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REVIEW ARTICLE

Nutritional approaches to modulate oxidative stress that induce Alzheimer's disease. Nutritional approaches to prevent Alzheimer's disease

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Abstract

Alzheimer´s disease is the most common cause of dementia in the world; symptoms first appear after age 65 and have a progressive evolution. Expecting an increase on its incidence and knowing there is currently no cure for Alzheimer's disease, it is a necessity to prevent progression. The change in diet due to globalization may explain the growth of the incidence in places such as Japan and Mediterranean countries, which used to have fewer incidences. There is a direct correlation between disease progression and the increased intake of alcohol, saturated fats, and red meat. Therefore, we find obesity and higher serum levels in cholesterol due to saturated fat as a result. A way to decrease the progression of Alzheimer´s is through a diet rich in poliphenoles (potent antioxidants), unsaturated fats (monounsaturated and polyunsaturated), fish, vegetable fat, fruits with low glycemic index, and a moderate consumption of red wine. Through this potent antioxidant diet we accomplish the prevention of dementia and the progression of Alzheimer´s disease. This article emphasizes the food and other components that have been demonstrated to decrease the oxidative stress related to these progressive diseases.
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Introduction

Alzheimer's disease (AD) is the main cause of dementia in the world. It is a neurological progressive disease and the most important degenerative disease[1], more common than Parkinson. It has generated a series of problems for society, since, currently, 35 million[2] people have it and this number of patients is expected to be doubled by the year 2030[3], and tripled by 2050[4]. It is more common for American-Africans to suffer from this disease than for Hispanics and Caucasians[5]. There is no cure as yet, since physiologically the brain starts deteriorating in old age; different approaches have been tried searching for some alternatives[6] for its prevention[7,8].

AD was described by Alois Alzheimer[9] in 1906, and its main symptoms are loss of memory and anterograde amnesia. These symptoms usually start after the age of 65 years. Clinically, AD is characterized by a progressive loss of memory, deterioration of all mental functions, loss of speech, disorientation and walking problems[10]; hallucinations, hypokinesis, rigor and tremors can also be observed[11].

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The disease can be genetic[12] or produced by inappropriate folding of a β-amyloid (βA) peptide[13], due to cleavage of the amyloid precursor protein (APP)[14] by three enzymes α, β and γ-secretase, which create βA peptide extracellular senile plaques and hyperphosphorylation of the tau protein, which in turn produces intracellular neurofibrillary tangles; especially, these accumulations create toxic substances against neurons gathering in the hippocampal region. This protein tau hyperphosphorylation is caused by overexpression of the enzyme glycogen synthase kinase-3 (GSK-3)[15]. Recent studies show that the hippocampus[16] is one of the parts of the brain where recent memory develops[17] and the one suffering more damage due to neuronal apoptosis, which results in the onset of the AD symptoms[18-21].

βA peptides are the principal molecules related to AD pathogenesis and, in general, to neurodegenerative diseases and to the production of neurotoxicity[22]. Although the precise molecular mechanisms are not yet fully elucidated, a body of evidence points at actions by reactive oxygen species[23], which are produced by the effect of βA soluble oligomers at nanomolar concentrations. Oxidative stress resulting from this reaction is considered to be the mediator and trigger of a cascade of degenerative and inflammatory events in this and other neurodegenerative diseases[24].

Recent epidemiological studies indicate that alimentary habits associated with a diet based on ontioxidants hinder oxidative stress, which can prevent the incidence of neurodegenerative diseases[25] such as Alzheimer or Parkinson. Recently, different research articles have demonstrated the neuroprotective effects of phenols due to their action as potent antioxidants[26].

Therefore, different phytochemicals are being studied, such as carnosic acid (CA), curcumin, catechin and resveratrol, which, according to recent publications, have antioxidant neuroprotective effects and inhibit βA buildup[27-30]. Different hormones, such as melatonin, corticosteroids and estradiol have also been reported to act as neuroprotective antioxidants[31-33]. The onset of this disease results from βA buildups, which subsequently create neurofibrillary tangles made up by hyperphosphorylated tau protein; therefore, all the compounds that will be later mentioned inhibit both these abnormal buildups.

