DOI: https://doi.org/10.53555/nnpbs.v1i10.562 **Publication URL: http://nnpub.org/index.php/PBS/article/view/562**

CURRENT RESEARCH ON THERAPY IN ALZHEIMER'S DISEASE EXPERIMENTAL MODEL: BETA-AMYLOID$_{1-42}$ INDUCTION

Felipe Carmo de Moura[1]*, Welton Daniel Godinho[2], Lucas Lima Vieira[3], Conceição da Silva Martins[4], Paula Matias Soares[5], Gerly Anne de Castro Brito[6]

*[1,2,3,5]*Superior Institute of Biomedical Science, Ceara State University, Fortaleza, Ceara, Brazil.*

*[4,5,6]*Postgraduate Program in Morphofunctional Sciences, Faculty of Medicine, Morphology Department, Ceara Federal University, Fortaleza, CE, Brazil.*

**Ceara State University, Superior Institute of Biomedical Science, 1700 Dr. Silas Munguba, Avenue, Fortaleza, Ceara, Brazil, E-mail: premium_rep@hotmail.com*

Corresponding Author: -
E-mail: premium_rep@hotmail.com

Abstract: -

Alzheimer's disease (AD) is a neurodegenerative disorder commonly associated with brain β-amyloid accumulation (Aβ). Early in disease, individuals have impairment in short-term memory, but keeps alert preserved sensory and motor functions, progressing to cognitive functions total loss. The aim of this study is to present main substances currently investigated in Alzheimer's disease experimental model induced by Aβ$_{1-42}$ and its possible therapeutic actions. For this, we realized an exhaustive literature research, and main results data compiled and analyzed. Thus, there were observed three agents' classes used to treat AD: antioxidants, anti-inflammatory, and calcium homeostasis regulators, with 15 substances found. In conclusion, it can be seen that these agents have beneficial results which suggest actions that may be used in clinical practice to pathology treatment.

Keywords: - *Alzheimer's disease, β-amyloid$_{1-42}$, treatment, hippocampus*.

INTRODUCTION

Dementia is characterized by progressive deterioration of cognitive function, memory loss and behavioral changes [1]. Alzheimer's Disease (AD) is the most dementia common form occurring progressive degeneration [2-4], and it is commonly associated with amyloid plaque accumulation (formed by β-amyloid protein aggregates - Aβ) in intracerebral regions, such hippocampus, amygdala, prefrontal cortex and striatum, being one of first identified structural features, followed by neurofibrillary tangles, associated with Tau protein hyperphosphorylation [1,2,4-6].

Aβ plays an important role in synaptic vesicle activity modulation, especially in hippocampus, wherein production, release, and degradation ratio is a possible mediator' synapses mechanism, probably indicating the initial disease pathological symptoms [1,7]. The Aβ hypothesis through amyloidogenic pathway, i.e., Amyloid Precursor Protein (APP) is cleaved initially by β-secretase enzyme and then by γsecretase one, is widely accepted by scientific community, and, through genetic, histological, and biochemical use on animal models, these findings are evidenced involving synaptic dysfunctions in several neurotransmitter systems, such as cholinergic, serotonergic, dopaminergic, and glutamatergic ones [8,9].

AD is still an incurable disease, the search for new therapeutic approaches has been widely studied. Thus, animal models enable new strategies use for humans' treatment. Among animal models that more closely resemble human disease physiopathology have been cholinergic dysfunction models, Aβ induction aggregate, APP or Tau protein gene mutations are described in literature [10-12].

The model based on Aβ induction aggregate can be through Aβ1-40, Aβ25-35 or Aβ1-42, the latter being the most used one due to increased propensity to amyloid aggregation and present resemblance to disease in few days[13-15]. The $A\beta_{1-42}$ model is done through a surgical procedure in rodents by intrahippocampal or intraventricular injection of this aggregate after animal anesthesia with assistance of a stereotactic apparatus [14,16].

The procedure starts with anesthesia, being a meticulous substances choice according to animal type, because intravenous injection use is impractical in mice and intraperitoneal, subcutaneous or intramuscular administration shows inconsistency in its absorption [17]. Among anesthetic, the most used are: ketamine, xylazine, diazepam, thiopentone e acepromazine, being combination of these substances frequently used [18-20].

