Monoamine Oxidase Inhibitory Effects of Medicinal Plants in Management of Alzheimer's Disease

Tuba Ege[1*] ✉ iD **, Hayriye Deniz Şelimen[2]** ✉ iD
[1]European University of Lefke, Faculty of Dentistry, Northern Cyprus TR-10 Mersin, Turkey.
[2]European University of Lefke, School of Health, Northern Cyprus TR-10 Mersin, Turkey.

Abstract: Alzheimer's disease is the most common progressive neurodegenerative disorder that effects large population of society, especially elderly people. Environmental and/or genetic factors contribute Alzheimer's disease to become a pivotal health problem but this relationship remains ambiguous. Globally growing prevalence of Alzheimer's disease requires to understand cellular pathways that lead to Alzheimer's disease and to develop new strategies for prevention and treatment. Elevated monoamine oxidase (MAO) enzymes activity with age is associated with etiology of Alzheimer's disease. Inhibition of monoamine oxidase enzyme can protect from neuronal damage, thus it became one of the key pathway for management of Alzheimer's disease. Using bioactive compounds from medicinal plants as potential monoamine oxidase inhibitors might be a better solution considering undesired side effects of synthetic drugs on human body. The purpose of this review is to implicate the importance of pharmacophore analysis which explains pharmacological properties of medicinal plants and interaction of bioactive compounds from plants with MAO enzyme.

INTRODUCTION

Alzheimer's disease (AD) has been an important health problem that needs to be researched, as it affects the quality of life of millions of people. According to Alzheimer's Association Report (March 2020), the number of people living with Alzheimer's dementia in United States is 5,8 million and is expected to be 13,8 million by 2050 (1). According to the "Dementia in Europe Yearbook 2019 by Alzheimer Europe" report, in Turkey there were 528,547 citizens suffering from dementia in 2018 and due to the increase in the proportion of the 65-and-elder population each year, the number is estimated to be triplicated (1,745,679) by 2050 (2).

Alzheimer's disease is an irreversible age-dependent neurodegenerative disorder that is characterized as lessening the size of brain and locally neuronal death in basal forebrain and hippocampus (3–5) of which common manifestations are progressive loss of memory, cognitive impairments, deterioration of learning and memory functions, disorientation and mood swings and communication problems (4,6–8).

ALZHEIMER PATHOPHYSIOLOGY

There are several hypotheses explaining risk factors (Figure 1) for developing AD such as long exposure to the environmental heavy metals, genetic factors, stress, depression, history of head injuries, hypertension and life styles, etc. but there is no clear consensus (9–11). Abnormal β-amyloid protein deposits outside of neurons and hyper-phosphorylated tau protein inside of neurons are two main factors which lead to develop AD because of misfolded protein accumulation (12).

The formation of senile plaques, (neuritic plaques) which are by products of biological aging, is associated with beta-amyloid protein deposits. β-amyloid precursor protein (APP) in the neuron cell membrane helps neurite outgrowth and repairs after injury (13). APP proteolysis contains two pathways as nonamyloidogenic and amyloidogenic. In nonamyloidogenic pathway, the product of cleavage APP by alpha and gamma secretase is soluble and is not causative agent of AD. However, amyloidogenic pathway produces amyloid beta monomer by beta and gamma secretase (3). In synaptic junction, insoluble sticky clumps of beta-amyloid monomer which form senile plaques-one of the major factors of AD-can block neuron-to-neuron signaling which eventually results in impaired memory and neuroinflammation (3,13). Also certain genetic analyses show that duplication and missense mutation in APP precursor causes certain AD cases. In some AD studies with Down syndrome (DS) showed that three copies of gene encoding amyloid precursor protein (APP) cause overexpression of APP, which is an another risk factor of AD (14,15).

Heat-stable and soluble tau protein in brain cell, which is a microtubule-associated protein (MAP) stabilizes microtubules. Hyper-phosphorylation by intracellular kinase such as cyclin-dependent kinase-5 (Cdk5), glycogen synthase kinase-3β (GSK-3β), Ca^{2+}/calmodulin activated protein kinase II, casein kinase-I elicits paired-helical-filament (PHF) tau and neurofibrillary tangles (NFTs) (16). Abnormal hyper-phosphorylated tau protein inside of the AD patients' brain results in disruption of neuronal signaling and programmed cell death (17).

Besides these two main factors, studied complementary elements which lead developing AD are shown in Figure 1. In addition to amyloid precursor protein (APP) gene mutation, presenilin 1 (PSEN1)-presenilin 2 (PSEN2) and apolipoprotein E (APO E) gene mutations, respectively on chromosome 1 and 19, are involved in progression of AD (11). Patients with presenilin 1 and 2 missense gene mutations and apolipoprotein E (APO E) mutations are prone to develop beta amyloid plaques (18).

Many studies show that genetic polymorphisms of interleukin(19), alpha-antichymotrypsin (20), ATP-binding cassette transporter A1, synaptosomal-associated protein (SNAP-25) (21) and choline O-acetyltransferase (22) are recognized as pejorative factor in developing AD. Also insulin resistance and type-2 diabetes are important risk factor of AD (23). Moreover, some diseases like COVID-19 can prompt neurocognitive alterations and affects neurons and neuroglia (24). Since COVID-19 fatality rate

rises by approximately 11.2% per year of age (25) and this rate is higher in older age(26), patients with Alzheimer and dementia are at risk (27).

The cholinergic hypothesis demonstrates that impairment of cholinergic system contributes cognitive decline (28). Diminished concentration and function of acetylcholine (ACh) which is related with both memory and learning, is one of the marker of AD. While acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) hydrolyzes choline esters like acetylcholine, choline acetyltransferase (ChAT) synthesizes neurotransmitter acetylcholine (28,29). In AD patients' cerebral neocortex and hippocampus, it has been observed that the concentration of ACh and ChAT are decreased (30). Since cholinergic hypothesis is related with reduced ACh concentration, cholinesterase (acetylcholinesterase and butyrylcholinesterase) inhibitors are one of the ameliorating strategies for AD treatment (31).

