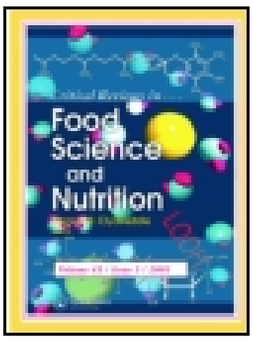

Taylor & Francis
Taylor & Francis Group

Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: http://www.tandfonline.com/loi/bfsn20

Effects of nutrient and bioactive food components on Alzheimer's disease and epigenetic

Elİf Celİk & Nevİn Sanlİer

To cite this article: Elİf Celİk & Nevİn Sanlİer (2017): Effects of nutrient and bioactive food components on Alzheimer's disease and epigenetic, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2017.1359488

To link to this article: http://dx.doi.org/10.1080/10408398.2017.1359488

Accepted author version posted online: 11 Aug 2017.

Effects of nutrient and bioactive food components on Alzheimer's disease and epigenetic

ELİF CELİK[1] and NEVİN SANLİER[1]

[1]Gazi University, Faculty of Health Sciences, Nutrition and Dietetics Department, 06500 Ankara, Turkey

Corresponding Author: Nevin SANLİER, PhD, Gazi University, Faculty of Health Sciences, Nutrition and Dietetics Department, Emniyet Mahallesi, Muammer Yaşar Bostancı Caddesi, No:16 Beşevler /ANKARA, TURKEY, **Telephone Numbers:** +90532 585 59 44, **Fax Numbers:** +903122162636

Alzheimer's disease (AD) is the most common form of dementia in the elderly and is a chronic neurodegenerative disease that is becoming widespread. For this reason, in recent years factors affecting the development, progression and cognitive function of the AD have been emphasized. Nutrients and other bioactive nutrients are among the factors that are effective in AD. In particular, vitamins A, C and E, vitamins B_1, B_6 and B_{12}, folate, magnesium, choline, inositol, anthocyanins, isoflavones etc. nutrients and bioactive nutrients are known to be effective in the development of AD. Nutrients and nutrient components may also have an epigenetic effect on AD. At the same time, nutrients and bioactive food components slow down the progression of the disease. For this reason, the effect of nutrients and food components on AD was examined in this review.

Key words

Alzheimer, nutrition, nutritional components, epigenetics

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia in the elderly and is becoming increasingly widespread throughout the world. The main cause of the disease is age although the factors affecting its development are multifactorial (Hickman, Faustin, and Wisniewski 2016). According to the data from the Alzheimer's Association, it is estimated that there will be 5.3 million AD patients in America in 2015, 5.1 million of those individuals being over 65 years old, and 200,000 of them being under 65 years of age (Association 2015). According to the World AD report, it is estimated that 46.8 million people worldwide, 4.9 million people in Asia and 2.5 million people in Europe live with dementia in 2015 (Dementia 2015).

AD is characterized by the presence of amyloid β peptide accumulation in many parts of the brain and the presence of neurofibrillary tangles (NFT) in brain regions (Davinelli et al. 2014). Amyloid-β (Aβ) peptides accumulate in the extracellular, whereas neurofibrillary tangles (NFTs) accumulate in the intracellular. Aβ peptides are synthesized from β-amyloid precursor proteins (APP). APP is shifted to the amyloidogenic pathway by β secretase (BACE1) and γ secretase complex, while α-secretase is involved in the synthesis of non-amyloidogenic pathway (Athanasopoulos, Karagiannis, and Tsolaki 2016; Sezgin and Dincer 2014). The neurotoxic properties of different Aβ isoforms is revealed. Aβ-42 residues are more likely to increase aggregation when compared to short Aβ peptides such as Aβ-40 and Aβ-38 (Xia and Mo 2016). NFTs are formed by the hyper-phosphorylation of tau proteins by the action of enzymes such as cyclin-dependent kinase 5 and glycogen synthase kinase 3β. While Aβ plaques are thought to

affect neuron-neuron transport in synapses, NFTs block transport of nutrients and other essential molecules to neurons (Athanasopoulos, Karagiannis, and Tsolaki 2016; Mach 2014). In addition, oxidative stress plays an important role in AD. Lipid peroxidation is associated with reactive oxygen species (ROS) formation and deficiency of antioxidant substances with oxidative stress. Excessive pro-inflammatory cytokine production is also associated with Aβ peptide production / accumulation, increased tau protein phosphorylation. At the same time, Aβ proteinsupports the release of ROS by suppressing the electron transport chain in mitochondria (Cardoso, Cominetti, and Cozzolino 2013; Xia and Mo 2016; Mohammadzadeh Honarvar et al. 2016).

The factors affecting AD can be divided into two groups as genetic factors and environmental factors. Diet, chemical exposure, smoking and traumatic brain injury are among the environmental factors. For example, the hyper-cholesterolemic diet may increase Aβ accumulation (Athanasopoulos, Karagiannis, and Tsolaki 2016; Xia and Mo 2016). The three genes responsible for AD are APP, presenilin 1 (PSEN1), and presenilin 2 (PSEN2). The polymorphism in these variations causes AD. In addition, apolipoprotein E (APOE) ε4 allele is effective in the formation of late onset AD. While APOE ε2 allele has protective effect against AD, APOE ε4 allele poses a risk for AD (Xia and Mo 2016). In recent years, epigenetic mechanisms is associated with AD. Epigenetic modifications can be described as inherited but reversible changes in chromatin structure in conjunction with changes in gene expression. DNA methylation, histone modification, and problems with microRNAs are associated with AD. DNA methyltransferase (DNMTs) is the most recognized chromatin modification. DNA methylation reduces in AD. DNMT1, DNMT2, DNMT3a and DNMT3B polymorphisms have been shown to be associated with AD. 5 methyltidine (5-mC) and 5-hydroxymethylidine (5-hmC), which are

effective in DNA methylation, reduced in AD and found to be negatively associated with amyloid plaque burden. Modification of histone acetylation (HAC), histone deacetylation (HDAC) (Sitruin (SIRT) 1,2,6,7), microRNA RNA dysfunction (microRNA 125b, microRNA 146a) were also found to be associated with AD (Athanasopoulos, Karagiannis, and Tsolaki 2016; Sezgin and Dincer 2014; Davinelli et al. 2014).

