EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 3
Issue: 8
153-157
Year: 2016

HERBS AND PHYTOCHEMICALS BENEFICIAL IN ALZHEIMER'S DISEASE

Rakesh K. Goyal* and Janardhan Singh

*Faculty of Pharmaceutical Sciences, Pt. B.D. Sharma University of Health Sciences, Rohtak 124 001, India.
Department of Pharmacology, Pt. B.D. Sharma Post Graduate Institute of Medical Sciences, Rohtak 124 001, India.

***Corresponding Author: Rakesh K. Goyal**
Faculty of Pharmaceutical Sciences, Pt. B.D. Sharma University of Health Sciences, Rohtak 124 001, India

Article Received on 11/06/2016 **Article Revised on 01/07/2016** **Article Accepted on 22/07/2016**

ABSTRACT
Alzheimer's disease (AD) is a complex neurodegenerative disorder associated with aging process of unknown etiology. It is characterized by cognitive impairment like amnesia, depression, schizophrenia with poor learning and memory. Currently, there is no cure for AD, although drugs (tacrine, donpezil, rivastigmine and galantamine) improve symptoms of this condition, but are associated with severe unacceptable side effects. Plants have been shown to possess antioxidant, anticholinesterase and neuroprotective properties which are beneficial for treatment of this neurodegenerative disease. The present review describes some important plants / phytochemicals possessing active ingredients beneficial for the treatment of AD.

KEY WORDS: Alzheimer's disease, Medicinal plants, β-amyloid, *Bacopa monnieri*, Galanthamine.

INTRODUCTION
Alzheimer's disease (AD) originally defined as pre-senile dementia, means an acquired organic mental disorder with loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning. It is associated with brain shrinkage and localized loss of neurons, mainly in the hippocampus and basal forebrain. Although other neurotransmitters decline during Alzheimer's-associated neurodegeneration, the degree of brain acetylcholine (ACh) reduction directly correlates with deterioration of cognition and of daily activity in AD patients. Since deficits in cholinergic function contribute to the pathology of Alzheimer's disease, attempts to delay the progression of the illness and improve patients' daily activities are based on pharmacological strategies to increase ACh levels by means of anti-cholinesterasic agents. Two microscopic features are characteristic of the disease namely extra cellular amyloid plaques consisting of amorphous extracelluar deposits of β-amyloid protein and intranuronal neurofibrillary tangles, comprising filaments of phosphorylated form of a microtubule associated protein.[1-3] It primarily affects elderly population and is considered to be responsible for about 60% of all dementia in people aged over 65 years. Due to its debilitating nature, an enormous social and economic burden is placed on the society. The significance of AD is further compounded as the number of identified cases is estimated to double or triple by 2050. Currently several acetylcholinesterase inhibitors, such as donepezil, galantamine etc. are available for the symptomatic treatment of patients with mild to moderate AD.[4, 5] Although acetylcholinesterase inhibitors was the most widely used medication in Alzheimer's disease treatment, some report propound that acetylcholinesterase inhibitors have inclement side effects such as anorexia, diarrhoea, fatigue, nausea, muscle cramps as well as gastrointestinal, cardiorespiratory, genitourinary and sleep disturbances.[6] This condition led the researchers in obtaining new acetylcholinesterase inhibitors with higher efficacy, improved bioavailability and reduced side effects, particularly from natural sources. This article describes some plants and their extracts, phytochemicals exhibiting beneficial pharmacological properties relevant to AD therapy.

METHODS
Data Collection: The data for present review was collected form internet, online journals and from various Ayurvedic texts like database on medicinal plants used in Ayurveda, central council for research in Ayurveda and Sidha, Department of ISH & H, Ministry of Health & Family Welfare, Govt. of India, New Delhi, Volumes 1-8, Reviews on medicinal plants, Volumes 1-9 (ICMR, New Delhi). Most of the papers reviewed herein pertinent to herbal medicine research were published in internationally recognized peer reviewed journals. Some of the medicinal plants / extracts and their isolated active phytochemicals reported to be useful for the prevention

and treatment of neurodegenerative disorders particularly Alzheimer‟s disease are**:**