Oxidative stress, high level reactive oxygen species, is admitted as pejorative factor in occurrence of AD. Oxidative stress in frontal cortex is accepted to be significant in cognitive impairment (3). Because of human brain's need for more energy than other tissues trigger more oxygen-consuming. This increases the possibility of free radicals production and tissue damage (32,33). In normal condition, excessive reactive oxygen level (ROS) can be eliminated by glutathione which is the most common endogenous antioxidant in brain. Attenuation of glutathione level is considered as a contributing factor to damage in hippocampus and frontal cortex (34). Also, ROS stimulates oxidation of lipids, proteins, and nucleic acids in neurons and deposition of amyloid beta and hyper-phosphorylated tau protein as well (32,33).

It is known that monoamine oxidase enzyme (MAO) interlink with oxidative stress mechanism. And it is related with monoaminergic pathway. Monoamine oxidase enzyme is flavin-dependent amine oxidase which include flavin adenine dinucleotide (FAD) in the active site (35). MAOs reside in the outer membrane of the mitochondria of the central nervous system, liver, lung, gastrointestinal tract, blood platelets, and placenta in mammals (36–38). Monoamine oxidase enzyme is responsible for oxidative deamination of several neurotransmitters and different exogenous and endogenous amines containing melatonin, serotonin, epinephrine, norepinephrine, dopamine, histamine, tryptamine, taurine and benzylamine (16,39). Monoamine oxidases exist in two isoforms (MAO-A and MAO-B), which have different substrates and different specific inhibitors on the other hand they have some overlapping substrates though (5). MAO-A and

MAO-B genes are located on X chromosome, and these two isoenzymes show 70% identity (40). MAO-A mainly catalyzes breakdown of serotonin, noradrenalin, norepinephrine, dopamine and tyramine while MAO-B catalyzes mainly breakdown of dopamine and phenylethylamine (38,41). In the brain, MAO-A is mainly expressed in catecholaminergic neurons but MAO B is expressed in serotonergic, histaminergic neurons and astrocytes (40). Both MAO A and B expression is regulated by diverse transcription factors and hormones and this expression increases with ages (42). Brain functions, regulation of concentration, emotional behaviors, adaption,

muscle coordination, protection of neurons from exogenous monoamines and storage of monoamines are regulated by monoamine oxidase enzymes subtypes. In recent studies, it shows that increase (or decrease) of MAO enzyme level which influences neurotransmitters metabolism leads to halting problems in brain and production of reactive oxygen species (ROS) (39). Furthermore, the importance of MAO enzymes is proved in several psychiatric conditions, including chronic stress, neurodegenerative disorders (Alzheimer's and Parkinson's diseases) and alcohol dependence (41,43).
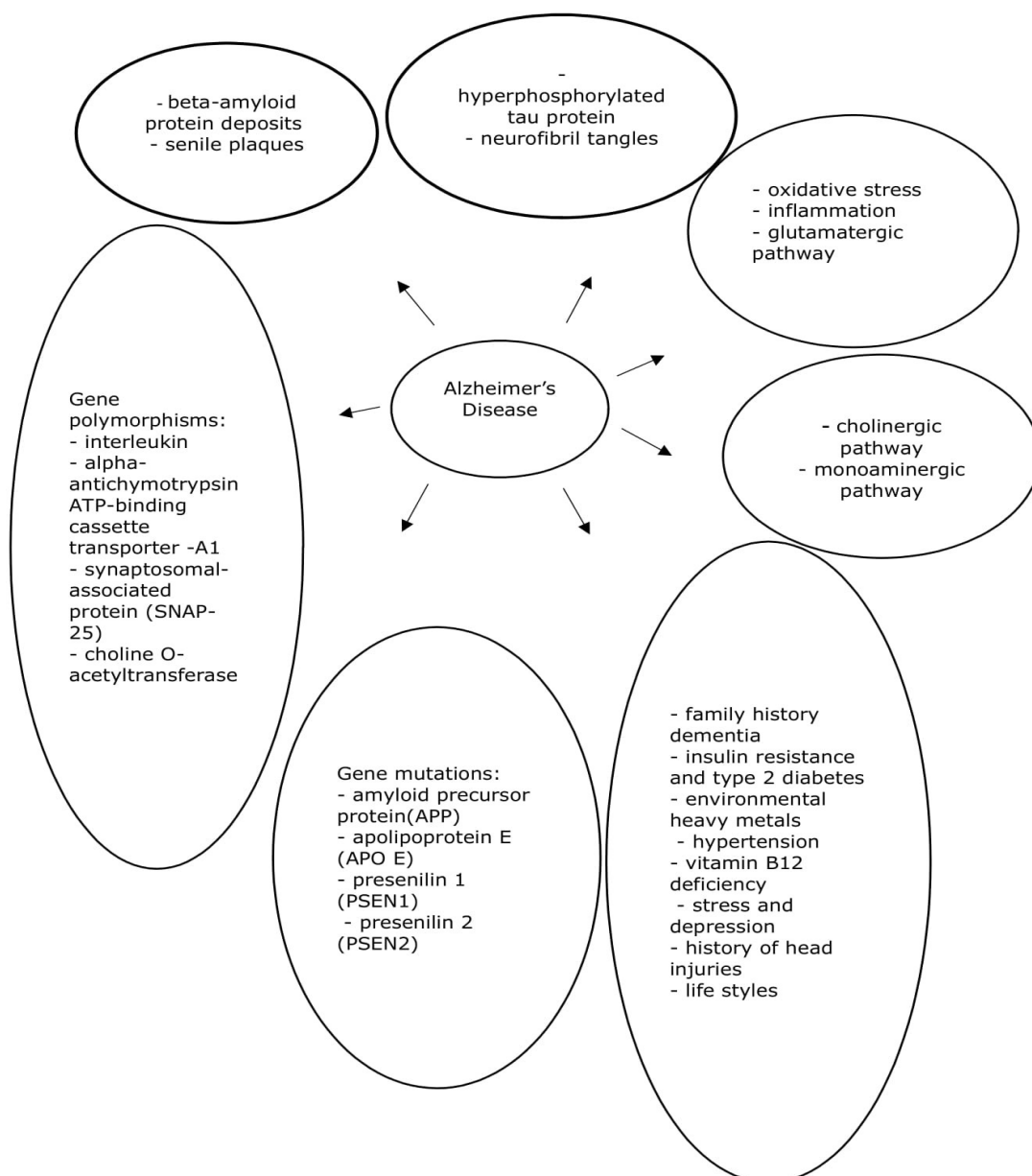

Figure 1. Risk Factors for developing Alzheimer's disease.

