Treatment of Alzheimer's disease by natural products

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Abstract

Alzheimer's disease is a neurological disorder that progressively affects the brain cells. It is sometimes accompanied with dementia and commonly seen in elderly people. It ultimately leads to impaired cognitive functions and loss of memory. Widely used drugs such as donepezil and galantamine successfully abate mild to moderate symptoms of the disease though they have profound side effects. Natural products have been a source of medicine for over thousands of years. Plant secondary metabolites such as alkaloids, flavonoids, terpenoids, etc. are major sources of such medicines. In recent times, the use of natural products to treat various diseases has gained a lot of popularity. Extensive research is being undertaken to identify and isolate various natural products that can be used to not only reduce the disease symptoms but also as a permanent cure. The review article aims to summarize the effects of various natural products and their neuroprotective mechanisms that can be helpful to cure Alzheimer's disease.

Keywords: AChE, AD, Aβ aggregation, resveratrol, plant secondary metabolites

1. Introduction

Earth's biodiversity is a major natural resource. The variation in the climatic conditions of the earth is what makes the living system so diverse. Biodiversity is considered as a major natural resource because of the various products obtained from it. Out of these products the ones that have the highest importance to us are the ones with medicinal properties. Such natural products form an important form of treatment and healthcare. Nature has been a continuous source of biological agents and natural products used as traditional medicines. These come from aquatic or terrestrial plants, animals, macro- and micro-organisms (1).

Herbal medicines were first used in China several thousands of years ago according to the records. Likewise, Ayurvedic medicine of India is also thought to be 5000 years old (2). There are many Islamic Hadiths that mention the curative properties of *Nigella sativa* also known as black cumin seeds. It specifically mentions that *N. sativa* has cure to every illness except death (3-5). World Health Organization (WHO) report suggests 75% of the global population still depends on herbal medicines for health care (2).

Natural products have therapeutic effects on many chronic as well as acute diseases (6). The plants as well as animal derived products have served as the base of many drug discoveries for many diseases. They have not only been used for the treatment of common diseases, but recent studies have shown that certain natural compounds extracted from plants may have the ability to treat chronic diseases like Alzheimer's Disease (AD) (1).

AD is progressive disorder that leads to the degeneration of brain cells and affects majority of the aged people globally. Most people affected with this disease lie in the age group of 65 to 75 years. Neuroprotective effects of biological agents against AD have been widely studied and further studies related to the mechanism of action may help us to gain an insight as to how these products can be used as drugs for efficient therapies. The knowledge of natural products as well the details regarding the onset of AD may open new vistas in the world of drug development using natural products (7).

2. Alzheimer's disease and its treatment

AD is related to aging. The progressive neuro-degeneration results in loss of memory and impaired cognitive functions. According to 2020 report of Alzheimer's Association, nearly 508 million people affected by AD in USA alone and the numbers are expected to increase with coming years. So far there is no satisfactory cure to this disease. The mechanism of the disease is completely unknown yet however, overproduction of β-amyloid proteins, involvement of oxidative stress and hyperphosphorylation of tau proteins are supposedly the main reasons. This causes disruption of synapsis and neurons in the hippocampus and cerebral cortex,

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decline in cognitive functions and loss of memory. Apart from these, many hypotheses have been postulated that aim at explaining the cause of AD (8).

The current drugs available in market for AD treatment are mainly designed based on the cholinergic hypothesis and the oxidative stress hypothesis. Donepezil, rivastigmine, galantamine, memantine are the FDA approved drugs for the treatment of this disease. These drugs alleviate the symptoms caused by the degeneration of cholinergic neurons and disrupted transmission but do not delay the onset of AD. Apart from memantine, all the other is mainly Alzheimer's disease (AChE) inhibitors. The efficacy of these drugs is poor to moderate and drug response varies individually based on various genetic factors (7, 9).

Metabolism of galantamine and donepezil takes place in the liver. Main enzymes involved in the metabolism are CYP3A4, CYP2D6 and CYPA12. Rivastigmine is bio transformed through carbamylation. Donepezil and galantamine primarily inhibit AChE but also act on BChE, whereas rivastigmine inhibits both equally. Memantine on the other is an antagonist of the NMDA (N-methyl-D-aspartate) receptor and inhibits the effect of increased glutamate levels which lead to neuronal cell death (9).

According to a study reported by Santamaria et al. (9), certain mild to moderate side effects of these drugs were observed over a certain period. It was noted that patients administered with donepezil developed nausea, bradycardia, abdominal pain, diarrhea, dizziness, orthostatic hypotension accompanied with headache, rhinitis, muscle cramps and cholinergic symptoms. Donepezil also causes syncopal episodes. Also due to enhanced activation of visual association cortex, donepezil has been known to cause nightmares during REM sleep (10).

Administration of rivastigmine led to anorexia, diarrhea, nausea and vomiting after about 26 weeks. Furthermore, people treated with a combination of donepezil, rivastigmine and galantamine suffered from epigastric pain, diarrhea, irritability, vertigo, dizziness, abdominal pain, nausea, cardiovascular events, rash, depression, perspiration, hallucination, falls, agitation, and insomnia. When administered with a combination of just donepezil and rivastigmine, patients suffered from vomiting, diarrhea, nausea, anorexia, abdominal pain, falls, anxiety, agitation, dizziness, headache, and urinary tract infection (9).

3. Natural products for the treatment of AD

As discussed earlier, the FDA approved drugs for AD cause a lot of side effects thus, researchers have undertaken studies to discover natural remedies that may not only alleviate the disease but have the potential to completely cure it. A promising cure for AD has not yet been found, but a number of natural compounds extracted from various plants have successfully been used to reduce the symptoms of AD.

These products belong to various classes of secondary metabolites produces by different plants. A brief classification of the products according to the class is given below.

3.1. Flavonoids

Flavonoids (Fig. 1) are plant secondary metabolites, which contain 15-carbons, two phenyl rings and a heterocyclic ring (11). All types of flavonoids have a capacity to act as antioxidant. They have an additive effect to endogenous scavenging compounds. In addition, flavonoids contain anti-AChE activity. Both of these properties can be harvested for the treatment of AD. Following flavonoids have been found to be effective against AD (12).
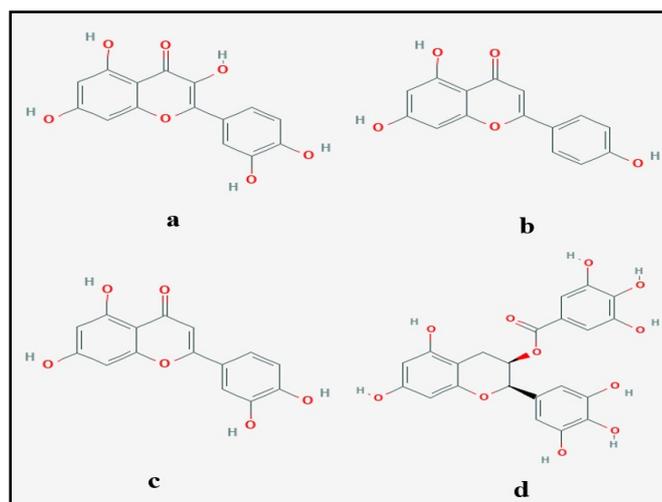

Fig. 1. Structures of flavonoids, (a) Quercetin (National Center for Biotechnology Information. PubChem Compound Database; CID=5280343), (b) Apigenin (National Center for Biotechnology Information. PubChem Compound Database; CID=5280443), (c) Luteolin (National Center for Biotechnology Information. PubChem Compound Database; CID=5280445), (d) Epigallocatechin gallate (National Center for Biotechnology Information. PubChem Compound Database; CID=65064)

3.2. Quercetin

Quercetin (Fig. 1a) is present in a variety of foods such as apples, onions, berries, tea, etc. It is a flavone type flavonoid that possesses antioxidant properties and scavenges ROS. This free radical scavenging property could inhibit lipid peroxidation (7). It shows strong inhibition of 5-lipoxygenase and cyclooxygenase-2 (COX-2), which are involved in the production of arachidonic acid and eicosanoids. It also inhibits prostaglandins production and nuclear factor κB (NF) activation (13).