1.*Acorus calamus* *L.* (Araceae) commonly known as sweet flag is a semi-aquatic, perennial, tuberous herb, with creeping rhizomes, sword shaped leaves, having a long history of medicinal use in different healthcare systems worldwide, and particularly in Indian herbal traditions. *A. calamus* essential oil and its major phytoconstituent, β-asarone, have been reported to possess significant acetylcholinesterase (AChE) inhibitory activity in vitro.[7] β-asarone has also been shown to possess capability of suppressing neuronal apoptosis in the beta-amyloid hippocampus injection in rats by attenuating amyloid β1-42-induced neuronal apoptosis in hippocampus by reversal down-regulation of Bcl-2, Bcl-w, caspase-3 activation and c-Jun N-terminal kinase (JNK) phosphorylation.[8] Ethonolic extract of *A. calamus* has significant effect against scopolamine induced Alzheimer in albino Wistar rats by regulating AchE activity and free radical scavenging activity.[9]

2.*Bacopa monnieri* **(***Scrophulariaceae*), commonly known as Brahmi is a small, annual, creeping, spreading, succulent herb with numerous prostrate branches, each 10-30 cm long, rooting at the nodes with small fleshy, oblong leaves. *B. monniera* has been reported to reverse (a) depletion of acetylcholine, (b) reduction in choline acetyltransferase activity, and (c) decrease in muscarinic cholinergic receptor binding in rat frontal cortex and hippocampus.[10] *B. monniera* extract protected neurons from beta-amyloid-induced cell death by suppressing cellular acetylcholinesterase activity.[11] *B. monnieri* has been shown to reduce beta-amyloid deposits in the brain of animal models of AD.[12] The alcoholic extract of *B. monnieri* inhibited cholinergic degeneration and displayed a cognition-enhancing effect in male Wistar rat model of AD induced by ethylcholine aziridinium ion.[13]

3.*Biota orientalis* L (Cupressaceae) is an evergreen plant that grows mainly in Sourth East Asia. A pinusolide derivative isolated from *B. orientalis* leaves, 15-methoxypinusolidic acid, is reported to prevent glutamate-induced excitotoxicity in primary cultured rat cortical cells in vitro.[14]

4.*Celastrus paniculatus* Willd. (Celastraceae), commonly known as black-oil tree, is a large, woody, climbing shrub, distributed almost all over India up to an altitude of 1800 m. Badrul and Ekramul 2011[15] had tested crude methanolic extract of the seeds of *C. paniculatus* along with its organic soluble fractions for their possible antioxidant and antialzheimer activity in vitro and found that the extract possessed antioxidant and moderate anticholinesterase activity.

5.*Centella asiatica* (L) Urban (Umbellifere, Apiaceae), commonly known as Gotu kola, is a clonal, perennial herbaceous creeper native to Asia and Australia which grows in moist places up to an altitude of 1800m. It is a tasteless, odourless plant that thrives in and around water. The leaves and other parts of the plant are used in cooking and for various medicinal purposes. Asiatic acid isolated from *C. asiatica* as well as withanolide A (from *withania somnifera*) positively modulate multiple targets associated with β-amyloid pathways and thus may be beneficial in attenuating β-amyloid levels in Alzheimer's disease by decreasing β-amyloid production and by increasing β-amyloid degradation.[16] Polyphenols and triterpenes from *C. asiatica* are useful detoxifying agents that decrease lipid peroxidation & enhance brain antioxidants, and are thus neuroprotective in nature. Aqueous extract of *C. asiatica* attenuated β-amyloid-associated behavioral abnormalities in the Tg2576 mouse, a murine model of AD. In vitro, aqueous extract of *C. asiatica* protected SH-SY5Y cells and MC65 human neuroblastoma cells from toxicity induced by exogenously added and endogenously generated β-amyloid, respectively.[17] Chen et al 2015[18] has attributed the protection mediated by ethanol extract of *C. asiatica* against aggregated β-amyloid-induced neurotoxicity to modulation of the antioxidative defense system in cells, including the activities of superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and levels of glutathione and glutathione disulfide by ethanol extract of *C. asiatica* and thus, emphasized the potential therapeutic and preventive value of *C. asiatica* in the treatment of AD.