Nutrition and risk for developing AD

A healthy diet, cognition-stimulating activities and constant physical activities reduce the risk for suffering from AD[32]. Conversely, diabetes, apolipoprotein E (APO-ε4), smoking and depression are associated with increased progression of AD[35].

Recently, evidence indicating that nutrition plays an important role in preventing the progression of this disease has increased. Epidemiological studies compellingly suggest that diet can be a modifiable factor among the risk factors for AD. A diet rich in antioxidants, vitamin B, polyphenols, polyunsaturated and monounsaturated fatty acids is beneficial against AD, and their consumption is achieved by ingesting fish, fruits, vegetables, coffee and red wine. Therefore, adhering to a healthy diet such as the Japanese and the Mediterranean is associated with lower risk for suffering from AD[36]. On the other hand, the Western diet, which is based on higher consumpton of saturated fatty acids, high caloric intake[37] and excess of alcoholic beverages, increases the risk of suffering from this incurable and progressive disease (Table 1)[38].

Fish

According to recent epidemiological studies, consumption of fish reduces the risk of sufering from AD[39], especially among patients lacking APOE-ε4, due to the eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA) omega-3 fatty acids it contains; when subjects consumed fish more than once a week, the risk decreased by 60%, as compared with subjects who never ate fish[40].

Fruits and vegetables

People who consume fruit and vegetables regularly have been compared with others who don't, and benefit and a decrease in the risk of AD have been found in consumers; this may be due to the fact that fruit and vegetables are a source of antioxidants and bioactive compounds, as well as to their low contents of saturated fat[41].

Strong protection against AD has been demonstrated for the consumption of vegetables, especially those with green leaves, which contain vitamin E. The consumption of certain grains related to the Mediterranean diet has also been proven useful[42].

Green tea

Observational studies suggest that green tea decreases the risk for cognitive problems. Polyphenols in green tea inhibit cognitive problems by modulating oxidative stress. Additionally, it has been shown to possess a potent antioxidant, epigallocatechin-3-gallate (EGCG), which reduces the generation

Table 1. Antioxidants

Antioxidant diet	
Fish	– Contains omega-3 fatty acids, EPA and DHA – Consumption > 2 times per week reduces the risk for AD by 60%
Fruits and vegetables	– Low saturated fat contents – Green leaf vegetables contain vitamin E
Phytochemicals	
Polyphenols	
Cranberries	– Increase cAMP – Improve synaptic transmission – Reduce βA toxicity
Turmeric curcumin	– Inhibits bA formation – Promotes fibrille and neurofibrillary tangles degradation – Inhibits APP
Tea catechines	– Modulate oxidative stress – Increase SOD enzyme activity – Modulate the α-secretase, β-secretase and γ-secretase enzymes – EGCG reduces the generation of βA and tau isoforms
• Resveratol from grapes	– Promotes βA intracellular buildup elimination – Activates proteasomal neurotoxic degradation – Decreases plaque formation – Protects from βA-induced neurotoxicity
• Peanuts	– Elevate cAMP – Improve synaptic transmission – Reduce βA toxicity
CA	– Increases α-secretase enzyme ADAM17 and ADAM10 – Prevents neuronal apoptosis and degradation – Suppresses βA production
Hormones	
Melatonin	– Protects the cholinergic system – Has an anti-inflammatory effect – Inhibits βA fibrilles generation and formation – Inhibits protein tau hyperphosphorylation – Has great capacity to capture free radicals – Inhibits βA precursor protein – Activates protein kinase C – Inhibits the GSK-3 enzyme
Estradiol, estrogen and progesterone	– Inhibit APP proteolysis – Prevent the formation of βA – Improve neuronal functioning and elasticity – Protect neurons from cell apoptosis – Prevent senile plaques and neurofibrillary tangles accumulation

of βA and tau isoforms in animal models. Therfore, consumption of green tea can be considered for the prevention of AD[43].

Alcoholic beverages

Epidemiological studies have suggested that moderate consumption of alcoholic beverages reduces the risk for developing AD, but high consumption is associated with increased risk. Different beverages yield different results: red wine, for example, contains high levels of resveratrol and other polyphenols that, since they are potent antioxidants, decrease plaque formation and protect against βA-induced neurotoxicity[44].

Phytochemicals

Food polyphenols

Polyphenols, which include green and white tea, are neuroprotective against AD; their anti-βA action has been demonstrated, especially in grape polyphenols.