In the brains of Sprague-Dawley rats, quercetin inhibited manganese (Mn) induced apoptosis and inflammatory response by the activation of nuclear factor E2-related factor 2 (Nrf2) and hem oxygenase (HO-1) and inhibits NF-κB activity (13, 14). Quercetin doses up to 10 μM showed anti-amyloidogenic effects thus inhibiting Aβ fibrils. It also reduces the apoptosis in neuronal cells due to Aβ, however induces cytotoxicity at levels higher than 40 μM. Recently, solid lipid nanoparticles of quercetin have shown better

penetration in the blood-brain barrier (15). The nano-encapsulated quercetin shows enhanced neuroprotective effect. The elimination of quercetin is exceptionally low which might lead to its accumulation in the body (16). Though neuroprotective in nature, increase in the levels of quercetin may lead to neurotoxicity and carcinogenicity. Therefore, further toxicology research is required to derive a successful drug from this compound (7).

3.3. Apigenin

Apigenin (Fig. 1b) is a yellow crystalline non mutagenic flavone obtained from *Apium graveolen* (celery), parsley, artichoke, and basil. When ingested, apigenin showed high intestinal permeability (7). It is absorbed in the duodenum. Apigenin exhibits strong potent chelating and antioxidant properties (15). It reduces the toxicity of β amyloid (Aβ) induced by copper by binding with transition metals (17). Thus, it controls free radical formation by preventing metal ion participation in the radical reaction. It is found to be effective in scavenging free radicals such as oxygen, nitric oxide, and superoxide anion (15). Apigenin also shows actions like that of estradiol because of which, apoptosis of human neuroblastoma cells induced by oxidative stress in controlled. It is also a potent inhibitor of CYP450 (17). In an experimental model, APP/PS1 double transgenic AD mice when treated with 40mg/kg apigenin for three months, mice showed improved memory retention and learning deficits which was tested using Morris Water Maze. Thioflavin-T (THT) staining proved that the mice showed reduced levels of amyloid deposits (18,19). A reduction of glutamate induced toxicity was seen in rat hippocampal brain and increased intracellular Ca^{+2} by extracellular-signal-regulated kinase/cAMP-response element binding protein/brain derived neurotrophic factor (ERK/BDNF/CREB) pathway (17). 10-50 μM apigenin was able to reduce apoptosis induced by ER stress inducer thapsigargin and brefeldin A. This was achieved by scavenging ROS and inhibiting the activation of caspase-12 (7).

3.4. Luteolin

Luteolin (Fig. 1c) is a yellow crystalline flavonoid found in many plants of bryophyte, pteridophyta, pinophyta and magnoliophyte families. Among dietary products, it is found in celery, oregano, carrots, peppers, olive oil, thyme, etc. (20). It has antioxidant, anti-inflammatory, and antimicrobial activities (7). It can cross the blood brain barrier. HepG2 cells when treated with 50 μM luteolin, showed reduced levels of tumor necrosis factor α (TNF-α) induced inflammation. This was done by suppression of NF-κ light chain enhancer of B cells (20). In several *in vitro* and in vivo models luteolin has been seen to regulate various cytokines (21). Results of an experiment conducted by Ali et al. (22) on Drosophila revealed that luteolin bound to AChE and Aβ peptides which led to the inhibition of AChE and prevented Aβ aggregation. Through THT staining, they also reported decreased Aβ aggregation. Luteolin action also partly includes inducible

nitric oxide synthase (iNOS) function, iNOS expression and NO production (22). Reports suggest that 20-100 μM luteolin reduces zinc induced hyperphosphorylation of tau proteins by its antioxidant activity and regulation of tau phosphatase/kinase system. Moreover, luteolin can control the expression of amyloid precursor protein (APP), reduce the formation of Aβ proteins (15), inhibits caspase-dependent apoptosis (23). It relieves the learning and understanding problems, strengthens the antioxidant system, decreases the lipid peroxidation and inflammation of the brain tissue (16).

3.5. Epigallocatechin-3-gallate

Epigallocatechin-3-gallate (Fig. 1d) is a flavonoid-type catechin found in *Camellia sinensis*, carob flour. Apples, berries like blackberries, strawberries and raspberries, nuts, plums, peaches, avocados, onions have lower amounts of epigallocatechin-3-gallate (7, 15). The strong antioxidant effects of catechins have been studied in cancer, and AD. Activation of antioxidant enzyme, protein survival genes and APP processing are some of its biological roles. Several *in vitro* studies have reported neuronal protection from Aβ induced damages (13). Certain reports indicate an enhanced synaptic plasticity in brain due to epigallocatechin-3-gallate's interaction with AChE receptors and its direct binding with Aβ protein inhibits β sheet formation (17). Epigallocatechin-3-gallate is absorbed at the small intestine by passive diffusion; however, high concentrations saturate these tissues. Important roles of Epigallocatechin-3-gallate include:

- Enhancement of glutathione peroxidase activity
- Inhibition of AChE activity, NO metabolite formation and ROS generation (7)
- Inhibition of γ-secretase enzyme activity
- Prevention of lipopolysaccharide induced memory loss and apoptosis
- Reduction of the expression of inflammatory factors; TNF-α, IL 1β, IL-6, inducible nitric oxide synthase (iNOS), COX-2
- Prevention of astrocyte activation in neuronal cells (15)
- Enhancement of neurite outgrowth (24)
- Cholinergic transmission enhancement (24)
- Cognitive function improvement (24)

3.6. Alkaloids

Alkaloids (Fig. 2) are naturally occurring organic compounds containing basic nitrogen atom. They can be extracted from a several organisms such as bacteria, fungi, plants, and animals. The pharmacological properties of alkaloids include antiasthma, anticancer, antimalarial, analgesic, etc. Alkaloids exert anti-AD effect by activating the cholinergic system and exciting the central nervous system (25). Alkaloids that can be used in treatment if AD are:
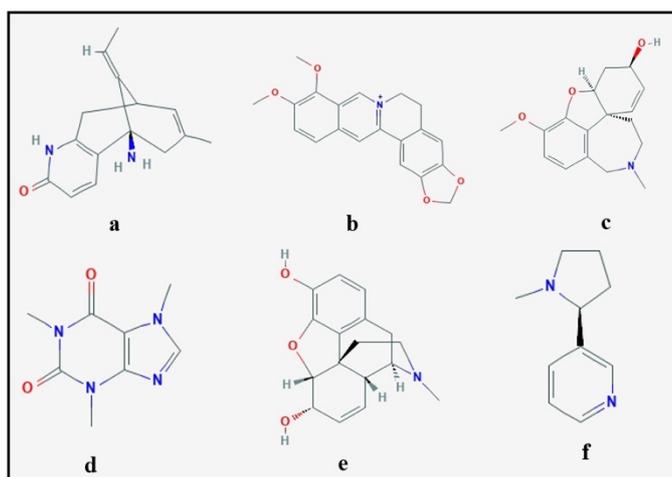
Fig. 2. Structures of alkaloids, (a) Huperzine A (National Center for Biotechnology Information. PubChem Compound Database; CID=44461111), (b) Berberine (National Center for Biotechnology Information. PubChem Compound Database; CID=2353), (c) Galantamine (National Center for Biotechnology Information. PubChem Compound Database; CID=9651), (d) Caffeine (National Center for Biotechnology Information. PubChem Compound Database; CID=2519), (e) Morphine (National Center for Biotechnology Information. PubChem Compound Database; CID=44461111), (f) Nicotine (National Center for Biotechnology Information. PubChem Compound Database; CID=86594)