However, a careful conversion rate between humans and animals is extremely important for treatment after induction model [21]. Therefore, after anesthesia, animal is fixed in stereotaxic through ear bars and nose fixer, then an incision is made to skull expose to bregma and lambda visualization. With an atlas coordinates assistance[22], hippocampus or third ventricle region are located, where $A\beta_{1-42}$ aggregate application are performed, being approximately 5µl per application. For this purpose, $A\beta_{1-42}$ peptide, lyophilized powder, needs to be prepared by dilution and centrifugation with physiological or fetal bovine serum (FBS)[14,23]. Surgery total time may vary according to anesthesia (10-20 minutes), and/or selected pre-anesthesia, with apparatus fixing animal (15-20 minutes), with intracerebral injection (20-30 minutes), suture and anesthesia recovery (10-30 minutes)[24].

The necessity to studies and research on finding new therapies that control, reverse or even cure this disease in humans make animal models important in preclinical studies. Additionally, $A\beta_{1-42}$ model promotes na important research source for new therapeutic approaches in scientific community. Thus, the study aims to conduct a literature review in order to identify new therapies being more invested in $A\beta_{1-42}$ experimental model by researchers.

Materials and Methods

This study constituted in a relevant literature survey on subject, for that the following keywords were related to each other: Alzheimer, $A\beta_{1-42}$ and Treatment considering their appearance in Title, Abstract, and/or text words. Publications were considered in different databases, such as SciELO, LILACS, PubMed, ScienceDirect, and BIREME in the last 05 years. Articles with humans' treatment and cell culture were excluded, as well as others animal models which did not use $A\beta_{1-42}$ protein. After initial survey, Title and Abstract had been read, and it was considered only new substances not used in AD standard clinical practice or even those ones which were not approved for human use and it were disconsidered papers in duplicate, exposing forward obtained results

Results and Discussion

A scientific analysis previously done with drugs under development for Alzheimer treatment observed a 99% failure rate between years 2002-2012[25]. Currently there are five drugs approved by Food and Drug Administration (FDA) for disease treatment, such Tacrine, Donepezil, Galantamine, Rivastigmine (acetylcholinesterase inhibitors), Memantine (NMDA glutamatergic receptor antagonist), and association between Donepezil and Memantine [26].

Understand mechanisms involved in disease onset and progression can contribute to search for more effective treatments. Studies demonstrated, besides Aβ aggregates and Tau hyperphosphorylation, reactive oxygen (ROS) and nitrogen species (RNS) production, inflammation, and excitotoxicity related to calcium homeostasis deregulation are also involved in disease pathogenesis [27]. This section presents subgroups and substances used in interest experimental model and their results.

Antioxidants

Oxidative stress can be defined as na imbalance between pro and antioxidants substances. ROS and RNS are aerobic cellular metabolism products, involved with redox balance, together with antioxidant substances and enzymes, thus playing na important role in neurodegenerative diseases [28] and aging process [29].

Among antioxidants substances recently studied, Resveratrol, a polyphenol derived from plants and found elevated level in red grapes and wine, possibly activate directly sirtuins, which have similar effect to caloric restriction affecting pathway

regulation related diseases aging, such AD [30]. It is believed it is a substance with antioxidant properties and when administered in an AD experimental model in mice may promote reduction $A\beta_{1-42}$ levels in hippocampus region after treatment [31].

Another antioxidant compound, 5-Hydroxymethylfurfural (5-HMF) produced from natural ones, such as fructose, glucose, sucrose, and cellulose, has been studied under various extraction processes, as well as its production from wood, straw rice or corn [32]. Currently it is extracted from Alpinia oxyphylla Miq. and in a study involving mice treated for Five consecutive days showed positive results in relation to memory and learning in Morris Water Maze (MWM), and antioxidant enzymes increase, indicating as a possible therapeutic agent in AD treatment [33].

Minocycline, a second-generation tetracycline derivative, has been used for over 40 years for its characteristic to overcome blood brain barrier and prevent caspase upregulation, possibly reducing neuronal apoptosis in Huntington experimental model and Amyotrophic Lateral Sclerosis [34]. Evidences indicate this agent has anti-inflamatory and antioxidant properties, observing a reduction in 3-nitrotyrosine

(3-NT) levels, a peroxynitrite formation marker, in rats' glial cells, and possible reduction in oxidative enzymes activity, such cycloxygenase-2 (COX-2), NADPH-oxidase e calcium-insensitive nitric oxide synthase (iNOS)[35].

Since Chitosan discovery in mid-1850s, numerous studies have been conducted since application in reducing blood cholesterol levels, lower blood pressure, as well as diseases related to inflammation [36]. Chitosan oligosaccharides (COS) are a Chitosan hydrolyzed product, abundant in crustaceans' exoskeletons and fungi and insects cell wall. In a study with rats, using MWM and biochemical methods, it was observed in treated group there was na improvement in memory and indexes decrease in malondialdehyde (MDA) levels, as well as increased antioxidant enzymes levels [37].