Neurotoxic byproducts of monoamine oxidase enzyme catalyzed reactions are aldehyde, ammonia, and hydrogen peroxide (H_2O_2)(16). Hydrogen peroxide can be converted to hydroxyl radical, an example of ROS, which leads to oxidative stress in brain (37,44). Hydroxyl radical produces an affliction in neuronal membrane and DNA of the mitochondria. Elevated H_2O_2 level activates cell acidosis resulting neuro-inflammation in brain. Immune cells produce interleukins which are a group of cytokines and they are linked to different diseases ranging from schizophrenia, major depression, and Alzheimer's disease (5). Also, throughout aging of brain, increased MAO enzyme activity produces more H_2O_2 which results in increased oxidative stress (31). Elevated oxidative stress has also an important function on progression of Alzheimer's disease (38). Recent discoveries demonstrate that both astrocytes and pyramidal neurons of AD brain include abnormal elevated level of MAO-B activity (39,45). It is stated that increased formation of beta plaque and ROS and dopamine metabolism is one of the hallmarks of monoamine oxidase activity and/or transcription rate (9,46).

The overexpression of MAO-B enhances amyloid β-peptide production and MAO-B is a main component of regulation of amyloid β-peptide by means of γ-secretase (45). High level of glucocorticoids is related with elevated MAO-B activity, which will increase amyloid-β and tau protein in rat model of AD (47). Neuropsychiatric disorders management is related with two isomers of MAO. Inhibition of MAO-A is widely used for clinical treatment of depression and anxiety since MAO-A possess high affinity to serotonin and norepinephrine, whilst MAO-B inhibition is an effective molecular target for AD (41,43).

There are several phytochemical analyses and pharmacological studies to research therapeutic potential and mechanism of folk medicinal plants about AD management. In this review, we will discuss plant-based MAO inhibitors that reveal anti-Alzheimer activity and neuroprotection. Studies suggest that bioactive compound from medicinal plants have promising multifunctional agent including monoamine oxidase inhibitors (MAOIs) for AD management to improve brain functions.

PLANTS AND DERIVATIVE COMPOUNDS WITH MAO INHIBITORY POTENTIAL

Phytochemicals are known as bioactive compounds in plants which have preventive and curative properties as enzyme inhibitory, anti-oxidant, anti-cancer and anti-inflammatory. Herbs which contain phenolic and polyphenolic bioactive compounds have been used throughout human history to avert and treat disparate diseases (48).

Polyphenols, flavonoids and phenolic acids, have natural antioxidant activity to scavenge ROS and chelate metal ions, to inhibit different enzyme activities and to keep from protein aggregation (10). The phenolic hydroxyl groups (Phe-OH) are hydrogen donating antioxidants and they disrupt production of new radicals. Also, phenolics show high affinity to interact with protein due to their structure which includes hydrophobic benzenoid rings and hydrogen-bonding potential of Phe-OH groups. This unique structure provides possibility of inhibiting some enzymes related with ROS production such as MAOs and CYPs (49).

Quercetin, a flavonoid found in wine and green tea, is an inhibitor of monoamine oxidase A (IC50 = 0.01 µmol/L)/monoamine oxidase B (IC50 = 10.89 µmol/L) and a stonewall for amyloid beta and tau protein aggregation with IC50 < 1 µmol/L (50–52).

Epigallocatechin gallate (EGCG) in green tea has anti-Alzheimer effect by displaying inhibitor function for amyloid beta aggregation (IC50 = 0.18 µmol/L) and MAO enzyme activity (IC50 = 10 µmol/L) (49,53).

Resveratrol, a popular phenol in wine, decreases amyloid beta production and inhibits monoamine oxidase A (MAO-A) with an IC50 of 26.6 µmol/L (49,54).

Curcumin (500.46 nM) and ellagic acid (412.24 nM) strongly inhibit MAO-B enzyme isolated from rat brain, compared to standard drug which is selegiline, MAO-B inhibitor. Both curcumin and ellagic acid inhibit MAO enzyme in a competitive and non-competitive way, but ellagic acid has more efficacious inhibitory effect on MAO-B than curcumin (55).

Curcumin, luteolin, apigenin, quercetin, and chlorogenic acid from medicinal plants have as good binding affinity as standard drugs due to having similar binding amino acid residue with drug rasagiline and selegiline, which are selective and irreversible MAO-B inhibitors (5).

MAO inhibitory potential of five coumarin derivatives from the roots of *Angelica gigas* Nakai (AG) and eight flavonoids from *Scutellaria baicalensis* Georgi (SB) is studied. Decursin isolated from AG strongly inhibits MAO-A with IC50 = 1.89 µM but not MAO-B (IC50 = 70.5 µM), thus decursin is selective, reversible, and competitive inhibitor of human MAO-A. Wogonin isolated from SB is non-selective, reversible, and competitive inhibitor of MAO-A and moderate inhibitor of MAO-B (IC50 = 6.35 and 20.8 M, respectively). Decursinol angelate and

baicalein show selective and moderate inhibitory activity against MAO-A. Molecular docking analyses exhibit that decursin forms hydrogen bond with Asn116 residue of MAO-B and Asn181 residue of MAO-A, which H-bonds promote ligand binding affinity (56). Authors suggest that decursin and wogonin may be a remedy for Alzheimer disease, due to their reversible MAO-A inhibitor activity (57).