3.7. Huperzine A

Huperzine A (Fig. 2a) is a sesquiterpene alkaloid isolated from the moss *Huperzia serrata* belonging to the family Lycopodiaceace (17). The *H. serrate* extracts are used for improving the memory (7). It is a reversible and selective cholinesterase inhibitor. It is highly non-polar and hence passes through the blood-brain barrier easily (16). It reduces inflammatory loss induced D-galactose-induced in rat hippocampus via NF-kB and inhibiting neurovascular damage and blood brain barrier impairment. In neonatal rats having hypoxia-ischemia induced brain injury, huperzine A prevented cognitive decline and brain damage. In rats with transient focal cerebral ischemia huperzine A is involved in protection through cholinergic anti-inflammatory pathway (13). In streptozotocin induced diabetic rats, it protects full stop is not required against cognitive damage (23). Via activation of Wnt/β-catenin and increasing phosphorylation of GSK-3β and PKC/MAPK pathways by triggering β secretases. Huperzine A (0.1 mg/kg) enhances cognitive impairment (17).

The important roles of Huperzine A in the body include:

● Inhibition of several apoptotic factors, including caspase 3, Bax, and p53.

● Regulation of the production and secretion of the nerve growth factor.

● Restoration of the activity of respiratory chain complexes and prevention of Aβ-induced ATP reduction and mitochondrial swelling (7).

● Reduction of the clumping of β-amyloid and oligomeric A amount in the cortex and hippocampus.

● Inhibition of the NMDA receptor and potassium channel in the brain (15).

Clinical trials of Huperzine A gave good results without any side effects such as dizziness, nausea, gastroenteric problems, headaches, and low heart rate which gives an advantage to Huperzine A compared to other AChE inhibitors for the treatment of AD (16).

3.8. Berberine

Berberine (Fig. 2b) is a chemical found in plants. It is an isoquinoline alkaloid and the main sources are *Coptis chinensis*, *Berberis aquifolium, Berberis vulgaris, Berberis aristata,* etc (8). It is used as a natural yellow dye due to its characteristic yellow fluorescence upon UV activation (15). Berberine is mainly isolated from the *Coptis* rhizome. It mainly has anti-inflammatory, cardio-protective, neuroprotective and antioxidant effects. Berberine in male Wistar rats with focal cerebral ischemia reduced infarct volume and brain edema by acting as an anti-inflammatory agent (26, 27). In rats with memory impairments induced by scopolamine, berberine reduced the production of TNF-α, COX-2, and IL-1β. It also restored the levels of CREB and BDNF (13). Other major roles of berberine include:

● Potent AChE inhibitor, butyrylcholinesterase and monoamine oxygenase.

● Prevention of Aβ plaques formation and aggregation in neuronal cells.

● Inhibition of the production of pro-inflammatory cytokines such as IL-6 in Aβ-activated primary microglia and murine microglial cell line (7).

● Reduction of the expressions of COX-2 and iNOS.

● Prevention of inflammation via by inhibiting NF-κB, phosphoinositide 3-kinase and MAPK signaling pathways.

● Scavenging free radicals such as nitric oxide, peronitrite (ONOO-), hydrogen peroxide, and 1, 2-diphenyl-2-picryl hydrazyl radicals.

● Reducing lipid peroxidation (28).

● Activation of anti-oxidative enzymes such as superoxide dismutase and glutathione peroxidase to protect against oxidative stress (7).

3.9. Galantamine

Galantamine (Fig. 2c) is an alkaloid obtained from *Galanthus* and *Narcissus* species of the family Amaryllidaceae. The structure of galantamine suggests it is a phenylalanine and tyrosine derivative. This compound exhibits many types of pharmacological activities, particularly on central nervous system. It is a potent AChE inhibitor and is thus useful for symptomatic treatment of AD. Galantamine controls the oxidative neuronal damage by scavenging ROS through: (1)

inactivation of P2X7 receptors, (2) protecting mitochondrial membrane potential, and (3) preventing changes in the membrane fluidity (29).

3.10. Caffeine

Caffeine (Fig. 2d) is a common dietary product found abundantly in tea, coffee, cola, and cocoa. It has been reported as a selective non-competitive inhibitor of AChE (24). It is a strong stimulant of the central nervous system via its ability to antagonize adenosine A2A receptors (30). Depletion of AChE from the cerebral cortex is also reduced by caffeine (31). It promotes behavioral functions such as alertness, attention, mood as well as improved learning. All these behavioral functions are stimulated at a low dose. High doses cause anxiety, insomnia, restlessness, and increased heart rate. At low doses, caffeine reduced levels of Aβ and Aβ induced toxicity by reducing caspase-3 expression which was seen in neuroblastoma 2a cells expressing Swedish Mutant APP and protected basal forebrain neurons and cerebellar granule neurons from neurotoxicity due to Aβ. It reduces β-secretase levels, presenilin 1 and controls the level and deposition of Aβ in the hippocampus and entorhinal cortex (30). It scavenges hydroxide and methoxy free radicals thus control the oxidative stress. In addition, caffeine reduces hippocampal tau phosphorylation and the respective proteolytic products (25). It also increases the activity of Protein Kinase A (PKA) and pCREB levels by stimulating the survival pathway which leads to the blocking of p-ERK and p-JNK expression (25).

3.11. Morphine

Morphine (Fig. 2e), type of opioid, widely used as reliable analgesic. Opioids act through G protein-coupled receptors named μ, δ, κ, and the nociceptin orphanin peptide receptor. Heroin, morphine, and oxycodone target the μ-opioid receptors to exert the analgesic effects. Reports on the therapeutic effect of morphine for treatment of AD suggest that morphine protects against microglia-mediated neuroinflammation and oxidative stress. Morphine plays an important role in controlling the intracellular amyloid toxicity by inducing estradiol release and the activation of heat shock protein. Activation of μ-opioid receptor weakens the Aβ oligomer-induced neurotoxicity. Hence, opioid receptors are potential therapeutic targets for AD. However, the use of opioids as therapeutics is strictly restricted due to its addictive property (25).

3.12. Nicotine

Nicotine (Fig. 2f) has been investigated extensively for its therapeutic value as it supports cholinergic functions of the body. It binds to and prevents the aggregation of Aβ, exerting a neuroprotective effect. Therapeutic effect of nicotine in animal models has shown encouraging results. Unlike the effect on memory nicotine demonstrated promising result on attention in AD patients. Cotinine, metabolite of nicotine, is also considered as an effective alternative to nicotine. Cotinine possesses similar effects as nicotine, without the

negative side-effects. Results with AD mouse model have shown that it prevents working and reference memory loss. This is achieved by preventing the aggregation of Aβ peptides both *in vitro* and *in vivo*, inhibiting GSK-3β activity, and activating the pro-survival enzyme Akt. Thus, cotinine may become a promising compound for AD treatment (25).