Canola seeds are rich in phenolic compounds when compared to other oil ones. The most significant component is extracted from this seed is sinapic acid (SA), and the acid component main antioxidant derivative was identified as 1-O-β-D-glucopyranosyl sinapate[38]. O SA is a phenylpropanoid compound which can also be found in wheat bran or plants, such as Sinapis alba, and mustard seeds. It presents antioxidant and anti-inflammatory actions. In a study with mice, it was observed reduction in iNOS expression when treated with SA for a week [39].

Orientin (ORI) is a flevonoid component found in abundance in passion fruit peel and bamboo leaves, with a long history in Asian medicine for possible exerts antioxidant and anti-inflammatory properties [40]. In a study that demonstrate antioxidant properties by lowering mitochondrial apoptotic pathway in mice brain, it was observed, after 15 days of treatment with ORI intraperitoneally, there was improvement in memory and learning tests using MWM, as well as reduction in 3-NT levels, lipid peroxidation (4-hydroxy-nonenal, 4-HNE) and DNA oxidation (8-hydroxy-2'-deoxyguanosine, 8-OHdG), related oxidative stress [41].

Calcium Homeostasis Regulators

Among some features related to AD pathogenesis, calcium homeostasis imbalance can promote deficits in memory and learning [3], being suggested as a theory in relationship between AD high rates in individuals with Diabetes Mellitus type 2[3,4].

Exendin-4 is a peptide of 39-amino, an acid glucagon-like peptide (GLP-1) analog, and it is present in Gila monster (Heloderma suspectum) saliva [42]. In a recent study of this substance as diabetes mellitus type 2 treatment, since it has an action to stimulate insulin secretion by increasing calcium inflow. This turned out to support the Exendin-4 theory use in AD treatment [43].

Anthocyanins are a group derived from flaviliium salts polihydroxy compounds which belongs to

flavonoid family and they are responsible for blue, purple and red pigments in higher plants' leaves, fruits and flowers. Usually, plants produce these substances as a defense mechanism against environmental stress factors as ultraviolet rays, low temperatures and droughts [44]. In a study using anthocyanins in AD experimental model was observed that treated animals showed reduction in Aβ levels in hippocampus when compared to control group, as well as calcium levels normalization in a study with cell culture. Thus, it is suggested that treated animals' Aβ levels reduction in hippocampus is due to an intracellular calcium levels' normal balance [45].

Anti-inflammatory

Evidences indicate that neuritic plaques formed by Aβ accumulation in brain are responsible for synaptic dysfunction followed by neuronal damage [46]. Aβ possibly promotes neurodegeneration through parallel mechanism via microglial cells and astocytes activation [47]. Microglia makes up about 10% of cells in Central Nervous System (CNS) and plays an important role in most immune cell defense in this system, representing the defense first line against pathogens and other lesions types [48,49].

Thus, with microglia activation and astrocytes recruitment occurs na acute inflammatory response with cytokines release, activating a neuroinflammation cascade. These inflammatory mediators are involved in AD and when released in excess promote neurotoxicity [50]. During brain lesions or neurodegenerative processes, Tumor Necrosis Factor (TNF-α) release, inflammatory cytokines, nitric oxide and ROS activate microglia [47-49]. Thus, evidences suggest that inflammatory mechanisms are involved in disease pathogenesis, contributing to its progression, leading to extensive research on antiinflammatory substances use as a treatment option that offer benefits in AD [51].

Soybean isoflavone has been cultivated for about 5,000 years in China and it was introduced in Europe and America in the 18th and 19th centuries, respectively. This substance is biosynthesized through a general phenylpropanoid pathway, which initiates from naringenin phenylalanine, na pathway intermediate amino acid, converted sequentially in genistein isoflavone by isoflavone synthase enzyme and dehydratase [52]. In a recent study, this substance was able to reduce

Interleukin-1 (IL-1) and TNF-α level, and thus it can be an effective component in inflammatory processes' reduction treatment related to AD [53].

Dipsacus asper wall is a substance extracted from Chinese plants with various therapeutic applications, such low back pain, traumatic hematomas and bone fractures. Evidences indicate that this substance could reduce cognitive impairment and decrease Aβ production in hippocampus induced by chronic exposure of rats to aluminum[54,55]. Akebia Saponin D is extracted from this medicinal herb above mentioned and it has been studied like an anti-inflammatory substance. A recent study showed this activity, by histochemical and biochemical methods, with reduction in IL-1 and TNF-α levels [56].