6.*Coptis chinensis* Franch (Ranunculaceae), commomly known for 'Huang Lian' is an evergreen perennial plant. Rhizoms of *C. chinensis* and its isolated alkaloids are reported to possess a variety of activities, including neuroprotective and antioxidant effects. Zhu and Qian, 2006[19] has demonstrated that intragastric administration of berberine (50 mg/kg), a natural isoquinoline alkaloid isolated from this plant, once daily for 14 days significantly ameliorated the spatial memory impairment in the rat model of AD. Various alkaloids derived from this plant (berberine, palmatine, jateorrhizine, epiberberine, coptisine, and groenlandicine) have been reported to possess strong potential for inhibition and prevention of AD mainly through both cholinesterases and β-amyloids pathways, and additionally through antioxidant capacities. In particular, groenlandicine possessed a promising anti-AD agent due to its potent inhibitory activity on both cholinesterases and β-amyloids formation, as well as marked peroxynitrite scavenging and good reactive oxygen species inhibitory capacities.[20] Berberine significantly ameliorated learning deficits, long-term spatial memory retention, as well as plaque load compared with vehicle control treatment in TgCRND8 mice, a well established transgenic mouse model of AD. In addition, enzyme-linked immunosorbent assay (ELISA) measurement showed that there was a profound reduction in levels of detergent-soluble and -insoluble β-amyloid in brain homogenates of berberine-treated mice. Berberine also significantly inhibited glycogen synthase kinase 3, a major kinase involved in amyloid precursor protein

(APP) and tau phosphorylation and significantly decreased the levels of C-terminal fragments of APP and the hyperphosphorylation of APP and tau via the Akt/glycogen synthase kinase 3 signaling pathway in N2a mouse neuroblastoma cells expressing human Swedish mutant APP695 (N2a-SwedAPP).[21]

7. *Curcuma longa* L (Zingiberaceae, the ginger family) commonly known as turmeric, is a sterile plant and does not produce any seeds. The plant grows up to 3-5 ft tall and has dull yellow flowers. The underground rhizomes or roots of the plant are used for food and medicinal purposes. A cross-cultural study of India and the United States of America found that the Indian population aged between 70-79 years had a 4.4 time lower prevalence of AD compared to the same population in the USA.[22] Lower incidence of AD in part has been attributed to increased consumption of curry, and thus curcumin in India. Further, other epidemiological studies in India, a country where turmeric consumption is widespread, suggest it has one of the lowest prevalence rates of AD in the world.[23, 24] To further substantiate this, one more study reported improved cognitive function among populations that consume curry, containing curcumin, on a regular basis than those who don't.[25] Yang et al. 2005[26] has shown that curcumin directly binds small β-amyloid species to block aggregation and fibril formation in vitro and in vivo, suggesting that low dose curcumin effectively disaggregates Aβ as well as prevents fibril and oligomer formation, supporting the rationale for curcumin use in clinical trials for preventing or treating AD.

8. *Galanthamine,* an alkaloid of *Galanthus nivalis*, (common known as snowdrop) and several other members of the Amaryllidaceae family. All species of *Galanthus* are perennial, herbaceous plants that grow from bulbs. Galanthamine is a long-acting, selective, reversible and competitive inhibitor of acetylcholinesterase and an allosteric modulator of the neuronal nicotinic receptor for acetylcholine.[27,28] Galanthamine hydrobromide has superior pharmacological profiles and higher tolerance as compared to the original AChE inhibitors, physostigmine or tacrine.[29] After establishing the effectiveness of galanthamine in preclinical trials for AD, a large number of clinical studies were carried out to see its beneficial effects in the diseased patients. From all the clinical trials, it was predicted that galanthamine was specifically effective in patients with mild AD by improving cognition in patients with mild AD.[30] After the successful clinical trials, it was first launched in market as "NIVALIN" in 1996 by Sanochemia Pharmazeutika of Austria for treatment of AD, and later as "REMINYL" in many countries such as Argentina, Australia, Belgium, Canada, Denmark, France, Germany, Greece, Italy, U.S. etc. from 2000 to 2003.[28] Nowadays, galanthamine is marketed under the name "Razadyne". which was approved in 2001 by FDA.