Berberine is an alkoloid which is found in many plants including goldthread, goldenseal, and oregon grape. It has been substantiated that berberine has distinct pharmacological properties such as being antioxidant, antidepressant, and anticancer. Berberine has a neuroprotective effect against long term exposure to heavy metals, which are aluminum, cadmium, and fluoride anion. After rats are orally exposed to these three metals (50 mg/kg, 5 mg/kg and 20 mg/kg, respectively) for three months, 50 mg/kg/day berberine is orally given for one month. Berberine penetrates blood-brain barrier, and inhibits AChE, BchE, and MAOs enzyme activities and also it reduces amyloid beta and neural fibril tangle production (9). It is observed that since berberine has a large hydrophobic surface, it has binding affinity to monoamine oxidase A and B because of their hydrophobic substrate recognition site (58). The inhibitory potential of berberine against MAO enzymes stems from these hydrophobic interactions. In drug design, hydrophobic interaction is very important by virtue of its ability to elevate binding affinity between target-drug interfaces (59). Both of their findings show that berberine can be used for anti-Alzheimer drug design.

Danshensu (salvianic acid A), a water-soluble compound, is a phenolic acid isolated from herbs. Scopolamine and amyloid-β (Aβ) protein-induced cognitive impairments in rat model, oral administration of danshensu (3 or 10 mg/kg) inhibits monoamine oxidase A (MAO-A) activity but not MAO-B and it elevates dopamine level and phosphorylation level of protein kinase A. It is suggested that danshensu may be a new therapeutic agent against cognitive dysfunction by MAO-A inhibition and dopamine level related PKA-CREB activation (7).

Another multi-target agent is sarsasapogenin (SRS) which is a steroidal saponin from *Asparagus racemosus*. *Asparagus racemosus* (satavar) spreads over Sri Lanka, India, and the Himalayas. Satavar has a wide range of biologically active compounds and shows pharmacological activities such as immunomodulatory activity, antihepatotoxic activity, antidepressant activity, aphrodisiac activity, and antioxidant effects. Satavar, one of the ancient ayurvedic medicine of India, has also been used to control AIDS symptoms (60).

Sarsasapogenin inhibits not only MAO-B but also acetylcholinesterase (AChE), butyrylcholinesterase (BuChE) and Beta-secretase 1 (BACE1). Their inhibition rates raise when concentration of sarsasapogenin is increased. Forty μM SRS inhibits MAO-B enzyme by 68% as compared to control seleginine (85% inhibition). Molecular docking analysis carries out that SRS interacts only with hydrophobic residues (Tyr 326 and Gln206) of MAO-B (1).

Synthetic analogues synthesis of plants bioactive compounds is very important for drug production to combat neurodegenerative disease. Anti-Alzheimer's and anti-depressant benefits of dibenzylidene ketone derivatives (2,6-dibenzylidene cyclohexanone (A1K1) and 5-(2,3-dichlorophenyl)-1-(4-methoxyphenyl)-2-methylpenta-1,4-diene-3-one (A2K2)), which are analogues of curcumin, are evaluated in mice models. In mice, anti-Alzheimer activity are investigated by Y-maze test and Morris water maze test (MWM). Anti-depressant activity is investigated by forced swim test, tail suspension test and open field test. In the Y-maze test, administration of A1K1 and A2K2 (0.5 mg/kg and 1 mg/kg respectively for 3 days) intraperitoneally improves spontaneous alteration behavior, which increases cognitive performance. In Morris water maze test (MWM), mice are administered same concentrations as Y-maze test for 5 days instead of 3 days. Both doses (0.5 mg/kg and 1 mg/kg) of A1K1 and A2K2 minimize escape latency time as compared to control group. The molecular docking results reveal that both derivatives have high binding affinity to MAOB, which is related with hydrogen binding between ligand and protein (8).

Six synthetic α,β-unsaturated carbonyl-based tetralone derivatives (3f, 3o, 3u, 3ae, 3af, and 3ag) exhibit defense against Aβ-induced cell death in pheochromocytoma cells (PC12 cell). One hundred μm tetralone derivatives are treated to PC12 cells. These derivatives protect 88 percent of the cells from Aβ-induced cell death. Compound 3f shows both MAO-B (IC50 = 0.88 ± 0.12 μm) and AChE (IC50 = 0.045 ± 0.02 μm) inhibitory potential. These α,β-unsaturated carbonyl-based tetralone derivatives have potency to develop multi-target-drugs (43).

Spondias mombin (S. mombin), also known as yellow mombin, has historically been used as an alternative medicine because of its polyphenol content. *S. mombin* leaves' chemical profile, phytochemical–protein mechanism and inhibitory properties on some enzymes (MAO-A, phosphodiesterase- 5, arginase, angiotensin I-converting enzyme, cholinesterase, ecto-5′ nucleotidase, tyrosinase, and stimulated sodium–potassium ATPase) which are related with erectile and cognitive dysfunction are

analyzed. 3.125 µg/mL, 6.25 µg/mL, 12.5 µg/mL and 25 µg/mL of *S. mombim* fractions inhibit monoamine oxidase A (MAO). While the concentration increases, enzyme inhibition has also increased. HPLC/MS analysis proves that its chemical profile include lutein, zeaxanthin, β-cryptoxanthin, α-carotene, β-carotene, chlorogenic acid, and ellagic acid. Chlorogenic acid has the lowest binding score to MAO-A with lowest atomic contact energy (AtCE = -139.08). There are many studies associated with chlorogenic acid and ellagic acid consumption that provide a lot of benefits relevant to neurological degeneration (61).

Aloe vera (*Aloe barbadensis*-AV), a cactus-like plant, is a popular ingredient in pharmaceutical industry and cosmetics. Different alcohol extract concentrations of AV (0.001 M, 0.005 M, 0.01 M, 0.05 M, 0.1 M) exhibit good enzyme inhibition for MAO (4.46, 20.08, 43.91, 53.17, and 81.13%). The results have revealed that AV is an uncompetitive inhibitor for MAO. Owing to inhibition potential on MAO/AchE and reducing Alzheimer's disease symptoms and increasing cognition scores, AV can be recommended as a food supplement for treatment of Alzheimer's disease (62).