3.13. Terpenoids

Terpenoids (Fig. 3) are a diverse class of secondary metabolites which are derived from terpenes. They are multicyclic with oxygen containing functional groups. Terpenoids are responsible for imparting scent, colour, flavor etc. to different plants. Terpenoids that can be used for the treatment of AD are.
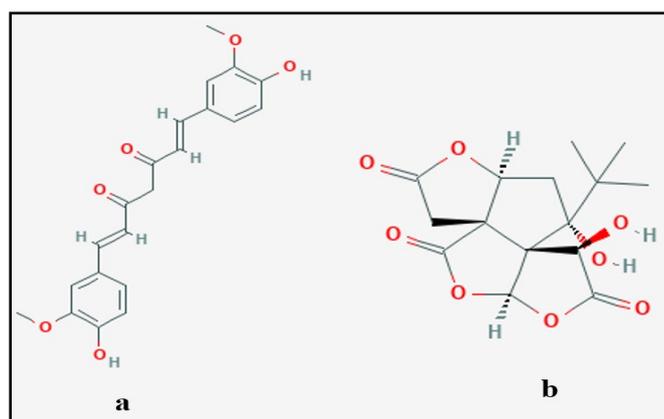

Fig. 3. Structures of Terpenoids, (a) Curcumin (National Center for Biotechnology Information. PubChem Compound Database; CID=969516), (b) Bilobilade (National Center for Biotechnology Information. PubChem Compound Database; CID=73581)

3.14. Curcumin

Curcumin (Fig. 3a) is a principal diarylheptanoid isolated from the rhizome of *Curcuma longa* which belongs to the Zingiberaceae family (7). The other curcuminoids present are demethoxycurcumin and bis-demethoxycurcumin. Curcumin imparts the characteristics yellow color to the rhizome. It is useful in the prevention and treatment of several diseases such as cystic fibrosis, inflammatory diseases, neurodegenerative diseases, etc. (15). It is an efficient antioxidant, antibacterial and antitumor agent. Curcumin suppresses the formation of amyloid plaques. It not only interferes with Aβ aggregation which leads to formation of Aβ fibrils, but also destabilizes preformed Aβ fibrils. It suppresses the formation of APP and β-secretase mRNA (16). In mice models, intragastric administration of curcumin showed reduced Aβ formation. This was done by downregulating the BACE1 expression which is responsible for cleaving APP to Aβ (32). Curcumin at a concentration range of 12.5-2 μM reduces the expression of cytokines TNF-α and IL-1β and chemokines. Curcumin inhibits AChE activity (28). The distance between the two aromatic rings of curcumin molecule allows it to favorably interact with quaternary and peripheral sites of AChE (24). Curcumin posseses strong antioxidant, anti-inflammatory and free

radical scavenging properties which help to control some AD symptoms. In vitro curcumin competes with vitamin E in controlling lipid peroxidation and ROS levels which reduces amyloid accumulation and neurotoxicity (33). Curcumin at a dose of 5–10 μM protects cells against Aβ-induced neurotoxicity by inhibiting oxidative damage and tau hyperphosphorylation (7). It is also involved in suppressing Presinilin-1 activity stimulated by GSK-3β and thus inhibits further Aβ formation (33). Though curcumin does not show any major side effects, however, excess use of it may damage the gut microbiota, and disturb the immune functions (16).

3.15. Bilobalide

Bilobalide (Fig. 3b) is a principle terpenoid obtained from the leaves of Ginko biloba. It is a sesquiterpene trilactone which gives strong protection to neurons and Schwann cells (16). It reduces the expression of p53, Bax, and caspase-3 proteins as well as inhibits ROS-induced apoptosis. It blocks the β-secretase activity of cathepsin B and in turn brings down the production of two β-secretase cleavage products of APP, Aβ and soluble APP, via PI3K dependent pathway (15). To achieve this bilobalide acts through GSK-3 signaling as a downstream target of the activated PI3K pathway. In hippocampal neurons, BB activates neurogenesis and synaptogenesis by increasing the levels of cAMP-response element binding protein (pCREB) and brain derived neurotrophic factor (BDNF) (7). Overdose of BB may initiate adverse effects on the recovery of regenerated nerves (28).

3.16. Phenylpropanoids

Phenylpropanoids are a vast class of compounds which are synthesized from amino acids tyrosine and phenylalanine. They are found throughout the plant kingdom and provide protection to the plant from ultraviolet light and pathogens. Stilbenoids, derivatives of stilbenes, is a class of phenylpropanoids. The stilbenoids involved in the treatment of AD are:

3.17. Resveratrol

Resveratrol (Fig. 4) is a compound found in red wine, nuts, skin of grapes and various plants belonging to the class Vitaceae (28). It has good anti-cancer, anti-inflammatory, antioxidant and neuroprotective properties (7). It helps in lowering the blood pressure and blood glucose levels. Resveratrol is taken up effectively in gastrointestinal lumen, but it does not remain in the body due to rapid metabolism and clearance. To overcome this problem Bui and Nguyen reported the use of resveratrol loaded lipid core nano-capsules to increase its concentration in brain tissue, compared to free resveratrol (15). The strong antioxidant activity of resveratrol increases glutathione as well as antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase levels and improves the levels of endogenous antioxidants (34). It inhibits lipopolysaccharide induced inflammatory mediators such as NO, TNF-α, variety of interleukins, C-reactive protein and chemokine monocyte chemotactic protein-1 in astrocytes (34). Resveratrol can also lower the

level of β-amyloids by promoting the cleavage of APP and its rapid elimination. It also enhances the binding of transthyretin, a transporter protein to Aβ oligomers by structure stabilization, and thus prevents Aβ aggregation (35). It inhibits AChE activity in neuronal cells. In a helminth parasite *Raillietina echinobothrida*, after treatment with 135μg resveratrol, it showed about 46% inhibition of AChE (24). Resveratrol prevents hyperphosphorylation and mediates dephosphorylation of tau proteins. It is a strong antioxidant and scavenges ROS, increases GSH level and enhance overall antioxidant capacity of the cell (7). Resveratrol increases intracellular Ca^{2+} in cortical neurons via modulating second messengers, cGMP, cAMP, and NO. This rise in Ca^{2+} enhances the cellular glucose utilization by calcium dependent AMP-activated protein kinase (28). It is also an activator of various sirtuins such as SIRT1, SIRT2 and SIRT3. Sirtuins are involved in neuronal cell survival and longevity. Thus, resveratrol reduces Aβ aggregation via activation of sirtuins (36).
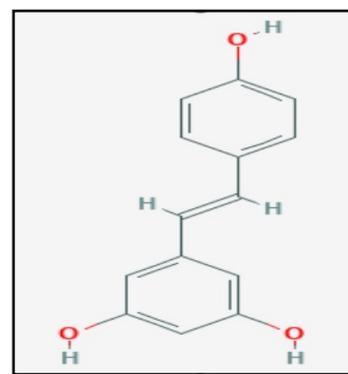

Fig. 4. Structure of Resveratrol (National Center for Biotechnology Information. PubChem Compound Database; CID=445154)

3.18. Carboxylic acids

Carboxylic acids are organic acids containing a hydroxyl group. As the name suggests, these are acidic in nature and are generally weaker than mineral acids. These acids occur widely in nature. They are found in milk, citrus fruits and also in the bodies of many animals such as ants. Carboxylic acids useful in treatment of AD are:

3.19. Rosmarinic acid

Rosmarinic acid (Fig. 5) is a polyphenol carboxylic acid found in many Lamiaceae herbs which are commonly used in food such as *Mellisa officinalis* (Lemon Balm), *Rosmarinus officinalis* (Rosemary), *Origanum vulgare* (Oregano), *Salvia officinalis* (Sage), etc. It is an ester of caffeic acid and dihydroxyphenyl lactic acid (37). Taguchi et al. (38) conducted an experiment using docking simulation and direct binding studies and showed that the catechol functional group on caffeic acid is important for binding. It is used in many pharmacological activities. Rosmarinic acid is a strong antioxidant, antibacterial, anti-inflammatory, anticancer, antiviral, and neuroprotective. 10 μM of rosmarinic acid suppressed Aβ cytotoxicity, ROS generation, caspase3 activity, DNA fragmentation, lipid peroxidation and tau

hyperphosphorylation in cultured PC12 cells (39). It has been observed to prevent β-amyloid induced memory loss. This is because of its ability to inhibit NF-κB and TNF-α expressions (7). It protects neuronal cells by protecting against cytotoxicity induced by β-amyloid. It reduces the hyperphosphorylation of tau proteins. Rosmarinic acid inhibits apoptotic pathways by preventing ROS formation, caspase-3 activation, and DNA fragmentation. Rosmarinic acid by controlling lipid peroxidation and inflammation is able to prevent locomotor activity, short-term spatial memory and alterations of brain tissue found in a rat model of AD. These results further need to be supported by clinical trials to demonstrate the effect of rosmarinic acid against AD (16). Rosmarinic acid also showed 28% inhibition of AChE and 80% inhibition of BChE at a concentration of 10 µg/ml (39, 40).
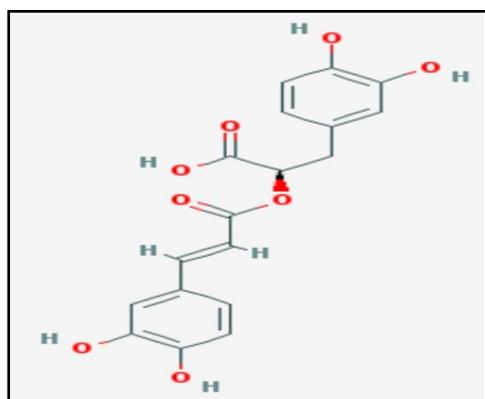

Fig. 5. Structure of Rosmarininc Acid (National Center for Biotechnology Information. PubChem Compound Database, CID-5281792)

3.20. Polysaccharides

Polysaccharides are long chain of monomers joined together by glycosidic bonds. These are basically sugar molecules bound to each other. Polysaccharides can be linear or branched depending upon the monomers that make them up. Polysaccharides that are active against Alzheimer's Disease are:

3.21. Chitosan

Chitosan (Fig. 6) is a polysaccharide of D-glucosamine and N-acetyl-D-glucosamine. It is produced by deacetylation of chitin, component of the exoskeleton of crustaceans and cell wall of fungi (7, 41). It is a potent coagulant and is used in making of bandages. Chitosan nanoparticles have been studied for the delivery of rivastigmine and tacrine to CNS for the treatment of AD (7, 42). More interestingly, a chitosan nanocarrier is designed as a nano-vaccine to deliver Aβ into brain (43). Recent studies suggest that chitosan itself could protect neurons against H_2O_2-induced apoptosis by preventing Aβ formation and blocking intrinsic apoptosis pathway (44). It upregulates Nrf2 and inhibits NF-κB in neural cells. Chitosan protects the cells by reducing the intracellular ROS and Ca^{+2} levels and suppressing apoptosis. It inhibits Aβ induced AChE activity as well as the phosphorylation of

MAPK whose aberrant phosphorylation has been implicated in AD. Water soluble chitosan (10 µg/ml) was able to prevent inflammation in Aβ-stimulated human astrocytoma cells by reducing the TNF-α and IL-6 levels, and suppressing iNOS expression (45). However, the clinical studies did not report any serious side effects of chitosan (7).
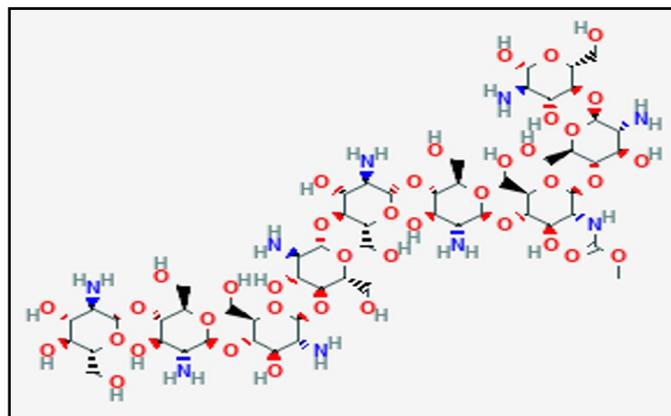

Fig. 6. Structure of Chitosan (National Center for Biotechnology Information. PubChem Compound Database; CID-71853)

3.22. Other Plants

Apart from these above-mentioned compounds, there are other plants which have been identified to have potential to cure AD. These plants belong to various families and the compounds that possess the capability to treat AD has not been classified or tested. These plants are:

3.23. *Zingiber officinale* (Ginger)

Zingiber officinale (Fig. 7a) has been widely used in food supplements and beverages. Principal compounds present in *Z. officinale* are gingerols, shagaols, bisabolene, zingiberene (Fig. 7b) and monoterpenes (46). The main biological effect includes inhibiting the AChE enzyme resulting in higher ACh release in synapses, higher activity of cholinergic pathways, and thereby improved cognitive functions in AD patients. Grzanna et al. (47) reported that treatment of human monocytic THP-1 cells with ginger prevents pro inflammatory cytokines and chemokines (47, 48). It also reduces NF-κβ and IL-1β levels, thus attenuating Aβ induced neuronal cell death and behavioral dysfunction (48). Shagaol, a constituent of ginger inhibits release of NO and the expression of iNOS (46). 6-gingerol treatment protects neuronal cells from Aβ induced cytotoxicity (48). Gingerol treatment led to reduction of oxidative stress and inflammation while it enhanced learning and memory in rat model (49, 50). Furthermore, *Z. officinale* can inhibit lipid peroxidation, reducing the overstimulation of NMDA receptors and prevent the formation of oxidative free radicals (15). In human chondrocyte cells with IL-1 induced oxidative stress, treatment with ginger decreased ROS and lipid peroxidation and increased the levels of catalase, superoxide dismutase. This activity protects against AD.
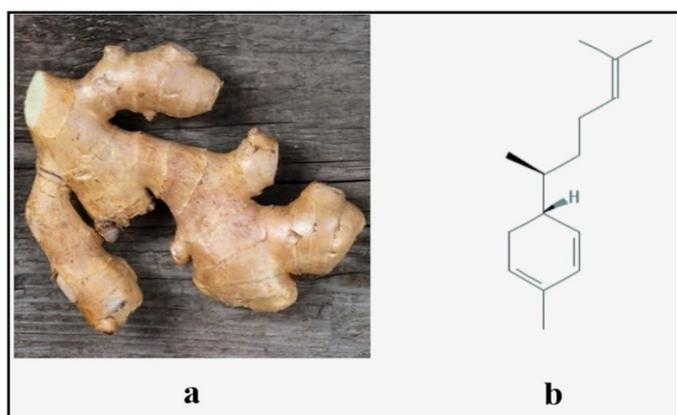
Fig. 7. (a) Rhizome of *Zingiber officinale* (National Center for Complementary and Integrative Health), (b) Structure of Zingiberene (National Center for Biotechnology Information. PubChem Compound Database, CID-71853)