Another option discussed in literature with anti-inflammatory effects is hydrogen-rich saline, an option to hydrogen gas use, because transport and handle tanks difficulty, as well as itself is safe and costeffective option. Studies demonstrate beneficial therapeutic effect on ROS production and inflammatory processes in several brain injury types and neurodegenerative diseases [57]. In a 2011 study, they examined these saline effects in reducing neuroinflammation, which they found decrease in IL-1β levels, concluding that it may attenuate inflammatory effects on AD [58].

Ginseng is an important medicinal herb related to longevity, especially in Asian countries. In traditional Chinese medicine, this plant is widely used for improving cognitive functions like memory and slow processes related to dementia. The main pharmacologically active ingredients in ginseng are ginsenosides Rg1 e Rb1, involved in inhibiting neuroinflammation and reduced Aβ aggregation [59,60].

Thus, Rb1 effects were studied in AD experimental model in rats induced by $A\beta_{1-42}$ and through MWM it was observed a damage in memory reversal caused after surgery, suggesting an indirect mechanism for drugs development that promote reversal neuroinflammation on hippocampus [61].

Hydroxy-safflor yellow A (HSYA) is the main chemical component of isolated yellow pigment from Carthamus tinctorius L. and it has demonstrated antithrombotic properties and has been used for treating cardiovascular diseases and pulmonary inflammatory lesions minimization [62]. Evidences suggest that this substance has anti-inflammatory properties and a study model induced by Aβ1-42 was demonstrated significant reductions in IL-1 e TNF-α level, suggesting an inflammatory response inhibition in AD [63].

Tetrandine, an isolated alkaloid extracted from Chinese herb Stephania tetranda root, presents antihypertensive, hepatoprotective, and anti-inflammatory effects [64,65]. In a recent study, this alkaloid decreased proinflammatory mediators' expression by inhibiting Nuclear Factor-kB (NF-kB) activation. By reducing IL-1 e TNF-α, spatial learning and memory could be improved in rats by NF-kB downregulation, suggesting that this substance administration might be used on patients with AD treatment [66].

Carotenoids are present in considerable amounts in human plasma and tissues due to tomatoes, red vegetables and watermelons dietary intake [67]. Lycopene, a carotenoid type, has antioxidant and antiinflammatory effects. In AD, a study demonstrated a proinflammatory cytokines significant reduction, such as TNF-α, TGF-β and IL-1β in rats' brain after 14 days of treatment. The improvement in relation to learning and spatial memory was confirmed through WMW [68].

Tabel 01 – Screened substances in different papers with their methodological characteristics (animal species, effective doses, treatment duration, methods used) and results obtained (action and effects) in an experimental model induced by $A\beta_{1-42}$.

Substances	Animal species	Doses	Treatment duration	Methods used	Action	Effects	Paper number
Resveratrol	Rats	40, 80 mg/kg	12 weeks	IA, Wb	Antioxidant	↓NF-κB, Aβ1-42	[31]
5-Hydroxymethylfurfural (5-HMF)	Mice	15, 150 µg/kg	05 days	MWM	Antioxidant	↓Cognitive impairment	[33]
Minocycline	Rats	25 mg/kg	07 days	IH	Antioxidant	↓3-NT	[35]
Chitosanoligosaccharides (COS)	Rats	200, 400, 800 mg/kg	14 days	BCH	Antioxidant	↓MDA	[37]
Sinapicacid	Mice	10 mg/kg	07 days	Wb	Antioxidant	↓iNOS	[39]
Orientin	Mice	20, 40 mg/kg	3 weeks	IH	Antioxidant	↓3-NT	[41]
Exendin-4	Rats	1 µl	Injection 15 minutes after surgery	IH	Calcium homeostasis regulators	↓Ca^{2+}	[43]
Anthocyanins	Rats	0.2 mg/kg	30 days	Wb	Calcium homeostasis regulators	↓Aβ1-42	[45]
Soybeanisoflavone	Rats	80 mg/kg	14 days before surgery	RT-PCR, Wb	Antiinflammatory	↓IL-1, TNF-α	[53]
AkebiaSaponin D	Rats	30, 90, 270 mg/kg	4 weeks	BCH, HCH	Antiinflammatory	↓IL-1, TNF-α	[56]
hydrogen-rich saline	Rats	5 ml/kg,	10 days	IH, Wb	Antiinflammatory	↓IL-1	[58]
Ginseng Rb1	Rats	10 mg/kg		MWM	Antiinflammatory	↓Cognitive impairment	[61]
Hydroxy-saffloryellow A	Mice	20 mg/kg	14 days	RT-PCR, Wb	Antiinflammatory	↓IL-1, TNF-α	[63]
Tetrandine	Rats	40 mg/kg	14 days	BCH, HCH	Antiinflammatory	↓IL-1, TNF-α	[66]
Licopeno	Rats	1,2,4 mg/kg	14 days	Imunoass ay-kit	Antiinflammatory	↓TNF-α, TGF-β, IL-1β	[68]