9. *Ginkgo biloba* L (Ginkgoaceae) A tree with pyramidal form, reaching a height of 30 m; leaves petiolar, lamina fan-shaped, bilobed; dioecious; mature seeds orange coloured and are about the size of an apricot. *G. biloba* is currently the most investigated and adopted herbal remedy for cognitive disorders and AD.[31] It is looked as polyvalent agent with a possible therapeutic use in the treatment of neurodegenerative diseases of multifactorial origin, such as AD. The extract of *G. biloba* leaves (EGb761) has been standardized to contain 24% flavonoid glycosides (containing quercetin, kaempferol, isorhamnetin *etc.*), 6% terpenoids (in which 3.1% are ginkgolides A, B, C, and J and 2.9% is bilobalide), and 5–10% organic acids. Bastianetto et al. 2000[32] has demonstrated that EGb761 is able to completely protect rat hippocampal primary cultured cells, the area severely affected in AD, against beta-amyloid and H_2O_2 induced toxicity and apoptosis. A number of other studies have indicated that EGb761 protects against Aβ-induced neurotoxicity by blockade of Aβ-induced events, such as ROS accumulation, glucose uptake, mitochondrial dysfunction, activation of AKT, JNK and ERK ½ pathways and apoptosis.[33,34] In addition to the protective effects against Aβ, EGb761 has also been shown to prevent amyloidogenesis.[35] Canevellia et al. 2014[36] has suggested that *G. biloba* may provide some added cognitive benefits in AD patients already under cholinesterase inhibitors treatment.

10. *Huperzia serrata* (Huperziaceae)- A traditional Chinese medicine has attracted intense attention since its marked anticholinesterase activity was discovered by Chinese scientists. Huperzine A, a sesquiterpene alkaloid isolated from *H. serrata* has been marketed in China as a new drug for AD treatment. Huperzine A inhibited acetylcholinesterase and protects the neuronal cells against the protein β-amyloid, offering a good alternative for treatment of AD.[37]

11. *Magnolia officinalis* (Magnoliaceae), commonly known as Houpu in Chinese, a deciduous tree growing to 20 m in height is native to the mountains and valleys of China at altitudes of 300–1500 m. Lee et al. 2010[38] has demonstrated that oral pretreatment of ethanol extract of *M. officinalis* (2.5, 5 and 10 mg/kg) and its major active constituent, 4-*O*-methylhonokiol (1 mg/kg), into drinking water for 5 weeks suppressed Aβ1–42 (0.5 μg/mouse, i.c.v.)-induced memory impairments. 4-*O*-methylhonokiol has also directly inhibited β-secretase activity and Aβ fibrilization in vitro. Thus, ethanol extract of *M. officinalis* might be useful for treating AD. Oral pretreatment of ethanol extract of *M. officinalis* has also been reported to inhibit memory impairment and Aβ deposition in the brain of Tg2576 mice and decreased activity of β-secretase, cleaving Aβ from amyloid precursor protein (APP).[39]

12. *Ptychopetalum olacoides* Benth (Olaceae)- A small tree native of Amazon region of Brazil where it is commonly known as muirapuama, is used to treat

chronic neurodegenerative conditions of nervous system. Alcoholic infusions are prepared from the roots of *P. olacoides* to treat nerve weakness by Amazonian Indians. Clerodan-type diterpenoids present in this plant showed nerve growth factor potentiating activity on PC-12 cells (in vitro) in a dose dependent manner suggesting that they may be useful for developing drugs for treatment of neurodegenerative diseases such as AD.[40]