Nutrients and bioactive nutrients have been found to be related to AD-related factors such as epigenetic, Aβ, tau proteins, oxidative stress, and ROS (Athanasopoulos, Karagiannis, and Tsolaki 2016; Cardoso, Cominetti, and Cozzolino 2013). For this reason, this review was carried out to investigate the effects of nutrients and bioactive nutrients on development, progression, cognitive function and genes of AD.

1. The Relationship between Essential Elements and Bioactive Nutritional Compounds with Alzheimer's and Effective Genes

1.1. Fatty Acids

Polyunsaturated fatty acids (PUFAs) are essential fatty acids for optimal brain function. Essential fatty acids, eicosopentonoic acid (EPA) and docosohexonic acid (DHA) have been associated with AD, especially neuronal cell structure, anti-inflammatory properties, recall, memory, cognitive functioning role (Rashid, Haque, and Akbar 2016; Belkouch et al. 2016). Serum EPA, EPA + DHA levels associate with cognitive function. Serum DHA level decreases with age. Serum EPA increased at cognitive function levels as the levels of EPA + DHA increased (Nishihira et al. 2016). EPA and DHA have been shown to reduce the expression of lipopolysaccharide-induced TNF-α, IL-6 and IL-1β leading to the progression of AD (Rey et al.

2016). Additionally, EPA and DHA may increase Aβ degradation by affecting the insulin degrading enzyme (IDF) secreted from the extracellular space of neuronal and microglial cells that are effective in Aβ degradation. While EPA directly enhanced enzyme and gene activity of IDE, DHA affected enzyme activity and elevated extracellular IDE levels and EPA and DHA might contribute to the recovery of AD pathology (Grimm, Mett, et al. 2016). In addition, DHA may affect APP and BACE1 and regulate Aβ production. The unsaturated fatty acids in neuronal cells may alter the neuronal composition and may affect APP and BACE1 (Thomas et al. 2016). Dietary supplementation of 0.6% DHA for four months resulted in increased DHA, decreased arachidonic acid, decreased Aβ plaque formation, and improved cognitive function in the brain (Teng et al. 2015). Similarly, 15 mg / kg / day 2-hydro DHA supplementation reduced Aβ accumulation and reduce Aβ-induced tau protein phosphorylation in rats and cognitive function development was detected (Torres et al. 2014).

EPA and DHA can influence DNA methylation resulting from properties such as its role in lipid metabolism, anti-inflammatory properties. EPA and DHA-enriched diets regulated DNA methylation during pregnancy and prevented hyper-methylation in pigs (Boddicker et al. 2016). Moreover, EPA and DHA are effective in histone modification and histone demethylation. H3K9 may increase and HDAC1, HDAC2 and HDAC3 decrease with DHA (Athanasopoulos, Karagiannis, and Tsolaki 2016).

1.2. Vitamins A, C, E

The nutritional components of vitamin A are retinol, retinoic acid and β-carotene, which are antioxidants and anti-inflammatory agents. Due to these properties of the components, they

have neuron protective effects and they association with AD (Athanasopoulos, Karagiannis, and Tsolaki 2016; Mohammadzadeh Honarvar et al. 2016). Retinoic acid and its receptors are effective in regulating gene expression of constructs such as ADAM10, α-secretase, which are effective in AD, APP regulation, tau phosphorylation and Aβ (Chakrabarti et al. 2016; Lerner et al. 2012). As a result of pretreated all-trans retinoic acid supplementation for 150 mcg / mL for 30 days, production of lipopolysaccharide-induced Aβ, nitric oxide production was suppressed and ATRA significantly downregulated NOS2 expression in the cerebral cortex and the hippocampus (Behairi et al. 2016). Likewise, all-trans retinoic acid reduced the IL-17A inflammatory cytokine and NO-induced iNOS production (Behairi et al. 2015).As a result of the 20 mg / kg all-trans retinoic acid supplementation, the activity of the two enzymes effective in tau hyper-phosphorylation (cyclin-dependent kinase 5 (Cdk5) and glycogen synthase kinase 3b (GSK3b)) reduced and less tau aggregation occurred (Watamura et al. 2016). In addition, all-trans retinoic acid was effective in reducing BACE1 expression by 30% by suppressing NF-kβ signaling (suppresses inflammation) and regulating BACE gene expression (Wang et al. 2015). Besides, retinoic acid receptors (RAR) and retinoid X receptor (RXR) have some physiological functions in the brain. Retinoic acid signal is present in the central nervous system in amygdala, cortex, hypothalamus, hippocampus and other parts of the brain. Retinoic acids are involved in the formation and differentiation of nerve cells and in the formation of axons. Deterioration of the retinoic acid signal may cause neurodegeneration and progression, and learning and memory may be negatively affected (Chakrabarti et al. 2016). In addition to these effects of retinoic acid, lutein, lycopene and zeo-xanthine are significantly lower in AD individuals and carotenoids supplement (10 mg meso-zeaxanthin, 10 mg lutein, 2 mg zeaxanthin) significantly increase

serum levels of carotenoids, AD is positively affected and a negative correlation is found between high serum lycopene and lutein + zeo-xanthine levels and AD mortality risk. (Nolan et al. 2015; Min and Min 2014; Dias et al. 2014). At the same time, the deficiency of vitamin A in the diet can change DNA methylation and that lycopene can suppress DNMT3B (Athanasopoulos, Karagiannis, and Tsolaki 2016; Huang et al. 2016).

Vitamin C is one of the vitamins associated with AD. It may protective effect against AD by inhibition of LDL oxidation, ROS reduction, inhibition of oxidative stress, role in norepinephrine and epinephrine synthesis. Plasma ascorbic acid deficiency and low dietary intake are associated with a significant reduction in cognitive performance and an increase in neurofibrillary tangles and plaques (Harrison, Bowman, and Polidori 2014; Heo, Hyon, and Lee 2013). In a study conducted in mice with APP / PSEN1 mutation, the concentration of vitamin C decreased. Oxidative stress increased in rats when sodium-dependent vitamin C transporter was also deficient. The accumulation of Aβ 1--42 and 40 was increased in mice with APP / PSEN1 + SVCT2 deficiency rats than with APP / PSEN1 mutation alone (Dixit et al. 2015). Furthermore, when AD rats were given 125 mg / kg ascorbic acid for 1 week, learning and memory were positively affected (Harrison et al. 2009). However, the effect of ascorbic acid supplementation on amyloid plaque formation should be discussed. Reducing supplementation, does not, or only slightly affects the formation of amyloid plaques (Chan et al. 2016; Kook et al. 2014; Harrison et al. 2009).