The antioxidant potential of polyphenols obtained from the diet (anthocyanins from cranberries, catechins from tea, curcumin from turmeric, resveratrol from grapes and peanuts) has neuroprotective effects that have been demonstrated in preclinical models. The capability of polyphenols to improve synaptic transmission by elevating cyclic adenosine monophosphate (cAMP), by targeting several signaling pathways and reducing βA toxicity, suggests their therapeutic utility against diseases related to age, such as AD and dementia[45].

CA

A member of the phenolic compounds family, CA is a diterpene with the formula $C_{20}H_{28}O_4$ that is found in *Salvia officinalis* and *Rosmarinus officinalis.* It is known to act as an antibiotic against *Staphylococcus aureus* and has been found to have anti-cancer effects that mainly prevent the proliferation of some malignant cells.

CA is a potent antioxidant with neuroprotective effect, which prevents neuronal apoptosis and degradation. The treatment with CA suppresses the production of βA and, therefore, increases the expression of messenger RNA (mRNA) of the α-secretase tumor necrosis factor-alpha-converting enzyme (TACE), better known as ADAM17, and α-secretase ADAM10, with no changes in β-secretase (BACE1), and, therefore, it doesn't promote it, thus avoiding βA generation. CA was tested in the University of Teheran of Medical Sciences in an experiment with ill transgenic rats, which were divided into two groups: surgery with CA and no surgery with CA, each one with a corresponding control group. The CA was dissolved in dimethyl sulfoxide and stored at –20 °C; then, 10 mg/kg were intraperitoneally injected. Histological results showed that the number of pyramidal cells from the CA1 region of the hippocampus was quantitatively higher than in the control group and, thus, the sample was statistically significant and confirmation was obtained that CA decreases hippocampal neurons death in the presence of βA, acting as a potent neuroprotector[27,46,47].

Curcumin

Extracted from the turmeric plant, it is a yellow colorant with great affinity for βA fibrils and hence it binds in the enol form. Curcumin inhibits βA formation and promotes fibrils and neurofibrillary tangles degradation. Additionally, direct interaction with βA is captured by macrophages, which affects APP maturation and the enzymes for its processing. Curumin is a potent antioxidant that can be administered orally, but due to its low bioavailability, it is inadequate in aqueous solutions; therefore, it has been modified and formulated in high concentrations of cyclodextrin, in order to improve it and to enable its availability in aqueous solutions.

In order to observe the prevalence of amyloid plaque, experiments were conducted with mice, which were injected in the tail with a 0.1 ml solution of curcumin and cyclodextrin solubilized in 4 mM until they were 4 months of age. Injections were resumed at 10 months with 6 mM, and during the last six weeks the animals were injected twice-weekly with 24 nM. Twice-weekly-injected mice developed 70% less amyloid plaques than the control group[28-30].

Catechin (EGCG)

It is a phenolic compound, originating from green tea, with potent capacity to capture free radicals, which is attributed to the presence of a trihydroxy group in the B-ring. EGCG increases the activity of the superoxide dismutase (SOD) enzyme that protects neurons, thus decreasing their oxidative stress and a glutathione (GSH) cluster owing to the γ-glutamylcysteine ligase mRNA, therefore providing protection to the neurone against βA cytotoxic substances. On the other hand, it is able to modulate the α-secretase, β-secretase and γ-secretase enzymes involved in the APP processing, since βA is synthesized from it. In particular, catechin inhibits βA fibrinogenesis and prevents the formation of substances that are toxic to neurons. Furthermore, the compound improves spatial memory and prevents the development of AD.

In a recent experiment performed with two groups of transgenic mice with the disease, catechin (20 mg/kg) was applied to one group by intraperitoneal injection and orally to the other in a solution with water (50 mg/kg). When the experiment was concluded at six months, both groups were found to have reduced senile plaques by more than 50%, but the intraperitoneal injection attenuated cerebral βA and improved the cognitive function. It should be noted that high concentrations of this antioxidant are associated with neuronal apoptosis and hippocampal degeneration. This evidence suggests that green tea catechin can be used to prevent the development of AD[48,49,30].