REFERENCES

1. Sandhya S, Vinod KR, Kumar S. Herbs used for brain disorders. Hygeia J D Med, 2010; 2: 38-45.
2. Auld D S, Kornecook T J, Bastianetto S, Quirion R. Alzheimer's disease and the basal forebrain cholinergic system: relations to beta-amyloid peptides, cognition and treatment strategies. Prog Neurobiol, 2002; 68: 209-45.
3. Giacobini E R, Spiegel A, Enz Veroff A E, Cutler N R. Inhibition of acetyl – and butyryl – cholinesterase in the cerebrospinal fluid of patients with Alzheimer's disease by rivastigmine: Correlation with cognitive benefit. J Neurol Transm, 2002; 109: 1053-65.
4. Kelly CA, Harvey RJ, Cayton H. Drug treatments for Alzheimer's disease. Br Med J, 1997; 314: 693–4.
5. Scott LJ, Goa KL. Galantamine: a review of its use in Alzheimer's disease. Drugs, 2000; 60: 1095–122.
6. Chattipakorn S, Pongpanparadorn A, Pratchayasakul W, Pongchaidacha A, Ingkaninan K, Chattipakorn N. Tabernaemontana divaricata extract inhibits neuronal acetylcholinesterase activity in rats. J Ethnopharmacol, 2007; 110: 61–8.
7. Mukherjee PK, Kumar V, Mal M, Houghton PJ. In Vitro acetylcholinesterase (AChE) inhibitory activity of the essential oil form *Acorus calamus* and its main costituents. Planta Medica, 2007; 73: 283-5.
8. Geng Y, Li C, Liu J, Xing G, Zhou L, Dong M, Li X, Niu Y. Beta-asarone improves cognitive function by suppressing neuronal apoptosis in the beta-amyloid hippocampus injection rat. Biol Pharm Bull 2010; 33: 836-43.
9. Swathi V, Ragavendra M, Sushma M, Rao VUM. Evaluation of nootropic activty of *Acorous calamus* against scopolamine induced Alzheimer's. world J Pharm pharm sci, 2015; 4: 1743-58.
10. Bhattacharya SK, Bhattacharya A, Kumar A, Ghosal S. Antioxidant activity of *Bacopa monniera* in rat frontal cortex, striatum and hippocampus. Phytother Res, 2000; 14: 174-9.
11. Limpeanchob N, Jaipan S, Rattana karuna S, Phrompittayarat W, Ingkaninan K. Neuroprotective effect of *Bacopa monnieri* on beta-amyloid-induced cell death in primary cortical culture. J Ethnopharmacol, 2008; 120: 112-7.
12. Dhanasekaran M, Tharakan B, Holcomb LA, Hitt AR, Young KA, Manyam BV. Neuroprotective mechanisms of Ayurvedic antidementia botanical *Bacopa monniera*. Phytother Res, 2007; 21: 965-9.
13. Uabundit N, Wattanathorn J, Mucimapura S, Ingkaninan K. Cognitive enhancement and neuroprotective effects of *Bacopa monnieri* in Alzheimer‟s disease model. J Ethnopharmacol, 2010; 127: 26-31.
14. Koo KA, Kim SH, Lee MK, Kim YC. 15-methoxypinusolidic acid from *Biota orientalis* attenuates glutamate-induced neurotoxicity in primary cultured rat cortical cells. Toxicol Vitro, 2006; 20: 936–41.
15. Badrul A, Ekramul H. Anti-alzheimer and antioxidant activity of *Celastrus paniculatus* seed. Iran J Pharm Sci, 2011; 7: 49-56.
16. Patil SP, Maki S, Khedkar SA, Rigby AC, Chan C. Withanolide A and Asiatic acid modulate multiple targets associated with amyloid- beta precursor protein processing and amyloid- beta protein clearance. J Natl Prod, 2010; 73: 1196-1202.
17. Soumyanath A, Zhong YP, Henson E, Wadsworth T, Bishop J, Gold BG, Quinn JF. *Centella asiatica* extract improves behavioral deficits in a mouse model of Alzheimer‟s disease: investigation of a possible mechanism of action. Int J Alzheimer‟s Dis, 2012; 1-9.
18. 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 Compl Med, 2015; 1-8.
19. Zhu F, Qian C. Berberine chloride can ameliorate the spatial memory impairment and increase the expression of interleukin-1beta and inducible nitric oxide synthase in the rat model of Alzheimer's disease. BMC Neurosci. 2006; 7: 78-86.
20. Jung HA, Min BS, Yokozawa T, Lee JH, Kim YS, Choi JS. Anti-alzheimer and antioxidant activities of *Coptidis rhizoma* alkaloids. Biol Pharm Bull, 2009; 32: 1433-8.
21. Durairajan SSK, Liu LF, Lu JH, Chen LL, Yuan Q, Chung SK, Huang L, Li XH, Huang JD, Li M. Berberine ameliorates β-amyloid pathology, gliosis, and cognitive impairment in an Alzheimer's disease transgenic mouse model. Neurobio Aging, 2012; 33: 2903-19.
22. Ganguli M, Chandra V, Kamboh MI, Johnston JM, Dodge HH, Thelma BK, Juyal RC, Pandav R, Belle SH, Dekosky ST. Apolipoprotein E polymorphism and Alzheimer's disease: The Indo-US cross-national dementia study. Arch Neurol, 2000; 57: 824-30.
23. Chandra V, Pandav R, Dodge HH, Johnston JM, Belle SH, De-Kosky ST, Ganguli M. Incidence of Alzheimer's disease in a rural community in India: the Indo-US study. Neurology, 2001; 57: 985-9.
24. Vas CJ, Pinto C, Panikker D, Noronha S, Deshpande N, Kulkarni L, Sachdeva S. Prevalence of dementia in an urban Indian population. Int Psychogeriatr, 2001; 13: 439-50.