Vitamin C is known to protect DNA against oxidative stress and hydrogen peroxide damage and to be associated with AD by the effect of DNA demethylation. 5-

hydroxymethylcysteine, a component of DNA methylation and demethylation, decreases in the hippocampus in AD patients. This may be related to DNA hyper-methylation (Shu et al. 2016). Ascorbic acid acts as a coenzyme for an eleventh translocation (TET) enzyme which is effective at converting 5-methylcytidine to 5-hydroxymethylcytidine during demethylation of DNA. In this respect it is stated that it may be with AD (Camarena and Wang 2016).

Vitamin E is an antioxidant affective on AD. Its supplementation can reduce oxidative stress, affect DNA methylation and histone modification, oral administration of α-tocopherol quinine can ameliorate memory impairment, inhibit pro-inflammatory cytokines such as IL-6 and IL-1β by inhibiting the oxidative stress-mediated NF-kβ pathway. However, its excess intake is associated with an increase in β and γ secretase activity and may increase the level of Aβ in tocopherol (Wang, Yang, et al. 2016; Grimm, Regner, et al. 2016; Athanasopoulos, Karagiannis, and Tsolaki 2016).

1.3. Vitamin D

Vitamin D has an important role in the physiological function and protection of the central nervous system due to their role as anti-oxidative, anti-inflammatory, Aβ metabolism and providing calcium homeostasis. Hypovitaminosis D is associated with brain changes and dementia (Grimm, Mett, and Hartmann 2016). Serum / plasma 25 (OH) D_3 levels decrease in AD and demented individuals and low plasma vitamin levels are associated with a decrease in cognitive function (Gangwar et al. 2015; Shen and Ji 2015; Littlejohns et al. 2014). Vitamin D supplementation can improve cognitive and memory functions in AD and demented individuals. A significant increase in cognitive performance of individuals was observed when 4,000 IU D

vitamin supplementation was administered for 3--6 months in demented individuals with D vitamin deficiency (<30 ng / mL) (Gangwar et al. 2015). Vitamin D can be effective in the cleavage, phagocytosis, polymorphism and enzymatic synthesis of Aβ peptides which are effective in AD mechanism (Grimm, Mett, and Hartmann 2016). It regulates calcium homeostasis to reduce Aβ peptides and protect against glutamate neurotoxicity by vitamin D receptor (VDR) expression and antioxidant effect (Annweiler 2016). In a study where a drug used in AD was given together with vitamin D supplementation (100 nM 1,25 $(OH)_2$ D_3), this combination was reported to protect neuronal axons against Aβ and glutamate indulgent degeneration (Annweiler et al. 2014). At the same time, in the supplement of 2.5 μg / kg 1.25 $(OH)_2$ D_3, short-term and long-term Aβ load decreased significantly and cognitive functioning improved (Durk et al. 2014). Vitamin D active form 1,25 $(OH)_2$ D_3 suppresses Aβ secretion by decreasing gene expression of APP activity. It also increases neprilysin (NEP) enzyme activity, which causes deterioration of Aβ plaques (Grimm, Mett, and Hartmann 2016). In addition, vitamin D_2 inhibited Aβ-25-35 stimulation by suppressing NF-kβ inflammation signals and Aβ-25-35 induced İNOS expression in microglia cells. It attenuated Aβ-induced pro-inflammatory cytokines IL-1β, IL-6, TNF- α and reduced ROS production (Raha et al. 2016). Studies suggest that VDR and VDR gene polymorphisms may be effective in genetic susceptibility of AD. The low sensitivity of some VDRs to vitamin D may be associated with cognitive decline. VDR is associated with AD, recall and cognitive decline of Taq1 G allele, Apal T allele, BSM1 gene polymorphisms (Lehmann et al. 2011; Gezen-Ak et al. 2012; Laczmanski et al. 2015). Apal A allele was found to be higher in the control group than AD group, and these allele carriers had a 30% less risk for AD (Laczmanski et al. 2015).

1.4. Vitamin K

Vitamin K is effective in cell growth, myelinization, mitogenesis and neuronal protection. The menaquinone-4 form of vitamin K is excess ın the central nervous system (Ferland 2012).

Individuals with memory complaints is found lower dietary intake of vitamin K vitamins than non-individual memory complaints and increased intake of vitamin K may lead to a positive development in memory (Soutif-Veillon et al. 2016; Presse et al. 2013). In patients with AD, the serum vitamin K concentration decreases and there is a positive correlation between the its serum level and cognitive function. Cognitive dysfunction is more prevalent in geriatric patients using anticoagulant medication (Vitamin K antagonist), and may decrease in brain volume and gray matter (Annweiler, Ferland, et al. 2015; Annweiler, Denis, et al. 2015). The use of vitamin K antagonists, brain sulphate metabolism impair and brain galactoserbroside sulphotransferase activity decrease. In addition, 3-ketodihydrosphingosine synthase enzyme which is effective in sphingolipid metabolism decreases and as a result of the supplementation, the level of sulfatide increases and sulfatide enzyme activation can return to normal (Ferland 2012; Sundaram et al. 1996).

Protein S, which protects nerves and cells against brain antithrombotic activity, protein S, which is effective in apoptosis, and Gas 6, which is effective in chemotaxis, mitogenesis, cell growth and myelination, and prevents apoptosis, is vitamin K dependent and vitamin K can also affect the central nervous system (Ferland 2012). Besides these properties, menadione (vitamin K3) plays a role in redox activity and regulate the NADPH cytochrome P450 reductase reaction to reduce cholinesterase inhibition due to pesticide damage (Jan et al. 2015). It has also been

suggested that vitamin K3 anologists prevented Aβ accumulation and protected against Aβ-induced toxicity and thus may be used as anti-amyloidogenic drugs (Huy et al. 2013).