IA- Immunosorbent assay; Wb- Western blot; Ih- Immunohistochemistry; RT-PCR- Reverse transcriptionpolymerase chain reaction; MWM- Morris Wate Maze; BCH- Biochemistry; HCH- Histochemistry; MDA- malondialdehyde; ↓- reduction; NF- Nuclear Factor; $A\beta_{1-42}$- β-amyloid$_{1-42}$; 3-NT- 3-nitrotyrosine; MDA- malondialdehyde; iNOS- calcium-insensitive nitric oxide synthase; Ca^{2+}- calcium levels; IL- Interleukin; TNF- Tumor Necrosis Factor; TGF- Tumor Growth Factor.

Conclusion

AD, because it is a multifactorial disease and its origin remains Unknown, presents a variety of research related to treatment, but insufficient in complete remission. It is observed, among animals' models similar to AD, $A\beta_{1-42}$ experimental model has been extensively studied in recent years with several substances, which promote positive effects, mainly antioxidant, anti-inflammatory, and calcium homeostasis regulators.

Acknowledgment

Scientific and Technological Development Nacional Brazilian Council (CNPq), Higher Education Personnel Improvement Coordination (CAPES), Cearense Foundation for Support of Scientific and Technological Development (FUNCAP), Post-graduate Program in Morphofunctional Sciences (PPGCM), Center for Studies in Microscopy and Image Processing (NEMPI), and Post-graduate Program in Physiological Sciences (PPGCF) of Biomedical Sciences Higher Institute (ISCB).

References

[1] Selkoe D. J. Alzheimer's Disease: Genes, Proteins, and Therapy. Physiological Reviews 81, 2, (2001).
[2] Bombois S, Duhamel A, Salleron J, Deramecourt V, Mackowiak M-A, Deken V. A New decision tree combining abeta 1-42 and p-tau levels in Alzheimer's Disease. Current Alzheimer Research 10, 357-364, (2013).
[3] Querfurth H. W, Laferla F. M. Mechanism of disease Alzheimer's Disease. The New England Journal of Medicine 362, 329-344, (2010).
[4] Reitz C, Mayeux R. Alzheimer's disease: Epidemiology, diagnostic criteria, risk factors and biomarkers. Biochemical Pharmacology 88, 640-651, (2014).
[5] Morishima-Kawashima M, Ihara Y. Alzheimer's Disease: β-Amyloid Protein and Tau. Journal of Neuroscience Research 70, 392-401, (2002).
[6] Magistri M, Velmeshev D, Makhumutova M, Faghihi M. A. Transcriptomics profiling of alzheimer's disease reveal neurovascular defects, altered amyloid-β homeostasis, and desregulated expression. Of long noncoding RNAs. Journal of Alzheimer's Disease 48, 647-665, (2015).
[7] Abramov E. et al. Amyloid-B as a positive endogenous regulator of release probability at hippocampal synapses. Nature Neurosciece 12, 12, 1567-1576, (2009).
[8] Selkoe J. D**.** The therapeutics of Alzheimer's Disease: Where we stand and where we are heading. Ann Neurol 73, 328-336, (2013).
[9] Hardy, J.; Selkoe, D.J. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 297(5580), 353-356. (2002).
[10] Benedikz E, Kloskovwka E, Winblad B. The rat as model of Alzheimer's Disease. J Cell. Mol. Med 13, 6, (2009).
[11] Belarbi K, Burnouf S, Fernandez-Gomez F, Laurent C, Lestavel S, Figeac M, et al. Beneficial effects of exercise in a trangenic mouse modelo f Alzheimer's disease-like Tau pathology. Neurobiology of disease 43, 486-494, (2011).
[12] Bagheri M, Joghataei M-T, Mohseni S, Roghani M. Genistein ameliorates leaqrning and memory déficits in amyloid β $_{(1-42)}$ rat modelo f Alzheimer's disease. Neurobiology of Learning and Memory 95, 270-276, (2011).
[13] Cetin F, Dincer S. The effect of intrahippocampal beta amyloid (1-42) peptide injection on oxidant and antioxidante status in rat brain. Ann. N. Y. Acad. Sci. 1100, 510-517, (2007).
[14] Perez J. L, Carrero I, Gonzalo P, Arevalo-Serrano J, Sanz-Anquela J. M, Ortega J, et al. Solube oligomeric forms of beta-amyloid (Aβ) peptide stimulate Aβ production via astrogliosis in the rat brain. Experimental Neurology 223, 410-421, (2010).
[15] Richardson R. L, Kim E-M, Shephard R. A, Gardiner T, Cleary J, O'Hare E. Behavioural and histopathological analyses of ibuprofen treatment on the effect of aggregated $A\beta_{(1-42)}$ injections in the rat. Brain Research 954, 1-10, (2002).
[16] Lee H. E, Kim D. H, Park S. J, Kim J. M, Lee Y. W, Jung J. M, et al. Neuroprotective effect of sinapic acid a mouse modelo of amyloid $A\beta_{1-42}$ protein-induced Alzheimer's Disease. Pharmacology, Biochemistry and Behavior 103, 260-266, (2012).
[17] Messier C, Émond S, Ethier K. New techniques in stereotaxic surgery and anestesia in the mouse. Pharmacology Biochemistry and Behavior 63, 2, 313-318, (1999).
[18] Moghaddam A. H, Hosseini R. S, Roohbakhsh A. Anxiogenic effect of CCK8s in the ventral hippocampus of rats: possible involvement of $GABA_A$ receptors. Pharmacological Reports 64, 4553. (2012).
[19] Green C. J, Knight J, Precious S, Simpkin S. Ketamine alone and combined with diazepam or xylazine in laboratory animals: a 10 year experience. Laboratory Animals 15, 163-170, (1981).
[20] Welberg L. A. M, Kinkead B, Thrivikraman K. V, Huerkamp M. J, Nemeroff C. B, Plotsky P. M. Ketamine-Xylazine-Acepromazine Anesthesia and Postoperative Recovery in Rats. Journal of the American Association for Laboratory animal Science 45, 2, 13-20, (2006).

