amurensis</i> P. Smirn. (Valerianaceae)	Inhibits the formation of senile plaques decreases. Reduces pro-inflammatory cytokines and cellular fate of cortical and hippocampal neurons in rat model of AD.
39.	<i>Vitis amurensis</i> Rupr. (Vitaceae)	Inhibits neuronal apoptosis and exhibit antioxidant activity in cultures of rat cortical neurons. Improves learning and memory in mice models of AD
40.	<i>Withania somnifera</i> (L) Dunal (Solanaceae)	Semipurified extract of <i>Withania somnifera</i> reverses AD pathology. Nerving tonic, aphrodisiac, rejuvenative, antioxidant activity, calming effect, reverses behavioural deficit.
41.	<i>Zingiber officinalis</i> Rosc.	Exerts A β aggregating, antioxidant and AChE

	(Zingiberaceae)	inhibitory activity.
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2. Conclusion:

AD is the most common neurodegenerative disease in current scenario over the world with no effective drugs or therapy to treat the disease. Traditional oral-based AD therapies were failed due to several limitations, now a hope to new chemical entities where medicinal plants can play a vital role being the rich source of pharmacological principles and vast diversity. Many valuable medicinal plants applied to reduce dementia and treat AD. But The main chemical compounds, such as flavonoids and alkaloids, have been shown to have strong effects against AD. The pathogenesis of the Alzheimer disease involves amyloid- β cascade, protein misfolding, tau hyperphosphorylation, inflammation, gene mutation, mitochondrial dysfunction, and oxidative stress etc. It has been suggested that the multi-factorial nature of AD pathogenesis requires the design of medicines with a wide spectrum of activity. Herbal drugs are known to consist of multiple compounds and may implicate multiple mechanisms, thus being advantageous over the simple single-target drugs in the treatment of complex diseases. Due to capability of multiple target regulation compared with the single-target antagonist in the view of traditional medicine natural drugs will hopefully show promising results for treating AD in the near future.

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