1.5. Vitamins B_6, B_{12}, Folic Acid

Vitamins B6, B12 and folic acid are associated with the methionine cycle and have roles as coenzymes in the formation of homocysteine, methionine and S-adenosylmethionine (SAM) (Athanasopoulos, Karagiannis, and Tsolaki 2016). The association of these vitamins with AD is related to their role in DNA methylation. DNA methylation occurs in the folate / methionine / homocysteine metabolism and in the coenzyme of folate, methionine, choline, B6 and B12. The intake of dietary methyl groups can affect the methylation of DNA and histones and gene expression (Sezgin and Dincer 2014). Plasma homocysteine levels were found to be higher in subjects with AD and moderate cognitive problems than in the control group (Madsen et al. 2015). Plasma homocysteine levels and B_6, B_{12} and folic acid plasma levels and diet intake are negatively associated. Group B vitamin supplementation reduce homocysteine levels and B_6, B_{12} suplementations improve cognitive function (Kim, Kim, et al. 2014; Molina-Lopez et al. 2016). Besides, the presence of a mutation in the genes of methyl methylene tetrahydrate reductase (MTHFR), cystathionine β synthase (CβS), trans-cobalamin 2 receptor (TCN2) and methionine synthase reductase (MTRR) enzymes involved in folate / methionine / homocysteine metabolism can lead to increased homocysteine levels and decreased cognitive function (Mitchell, Conus, and Kaput 2014). Increase in homocysteine levels are associated with situations such as decrease in gray matter in cerebral cortex, increase oxidative stress, suppression of methylation reactions, DNA dysregulation, inhibition of gamma amino butyric acid (GABA) receptors, lipid

peroxidation, neuron conduction and kynurenine suppression, neurotoxicity induced cell death and apoptosis (Madsen et al. 2015; Hainsworth et al. 2016; Cheng et al. 2014). Homocysteine exposure is linked to DNA hypo-methylation and histone hyper-acetylation. The increase in homocysteine levels affects DNA methylation by suppressing methyltransferase activity (Jin et al. 2011). Decrease in vitamin B6, B12 and folic acid levels, MTHFR deficiency and polymorphism may increase homocysteine levels. Homocysteine increased secretase activity by increasing BACE and presenilin 1 expression, protein phosphate 2A suppresses methyltransferase, which leads to increased DNA methylation, increased tau phosphorylation (Fuso et al. 2011; Sontag et al. 2014). Vitamin B6, B12 and folic acid supplementation can prevent the elevation of homocysteine levels and reduce the harmful effects of homocysteine (Marti-Carvajal, Sola, and Lathyris 2015). However, in one study, the effect of B-vitamins alone may be less effective and omega-3 plus B group vitamins may be more effective. Mid-level demented individuals was not effective in decreasing cognitive function when omega-3 concentration was low, but group B vitamins slowed cognitive decline in w-3 presence in normal range (Oulhaj et al. 2016). According to the result of the meta-analysis, w-3, especially DHA, with group B vitamins is associated with an increase in cognitive function and decreased in homocysteine level. DHA is effective in decreasing homocysteine levels by decreasing betain-dependent re-myelination pathway by increasing the expression of methionine adenosyl transferase, 5-methionine tetrahydrofolate reductase and choline-phosphate cytidyltransferase, which are involved in homocysteine degradation (Dawson, Bowe, and Crowe 2016).

Vitamin B_6 plays a role of coenzymes in the formation of dopamine, GABA, serotonin and noradrenaline as well as coenzymes in folate metabolism (Kennedy 2016). Another feature

of vitamin B6 is association with inflammation. Due to this properties vitamin B6 is associated with AD. The pyridoxal phosphate form of vitamin B6 suppress the production of pro-inflammatory cytokines such as IL-1β and mitochondrial ROS production decreases and the deficiency is associated with a decrease in total antioxidant capacity (Zhang et al. 2016; Molina-Lopez et al. 2016). In addition, the pathway of B6 dependent in tryptophan metabolism is also associated with inflammatory cytokines. The plasma concentration of IL-10 cytokine was positively correlated with the level of kynurenine (Deac et al. 2016). Enzymes which are effective in sphingosine-1-phosphate metabolism, sphingolipid formation, trans-sulfuration pathway, serine and glycine metabolism, and hydrogen sulphide formation in the inflammatory response are dependent on pyridoxal phosphate. Because of these pathways, vitamin B6 is associated with inflammation (Ueland et al. 2016).

1.6. Thiamine

One of the important clinical manifestations of AD is the reduction in glucose metabolism. This decrease in glucose metabolism is associated with a decrease in cognitive function and loss in synapses. Glucose metabolism is higher in the brain than other tissues, so the requirement for thiamine is also excessive and thiamin deficiency is linked to the inability to metabolize glucose. Glucose metabolism disorder is associated with neurochemical dysfunction in brain regions. Cognitive function may be adversely affected as the level of choline esterase enzyme decreases in the presence of thiamin (Gibson et al. 2016). In addition, in thiamine insufficiency lead to increased protein levels and Aβ production by increasing β-secretase activity. Accordingly, Aβ1-40 and Aβ1-42 increased in plaque formation. In case of insufficiency, it can also cause neuron

loss with various mechanisms such as oxidative stress, eNOS-induced free radical formation, inflammation, APP overexpression, increasing the accumulation of Aβ plaques originating from ROS increase (Karuppagounder et al. 2009; Zhang et al. 2011). In the case of thiamine insufficiency, glycosylated end products and dephosphorylation of tau proteins may increase due to the pruvat dehydrogenase cofactor (Gibson et al. 2013; Gibson et al. 2016). The glycogen synthase kinase 3β (GSK3β) is one of the enzymes that the thiamin acts on. In the presence of memory impairment, GSK may decrease and may increase in depression. The administration of 200 mg / kg of the benfotiamine of thiamin derivatized reduced GSK3β expression and conditioning of adverse memories (Markova et al. 2016).