3.24. *Crocus sativus* (Saffron)

Croccus sativus (Fig. 8a) or saffron is a small perennial plant cultivated in Afghanistan, Iran, Spain, and Turkey. It is traditionally used as antispasmodic, stimulant, expectorant, etc. The stigmas (Fig. 8b) of the flowers are a rich source of many compounds such as lycopene, α-crocetin, safranal, etc. These compounds show antioxidant properties as well as inhibit the Aβ fibrilogenesis. It shows moderate AChE inhibitory activity thus inhibiting the ACh breakdown. It also inhibits nitric oxide induced astrocyte cytotoxicity (29). In a study conducted by Akhondzadeh et al. (51), a group was given 15 mg saffron capsules for 16 weeks twice a day. This group showed improved cognitive functions as compared to the placebo group (51, 52). In a time and concentration dependent manner, saffron is also involved in inhibition of Aβ fibrillogenesis. Crocin a component of C. sativus reduced Bax/Bcl-2 ratio and cleaves Caspase-3 and thus inhibits apoptosis (53). By inhibition of LPS induced NO release in rat brain microglial cells, crocin and crocetin provide neuroprotection (46). Reduced levels LPS induced TNF-α, IL-1β and ROS, as well as NF-κβ activation was also observed because of these compounds (53).
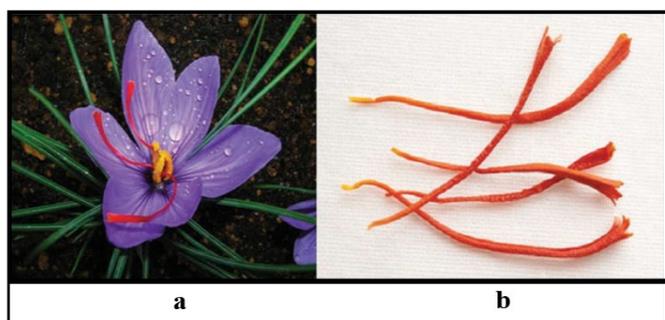

Fig. 8. (a) Flower of *Croccus sativus*, (b) Stigma of *Croccus sativus* (Adapted from Abd-Razak et al., 2017)

3.25. *Allium sativum* (Garlic)

Allium sativum (Fig. 9) belonging to the Amaryllidaceae family is extensively used in food and medicines (53). The components of *A. sativum* are active free radical scavengers.

They increase the levels of antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase; glutathione levels; inhibit lipid peroxidation; and reduce inflammatory prostaglandins. S-allyl cysteine, an organo-sulphur component of garlic protects PC12 cells against Aβ toxicities in a dose dependent manner (54). Aged garlic extracts inhibit 3-hydroxy-3-methylglutaryl-CoA reductase and reduce cholesterol synthesis. They also protect neurons from β-amyloid neurotoxicity and death; prevent cognitive damage, ischemia, and enhance learning and memory (15). Neuronal cultures treated with aged garlic extract and S-allyl cysteine resulted in protection against H2O2 induced oxidative stress (54). This treatment also decreases GSK-3β activity thereby reducing hyperphosphorylated tau in brain of APP-Tg mice. It can also increase insulin and insulin like growth factor in brain which in turn can help decrease Aβ burden in the brain (55).

Fig. 9. Bulb of *Allium sativum* (National Center for Complementary and Integrative Health)

3.26. *Bacopa monnieri* (Brahmy)

Bacopa monnieri plant (Fig. 10) is commonly used in traditional medicine as a nerve tonic, diuretic, cardiotonic agent and for the treatment of asthma and rheumatism (56). Compounds found in *B. monnieiri* are bacopasides III, bacopasides IV, bacopasides V, bacosides A, bacosides B, bacosaponins A, B, C, D, E and F. Saponin glycosides such as jujubogenin and bisdesmosides are also found. It is also applied as paste for epilepsy and insomnia treatment. Saponins and triterpenoids in *B. monnieri* have antioxidant properties thus reducing the oxidative stress in brain (15). It is used as a nootropic drug, i.e., it is used to enhance memory and cognitive functions. It augments protein kinase activity in the hippocampal region to induce the nootropic effect. Consumption of *B. monnieri* decreases cholinergic degradation and enhances cognition. It increases the ACh levels by inhibiting AChE. *B. monnieri* extracts also protect neuronal cells from damage caused by Aβ fibrils. It is known to inhibit lipid peroxidation in hippocampus, striatum areas and frontal cortex of rat brain (57). It also enhances the

expression of SOD and GSH as well as quenches H_2O_2 mediated oxidative stress along with downregulation of lipoxygenase and thus rescues cells from oxidative stress (58). In a study carried out by Nemetchek et al. (59) in cell free assay system, complete inhibition of caspase 1 and 3 was seen while, significant inhibition of TNF-α and IL-6 release from LPS-activated microglia was observed (59).

Fig. 10. Plant of *Bacopa monnieri* (Adapted from Pant et al., 2015)

3.27. *Centella asiatica*

Centella asiatica (Fig. 11) is a plant which has been used traditionally for rejuvenating neuronal cells. It is shown to increase intelligence, longevity, and memory. Asiatic acid and asiaticoside are the bioactive compounds found in this plant. They can control H_2O_2-induced cytotoxicity, reduce free radicals and prevent Aβ induced cell damage. These compounds reduce β amyloid pathology and the oxidative stress response in brain. *C. asiatica* can also reduce oxygen radical production and strengthen the antioxidative defense system by upregulating the activities of antioxidative enzymes and levels of glutathione and glutathione disulfide. Hence, *C. asiatica* can serve important role in the prevention and treatment of AD (15). Asiatic acid, a component of *C. asiatica* demonstrated neuroprotective effects in AlCl3 induced rat model of Alzheimer's disease (60). Asiatic acid also demonstrated improved memory as well as learning in male Sprague-Dawley rats (61). Certain studies have also reported that this plant shows excellent neuritogenic ability by stimulation of neurite outgrowth in human neuroblastoma cells (56).

Fig. 11. Leaves of *Centella asiatica* (Adapted from Tripathi et al., 2015)

3.28. *Olea europaea* (Olives)

Olea europaea is found mainly in the Mediterranean region. The fruits are mainly cultivated to obtain extra virgin olive oil and olive oil. Olive oil alleviates cognitive decline resulting from neurodegeneration. It enhances the activity of glutathione reductase and superoxide dismutase. High doses of extra virgin olive oil reduce the Aβ burden in brain as well as increases Aβ clearance in the blood brain barrier. Oleocanthal, a compound found in extra virgin olive oil removes fibrillation of tau proteins. At low concentrations, it has the capacity to depolymerize Aβ oligomers and protect the neurons (29).

4. Conclusion

Recently, there has been an increase in the cases of neurodegenerative diseases. With synthetic drugs having their side effects, natural products have become the key to the treatment. Several natural products are used alone or in combination to improve memory, alertness and learning in AD patients. The therapeutic effect of herbs and medicinal plants has drawn researchers' attention to study natural products as potentially promising compounds for drug discovery to replace chemically synthesized drugs. This review aims at listing the natural products that can be a cure for AD. Various alkaloids and flavonoids have properties such as anti-AChE, degradation if Aβ fibrils, reduction of hyperphosphorylation of Tau proteins etc. Due to these properties, such compounds have become top candidates for treatment of AD. The major advantage of these products is that they have minimum side effects with high efficacy. Though they are still not fully capable of treatment, they can be used to reduce the symptoms and pathology of the disease.