Ipomoea aquatica is known as water spinach. Meliorating effect of *Ipomoea aquatica* extracts is observed on mice with amyloid beta induced cognitive deficit. After 10 µL single intracerebroventricular injection of AB peptide, MAOs level increases in mice brain. Treatment with 200 mg/kg and 400 mg/kg of hydroalcoholic extract of *Ipomoea aquatica* (HAEIA) significantly increases neurotransmitter level, inhibits MAOs and AChE (acetylcholinesterase) enzyme activity and reduces glutamate level. In addition, both doses of HAEIA improve learning memory by reducing the negative effects of Alzheimer's disease (4).

Ammodaucus leucotrichus (A. leucotrichus) is a member of Apiaceae family. It is an endemic flouring plant found in North Africa, Morocco, Algeria, and Tunisia. It is traditionally used for cardiac diseases, stomach diseases, fever, vomits, and allergies. To illuminate the effects of *Ammodaucus leucotrichus* against neurological disorders, the anti-monoamine oxidase activities of the content of the essential oil that gathered from *A. leucotrichus* aerial parts is analyzed. Chemical analysis shows that perillaldehyde (58.3%) and limonene (23.33%) are the main components of essential oil. Essential oil and perillaldehyde have an inhibitory effect on both MAO-A with IC50 value 112.5 and 159.1 µg/mL respectively and MAO-B with IC50 values of 40.5 and 98.9 µg/mL in order. Essential oil and perillaldehyde show potent inhibitory activity for MAO-B than MAO-A (38).

Chinese herbal Naodesheng formula (ND) has been used as a therapeutic agent to treat mainly cardiovascular diseases. Naodesheng formula includes five different plants. Those are *Rhizoma Chuanxiong*, *Lobed Kudzuvine*, *Carthamus tinctorius*, *Radix Notoginseng* and *Crataegus pinnatifida*. When ND formula is studied for AD prevention, a biological pathway network is established. According to this network, it is found that albeit AChE is in the center, MAO-B is one of the nodes of this network and ND has drug-like properties. It can be utilized for treatment of central nervous system diseases by the virtual screening and network pharmacology methods (63).

Ethanolic extract of arecanut (4-80 mg/kg) inhibits monoamine oxidase in albino rats (64). In mice brain, treatment of 200 and 400 mg/kg hydroalcoholic extract of arecanut reduce MAO level (65). The dichloromethane fraction of arecanut elevates serotonin and dopamine in the brain by inhibiting MAO-A (66).

In another study, methanol extract of *Plantago major* strongly inhibits MAO-A enzyme more than MAO-B with IC50 values 2.174 µg/mL and 21.051 µg/mL, respectively (67).

Ginkgo biloba has been utilized in alternative medicine and as a dietary supplement. EGb 761 is an extract isolated from *Ginkgo biloba* leaves. Main ingredients of EGb 761 are flavanol glycosides and terpene trilactones. Information related with its radical scavenger and antioxidant properties and low side effects supported that EGb741 can be regarded amenable to treatment for Alzheimer's disease (68). Long term daily administration (50 mg/kg oral) of EGb741 reduced cerebral MAO-A and MAO-B activity by down-regulation in age-induced and stress-induced mice (69).

Gardenia jasminoides is a member of Rubiaceae family that is grown in South Korea and Southern China. It is envisioned that ethyl acetate, methanol, and total extracts of *G. jasminosides* inhibit both monoamine oxidase-A (MAO-A) and monoamine oxidase-B (MAO-B) activities (70,71). To elucidate which components of *G. jasminoides* play a major role in MAO inhibition mechanism, bioactive compounds (protocatechuic acid, geniposide, 6'-O-trans-p-coumaroylgeniposide, 3,5-dihydroxy-1,7-bis(4-hydroxyphenyl) heptanes and ursolic acid) of ethyl acetate fraction *Gardenia jasminoides* are identified. 6'-O-trans-p-coumaroylgeniposide (127 mmol/L), 3,5-dihydroxy-1,7-bis (4-hydroxyphenyl) heptane (IC50 = 196 µmol/L), geniposide (IC50 = 223 µmol/L) and protocatechuic acid (IC50 = 300 µmol/L), are strong MAO-B inhibitors whereas ursolic acid (IC50=780 µmol/L) is a weak MAO-B

inhibitor. Protocatechuic acid has weak inhibition (IC50 = 2411 μmol/L), but 3,5-dihydroxy-1,7-bis(4-hydroxyphenyl)heptane (IC50 = 400 μmol/L) have modest inhibition against MAO-A. Ursalic acid does not exhibit any inhibition against MAO-A. Ursolic acid (IC50 = 214 μmol/L) and Protocatechuic acid (IC50 = 334 μmol/L) show significant inhibition against dopamine β-hydroxylase which converts dopamine into norepinephrine. 3,5-dihydroxy-1,7-bis (4-hydroxyphenyl) heptane exhibits more specific activity to MAO-B (16,129) than MAO-A (7,937), because it has a hydroxyl group and it makes it having great inhibitory potential on MAO-B over MAO-A. Protocatechuic acid shows about 8 times more specific activity on MAO-B (21,739) than on MAO-A (2,695). This decreases affinity to MAO-A related with protocatechuic acid structure which includes an additional hydroxy group at the ortho-position. Even if 6'-*O*-trans-p-coumaroylgeniposide has a hydroxy group, it has a lack of inhibition against MAO-A. It is explained with 6'-*O*-trans-p-coumaroylgeniposide structure which masking hydroxyl proton with methyl and glycosyl groups (72). The pharmacophore analysis gives an information interaction of bioactive compounds to the target protein (73). Determination of bioactive compounds of high binding affinity to MAOs is a useful approach for anti-Alzheimer drug development.