Resveratrol

It is a phenol found in grapes. Resveratrol modulates different systems that protect and favor neuronal cells

neuroprotective functions. There are studies that show that the primary objective of resveratrol is the central nervous system, since it is able to cross the blood-brain barrier. Nevertheless, its bioavailability is low, since it is quickly metabolized. In an experiment with mice that were administered 0.5 µl/min in the right ventricle and then injected βA for 7 days, at the end, resveratrol was shown to have reduced neurodegeneration through the SIRT1 deacetylase enzyme. Therefore, resveratrol activates SIRT1 and is able to protect against oxidative stress exerted by βA buildups on neurons. Consequently, it promotes βA intracellular buildup elimination by activating proteasomal neurotoxic degradation. SIRT1 overexpression reduces AD pathogenesis, since it prevents the synthesis of βA from APP. Finally, resveratrol disrupts βA hydrogens and, by getting adhered, it prevents the formation of fibrils and destabilizes those already existing. The best administration route for this phytochemical is by injection, due to its bioavailability, since resveratrol regulates some enzymes, such as SOD and chloramphenicol acetyltransferase. The above mentioned studies demonstrate that resveratrol modulates AD pathogenesis[29,30,50].

Hormones

Melatonin

Secretion of the melatonin hormone is reduced in AD and this has been proposed to be owing to circadian disturbance, decreased efficiency of sleep and worsening of cognitive functions of these patients. Melatonin is a hormone secreted by the pineal gland in the human brain, synthetized from serotonin; secretion increases at night, with the absence of light. Melatonin plays an important role in the protection of the cholinergic system and as an anti-inflammatory; additionally, it efficaciously protects neurons from βA toxicity. The most recent studies of this hormone show that it acts by improving the levels of sleep and, most importantly, it delays cognitive deterioration in patients already suffering from Alzheimer and inhibits the generation and formation of βA fibrils. Its efficacy to inhibit tau protein hyperphosphorylation and its significant capacity to capture free radicals and prevent oxidation, which is another factor that has been found to influence on tau protein hyperphosphorylation, have been demonstrated. Melatonin has also been found to inhibit βA precursor protein normal levels and, although the results show that it prevents the formation of senile plaques, it doesn't stop the deterioration of those already existing. Additionally, it activates the kinase C protein, which intervenes in the first cleavage of APP and, by inhibiting the GSK-3 enzyme, protein tau hyperphosphorylation is prevented.

This hormone is a good preventive option; in recent experiments with old transgenic mice with AD it was shown to prevent the formation of senile plaques and neurofibtillary tangles. Unfortunately, it is not an actual treatment, since it fails to supress already originated buildups[31,332,51].

Sexual hormones

Sexual hormones, such as estradiol, estrogen and progesterone, have positive effects on cognitive health. Menopause entails low levels of sexual hormones, which explains why postmenopausal women tend to suffer more rapidly from AD symptoms. In general, there is a correlation between reduced hormonal levels and an increased risk to suffer from AD.

Estradiol

Estradiol can inhibit APP proteolysis by activating the microtubule affinity regulating kinase (MARK)/extracellular signal-regulated kinases (ERKs) and thus intervene in β and γ-secretase by reducing substrate levels and this way preventing βA formation. On the other hand, sexual hormones improve neuronal function and elasticity, and protect neurons from toxic substances-induced apoptosis. Estrogen and testosterone are required to avoid senile plaques and neurofibrillary tangles accumulation but, over time, these hormones reduce their levels; therefore, the risk of gradually contracting this disease increases as age advances in older adults. This was confirmed in an experiment with 1,357 men and 1,889 women with ages older than 73 years who received hormone therapy; the incidence of the disease was observed to decrease. Therefore, hormone therapy administration 10 years before 65 years of age can be of vital importance for senile plaques and tangles not to be formed[31].

Testosterone

Testosterone is a male sex steroid hormone produced in the testicles by the Leydig cells and regulated by gonadotropin hormones (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]). In a recent study conducted in 94 men older than 80 years,

testosterone was found to be lower in men with AD than in the control group; this way, a positive correlation between testosterone levels and cognition was demonstrated. This confirms that individuals with hypogonadism are more prone to the development of AD because testosterone levels decrease and, consequently, luteinizing hormone levels rise and this produces a βA increase[33,41-48,52-57].