The increase in the cases of people affected with AD put into sharp focus an urgent need to find a cure for the disease. The many synthetic drugs available in market do a good job of mitigating the effects of the disease, but synthetic drugs are known to have adverse effects on health of a person. The side effects of these drugs are the driving force that majority of the population is looking for an alternative to allopathic medicines. Thus, to avoid these adverse effects, natural products are desirable candidates. Right now, none of the mentioned natural products can fully cure the disease, but in coming years, they can form base for designing a drug which has the potential of eradicating AD. Further research and advanced technological knowledge will surely pave a path for creating such a drug which will be highly efficient with minimum side effects.

Conflict of interest

Authors have no conflict of interest.

References

1. Dar RA, Shahnawaz M, Rasool S, Qazi PH. Natural product medicines: a literature update. J Phytopharmacol. 2017; 6, 340-342.

2. Yuan H, Ma Q, Ye L, Piao G. The traditional medicine and modern medicine from natural products. Molecules. 2016; 21, 559.

3. Ali A. Herbs that heal: the philanthropic behavior of nature. Ann Phytomed. 2020; 9(1), 7-17.

4. Darakhshan S, Pour AB, Colagar AH, Sisakhtnezhad S. Thymoquinone and its therapeutic potentials. Pharmacol Res. 2015; 96, 138-158.

5. Ijaz H, Tulain UR, Qureshi J, Danish Z, Musayab S, Akhtar MF, et al. (prophetic medicine): a review. Pak J Pharm Sci. 2017; 30, 229-234.

6. Memariani Z, Farzaei MH, Ali A, Momtaz S. Nutritional and bioactive characterization of unexplored food rich in phytonutrients. In Phytonutrients in Food SM Nabavi, I Suntar, D Barreca, H Khan, eds. Woodhead Publishing. 2020; 157-175.

7. Ansari N, Khodagholi F. Natural products as promising drug candidates for the treatment of Alzheimer's disease: molecular mechanism aspect. Curr Neuropharmacol. 2013; 11, 414-423.

8. Sanabrio-Castro A, Alvarado-Echeverría I, Monge-Bonilla C. Molecular pathogenesis of Alzheimer's disease: an update. Ann Neurosci. 2017; 24, 46-54.

9. Santamaría TZ, Gómez PY, Galindo IF, González MG, Vázquez AO, López ML. Pharmacogenetic studies in Alzheimer disease. Neurología. 2018; 1-15.

10. Kumar A, Sharma S. Donepezil. In: StatPearls (Internet). Treasure Island (FL), StatPearls Publishing LLC. 2010.

11. Khatri S, Paramanya A, Ali A. Phenolic acids and their health promoting activity. In Plant and Human Health, Volume 2-Phytochemistry and Molecular Aspects, Munir Ozturk and Khalid Rehman Hakeem (Eds.). Springer Switzerland. 2018; pp. 661-680.

12. Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. J Nutr Sci. 2016; 5, e47.

13. Shal B, Ding W, Ali H, Kim YS, Khan S. Anti-neuroinflammatory potential of natural products in attenuation of Alzheimer's disease. Front Pharmacol. 2018; 9, 548.

14. Bahar E, Kim JY, Yoon H. Quercetin attenuates manganese induced neuroinflammation by alleviating oxidative stress through regulation of apoptosis, iNOS/NF-kB and HO-1/Nrf2 pathways. Int J Mol Sci. 2017; 18, 1989.

15. Bui TT, Nguyen TH. Natural product for the treatment of Alzheimer's disease. J Basic Clin Physiol Pharmacol. 2017; 28, 413-423.

16. Gao J, Inagaki Y, Li X, Kokudo N, Tang W. Research progress on natural products from traditional Chinese medicine in treatment of Alzheimer's disease. Drug Discov Ther. 2013; 7, 46-57.

17. Sathya S, Kasi PD. The use of polyphenols for the treatment of Alzheimer's disease. In Role of the Mediterranean Diet in the Brain and Neurodegenerative Diseases, T. Farooqui and A. Farooqui, eds. Academic Press. 2018; pp. 239-252.

18. Zhao L, Wang JL, Liu R, Li XX, Li JF, Zhang L. Neuroprotective, anti-amyloidogenic and neurotrophic effects of apigenin in an Alzheimer's disease mouse model. Molecules. 2013; 18, 9949-9965.

19. Nabavi SF, Khan H, D'Onofrio G, Šamec D, Shirooie S, Dehpor AR, et al. Apigenin as neuroprotective agent: of mice and men. Pharmacol Res. 2017; 128, 359-365.

20. Kwon Y. Luteolin as a potential preventive and therapeutic candidate for Alzheimer's disease. Exp Gerontol. 2017; 95, 39-43.

21. Aziz N, Kim MY, Cho JY. Anti-inflammatory effects of luteolin: a review of in vitro, in vivo, and in silico studies. J Ethanopharmacol. 2018; 225, 342-358.

22. Ali F, Rahul Jyoti S, Naz F, Ashafaq M, Shahid M, Siddique YH. Therapeutic potential of luteolin in transgenic Drosophila model of Alzheimer's disease. Neurosci Lett. 2019; 692, 90-99.

23. Dey A, Bhattacharya R, Mukherjee A, Pandey DK. Natural products against Alzheimer's disease: pharmacotherapeutics and biotechnological interventions. Biotechnol Adv. 2017; 35, 178-216.

24. Jabir NR, Khan FR, Tabrez S. Cholinesterase targeting by polyphenols: a therapeutic approach for the treatment of Alzheimer's disease. CNS Neurosci Ther. 2018; 24, 753-762.

25. Ng YP, Or TCT, Ip NY. Plant alkaloids as drug leads for Alzheimer's disease. Neurochem Int. 2015; 89, 260-270.

26. Chen CL, Tsai WH, Chen CJ, Pan TM. Centella asiatica extract protects against amyloid β1-40-induced neurotoxicity in neuronal cells by activating the antioxidative defence system. J Trad Complement Med. 2015; 6, 362-369.

27. Maleki SN, Aboutaleb N, Souri F. Berberine confers neuroprotection in coping with focal cerebral ischemia by targeting inflammatory cytokines. J Chem Neuroanat. 2018; 87, 54-59.

28. Vazhayll BK, Sundaram RS, Annapadian VM, Abhirama BR, Sudha M, Thiyagarajan T, et al. Natural products and its derived drugs for the treatment of neurodegenerative disorders: Alzheimer's disease a review. Br Biomed Bull. 2014; 2, 359-370.

29. Tundis R, Loizzo MR, Nabavi SM, Orhan IE, Skalicka-Wozniak K, D'Onofrio G, et al. Natural compounds and their derivatives as multifunctional agents for the treatment of Alzheimer disease. In discovery and development of neuroprotective agents from natural products: Natural products drug discovery G Brahmachari, eds. Elsevier. 2018; 63-102.

30. D'Onofrio G, Sancarlo D, Ruan Q, Yu Z, Panza F, Daniele A., Greco A, Seripa Det al. Phytochemicals in the treatment of Alzheimer's disease: a systematic review. Curr Drug Targets. 2017; 18, 1487-1498.

31. Hussain A, Tabrez ES, Mavrych V, Bolgova O, Peela JR. Caffeine: a potential protective agent against cognitive decline in Alzheimer's disease. Crit Rev Eukaryot Gene Expr. 2018; 28, 67-72.