[21] Reagan-Shaw S, Nihal M, Ahmad N. Dose translation from animal to human studies revisited. The FASEB Journal 22, 659-661, (2007).
[22] Paxinos G, Watson C, Pennisi M, Topple Ann. Bregma, lambda and the interaural midpoint in stereotaxic surgery with rats of different sex, strain and weight. Journal of Neuroscience Methods 13, 139-143, (1985).
[23] O'Hare E, Weldon D. T, Mantyh P. W, Ghilardi J. R, Finke M. P, Kuskowski M. A. et al. Delayed behavioral effects following intrahippocampal injection of aggregated Aβ $_{(1-42)}$. Brain Research 815, 1-10, (1999).
[24] Cetin A, Komai S, Eliava M, Seeburg P. H, Osten P. Stereotaxic gene delivery in the rodent brain. Nature Protocols 1, 6, 3166-3173, (2006).
[25] Cummings J. L, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: few candidates, frequente failures. Alzheimer's Research & Therapy 6, 1-7, (2014).
[26] Hyde C, Peters J, Bond M, Rogers G, Hoyle M, Anderson R. et al. Evolution of the evidence on the effectiveness and cost-effectiveness of acetylcholinesterase inhibitors and memantine for Alzheimer's disease systematic review and economic model. Age and Ageing 42, 14-20, (2013).
[27] Mattson M. P. Pathways Towards and Away from Alzheimer's Disease. Nature 430, 631-639, (2004).
[28] Jones D. P. Redefining Oxidative Stress. Antioxidants & Redox Signaling, 8, 9, 1865-1879, (2006).
[29] Mariani E, Polidori M. C, Cherubini A, Mecocci P. Oxidative stress in brain aging, neurodegenerative and vascular diseases: An overview. Journal of Chromatography B 827, 65-75, (2005).
[30] Albani D, Polito L, Forloni G. Sirtuins as novel target for Alzheimer's disease and other neurodegenerative disorders: experimental and genetic evidence. Journal Alzhimer's Disease 19, 1, 11-26, (2010).
[31] Zhao H. F, Li N, Wang Q, Cheng, X. J, Li X. M, Liu T. T. Resveratrol decrease the insoluble $A\beta_1$42 level in hippocampus and protects the integrity of the blood-brain barrier in AD rats. Neuroscience 310, 641-649, (2015).
[32] Yan L, Liu N, Wang Y, Machida H, Qi X. Production of 5-hydroxymethylfurfural from corn stalk catalized by corn stalk-derived carbonaceous solid acid catalyst. Bioresource Technology 173, 462-466, (2014).
[33] Liu A, Zhao X, Li H, Liu Z, Liu B, Mao X, et al. 5-Hydroxymethylfurfural, na antioxidante agente from Alpinia oxyphylla Miq. Improves cognitive impairment in $A\beta_{1-42}$ mouse model of Alzheimer's disease. International Immunopharmacology 23, 2, 719-725, (2014).
[34] Festoff B. W, Ameenuddin S, Arnold P. M, Wong A, Santacruz K. S, Citron B. A. Minocycline neuroprotects, reduces microgliosis, and inhibits caspase protease expression. Early after spinal cord injury. J Neurochem 97, 5, 1314-1326, (2006).
[35] Ryu J. K, McLarnon J. G. Minocycline or iNOS inhibition block 3-nitrotyrosine increases and blood-brain barrier leakiness in amyloid beta-peptide-injected rat hippocampus. Experimental Neurology 198, 2, 552-557, (2006).