The level of thiamine diphosphate (TDP) was found to be significantly lower in AD patients than in the control group and vascular demented individuals. The level of thiamine diphosphate (TDP) was found to be significantly lower in AD patients than in the control group and vascular demented individuals. Thiamine monophosphate (TMP) and thiamine levels were low in the control group. TMP was higher in AD patients than in control group and vascular demented individuals. TDP is the active form of thiamine. The fact that TDP and TDP enzymes were low in AD may be a problem in conversion to active form. For this reason, TDP and TMP could be used in the diagnosis of Alzheimer (Pan et al. 2016).

1.7. Riboflavin and Niacin

Niacin is responsible for mechanisms such as energy metabolism, DNA metabolism and repair, oxidative stress, folate – tetrahydrofolate conversion. It can be related to the disease due to the role of coenzymes in many cases that are effective in the formation and progression of AD.

Niacin is responsible for mechanisms such as energy metabolism, DNA metabolism and repair, oxidative stress, folate to tetrahydrofolate conversion. Riboflavin can likewise be associated with AD and dementia due to the role of coenzymes in the metabolic pathways such as brain lipid fatty acid synthesis, RNA structure, glutathione redox cycle (Kennedy 2016). It was found that high niacin intake had a positive effect on cognitive function and AD patients were significantly inadequate dietary intake compared to the control group (Morris et al. 2004).

Niacin supplementation affects AD and symptoms positively (Wang, Hu, et al. 2016; Couturier et al. 2014; Yang et al. 2014).In one study, the precursor of NAD which is nicotinamide mononucleotide (NMN) was given 500 mg / kg. It prevented Aβ-1-42 induced learning and memory impairment, decreased Aβ-1-42 induced neuronal cell death and ROS levels and accumulation (Wang, Hu, et al. 2016). Similarly, 100 mg / kg nicotinamide supplementation increased the mRNA activation of SIRT1, 2 and 6 in rats (Yang et al. 2014). Niacin 30 mg / kg and 780 mg / kg 4 week supplementation regulated the transcription of DNA by obese rats on the skeletal muscle miRNA expression (Couturier et al. 2014).

Riboflavin and niacin are also effective at homocysteine metabolism. For this reason, it is suggested that these vitamins are related to AD. Riboflavin plays a role in MTHFR and MTRR enzymes in homocysteine metabolism and niasin acts as a coenzyme for dihydrofolate reductase and S-adenosyl homocysteine synthase enzymes (Kennedy 2016). In one study, 1.6-mg / day riboflavin supplementation for 16 weeks in individuals with MTHFR polymorphism reduced homocysteine levels and blood pressure (Horigan et al. 2010).

Niacinin acts on betaine-homocysteine S-methyl transferase, methonine synthase and cytotin β-synthase, nicotinamide N-methyltransferase, DNA methyltransferase enzymes and high dose of niacin in nicotinamide form is associated with an increase in DNA methylation (Li et al. 2013).

1.8. Selenium

Selenium has antioxidant properties. It is involved in the structure of some seleno proteins as selenocysteine. Selenoproteins have diverse roles throughout the body, acting as antioxidants, modulators of immune function, detoxification agents for heavy metals etc. (Cardoso et al. 2015). Selenoprotein deficiency and selenocysteine synthase gene mutation are associated with increased oxidative stress, reduced cognitive function, and poor motor control (Steinbrenner and Sies 2013). In one study, the level of erythrocyte selenium was lower in the AD group than in the control group and mild cognitive impairment, which was associated with a decrease in cognitive performance (Rita Cardoso et al. 2014). In another study, serum and hair selenium levels were similarly found to be lower in AD patients than control group (Koc et al. 2015).

Selenium may be associated with the disease due to its role of oxidative stress, ROS mitochondrial effect, synaptic transmission and neuroinflammation. The antioxidant property of selenium is due to the role of glutathione peroxidase in the cofactor (Cardoso et al. 2015). Selenium can reduce H_2O_2-induced calcium release, increase glutathione peroxidase activity, and prevent lipid peroxidation (Uguz et al. 2009). In aluminum chloride-induced AD, 1 mg / kg selenium supplementation resulted in reduction loss of motor activity, lipid peroxidation and

oxidative stress. (Lakshmi, Sudhakar, and Prakash 2015). Selenium therapy and selenoprotein M affects the protein profile in the brain, increases enzyme activity, and secretase activity, and reduces the formation and accumulation of Aβ peptide for antioxidant proteins (Kim, Goo, et al. 2014). In one study was found that Se deficient diet characterized by the accumulation of Aβ plaques and progress are associated with AD. In the case of Se insufficiency, the formation of Aβ plaques Aβ plaque was more common due to the activity of glutathione peroxidase and β-secretase was high (Haratake et al. 2013). Selenium in the form of sodium selenate reduced the hyperphosphorylation of tau proteins, activates the serine / threonine specific protein phosphatase 2A, resulting in the dephosphorylation of tau proteins (van Eersel et al. 2010). In addition, selenium may reduce copper accumulation of Aβ. This is due to the binding of copper with γ-hydroxy guidine containing selenium (Wang et al. 2014). Selenium also affects DNA methylation and histone modification. In the case of insufficiency, DNA methylation is reduced and histone modification can occur by reducing the HDAC activity of the seleno-α-ketoacids produced by selenium metabolism (Speckmann and Grune 2015; Joven et al. 2014; Sezgin and Dincer 2014).

1.9. Magnesium

Ionized form of magnesium (Mg) has protective properties for neurodegenerative diseases (Sezgin and Dincer 2014). Although the effect of magnesium is not fully understood, magnesium L-Thoronate may inhibit Aβ formation, synaptic loss and memory loss. Magnesium may regulate BACE-1 expression by inhibiting excessive calcium action. Aβ accumulation has reduced by reducing the activity of the APPβ and β-C terminals. (Li et al. 2014). In addition, magnesium

may suppress tau hyper-phosphorylation by suppressing GSK-3β, protecting cognitive function and protecting against synaptic deterioration. Magnesium provide structural functional regulation of hypocampal neural stem cells and synapses due to its role in energy metabolism (improving insulin sensitivity, increasing GLUT) (Xu et al. 2014; Sun et al. 2016; Jia et al. 2016).

