NEUROPROTECTIVE ACTIVITY OF SOME MEDICINAL PLANTS

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ABSTRACT

Alzheimer’s disease (AD) is a type of disease which is characterized by a disorder of the brain in which the memory and thinking skills are slowly destroyed. This makes it difficult for a person to carry out the simplest task. It is also a type of dementia. Until now still there is no perfect cure for Alzheimer’s disease. Drugs are available only to reduce or eliminate the symptoms of this disease. In this review article, Alzheimer’s disease will be explained briefly along with its symptoms. Most importantly, since the treatment related to this disease is very crucial, plants or plant extracts which can be used to treat Alzheimer’s disease will be discussed.

Key words: Alzheimer’s disease, dementia, treatment, plants, plant extracts

INTRODUCTION

Alzheimer’s disease is a brain disorder which is irreversable and progressive capable of destroying brain’s function such as memory and thinking skills. This disease got its name from Dr. Alois Alzheimer. In 1906, the changes in brain tissue of a woman who passed away due to an abnormal mental illness was noticed by Dr. Alzheimer. So, he examined her brain and realised that there were many unusual clumps fibres which were tangled. This is how he came to know that these clumps and tangles are one of the main causes of Alzheimer’s disease.

Currently, Alzheimer’s disease is ranked in 6th place for being the main cause of death in the United States, but recently it is known that this disease is ranked 3rd behind heart disease and cancer. Besides that, Alzheimer’s disease is a type of dementia. Dementia refers to the impairment in cognitive functioning such as thinking, remembering and reasoning as well as disturbance in behaviours to the extent that a person’s cannot carry out his or her daily activities normally.

Generally, Alzheimer’s disease is very dangerous because it is fatal within 5-10 years of its onset. Approximately, 5 million people in the United States currently have Alzheimer’s disease[1]. To date, there is no drugs to completely cure AD. The few agents that are approved by the FDA for the treatment of AD have only modest efficacy in terms of modifying clinical symptoms, and none appear to affect disease progression or prevention [2]. Many researches are being carried out by scientists throughout the world to find a way to prevent or treat this condition.

The symptoms of Alzheimer’s disease are as follows:

- forgetfulness
- mild confusion
- difficult to remember things
- difficult to organize thoughts
- disorientation
- decreased ability to speak and write
- difficult to think and make reasoning
- inability to perform routine task efficiently
- personality and behaviour changes

PLANTS AND PLANT EXTRACTS IN THE TREATMENT OF ALZHEIMER’S DISEASE

Various plants and plant extracts can be used in the treatment of Alzheimer’s disease. The plants or plant extracts are:

A. Ashwagandha

Ashwagandha (roots of Withania somnifera DUNAL) is one of the most valuable herbal drugs used in Indian traditional medicine (Ayurveda) as a rasayana drug that is capable of imparting long life, youthful vigor, and good intellectual powers[3]. Ashwagandha is clinically used for the treatment of general debility, consumption, nervous exhaustion, insomnia, loss of
memory, and so on \cite{4,5}. Furthermore, it can be used as anti-inflammatory, anti-tumour, anti-oxidant, immunomodulator and most importantly as anti-neuropsychiatric. The main constituent of Ashwagandha extract is withanolide. It is this constituent and its derivatives which play a major role in AD treatment. Once axon and synaptic regeneration are promoted, then neuronal networks will be reconstructed and AD recovery can be seen. Therefore, the effects of methanol extracts of Ashwagandha on neurite outgrowth using an in vitro culture system were investigated; methanol extract of Ashwagandha showed neurite outgrowth-promoting activity in human neuroblastoma SK-N-SH cells \cite{6}. Methanol extract contains active constituents such as withanolide A, withanoside IV and withanoside VI which causes neurite outgrowth in human neuroblastoma SH-SY5Y cells and rat cortical neurons. Each of these 3 compounds induced axonal growth even in the presence of Aβ25–35\cite{7,9} when were used individually to treat the neurons with degenerated axons. Table I shows the effects of Ashwagandha extracts, constituents and derivatives on Alzheimer’s disease \cite{10}.