25. Ng TP, Chiam PC, Lee T, Chua HC, Lim L, Kua EH. Curry consumption and cognitive function in the elderly. Am J Epidem, 2006; 164: 898-906.
26. Yang F, Lim GP, Begum AN, Ubeda OJ, Simmons MR, Ambegaokar SS, Chen P,Kayed R, Glabe CG, Frautschy SA, Cole GM. Curcumin inhibits formation of amyloid β oligomers and fibrils, binds plaques, and reduces amyloid in Vivo. J Biol Chem, 2005; 280: 5892-901.
27. Bastida J, Lavilla R, Viladomat F. Chemical and biological aspects of Narcissus alkaloids. In The Alkaloids; Cordell, G.A., Ed., Elsevier Scientific: Amsterdam, The Netherlands, 2006; 63: 87–179.
28. Heinrich M, Teoh HL. Galanthamine from snowdrop-the development of a modern drug against Alzheimer's disease from local Caucasian knowledge. J Ethnopharmacol, 2004; 92: 147-62.
29. Grutzendler J, Morris JC. Cholinesterase inhibitors for Alzheimer's disease. Drugs, 2001; 61: 41–52.
30. Raskind MA, Peskind ER, Wessel T, Yuan W. Galantamine in AD: A 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. Neurology, 2000; 54: 2261-8.
31. Weinmann S, Roll S, Schwarzbach C, Vauth C, Willich SN. Effects of Ginkgo biloba in dementia: systematic review and meta-analysis. BMC Geriatr, 2010; 10: 14-25.
32. Bastianetto, S.; Ramassamy, C.; Doré, S.; Christen, S.; Poirier, J.; Quirion, R. The *Ginkgo biloba* extract (EGb 761) protects hippocampal neurons against cell death induced by beta-amyloid. Eur J Neurosci, 2000; 12: 1882–90.
33. Shi C, Zhao L, Zhu B, Li Q, Yew DT, Yao Z, Xu J. Protective effects of *Ginkgo biloba* extract (EGb761) and its constituents quercetin and ginkgolide B against beta-amyloid peptide induced toxicity in SH-SY5Y cells. Chem Biol Interact, 2009; 181: 115-23.
34. Smith JV, Luo Y. Elevation of oxidative free radicals in Alzheimer's disease models can be attenuated by *Ginkgo biloba* extract EGb761. J Alzheimer‟s Dis, 2003; 5: 287–300.
35. Yao ZX, Han Z, Drieu K, Papadopoulos V. *Ginkgo biloba* extract (EGb761) inhibits beta-amyloid production by lowering free cholesterol levels. J Nutr Biochem, 2004; 15: 749-56.
36. Canevellia M, Adali N, Kelaiditi E, Cantet C, Ousset PJ, Cesari M, ICTUS/DSA Group. Effects of *Gingko biloba* supplementation in Alzheimer‟s disease patients receiving cholinesterase inhibitors: Data from the ICTUS study. Phytomedicine, 2014; 21: 888-92.
37. Adams M, Gmunder F, Hamburger M. Plants traditionally used in age related brain disorders--a survey of ethnobotanical literature. J Ethanopharmacol, 2007; 113: 363-81.
38. Lee JW, Lee YK, Lee BJ, Nam SY, Lee SII, Kim YH, Kim KH, Oh KW, Hong JT. Inhibitory effect of ethanol extract of *Magnolia officianalis* and 4-O-methylhonokiol on memory impairment and neuronal toxicity induced by beta-amyloid. Pharmacol Biochem Behav, 2010; 95: 31-40..
39. Lee YJ, Choi DY, Han SB, Kim YH, Kim KH, Hwang BY, Kang JK, Lee BJ, Oh KW, Hong JT. Inhibitory effect of ethanol extract of *Magnolia officinalis* on memory impairment and amyloidogenesis in a transgenic mouse model of Alzheimer's disease via regulating β-secretase activity. Phytother Res, 2012; 26: 1884-92.
40. Tang WX, Kubo M, Harda K, Hioki H, Fukuyama Y, Novel NGF-potentiating diterpenoids from a Brazilian medicinal plant, *Ptychopetalum olacoides.* Bioorg Med Chem Lett, 2009; 19: 882-6.