1.10. Choline

The choline has an important role in memory. In the central nervous system, many neurons have a choline (in the form of phosphotidyl choline) in their structure. These neurons and acetylcholine containing the cholinergic neurotransmitter are effective in nerve conduction and are called cholinergic system. Cholinergic systems are involved in many processes such as attention, learning, memory, stress response, sleep and wakefulness. In AD, these neurons may have specific degeneration. In addition, loss of cholinergic neurons and cholinergic alterations could be the main factors underling AD-related psychiatric symptoms. Aβ oligomers early neurotoxicity affects cholinergic synapses (Ferreira-Vieira et al. 2016). Decreasing the level of the choline in the diet can result in hypo-methylation of some genes that are responsible for brain function (Sezgin and Dincer 2014). It is stated that individuals with AD have cholinergic failure and this may cause cognitive impairment by affecting neuron formation in individuals. Plasma cholinergic levels increased in AD individuals at supplementation 400 mg / day choline at 24 weeks, which may be beneficial (Rijpma et al. 2015). Cholinergic failure in the maternal diet may alter histone methylation in fetal individuals. Therefore, gene expression and neurogenesis can be affected by insufficiency. At the same time, choline defiency can disrupt histone methylation especially H3 and E17, which are associated with AD (Mehedint et al. 2010). In

addition, cholinergic neuronal axons were adversely affected by excess accumulation of amyloid precursor proteins, leading to anxiety and unconsciousness (Foidl et al. 2016).

1.11. Inositol

Inositol is the second messaging system, which responsible for the metabolic and cellular signaling system. Myo-inositol is a form of inositol. Myo-inositol affects some enzymes involved in energy metabolism, lipogenesis, increasing the activity of glucose transport proteins (Kunjara et al. 2016). In addition, phosphotidyl inositol has a role in transmembrane communication. Inositol 1-4-5 triphosphate (IP3) provides intracellular calcium mobilization. Myocinositol levels may increase during asymptomatic periods of AD. Similarly, myoinositol is elevated in ApoE 4 carriers (Voevodskaya et al. 2016; Lim et al. 2012). High levels of inositol is associated with decreased levels of decision making (Jollant et al. 2016) and low cognitive performance (Lim et al. 2012). This effect of inositol is due to the association between the inositol pathway and the intracellular calcium homeostasis. Abnormal IP3 signal is effective in pathogenesis of AD. Aβ-induced AD increases release of Ca + 2 and induces passage of Ca into the cell membrane. Release of Ca from ER is a signal for cell death. MiRNA can affect the expression of IP3R, causing changes in physiological conditions (Takada et al. 2016). At the same time, the single gene polymorphism in IP63K is associated AD susceptibility (Crocco et al. 2016).

1.12. Resveratrol

Resveratrol is a bioactive compound which found in foods such as grapes, wine and nuts (Sezgin and Dincer 2014). It affects AD because of its many effects such as formation of Aβ plaques,

oxidative stress, aging-related genes. Resveratrol activates protein kinase C and activates α-secretase. It decreases the formation of Aβ plaque by providing non-amyloidogenic pathway (Mazzanti and Di Giacomo 2016). Resvatrol also acts on proinflammatory cytokines and genes. ROS formation decreases cytokines and myeloperoxidase such as TNF-α, IL-1β by inhibiting NF-kβ and related gene activation and signal transducer and transcription factor 1 (STAT1) and STAT3 phosphorylation. In addition, it increases SIRT-1 and BCL-2 gene expression and decreases FOXO1 and SIRT3 gene expression (An et al. 2016; Capiralla et al. 2012; Porquet et al. 2014; Yao et al. 2015). Administration of resveratrol 100 μM / 5 μL / day for 7 days IV regulated mRNA expression, suppressed Aβ production by decreasing iNOS formation and lipid peroxidation (Huang et al. 2011). In addition, resveratrol suppresses DNMT (DNMT1 and DNMT3B) activity and contributes to cognitive development by increasing SIRT-1 activation (Mazzanti and Di Giacomo 2016; Porquet et al. 2014; Huang et al. 2016). In a study conducted in healthy individuals, resveratrol 200 mg / day improved the memory of individuals at the end of 26 weeks (Witte et al. 2014). Similarly, in a study of rats with Alzheimer's disease, in rats given 10% red grape juice water for 21 days learning and memory improved positively than rats not given grape juice (Siahmard et al. 2012). The European Food Safety Authority (EFSA) has specified a resveratrol NOAEL of 750 mg / kg / day and an ADI (Acceptable Dietary Intake) value of 450 mg / day (EFSA 2016).

1.13. Anthocyanins

Anthocyanins are compounds which found in grape, blueberry, cherry etc. Due to its antioxidant and anti-inflammatory properties it can show protective effect against AD. It is stated that short-

term and long-term memory develops in cherry juice containing anthocyanin at 200 mL / day, 12 weeks of intervention, 70 years of age or older, and moderate dementia (Kent et al. 2015). Anthocyanins inhibit mitochondrial dysfunction and apoptosis, reduce glycosylated end product (AGE), ROS and lipid peroxidation, protect against ethanol-induced and D-galactose-induced oxidative stresses, and are effective on AD in these mechanisms (Rehman et al. 2016). It has also been shown that cyanide protects against DNA damage by reducing superoxide and hydroxyl radicals. At the same time it protects glucose and methyl glucose-induced protein glycolysis (Suantawee, Cheng, and Adisakwattana 2016). Supplementation of 10 mg / kg and 100 mg / kg of cyanidin and anthocyanins, respectively, modulated the signaling pathway of SIRT1 and FOXO1, shown anti-inflammatory effect by reducing TNF-α and IL-6 levels via iNOS and Nf-kβ (Rehman et al. 2016; Liu, Zhou, et al. 2016). Anthocyanins also provide the non-toxic pathway of APP by suppressing the conversion to Aβ protein formation. In this way it can be effective in reducing tau phosphorylation and protecting nerve cells against Aβ amyloid damage. Furthermore, anthocyanins are associated with accumulation of Aβ plaques, impaired Ca homeostasis, and neuronal apoptosis. The supplementation of anthocyanin (2 mg / kg-4 mg / kg anthocyanin) regulated Ca + 2 homeostasis, was effective at the return of protein expression in the mitochondrial apoptosis pathway, and affected the regulation of APP, BACE-1 Aβ and P-tau pathways (Yamakawa et al. 2016; Badshah, Kim, and Kim 2015). In addition, anthocyanins may also affect genes associated with AD. Pro-anthocyanin supplementation (15, 25, 50 mg / kg) at different doses modulated hepatic and pancreatic miRNA expression (Baselga-Escudero et al. 2014; Castell-Auvi et al. 2013), and suppressed DNMT1 and DNMT3B expression when given at different concentrations in the case of colon cancer. Since these genes are associated with AD,

anthocyanins may be thought to be epigenetic effects (Sezgin and Dincer 2014; Wang et al. 2013). The NOAEL value of anthocyanins by EFSA is 225 mg / kg / day. However, JECFA has indicated ADI 2.5 mg / kg / day, although EFSA reported that the data were insufficient to determine ADI (EFSA 2013).