Conclusions

From the new discoveries on AD, it can be concluded that oxidative stress is the triggering factor of the disease. Therefore, nutrients with large phenolic contents are potent antioxidants and extremely important, since they might prevent the progression of this chronic and degenerative disease. Currently, life expectancy is increasingly longer owing to the advances in medicine and biotechnology and, consequently, this neuropathology represents a challenge due to the large numbers of geriatric patients we will be facing in the near future. AD is an incurable disease; the patient progresses from cognitive deficit to dementia until he/she requires sedation with permanent medical care and support. Antioxidant phytochemicals and hormones, owing to their high anti-inflammatory capacity, prevent oxidative stress in the patient. It is vitally important to improve dietary habits in order to prevent this disease, since epidemiologists claim that AD will be the pandemic of 21st century, as it is the 6th cause of death world wide.

References

1. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Demnt. 2013;9(1):63-75.e2.
2. Corbett A, Williams G, Ballard C. Drug repositioning: an opportunity to develop novel treatments for Alzheimer's disease. Pharmaceuticals (Basel). 2013;6(10):1304-21.
3. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. Neurology. 2013;80(19):1778-83.
4. Wortmann M. Dementia: a global health priority - highlights from an ADI and World Health Organization report. Alzheimers Res Ther. 2012;4(5):40.
5. Reitz C, Jun G, Naj A, et al. Variants in the ATP-binding cassette transporter (ABCA7), apolipoprotein E ε4,and the risk of late-onset Alzheimer disease in African Americans. JAMA. 2013;309(14):1483-92.
6. Gandy S, DeKosky S. Toward the treatment and prevention of Alzheimer's disease: rational strategies and recent progress. Annu Rev Med. 2013;64:367-83.
7. Chin AL, Negash S, Hamilton R. Diversity and disparity in dementia: the impact of ethnoracial differences in Alzheimer disease. Alzheimer Dis Assoc Disord. 2011;25(3):187-95.
8. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. Neurology. 2013;80(19):1778-83.
9. Cipriani G, Dolciotti C, Picchi L, Bonuccelli U. Alzheimer and his disease: a brief history. Neurol Sci. 2011;32(2):275-9.
10. Singhal AK, Naithani V, Om Prakash Bangar. Medicinal plants with a potential to treat Alzheimer and associated symptoms. IJNPND. 2012; 2:84-91.
11. Iqbal K, Flory M, Soininen H. Clinical symptoms and symptom signatures of Alzheimer's disease subgroups. J Alzheimers Dis. 2013;37(3):475-81.
12. Blacker D, Haines JL, Rodes L, et al. ApoE-4 and age at onset of Alzheimer's disease: the NIMH genetics initiative. Neurology. 1997;48(1):139-47.
13. Jack CR Jr, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 2013;12(2):207-16.
14. Schedin-Weiss S, Winblad B, Tjernberg LO. The role of protein glycosylation in Alzheimer disease. FEBS J. 2014;281(1):46-62.
15. Medina M, Avila J. New insights into the role of glycogen synthase kinase-3 in Alzheimer's disease. Expert Opin Ther Targets. 2014;18(1):69-77.
16. Goutagny R, Krantic S. Hippocampal Oscillatory Activity in Alzheimer's Disease: Toward the Identification of Early Biomarkers? Aging Dis. 2013;4(3):134-40.
17. Brayda-Bruno L, Mons N, Yee BK, et al. Partial loss in septo-hippocampal cholinergic neurons alters memory-dependent measures of brain connectivity without overt memory deficits. Neurobiol Dis. 2013;54:372-81.
18. La Joie R, Perrotin A, de La Sayette V, et al. Hippocampal subfield volumetry in mild cognitive impairment, Alzheimer's disease and semantic dementia. Neuroimage (Amst). 2013;3:155-62.