CONCLUSION AND FUTURE CONCERNS

The effects of known MAO inhibitor drugs (selective MAO-A, selective MAO-B, or nonselective MAO-A/B inhibitors, and reversible/irreversible MAOs) are limited. *In vivo* and *in vitro* investigations reveal that pharmaceutical properties of medicinal plants and their bioactive components support good opportunity as candidates for drug discovery and management for Alzheimer due to their MAOs inhibitory effects. Although phytochemical and pharmacological researches highlight promising MAO inhibitory potential of therapeutic medicinal plant and their rich content, it is needed further extensive research especially binding affinity between MAO enzyme and phytochemicals.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

REFERENCES

1. Kashyap P, Muthusamy K, Niranjan M, Trikha S, Kumar S. Sarsasapogenin: A steroidal saponin from Asparagus racemosus as multi target directed ligand in Alzheimer's disease. Steroids [Internet]. 2020;153(October 2019):108529. Available from: https://doi.org/10.1016/j.steroids.2019.108529

2. Alzheimer Europe. Dementia in Europe Yearbook. Estimating the prevalence of dementia in Europe. 2019.

3. Patil P, Thakur A, Sharma A, Flora SJS. Natural products and their derivatives as multifunctional ligands against Alzheimer's disease. Drug Dev Res. 2020;81(2):165–83.

4. Sivaraman D, Panneerselvam P, Muralidharan P. Memory and brain neurotransmitter restoring potential of hydroalcoholic extract of ipomoea aquatica forsk on amyloid beta Aβ (25-35) induced cognitive deficits in alzheimer's mice. Int J Pharmacol. 2016;12(2):52–65.

5. Sivaraman D, Srikanth J. Discovery of novel monoamine oxidase-b inhibitors by molecular docking approach for alzheimer's and parkinson's disease treatment. Int J Pharm Sci Rev Res. 2016;40(1):245–50.

6. Alzheimer's Association. 2018 Alzheimer's disease facts and figures. Alzheimer's Dement. 2018;14(3):367–429.

7. Bae HJ, Sowndhararajan K, Park HB, Kim SY, Kim S, Kim DH, et al. Danshensu attenuates scopolamine and amyloid-β-induced cognitive impairments through the activation of PKA-CREB signaling in mice. Neurochem Int [Internet]. 2019;131(August):104537. Available from: https://doi.org/10.1016/j.neuint.2019.104537

8. Bashir MA, Khan A ullah, Badshah H, Rodrigues-Filho E, Din ZU, Khan A. Synthesis, characterization, molecular docking evaluation, antidepressant, and anti-Alzheimer effects of dibenzylidene ketone derivatives. Drug Dev Res. 2019;80(5):595–605.

9. Hussien HM, Abd-Elmegied A, Ghareeb DA, Hafez HS, Ahmed HEA, El-moneam NA. Neuroprotective effect of berberine against environmental heavy metals-induced neurotoxicity and Alzheimer's-like disease in rats. Food Chem Toxicol [Internet]. 2018;111(April 2017):432–44. Available from: https://doi.org/10.1016/j.fct.2017.11.025

10. Ji HF, Zhang HY. Multipotent natural agents to combat Alzheimer's disease. Functional spectrum and structural features. Acta Pharmacol Sin. 2008;29(2):143–51.

11. Riederer P, Danielczyk W, Grünblatt E. Monoamine Oxidase-B Inhibition in Alzheimer's Disease. Neurotoxicology. 2004;25(1–2):271–7.

12. Wang Y, Wang H, Chen H. AChE Inhibition-based Multi-target-directed Ligands, a Novel Pharmacological Approach for the Symptomatic and Disease-modifying Therapy of Alzheimer's Disease. Curr Neuropharmacol. 2016;14(4):364–75.

13. Cras P, Kawai M, Lowery D, Gonzalez-DeWhitt P, Greenberg B, Perry G. Senile plaque neurites in Alzheimer disease accumulate amyloid precursor protein. Proc Natl Acad Sci U S A. 1991;88(17):7552–6.

14. Tcw J, Goate AM. Genetics of β-Amyloid Precursor Protein in Alzheimer's Disease. Cold Spring Harb Perspect Med. 2017;7(6):1–12.

15. Wiseman FK, Al-Janabi T, Hardy J, Karmiloff-Smith A, Nizetic D, Tybulewicz VLJ, et al. A genetic cause of Alzheimer disease: Mechanistic insights from Down syndrome. Nat Rev Neurosci. 2015;16(9):564–74.

16. Fišar Z. Drugs related to monoamine oxidase activity. Prog Neuro-Psychopharmacology Biol Psychiatry. 2016;69:112–24.

17. Iqbal K, Liu F, Gong C-X, Tau in Alzheimer Disease and Related Tautopathies. Curr Alzheimer Res. 2010;8(7):656–64.

18. Hutton M, Hardy J. The presenilins and Alzheimer's disease. Hum Mol Genet. 1997;6(10 REV. ISS.):1639–46.

19. Mun MJ, Kim JH, Choi JY, Jang WC. Genetic polymorphisms of interleukin genes and the risk of Alzheimer's disease: An update meta-analysis. Meta Gene [Internet]. 2016;8:1–10. Available from: http://dx.doi.org/10.1016/j.mgene.2016.01.001

20. Ezquerra M, Blesa R, Tolosa E, Ballesta F, Oliva R. α-Antichymotrypsin gene polymorphism and risk for Alzheimer's disease in the Spanish population. Neurosci Lett. 1998;240(2):107–9.

21. Sumirtanurdin R, Thalib AY, Cantona K, Abdulah R. Effect of genetic polymorphisms on alzheimer's disease treatment outcomes: An update. Clin Interv Aging. 2019;14:631–42.

22. Xu X, Wang Y, Wang L, Liao Q, Chang L, Xu L, et al. Meta-Analyses of 8 Polymorphisms Associated with the Risk of the Alzheimer's Disease. PLoS One. 2013;8(9).