1.14. Ellagitannin Geraniin

Ellagitannin is a polyphenol. It has antioxidants (4 times more than ascorbic acid), antimicrobial, anti-inflammatory and antitumor effects Pomegranate, raspberry, walnut and almonds contain high amounts of Ellagitannin (Vahid et al. 2015; Cheng, Ton, and Abdul Kadir 2016). Geraniin provides modulation of pro-inflammatory cytokine secretions such as TNF-a and IL-8. It is stated that geranium may be a neuroprotective effect due to its antioxidant and anti-inflammatory properties as well as its effect on prolyl peptidase (Its over-regulation results in pre-plaque phase) and β-secretase activity (inhibition). It may have an effect on Alzheimer caused by these properties (Youn and Jun 2013; Yuan et al. 2016; Cheng, Ton, and Abdul Kadir 2016). The urolithins form, which is synthesized by intestinal bacteria of the ellagitannin geranin, could also prevent β-amyloid fibrillation and protect against amyloid β-12-induced neuronal damage (Yuan et al. 2016). Besides, Ellagitannins is associated via transcription factors, miRNA and signaling. For this reason, It may be associated with AD (Vahid et al. 2015).

The AD and epigenetic effects of the other bioactive compounds are shown in Table 1.

CONCLUSIONS

AD is a common neurodegenerative disease in the elderly. Nutrients and bioactive components have effects on the formation, progression, genetics and epigenetics of AD. Nutrients and bioactive compounds can affect Aβ formation, accumulation, tau phosphorylation, inflammation and oxidative stress through various mechanisms. Inadequate intake of nutrients affects the AD in the negative, and excessive intake of some can negatively affect AD. Antioxidant vitamins and nutrients rich in bioactive compounds have a positive effect on AD by preventing oxidative stress and inflammation. In addition, both antioxidant vitamins and bioactive compounds have an important role on Aβ and tau phosphorylation. Epigenetic modifications are also associated with AD. Nutrition can affect these modifications. B_6, B_{12} vitamins, folic acid, methionine and choline have an important place in AD due to their main roles in DNA methylation. Diet polyphenols have epigenetic effects as well as antioxidant properties. The formation of AD is also linked to the fetal period. Cholinergic failure in the maternal diet can affect histone modification and may lead to risk for AD in later life. Therefore, adequate and balanced intake of all nutrients, adequate consumption of each nutrient group, attention to food diversity, consumption of foods rich in antioxidants will contribute to reducing the formation of AD, inhibiting its progression and have positive effects on epigenetics. Studies on the epigenetic effect of AD are limited, though. For this reason, increasing the number of studies done in the subject and especially the studies which will determine the dose / activity relationship will contribute to the better evaluation.

REFERENCES

An, R., L. Zhao, J. Xu, C. Xi, H. Li, G. Shen, W. Zhang, S. Zhang, and L. Sun. 2016. 'Resveratrol alleviates sepsisinduced myocardial injury in rats by suppressing neutrophil accumulation, the induction of TNFalpha and myocardial apoptosis via activation of Sirt1', *Mol Med Rep*.

Annweiler, C. 2016. 'Vitamin D in dementia prevention', *Ann N Y Acad Sci*, 1367: 57--63.

Annweiler, C., B. Brugg, J. M. Peyrin, R. Bartha, and O. Beauchet. 2014. 'Combination of memantine and vitamin D prevents axon degeneration induced by amyloid-beta and glutamate', *Neurobiol Aging*, 35: 331--5.

Annweiler, C., S. Denis, G. Duval, G. Ferland, R. Bartha, and O. Beauchet. 2015. 'Use of Vitamin K Antagonists and Brain Volumetry in Older Adults: Preliminary Results From the GAIT Study', *J Am Geriatr Soc*, 63: 2199--202.

Annweiler, C., G. Ferland, P. Barberger-Gateau, A. Brangier, Y. Rolland, and O. Beauchet. 2015. 'Vitamin K antagonists and cognitive impairment: results from a cross-sectional pilot study among geriatric patients', *J Gerontol A Biol Sci Med Sci*, 70: 97--101.

Association, Alzheimer's. 2015. "Alzheimer's Disease Facts and Figures." In.

Athanasopoulos, D., G. Karagiannis, and M. Tsolaki. 2016. 'Recent Findings in Alzheimer Disease and Nutrition Focusing on Epigenetics', *Adv Nutr*, 7: 917--27.

Badshah, H., T. H. Kim, and M. O. Kim. 2015. 'Protective effects of anthocyanins against amyloid beta-induced neurotoxicity in vivo and in vitro', *Neurochem Int*, 80: 51--9.

Baselga-Escudero, L., C. Blade, A. Ribas-Latre, E. Casanova, M. J. Salvado, L. Arola, and A. Arola-Arnal. 2014. 'Chronic supplementation of proanthocyanidins reduces postprandial

lipemia and liver miR-33a and miR-122 levels in a dose-dependent manner in healthy rats', *J Nutr Biochem*, 25: 151--6.

Baum, L., and A. Ng. 2004. 'Curcumin interaction with copper and iron suggests one possible mechanism of action in Alzheimer's disease animal models', *J Alzheimers Dis*, 6: 367--77; discussion 443--9.

Beck, S. M., H. Ruge, C. Schindler, M. Burkart, R. Miller, C. Kirschbaum, and T. Goschke. 2016. 'Effects of Ginkgo biloba extract EGb 761(R) on cognitive control functions, mental activity of the prefrontal cortex and stress reactivity in elderly adults with subjective memory impairment – a randomized double-blind placebo-controlled trial', *Hum Psychopharmacol*, 31: 227--42.