19. Becker JA, Hedden T, Carmasin J, et al. Amyloid-β associated cortical thinning in clinically normal elderly. Ann Neurol. 2011;69(6):1032-42.
20. Zhang X, Li H, Mao Y, et al. An over expression APP model for anti-Alzheimer disease drug screening created by zinc finger nuclease technology. PLoS One. 2013;8(11):e75493.
21. Tyagi E, Fiorelli T, Norden M, Padmanabhan J. Alpha 1-Antichymotrypsin, an Inflammatory Protein Overexpressed in the Brains of Patients with Alzheimer's Disease, Induces Tau Hyperphosphorylation through c-Jun N-Terminal Kinase Activation. Int J Alzheimers Dis. 2013;2013:606083.
22. Kayed R, Lasagna-Reeves CA. Molecular mechanisms of amyloid oligomers toxicity. J Alzheimers Dis. 2013;33 Suppl 1:S67-78.
23. Parajuli B, Sonobe Y, Horiuchi H, Takeuchi H, Mizuno T, Suzumura A. Oligomeric amyloid β induces IL-1β processing via production of ROS: implication in Alzheimer's disease. Cell Death Dis. 2013;4:e975.
24. Schrag M, Mueller C, Zabel M, et al. Oxidative stress in blood in Alzheimer's disease and mild cognitive impairment: a meta-analysis. Neurobiol Dis. 2013;59:100-10.
25. Guerra-Araiza C, Álvarez-Mejía AL, Sánchez-Torres S, et al. Effect of natural exogenous antioxidants on aging and on neurodegenerative diseases. Free Radic Res. 2013;47(6-7):451-62.
26. Cimini A, Gentile R, D'Angelo B, et al. Cocoa powder triggers neuroprotective and preventive effects in a human Alzheimer's disease model by modulating BDNF signaling pathway. J Cell Biochem. 2013;114(10): 2209-20.
27. Hou CW, Lin YT, Chen YL, et al. Neuroprotective effects of carnosic acid on neuronal cells under ischemic and hypoxic stress. Nutr Neurosci. 2012. [Epub ahead of print]
28. Quitschke WW, Steinhauff N, Rooney J. The effect of cyclodextrin-solubilized curcuminoids on amyloid plaques in Alzheimer transgenic mice: brain uptake and metabolism after intravenous and subcutaneous injection. Alzheimers Res Ther. 2013;5(2):16.
29. Villaflores OB, Chen YJ, Chen CP, Yeh JM, Wu TY. Curcuminoids and resveratrol as anti-Alzheimer agents. Taiwan J Obstet Gynecol. 2012; 51(4):515-25.
30. Davinelli S, Sapere N, Zella D, Bracale R, Intrieri M, Scapagnini G. Pleiotropic protective effects of phytochemicals in Alzheimer's disease. Oxid Med Cell Longev. 2012;2012:1-11.
31. Lin L, Huang QX, Yang SS, Chu J, Wang JZ, Tian Q. Melatonin in Alzheimer's disease. Int J Mol Sci. 2013;14(7):14575-93.
32. Cardinali DP, Vigo DE, Olivar N, Vidal MF, Furio AM, Brusco LI. Therapeutic application of melatonin in mild cognitive impairment. Am J Neurodegener Dis. 2012;1(3):280-91.
33. Bernal-Mondragón C, Rivas-Arancibia S, Kendrick KM, Guevara-Guzmán R. Estradiol prevents olfactory dysfunction induced by A-beta 25--35 injection in hippocampus. BMC Neurosci. 2013;14:104.
34. Balsamo S, Willardson JM, Frederico Sde S, et al. Effectiveness of exercise on cognitive impairment and Alzheimer's disease. Int J Gen Med. 2013;6:387-91.
35. Ashare RL, Karlawish JH, Wileyto EP, Pinto A, Lerman C. APOE ε4, an Alzheimer's disease susceptibility allele, and smoking cessation. Pharmacogenomics J. 2013;13(6):538-43.
36. Hu N, Yu JT, Tan L, Wang YL, Sun L, Tan L. Nutrition and the risk of Alzheimer's disease. Biomed Res Int. 2013;2013:1-12.
37. Dhungana H, Rolova T, Savchenko E, et al. Western-type diet modulates inflammatory responses and impairs functional outcome following permanent middle cerebral artery occlusion in aged mice expressing the human apolipoprotein E4 allele. J Neuroinflammation. 2013;10:102.
38. Dodge HH, Buracchio TJ, Fisher GG, et al. Trends in the prevalence of dementia in Japan. Int J Alzheimers Dis. 2012;2012:956354.
39. Pallauf K, Giller K, Huebbe P, Rimbach G. Nutrition and healthy ageing: calorie restriction or polyphenol-rich «MediterrAsian» diet? Oxid Med Cell Longev. 2013;2013:707421.