23. Qiu WQ, Folstein MF. Insulin, insulin-degrading enzyme and amyloid-β peptide in Alzheimer's disease: Review and hypothesis. Neurobiol Aging. 2006;27(2):190–8.

24. Steardo L, Steardo L, Zorec R, Verkhratsky A. Neuroinfection may contribute to pathophysiology and clinical manifestations of COVID-19. Acta Physiol. 2020;229(3):10–3.

25. Hall RE, Klenow PJ, Jones CI. Trading Off Consumption and COVID-19 Deaths. Fed Reserv BANK Minneap Q Rev. 2020;42(1).

26. Bulut C, Kato Y. Epidemiology of covid-19. Turkish J Med Sci. 2020;50(SI-1):563–70.

27. Brown EE, Kumar S, Rajji TK, Pollock BG, Mulsant BH. Anticipating and Mitigating the Impact of the COVID-19 Pandemic on Alzheimer's Disease and Related Dementias. Am J Geriatr Psychiatry [Internet]. 2020;28(7):712–21. Available from: https://doi.org/10.1016/j.jagp.2020.04.010

28. Francis PT, Palmer AM, Snape M, Wilcock GK. The cholinergic hypothesis of Alzheimer's disease: A review of progress. J Neurol Neurosurg Psychiatry. 1999;66(2):137–47.

29. Greig NH, Lahiri DK, Sambamurti K. Butyrylcholinesterase: An important new target in Alzheimer's disease therapy. Int Psychogeriatrics. 2002;14(SUPPL. 1):77–91.

30. García-Ayllón MS, Small DH, Avila J, Sáez-Valero J. Revisiting the role of acetylcholinesterase in Alzheimers disease: Cross-talk with β-tau and p-amyloid. Front Mol Neurosci. 2011;4(SEP):1–9.

31. Sharma K. Cholinesterase inhibitors as Alzheimer's therapeutics (Review). Mol Med Rep. 2019;20(2):1479–87.

32. Huang WJ, Zhang X, Chen WW. Role of oxidative stress in Alzheimer's disease (review). Biomed Reports. 2016;4(5):519–22.

33. Tönnies E, Trushina E. Oxidative Stress, Synaptic Dysfunction, and Alzheimer's Disease. J Alzheimer's Dis. 2017;57(4):1105–21.

34. Pocernich CB, Butterfield DA. Elevation of glutathione as a therapeutic strategy in Alzheimer disease. Biochim Biophys Acta - Mol Basis Dis. 2012;1822(5):625–30.

35. Kachalova G, Decker K, Holt A, Bartunik HD. Crystallographic snapshots of the complete reaction cycle of nicotine degradation by an amine oxidase of the monoamine oxidase (MAO) family. Proc Natl Acad Sci U S A. 2011;108(12):4800–5.

36. Fiedorowicz JG, Swartz KL. The role of monoamine oxidase inhibitors in current psychiatric practice. J Psychiatr Pract. 2004;10(4):239–48.

37. Rendu F, Peoc'h K, Berlin I, Thomas D, Launay JM. Smoking related diseases: The central role of monoamine oxidase. Int J Environ Res Public Health. 2011;8(1):136–47.

38. Sadaoui N, Bec N, Barragan-Montero V, Kadri N, Cuisinier F, Larroque C, et al. The essential oil of Algerian Ammodaucus leucotrichus Coss. & Dur. and its effect on the cholinesterase and monoamine oxidase activities. Fitoterapia [Internet]. 2018;130(June):1–5. Available from: https://doi.org/10.1016/j.fitote.2018.07.015

39. Duncan J, Johnson S, Ou XM. Monoamine oxidases in major depressive disorder and alcoholism. Drug Discov Ther. 2012;6(3):112–22.

40. Bortolato M, Chen K, Shih JC. Monoamine oxidase inactivation: From pathophysiology to therapeutics. Adv Drug Deliv Rev. 2008;60(13–14):1527–33.

41. Lee HW, Ryu HW, Kang MG, Park D, Lee H, Shin HM, et al. Potent inhibition of monoamine oxidase A by decursin from Angelica gigas Nakai and by wogonin from Scutellaria baicalensis Georgi. Int J Biol Macromol [Internet]. 2017;97:598–605. Available from: http://dx.doi.org/10.1016/j.ijbiomac.2017.01.080

42. Maggiorani D, Manzella N, Edmondson DE, Mattevi A, Parini A, Binda C, et al. Monoamine Oxidases, Oxidative Stress, and Altered Mitochondrial Dynamics in Cardiac Ageing. Oxid Med Cell Longev. 2017;2017(3).

43. Leng J, Qin HL, Zhu K, Jantan I, Hussain MA, Sher M, et al. Evaluation of multifunctional synthetic tetralone derivatives for treatment of Alzheimer's disease. Chem Biol Drug Des. 2016;88(6):889–98.

44. Gaweska H, Fitzpatrick PF. Structures and mechanism of the monoamine oxidase family. Biomol Concepts. 2011;2(5):365–77.

45. Schedin-Weiss S, Inoue M, Hromadkova L, Teranishi Y, Yamamoto NG, Wiehager B, et al. Monoamine oxidase B is elevated in Alzheimer disease neurons, is associated with γ-secretase and regulates neuronal amyloid β-peptide levels. Alzheimer's Res Ther. 2017;9(1):1–19.

46. Xie SS, Wang X, Jiang N, Yu W, Wang KDG, Lan JS, et al. Multi-target tacrine-coumarin hybrids: Cholinesterase and monoamine oxidase B inhibition properties against Alzheimer's disease. Eur J Med Chem [Internet]. 2015;95:153–65. Available from: http://dx.doi.org/10.1016/j.ejmech.2015.03.040

47. Green KN, Billings LM, Roozendaal B, McGaugh JL, LaFerla FM. Glucocorticoids increase amyloid-β and tau pathology in a mouse model of Alzheimer's disease. J Neurosci. 2006;26(35):9047–56.

48. Ege T. The Pharmacological and Therapeutic Potentials of Epilobium hirsutum L. Int J Pharm Sci Rev Res. 2019;57(2):20–3.