[36] Kim S-K, Rajapakse N. Enzymatic production and biological activities of chitosan oligosaccharides (COS): A review. Carbohydrate Polymers 62, 4, 357-368, (2005).
[37] Jia S, Lu Z, Gao Z, An J, Wu X, Li X, et al. Chitosan oligosaccharides alleviate cognitive déficits in na amyloid-β_{1-42}-induced rat modelo f Alzheimer's disease. International Journal of Biological Macromolecules,article in press, (2015).
[38] Khattab R, Eskin M, Aliani M, Thiyam U. Determination of Sinapic Acid Derivatives in Canola Extracts Using High-Performance Liquid Chromatography. J Am Oil Chem Soc 87, 147-155, (2010).
[39] Lee H. E, Kim D. H, Park S. J, Kim J. M, Lee Y. W, Jung J. M. et al. Neuroprotective effet of sinapic acid in a mouse model of amyloid β_{1-42} protein-induced Alzheimer's disease. Pharmacology Biochemistry and Behavior 103, 2, 260-266, (2012).
[40] Wang S, Yu Y, Feng Y, Zou F, Zhang X, Huang J. et al. Protective effect of the orientin on noiseinduced cognitive impairments in mice. Behavioural Brain Research 296, 290-300, (2016).
[41] Yu L, Wang S, Chen X, Yang H, Li X, Xu Y, et al. Orientin alleviates cognitive déficits and oxidative stress in $A\beta_{1-42}$-induced mouse model of Alzheimer's disease. Life Science 121, 15, 104-109, (2015).
[42] Ding X, Saxena N. K, Lin S, Gupta N, Anania F. A. Exendin-4, a Glucagon-like Protein-1 (GLP1) Receptor agonist, reverses hepatic steatosis in ob/ob mice. Hepatology 43, 1, 173-181, (2006).
[43] Wang X, Wang L, Jiang R, Yuan Y, Yu Q, Li Y. Exendin-4 antagonizes $A\beta_{1-42}$-induced suppression of long-term potentiation by regulation intracelular calcium homeostasis in rat hippocampal neurons. Brain Research 1627, 101-108, (2015).
[44] Wallace T. C. Anthocyanins in Cardiovascular Disease. Advances in Nutrition 2, 1, 1-7, (2011).
[45] Badshah H, Kim T. H, Kim M. O. Protective effects of Anthocyanins against Amyloid betainduced neurotoxicity in vivo and in vitro. Neurochemistry International 80, 51-59, (2015).
[46] Rogers J, Webster S, Lue L, Brachova L, Civin W. H, Emmerling M et al. Inflammation and Alzheimer's disease Pathogenesis. Neurobiology of Aging, 17, 5, 681-686, (1996).
[47] Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole G. M. et al. Inflammation and alzheimer's disease. Neurobiology of Aging, 21, 383-421, (2000).
[48] Block M. L, Hong J. Microglia and inflammation-mediated neurodegeneration: Multiple trigger with a common mechanism. Progress in Neurobiology 76, 2, 77-98, (2005).
[49] Sastre M, Klockgether T, Heneka M. T. Contribuition of inflammatory processes to Alzheimer's disease: molecular mechanisms. International Journal of Developmental Neuroscience 24, 167176, (2006).
[50] Heneka M. T, O'Banion M. K. Inflammatory processes in Alzheimer's disease. Journal of Neuroimmunology 184, 69-91, (2007).