**B. Berberine**

Berberine is a natural isoquinoline alkaloid isolated from the Chinese herb *Rhizoma coptidis*, which has been widely used in Chinese herbal medicine \cite{11}. Due to its various biochemical and pharmacological effects such as anti-viral, anti-bacterial and anti-cancer activities, Berberine has been given a lot of attention for the past years. Accumulating evidences indicate that berberine also possesses potential to treat AD \cite{12,13}. For instance, it was demonstrated that intragastric administration of berberine (50 mg/kg) once daily for 14 days significantly ameliorated the spatial memory impairment in the rat model of AD \cite{13}. Not only that, recently it was suggested that Berberine may act as multipotent agent to overcome AD based on the various activities possessed by natural product’s such as anti-oxidant, AChE and BChE inhibitory, MAO inhibitory, Aβ level-reducing and cholesterol-lowering activities. Since oxidative stress is one of the causes of AD, Berberine acts by scavenging the free radicals. Berberine can scavenge reactive oxygen species (ROS) and reactive nitrogen species (RNS) \cite{12,14-18}. In RNS, peroxynitrates (ONOO−) are generated by the reaction between nitric oxide (NO−) and superoxide anion radical in vivo which results in formation of Aβ and its accumulation. Previous studies showed that berberine can scavenge both NO and ONOO− \cite{12,16}.

In addition, berberine inhibits acetylcholinesterase enzyme (AChE) and butyrylcholinesterase (BChE) activity. Basically, ACh is needed for proper brain functioning. As in Alzheimer’s disease, AChE breaks down acetylcholine to choline. This leads to lack of ACh. In this case, Berberine inhibits the activity of AChE which results in improved neurotransmission. In addition, BChE also plays an important role in the aetiology and disease progression of AD beyond regulation of synaptic ACh levels \cite{19}. It has been found that Aβ neurotoxicity is amplified when BChE is added to Aβ in tissue culture \cite{20}. Many studies proved that berberine exerts inhibitory effect against AChE \cite{12,21-23}. Jung and co-workers reported that berberine can inhibit AChE with an IC50 of 0.44 μM \cite{12} and a close value of 0.58 μM and 0.37 μM was reported by Ingkaninan et al. \cite{22} and Huang et al. \cite{22}, respectively. It is proposed that the binding of berberine to AChE is principally driven by a favourable entropy increase and the inhibition of AChE with berberine consists of the main contributions of interaction as well as minor conformation change of AChE induced by berberine \cite{26}. In addition, berberine is also found to be a BChE inhibitor and the corresponding IC50 was estimated to be 3.44 μM \cite{12}. This sufficiently indicates that Berberine has dual function which is inhibitors of both AChE and BChE.

**C. Cinnamon**

*Cinnamomum* (肉桂 ròu guì), which is derived from a Greek word that means sweet wood, comes from the inner bark of tropical evergreen cinnamon trees \cite{27}. *Cinnamomum* (cinnamon) is a genus of the Lauraceae family, many of whose members are used as spices \cite{28}. Cinnamon is divided into two different categories based on the places in which they grow. The first one is called Ceylon or true cinnamon (*Cinnamomum zeylanicum* Blume) which grows in South India and Sri Lanka whereas the second one is called cassia (*Cinnamomum aromaticum* Ness) which grows in Vietnam, China and Indonesia. Cinnamon has been extensively used in traditional medicines and preparation food ever since the ancient times by the Chinese and Egyptians. It possesses several activities such as anti-inflammatory, anti-pyretic, anti-oxidant and anti-bacterial besides being used to treat cardiovascular disease, cold, flatulence, diarrhoea. Not only that, it is also used in tea preparation as well as spice. Several studies have also found that cinnamon extract (CE) displays anticancer activity \cite{29}.

*Cinnamomum* (肉桂 ròu guì) contains components such as mucilage, tannin, sugar, resin, and essential oil. It is the essential oil which is the major constituent that plays an important role. It contains cinnamaldehyde...
or cinnamic aldehyde which provides the wonderful smell and taste of cinnamon. Many studies have proven that the accumulation of soluble oligomeric assemblies of β-amyloid polypeptides [amyloid-beta (Aβ)] play a key role in AD development [30]. Aβ plaques formation can be inhibited by compounds which are derived from natural sources. A study showed that toxic Aβ oligomers formation can be inhibited by Cinnamon (肉桂 蘇桂) extract (CEppt) thus preventing Aβ toxicity on neuronal PC12 cells. In another study, the oral administration of CEppt to an aggressive AD transgenic mice model led to the reduction of plaques and improvement in cognitive behaviour. The results showed that the use of natural compounds such as cinnamon can inhibit toxic oligomeric Aβ species formation in AD [30]. The development of AD can also be caused by extracellular plaques such as Aβ and intracellular neurofibrillary tangles of tau whereby these tangles are formed in the later stages of amyloid formation. Tau refers to a protein which in real condition have little or no structure and contains polyrich regions in its molecules. In this case, drugs are developed to inhibit tau accumulation. The actions of an aqueous extract of cinnamon containing proanthocyanidins was examined on tau aggregation, and it was found that the extract of the whole cinnamon effectively inhibited the aggregation of human tau in vitro, and this could be attributed to both proanthocyanidin timer and cinnamaldehyde in CE [31].