49. Pereira DM, Valentão P, Pereira JA, Andrade PB. Phenolics: From chemistry to biology. Molecules. 2009;14(6):2202–11.

50. Chimenti F, Cottiglia F, Bonsignore L, Casu L, Casu M, Floris C, et al. Quercetin as the active principle of Hypericum hircinum exerts a selective inhibitory activity against MAO-A: Extraction, biological analysis, and computational study. J Nat Prod. 2006;69(6):945–9.

51. Lee MH, Lin RD, Shen LY, Yang LL, Yen KY, Hou WC. Monoamine oxidase B and free radical scavenging activities of natural flavonoids in Melastoma candidum D. Don. J Agric Food Chem. 2001;49(11):5551–5.

52. Porat Y, Abramowitz A, Gazit E. Inhibition of amyloid fibril formation by polyphenols: Structural similarity and aromatic interactions as a common inhibition mechanism. Chem Biol Drug Des. 2006;67(1):27–37.

53. Mazzio EA, Harris N, Soliman KFA. Food constituents attenuate monoamine oxidase activity and peroxide levels in C6 astrocyte cells. Planta Med. 1998;64(7):603–6.

54. Zhou CX, Kong LD, Ye WC, Cheng CHK, Tan RX. Veratrum taliense. 2001;67:158–61.

55. Khatri D, Juvekar A. Kinetics of inhibition of monoamine oxidase using curcumin and ellagic acid. Pharmacogn Mag. 2016;12(46):116.

56. Chen D, Oezguen N, Urvil P, Ferguson C, Dann SM, Savidge TC. Regulation of protein-ligand binding affinity by hydrogen bond pairing. Sci Adv. 2016;2(3).

57. Lee HW, Kim YJ, Nam SJ, Kim H. Potent selective inhibition of monoamine oxidase a by alternariol monomethyl ether isolated from alternaria brassicae. J Microbiol Biotechnol. 2017;27(2):316–20.

58. Ji HF, Shen L. Molecular basis of inhibitory activities of berberine against pathogenic enzymes in Alzheimer's disease. ScientificWorldJournal. 2012;2012.

59. Varma AK, Patil R, Das S, Stanley A, Yadav L, Sudhakar A. Optimized hydrophobic interactions and hydrogen bonding at the target-ligand interface leads the pathways of Drug-Designing. PLoS One. 2010;5(8).

60. Alok S, Jain SK, Verma A, Kumar M, Mahor A, Sabharwal M. Plant profile, phytochemistry and pharmacology of Asparagus racemosus (Shatavari): A review. Asian Pacific J Trop Dis. 2013;3(3):242–51.

61. Ojo OA, Afon AA, Ojo AB, Ajiboye BO, Okesola MA, Aruleba RT, et al. Spondias mombim L. (Anacardiaceae): Chemical fingerprints, inhibitory activities, and molecular docking on key enzymes relevant to erectile dysfunction and Alzheimer's diseases. J Food Biochem. 2019;43(3):1–17.

62. Shakir MA. The effect of Aloe Vera extract on Acetylcholinesterase AchE and Monoamine Oxidase MAO enzymes. Al-Mustansiriyah J Sci. 2018;29(4):88–92.

63. PANG XC, KANG D, FANG JS, ZHAO Y, XU LJ, LIAN WW, et al. Network pharmacology-based analysis of Chinese herbal Naodesheng formula for application to Alzheimer's disease. Chin J Nat Med. 2018;16(1):53–62.

64. Dar A, Khatoon S, Rahman G, Atta-Ur-Rahman. Anti-depressant activities of Areca catechu fruit extract. Phytomedicine. 1997;4(1):41–5.

65. Kannan R, Sivaraman D, Muralidharan P, Deepakvenkataraman N. Neuroprotective effect of hydroalcoholic extract of areca catechu linn on β-amyloid (25-35) induced cognitive dysfunction in mice. Int J Res Ayurveda Pharm. 2013;4(5):747–53.

66. Khan S, Abbas G, Ahmed FS, Atta-Ur-Rahman, Dar A. Effect of dichloromethane fraction of Areca catechu nut on monoamines associated behaviors and tyramine pressor sensitivity in rodents. Pak J Pharm Sci. 2014;27(2):303–7.

67. Akıncıoğlu, H., Akbaş, M. and Aydın T. Determination of Inhibition Effect of Plantago Major Plant Extract on Monoamine Oxidase Isoenzymes (MAO-A and MAO-B). In: 4th INTERNATIONAL CONFERENCE ON ADVANCES IN NATURAL & APPLIED SCIENCES. 2019.

68. Rojas C, Rojas-Castañeda J, Rojas P. Antioxidant properties of a Ginkgo biloba leaf extract (EGb 761) in animal models of Alzheimer's and Parkinson's diseases. Curr Top Nutraceutical Res. 2016;14(1):1–16.

69. Pardon MC, Joubert C, Perez-Diaz F, Christen Y, Launay JM, Cohen-Salmon C. In vivo regulation of cerebral monoamine oxidase activity in senescent controls and chronically stressed mice by long-term treatment with Ginkgo biloba extrac3t (EGb 761). Mech Ageing Dev. 2000;113(3):157–68.

70. Hwang KH. Monoamine oxidase inhibitory activities of Korean medicinal plants classified to cold drugs by the theory of KIMI. Food Sci Biotechnol. 2003;12:238–41.

71. Park, T. K. and Hwang KH. Inhibitory activity of the fruit extract of Gardenia jasminoides on monoamine oxidase. Korean J Pharmacogn. 2007;38:108–12.

72. Kim JH, Kim GH, Hwang KH. Monoamine oxidase and dopamine β-hydroxylase inhibitors from the fruits of Gardenia jasminoides. Biomol Ther. 2012;20(2):214–9.

73. Pitchai D, Manikkam R, Rajendran SR, Pitchai G. Database on pharmacophore analysis of active principles, from medicinal plants. Bioinformation. 2010;5(2):43–5.