[51] Tuppo E, Arias H. R. The role of inflammation in Alzheimer's disease. The International Journal of Biochemistry & Cell Biology 37, 289-305, (2005).
[52] He F-J, Chen J-Q. Consumptiom of soybean, soy foods, soy isoflavones and breast câncer incidence: Differences between Chinese women and women in Western countries and possible mechanisms. Food Science and Human Wellness 2, 3-4, 146-161, (2013).
[53] Yuan L, Zhou X, Li D, Ma W, Yu H, Xi Y et al. Pattern reconigtion receptors involved in the inflammatory attenuating effects of soybean isoflavone in β-amyloid peptides 1-42 treated rats. Neuroscience Letters 506, 2, 266-270, (2012).
[54] Zhang Z-J, Qian Y-Q, Hu H-T, Yang J, Yang G-D. The herbal medicine Dipsacus asper wall extract reduces the cognitive déficits and overexpression of β-amyloid protein induced by aluminum exposure. Life Science 73, 2443-2454, (2003).
[55] Yu X, Wang L-n, Ma L, You R, Cui R, Ji D. et al. Akebia saponin D attenuates ibotenic acidinduced cognitive déficits and pro-apoptotic response in rats: Involvement of MAPK signal pathway. Pharmacology Biochemistry and Behavior 10, 3, 479-486, (2012).
[56] Yu X, Wang L, Du Q, Ma L, Chen L, You R, et al. Akebia Saponin D attenuates amyloid βinduced cognitive déficits and inflammatory response in rats: Involvement of Akt/NF-kB pathway. Behavioural Brain Research 235, 200-209, (2012).
[57] Hou Z, Luo W, Sun X, Hao S, Zhang Y, Xu F. et al. k. Brain Research Bulletin 88, 6, 560-565, (2012).
[58] Wang C, Li J, Liu Q, Yang R, Zhang H, Cao Y, et al. Hydrogen-rich saline reduces oxidative stress and inflammatory by inhibit of JNK and NF-kB activation in a rat model of amyloid-betainduced Alzheimer's disease. Neuroscience Letters 491, 2, 127-132, (2011).
[59] Li N, Zhou L, Li W, Liu Y, Wang J, He P. Protective effects of ginsenosides Rg1 and Rb1 on an Alzheimer's disease mouse model: A metabolomics study. Journal of Chromatography B 985, 5461, (2015).
[60] Chen F, Elizabeth A. E, Christopher B. E. Reductions in levels of the Alzheimer's amyloid β peptide after oral administration of ginsenosides. The FASEB Journal 20, 1269-1271, (2006).
[61] Wang Y, Liu J, Zhang Z, Bi P, Qi Z, Zhang C. Anti-neuroinflammatory effect of ginsenoside Rbl in a rat model of Alzheimer disease. Neuroscience Letters 487, 1, 70-72, (2011).
[62] Zhang Z, Wu Z, Zhu X, Hui X, Pan J, Xu Y. Hydroxy-safflor yellow A inhibits neuroinflammation mediated by $A\beta_{1-42}$ in BV-2 cells. Neuroscience Letters 562, 39-44, (2014).
[63] Zhang Z, Yu L, Hui X, Wu Z, Yin K, Yang H et al. Hydroxy-safflor yellow A attenuates $A\beta_{1-42}$induced inflammation by modulating the JAK2/STAT3/NF-kB pathway. Brain Research 1563, 72-80, (2014).
[64] Cai X-H, Wang S, Chen B-A. Research advances on the Pharmacological effects of Tetrandine. Chinese journal of natural Medicines 9, 6, 473-480, (2011).
[65] Shouk R, Abdou A, Shetty K, Sarkar D, Eid A. H. Mechanisms underlying the antihypertensive effects of garlic bioactives. Nutrition Research 34, 2, 106-115, (2014).
[66] He F. Q, Qiu B. Y, Zhang X. H, Li T. K, Xie Q, Cui D. J et al. Tetrandine attenuates spatial memory impairment and hippocampal neuroinflammation via inhibiting NK-kB activation in a rat model of Alzheimer's disease induced by amyloid-β(1-42). Brain Research 1384, 12, 89-96, (2011).
[67] Islamian J. P, Mehrali H. Lycopene as a carotenoid provides radioprotectant and antioxidante effects by quenching radiation-induced free radical single oxygen: An overview. Cell J 16, 4, 386391, (2015).
[68] Sachdeva A. K, Chopra K. Lycopoene abrogates Aβ(1-42)-mediated neuroinflammatory cascade in an experimental model of Alzheimer's disease. The Journal of Nutritional Biochemistry 26, 7, 736-744, (2015).