32. Tang M, Taghiblou C. The mechanisms of action of curcumin in Alzheimer's disease. J Alzheimers Dis 2017; 58, 1003-1016.

33. Bhat A, Mahalakshmi AM, Ray B, Tuladhar S, Hediyal TA, Manthiannem E, et al. Benefits of curcumin in brain disorders. BioFactors. 2019; 1-24.

34. Arbo BD, André-Miral C, Nasre-Nasser RG, Schimith LE, Santos MG, Costa-Silva D, et al. Resveratrol derivatives as potential treatments for Alzheimer's and Parkinson's disease. Front Aging Neurosci. 2020; 12, 103.

35. Ahmed T, Javed S, Javed S, Tariq A, Samec D, Tejada S, et al. Resveratrol and Alzheimer's disease: mechanistic insights. Mol Neurobiol. 2017; 54, 2622-2635.

36. Deshpande P, Gogia N, Singh A. Exploring the efficacy of

natural products in alleviating Alzheimer's disease. Neural Regen Res. 2019; 14, 1321-1329.

37. Fachel FNS, Schuh RS, Veras KS, Bassani VL, Koester LS, Henriques AT, et al. An overview of the neuroprotective potential of rosmarinic acid and its association with nanotechnology-based delivery systems: a novel approach to treating neurodegenerative disorders. Neurochem Int. 2019; 122, 47-58.

38. Taguchi R, Hatayama K, Takahashi T, Hayashi T, Sato Y, Sato D, et al Structure-activity relations of rosmarinic acid derivatives for the amyloid β aggregation inhibition and antioxidant properties. Eur J Med Chem. 2017; 138, 1066-1075.

39. Habtemariam S. Molecular pharmacology of rosmarinic and salvianolic acids: potential seeds for Alzheimer's and Vascular Dementia drugs. Int J Mol Sci. 2018; 19, 458.

40. Senol FS, Slusarczyk S, Matkowski A, Perez-Garrido A, Giron-Rodriguez F, Ceron-Carrasco JP, et al. Selective *in vitro* and *in silico* butyrylcholinesterase inhibitory activity of diterpenes and rosmarinic acid isolated from *Perovskia atriplicifolia* Benth and *Salvia glutinosa* L Phytochemistry. 2017; 133, 33-44.

41. Hao C, Wang W, Wang S, Zhang L, Guo Y. An overview of the protective effects of chitosan and acetylated chitosan oligosaccharides against neuronal disorders. Mar Drugs. 2017; 15, 89.

42. Chou CP, Wang YC, Chang SJ, Liu PH, Kuo SM. Evaluation of the effects of chitosan hemostasis dressings on hemorrhage caused by breast biopsy. Breast Care (Basel). 2017; 7, 220-224.

43. Songjiang Z, Lixiang W. Amyloid-beta associated with chitosan nano-carrier has favorable immunogenicity and permeates the BBB. AAPS Pharm Sci Tech. 2009; 10, 900-905.

44. Khodagholi F, Eftekharzadeh B, Maghsoudi N, Rezaei PF. Chitosan prevents oxidative stress-induced amyloid beta formation and cytotoxicity in NT2 neurons: involvement of transcription factors Nrf2 and NF-kappaB. Mol Cell Biochem. 2010; 337, 39-51.

45. Ouyang QQ, Zhao S, Li SD, Song C. Application of chitosan, chitooligosaccharide, and their derivatives in the treatment of Alzheimer's disease. Mar Drugs. 2017; 15, 322.

46. Mirmosayyeb O, Tanhaeu A, Sohrabi HR, Martins RN, Tanhaei M, Najafi MA, et al. Possible role of common spices as a preventive and therapeutic agent for Alzheimer's disease. Int J Prev Med. 2017; 8, 5.

47. Grzanna R, Phan P, Polotsky A, Lindmark L, Frondoza CG. Ginger extract inhibits beta-amyloid peptide-induced cytokine and chemokine expression in cultured THP-1 monocytes. J Altern Complement Med. 2004; 10, 1009-1013.

48. Choi JG, Kim SY Jeoung M, Oh MS. Pharmacotherapeutic potential of ginger and its compounds in age-related neurological disorders. Pharmacol Ther. 2018; 182, 56-69.

49. Zeng GF, Zhang ZY, Lu L, Xiao DQ, Zong SH, He JM. Protective effects of ginger root extract on Alzheimer disease-induced behavioral dysfunction in rats. Rejuvenation Res. 2013; 16, 124-133.

50. Sahardi NFNM, Makpol S. Ginger (*Zingiber officinale* Roscoe) in the prevention of ageing and degenerative diseases: review of current evidence. Evid Based Complement Alternat Med. 2019, 5054395.

51. Akhondzadeh S, Sabet MS, Harirchian MH, Togha M, Cheraghmakani H, Razeghi S, et al. Saffron in the treatment of patients with mild to moderate Alzheimer's disease: a 16-week, randomized and placebo-controlled trial. J Clin Pharm Ther. 2010; 35, 581-588.

52. Leone S, Recinella L, Chiavaroli A, Orlando G, Ferrante C, Leporini L, et al. Phytotherapic use of *Crocus sativus L.* (Saffron) and its potential applications: a brief review. Phytother Res. 2017; 32, 2364-2375.

53. Iranshahy M, Javadi B. Diet therapy for the treatment of Alzheimer's disease in view of traditional Persian medicine: a review. Iran J Basic Med Sci. 2019; 22, 1102-1117.

54. Farooqui A, Farooqui T. Garlic and its effects in neurological disorders. In Neuroprotective Effects of Phytochemicals in Neurological Disorders, First eds. John Wiley and Sons Inc. 2017; 113-131.

55. Calfio C, Gonzalez A, Singh SK, Rojo LE, Maccioni RB. The emerging role of nutraceuticals and phytochemicals in the prevention and treatment of Alzheimer's disease. J Alzheimers Dis. 2020; 77, 33-51.

56. Kaur N, Sarkar B, Gill I, Kaur S, Mittal S, Dhiman M, et al. Indian herbs and their therapeutic potential against Alzheimer's disease and other neurological disorders. In Neuroprotective Effects of Phytochemicals in Neurological Disorders, First eds. John Wiley and Sons Inc. 2017; 79-112.

57. Manap ASA, Vidyabalan S, Madhavan P, Chia YY, Arya A, Wong EH, et al. *Bacopa monnieri*, a neuroprotective lead in Alzheimer disease: a review on its properties, mechanisms of action, and preclinical and clinical studies. Drug Target Insights. 2019; 13, 1-13.

58. Dubey T, Chinnathambi S. Brahmi (*Bacopa monnieri*): An ayurvedic herb against the Alzheimer's disease. Arch Biochem Biophys. 2019; 676, 108153.

59. Nemetchek MD, Stierle AA, Stierle DB, Lurie DI. The Ayurvedic plant *Bacopa monnieri* inhibits inflammatory pathways in the brain. J Ethnopharmacol. 2016; 197, 92-100.

60. Rather MA, Thenmohzi AJ, Manivasagam T, Bharathi MD, Essa M, Guillemin GJ. Neuroprotective role of Asiatic acid in aluminium chloride induced rat model of Alzheimer's disease. Front Biosci. 2018; 10, 262-275.

61. Prakash V, Jaiswal N, Srivastava M. A review on medicinal properties of *Centella asiatica.* Asian J Pharm Clin Res. 2017; 10, 69-74.