40. Shinto L, Quinn J, Montine T, et al. A randomized placebo-controlled pilot trial of omega-3 fatty acids and alpha lipoic acid in Alzheimer's disease. J Alzheimers Dis. 2014;38(1):111-20.
41. Hu N, Yu JT, Tan L, Wang YL, Sun L, Tan L. Nutrition and the risk of Alzheimer's disease. Biomed Res Int. 2013;2013:524820.
42. Hjorth E, Zhu M, Toro VC, et al. Omega-3 fatty acids enhance phagocytosis of Alzheimer's disease-related amyloid-β42 by human microglia and decrease inflammatory markers. J Alzheimers Dis. 2013;35(4):697-713.
43. Lim HJ, Shim SB, Jee SW, et al. Green tea catechin leads to global improvement among Alzheimer's disease-related phenotypes in NSE/hAPP-C105 Tg mice. J Nutr Biochem. 2013;24(7):1302-13.
44. Pasinetti GM. Novel role of red wine-derived polyphenols in the prevention of Alzheimer's disease dementia and brain pathology: experimental approaches and clinical implications. Planta Med. 2012;78(15):1614-9.
45. Bhullar KS, Rupasinghe HP. Polyphenols: multipotent therapeutic agents in neurodegenerative diseases. Oxid Med Cell Longev. 2013;2013:894718.
46. Azad N, Rasoolijazi H, Taghi-Joghataie M, Soleimani S. Neuroprotective Effects of Carnosic Acid in an Experimental Model of Alzheimer's Disease in Rats. Cell J. 2011;13(1):39-44.
47. Meng P, Yoshida H, Matsumiya T, et al. Carnosic acid suppresses the production of amyloid-β 1-42 by inducing the metalloprotease gene TACE/ADAM17 in SH-SY5Y human neuroblastoma cells. Neurosci Res. 2013;75(2):94-102.
48. Hyung SJ, DeToma AS, Brender JR, et al. Insights into antiamyloidogenic properties of the green tea extract (-)-epigallocatechin-3-gallate toward metal-associated amyloid-β species. Proc Natl Acad Sci U S A. 2013;110(10):3743-8.
49. Lee YJ, Choi DY, Yun YP, Han SB, Oh KW, Hong JT. Epigallocatechin-3-gallate prevents systemic inflammation-induced memory deficiency and amyloidogenesis via its anti-neuroinflammatory properties. J Nutr Biochem. 2013;24(1):298-310.
50. Huang TC, Lu KT, Wo YY, Wu YJ, Yang YL. Resveratrol protects rats from Aβ-induced neurotoxicity by the reduction of iNOS expression and lipid peroxidation. PLoS One. 2011;6(12):1-9.
51. Comai S, Gobbi G. Unveiling the role of melatonin MT2 receptors in sleep, anxiety and other neuropsychiatric diseases: a novel target in psychopharmacology. J Psychiatry Neurosci. 2014;39(1):6-21.
52. Cižas P, Jekabsonė A, Borutaitė V, Morkūnienė R. Prevention of amyloid-beta oligomer-induced neuronal death by EGTA, estradiol, and endocytosis inhibitor. Medicina (Kaunas). 2011;47(2):107-12.
53. Barron A, Pike C. Sex hormones, aging, and Alzheimer's disease. Front Biosci. 2012;4:976-97.
54. Grimm A, Lim YA, Mensah-Nyagan AG, Götz J, Eckert A. Alzheimer's disease, oestrogen and mitochondria: an ambiguous relationship. Mol Neurobiol. 2012;46(1):151-60.
55. Seyedreza P, Alireza MN, Seyedebrahim H. Role of testosterone in memory impairment of Alzheimer disease induced by Streptozotocin in male rats. Daru. 2012;20(1):98.
56. Butchart J, Birch B, Bassily R, Wolfe L, Holmes C. Male sex hormones and systemic inflammation in Alzheimer disease. Alzheimer Dis Assoc Disord. 2013;27(2):153-6.
57. Rosario ER, Carroll JC, Pike CJ. Evaluation of the effects of testosterone and luteinizing hormone on regulation of β-amyloid in male 3xTg-AD mice. Brain Res. 2012;1466:137-45.