D. Red wine
Grape fruits and seeds contains polyphenolic extract which is effective against AD. In recent studies, it is found that grape seed polyphenolic extracts (GSPE) are capable of interfering with tau-mediated toxicity by interfering with the abnormal aggregation of tau [32-34]. Moreover, it is also found that dietary supplementation with GSPE in tau mouse models effectively reduced the severity of abnormal tau aggregation and neuropathology in the brain [32-34]. Although there are studies being conducted to evaluate the efficacy of preparations derived from grapes to preserve cognitive function, there is data which explains that GSPE also has protective activity against AD since tau is one of the major contributor of AD. Wine consumption in moderate amount is effective against AD. Besides having anti-oxidant activity, polyphenols in red wine and other grape-containing products act directly by Aβ modulation and tau-related action in the brain. Since there is no specific mechanism of action for red wine on how it is used to treat AD, there is urgent need to study on this field so that more information can be obtained regarding the biologically active phenols found in grape fruits and seeds.

E. Ferulic acid
The vastly distributed component of plants is ferulic acid which is 4-hydroxy-3-methoxycinnamic acid or FA. It got its name from a plant known as Ferula foetida in which FA was isolated from in the year 1866. It is most abundant in cereal grains where FA can reach the concentration of 2 g/kg dry weight [35, 36]. FA has several functions in plants such as:
- protection of cells against hydrolytic enzymes during germination [37]
- regulation of plant growth [38]
- inhibition of competing plants [38]
- uptake of minerals and water in roots [39]
- protects cereals against aphids [40], insects [41], and fungal infections [42]
Ferulic acid is capable of scavenging free radicals due to its anti-oxidant activity and prevent amyloid formation. These two factors are contributors for Alzheimer’s disease. As for anti-oxidant activity, the chemical structure of FA promotes very strong scavenging of free radicals. Since there is delocalization of unpaired electron across the whole molecule, a stabilized resonance phenoxy radical can be formed. The scavenging activity is increased when collision of ferulate radical occurs which results in curcuma molecule production. Not only that, the tertiary structure obtained by the carboxylic acid group with adjacent unsaturated C-C double bond can stabilize free radicals via resonance or by offering additional sites to prevent free radical membrane attack [43].
FA contains one phenolic ring and is one of the metabolites of the curcuma, which has been demonstrated to possess neuroprotective capabilities resulting from its ability to directly alter the kinetics of Aβ fibril formation, as well as its anti-oxidative and anti-inflammatory properties [44]. FA is similar in structure to curcuma which is a compound with anti-amyloidogenic and fibril-destabilizing activity. Therefore, it is shown that FA too can be an appropriate molecule to specifically bind to Aβ and prevent formation of fibril. In addition, this molecule can be of important value in case of interactions with mature fibrils of Aβ thus, causing continuous destabilization. Based on a study, FA was found to inhibit formation of fibril and extension as well as destabilizing preformed fibrils. However, the effect of FA was reported to be a little weaker than the curcuma’s inhibitory effects. On the basis of these results it was speculated that “FA could prevent the development of AD, not only through scavenging reactive oxygen species, but also through direct inhibition of the deposition of fibrils in the brain” [45].
FA has pleiotropic biological activities, including anti-inflammatory and antioxidant properties, suggesting that long-term administration could delay the progression of AD. It has been, indeed, reported that the long-term administration of FA to mice protected against learning and memory deficits induced by centrally administered β-amyloid [46].

F. Ginkgo biloba

Ginkgo biloba is a tree with a main constituent known as EGb761. EGb761 is extracted from the leaves of this tree. This is used widely in herbal supplements as well as for medicinal purposes. In the early 1970s, Dr. Willmar Schwabe Pharmaceuticals (Karlsruhe, Germany) successfully improved methodical procedures for the extraction and standardization of Ginkgo biloba preparation and produced highly concentrated and stable extracts from Ginkgo biloba leaves [47]. From that time onwards, Ginkgo biloba leaves’ extract contain:

- 24% flavonoid glycosides (consisting of quercetin, kaempferol, isorhamnetin etc.)
- 6% terpenoids (3.1% are ginkgolides A, B, C, and J and 2.9% is bilobalide)
- 5–10% organic acids

The active constituents of EGb761 which are pharmacologically active are found to be terenoids and flavonoids. The flavonoids and terenoids are suggested to be the pharmacologically active constituents of EGb761 [48, 49]. Ginkgo biloba has several activities such as anti-oxidant activity, protects function of mitochondria, prevents cell death, anti-inflammatory effect and protects against amyloidogenesis and aggregation of Aβ. The proposal that the beneficial action of EGb761 is mainly due to its free-radical scavenging action is supported by numerous in vitro and in vivo studies [50]. For example, pre-treating cerebellar granule cells with EGb761 effectively attenuated oxidative damage triggered by H2O2/FeSO4 [51]. In another study using two AD models, Aβ-expressing neuroblastoma cell lineN2a and Aβ-expressing transgenic Caenorhabditis elegans, EGb761 was found to be able to attenuate the basal as well as the induced levels of H2O2-related reactive oxygen species (ROS) [50,52]. In addition to direct attenuation of ROS, EGb761 may also stabilize the cellular redox state by up-regulation of the protein level and activity of antioxidant enzymes [53].

AD can also be caused by mitochondrial dysfunction. Recently, it was discovered that EGb761 possesses direct protective activity on mitochondria. This in a way may contribute to the anti-oxidant effect of Ginkgo biloba since the major target and major source of ROS is the respiratory chain of mitochondria. Using SH-SY5Y cells, it was reported that, EGb761 prevented amyloid β peptide (Aβ)-induced mitochondrial dysfunction, and thus reduced intracellular ROS generation [49]. It is clearly understood that Aβ plaques play a major role in the development of AD. Therefore, the treatment should aim to prevent or inhibit Aβ formation and aggregation. A number of recent reports indicate that EGb761 protects against Aβ-induced neurotoxicity by blockage of Aβ-induced events, such as ROS accumulation, glucose uptake, mitochondrial dysfunction, activation of AKT, JNK and ERK 1/2 pathways and apoptosis [49,54,55]. Not only that, EGb761 also prevents amyloidogenesis as mentioned previously. On hippocampal slices, Colciaghi et al. demonstrated that EGb761 could push amyloid precursor protein (APP) metabolism towards the α-secretase pathway, thereby increasing the release of the soluble form of APP (sAPPα) [56,57]. It was found that, after EGb761 treatment, Tg-2576 mice exhibited an enhancement of spatial learning and memory comparable to wild type mice [57, 59]. Moreover, due to the action of free circulating and intracellular cholesterol levels which affect processing of APP and amyloidogenesis, EGb761 prevents brain from producing Aβ by decreasing circulating free cholesterol level. Furthermore, EGb761 inhibits Aβ fibrils formation by inhibiting the β-sheet structure of Aβ fibrils which is responsible for the neuronal toxicity of Aβ besides helping Aβ to escape clearance by proteolytic degradation. In addition, when Aβ interacts with transition metal ions, aggregation of Aβ will occur. In this case, EGb761 will inhibit Aβ aggregation due to its iron chelating property.

CONCLUSION

Various studies are being conducted to discover an excellent drug which can permanently cure Alzheimer’s disease. However, till to date, there is no any drug with such characteristic. Although there are drugs in the market which are used in the treatment of AD, but these drugs can only be used to treat the symptoms of AD. Many factors contribute to the pathogenesis of AD. There are many scientific studies and reports which provide useful information regarding the factors associated with AD and the suitable type of treatments. Overall, in this review article, a better understanding of Alzheimer’s disease as well as the plants and plant extracts which can be used to treat AD is discussed. From this, the neuroprotective effects of several drugs obtained from plants are clearly understood. By this, there will be enhanced understanding regarding the effectiveness of these plants and will be useful when designing more drugs related to treatment of AD in the future.

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Table 1: The effects of Ashwagandha extracts, constituents and derivatives on Alzheimer’s disease \[^{[10]}\].

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<th>Functions</th>
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<td>Extract</td>
<td>Neurite outgrowth in vitro[^{[7]}]</td>
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<td></td>
<td>Memory improvement[^{[4]}]</td>
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<tr>
<td></td>
<td></td>
<td>Neuroprotective effects in vitro[^{[1,3]}]</td>
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<td>(\beta) clearance in vivo[^{[3]}]</td>
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<td>Withanolide A</td>
<td>Neurite outgrowth in vitro[^{[4,10]}]</td>
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<td>Axonal regeneration and synaptic reconstruction in vivo and in vivo[^{[2]}]</td>
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<td>Memory improvement[^{[2]}]</td>
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<td>Upregulation of BACE1, ADAM10 and IDE in vitro[^{[1]}]</td>
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<td>Withanoside IV</td>
<td>Neurite outgrowth in vitro[^{[4,10]}]</td>
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<td>Neurite outgrowth in vitro[^{[4,10]}]</td>
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