Behairi, N., M. Belkhelfa, H. Mesbah-Amroun, H. Rafa, S. Belarbi, M. Tazir, and C. Touil-Boukoffa. 2015. 'All-trans-retinoic acid modulates nitric oxide and interleukin-17A production by peripheral blood mononuclear cells from patients with Alzheimer's disease', *Neuroimmunomodulation*, 22: 385--93.

Behairi, N., M. Belkhelfa, H. Rafa, M. Labsi, N. Deghbar, N. Bouzid, H. Mesbah-Amroun, and C. Touil-Boukoffa. 2016. 'All-trans retinoic acid (ATRA) prevents lipopolysaccharide-induced neuroinflammation, amyloidogenesis and memory impairment in aged rats', *J Neuroimmunol*, 300: 21--29.

Belkouch, M., M. Hachem, A. Elgot, A. L. Van, M. Picq, M. Guichardant, M. Lagarde, and N. Bernoud-Hubac. 2016. 'The pleiotropic effects of omega-3 docosahexaenoic acid on the hallmarks of Alzheimer's disease', *J Nutr Biochem*, 38: 1--11.

Berger, A., S. Venturelli, M. Kallnischkies, A. Bocker, C. Busch, T. Weiland, S. Noor, C. Leischner, T. S. Weiss, U. M. Lauer, S. C. Bischoff, and M. Bitzer. 2013. 'Kaempferol, a new nutrition-derived pan-inhibitor of human histone deacetylases', *J Nutr Biochem*, 24: 977--85.

Boddicker, R. L., J. E. Koltes, E. R. Fritz-Waters, L. Koesterke, N. Weeks, T. Yin, V. Mani, D. Nettleton, J. M. Reecy, L. H. Baumgard, J. D. Spencer, N. K. Gabler, and J. W. Ross. 2016. 'Genome-wide methylation profile following prenatal and postnatal dietary omega-3 fatty acid supplementation in pigs', *Anim Genet*, 47: 658--71.

Camarena, V., and G. Wang. 2016. 'The epigenetic role of vitamin C in health and disease', *Cell Mol Life Sci*, 73: 1645--58.

Capiralla, H., V. Vingtdeux, H. Zhao, R. Sankowski, Y. Al-Abed, P. Davies, and P. Marambaud. 2012. 'Resveratrol mitigates lipopolysaccharide- and Abeta-mediated microglial inflammation by inhibiting the TLR4/NF-kappaB/STAT signaling cascade', *J Neurochem*, 120: 461--72.

Cardoso, B. R., C. Cominetti, and S. M. Cozzolino. 2013. 'Importance and management of micronutrient deficiencies in patients with Alzheimer's disease', *Clin Interv Aging*, 8: 531--42.

Cardoso, B. R., B. R. Roberts, A. I. Bush, and D. J. Hare. 2015. 'Selenium, selenoproteins and neurodegenerative diseases', *Metallomics*, 7: 1213--28.

Castell-Auvi, A., L. Cedo, J. Movassat, B. Portha, F. Sanchez-Cabo, V. Pallares, M. Blay, M. Pinent, and A. Ardevol. 2013. 'Procyanidins modulate microRNA expression in pancreatic islets', *J Agric Food Chem*, 61: 355--63.

Chakrabarti, M., A. J. McDonald, J. Will Reed, M. A. Moss, B. C. Das, and S. K. Ray. 2016. 'Molecular Signaling Mechanisms of Natural and Synthetic Retinoids for Inhibition of Pathogenesis in Alzheimer's Disease', *J Alzheimers Dis*, 50: 335--52.

Chan, S., S. Kantham, V. M. Rao, M. K. Palanivelu, H. L. Pham, P. N. Shaw, R. P. McGeary, and B. P. Ross. 2016. 'Metal chelation, radical scavenging and inhibition of Abeta(4)(2) fibrillation by food constituents in relation to Alzheimer's disease', *Food Chem*, 199: 185--94.

Cheng, Hong Sheng, So Ha Ton, and Khalid Abdul Kadir. 2016. 'Ellagitannin geraniin: a review of the natural sources, biosynthesis, pharmacokinetics and biological effects', *Phytochemistry Reviews*: 1--35.

Cheng, Y., Y. Jin, F. W. Unverzagt, L. Su, L. Yang, F. Ma, A. M. Hake, C. Kettler, C. Chen, J. Liu, J. Bian, P. Li, J. R. Murrell, H. C. Hendrie, and S. Gao. 2014. 'The relationship between cholesterol and cognitive function is homocysteine-dependent', *Clin Interv Aging*, 9: 1823--9.

Couturier, A., J. Keller, E. Most, R. Ringseis, and K. Eder. 2014. 'Niacin in pharmacological doses alters microRNA expression in skeletal muscle of obese Zucker rats', *PLoS One*, 9: e98313.

Crocco, P., A. Saiardi, M. S. Wilson, R. Maletta, A. C. Bruni, G. Passarino, and G. Rose. 2016. 'Contribution of polymorphic variation of inositol hexakisphosphate kinase 3 (IP6K3) gene promoter to the susceptibility to late onset Alzheimer's disease', *Biochim Biophys Acta*, 1862: 1766--73.

Davinelli, S., V. Calabrese, D. Zella, and G. Scapagnini. 2014. 'Epigenetic nutraceutical diets in Alzheimer's disease', *J Nutr Health Aging*, 18: 800--5.

Dawson, S. L., S. J. Bowe, and T. C. Crowe. 2016. 'A combination of omega-3 fatty acids, folic acid and B-group vitamins is superior at lowering homocysteine than omega-3 alone: A meta-analysis', *Nutr Res*, 36: 499--508.

Deac, O. M., J. L. Mills, C. M. Gardiner, B. Shane, L. Quinn, O. Midttun, A. McCann, K. Meyer, P. M. Ueland, R. Fan, Z. Lu, L. C. Brody, and A. M. Molloy. 2016. 'Serum Immune System Biomarkers Neopterin and Interleukin-10 Are Strongly Related to Tryptophan Metabolism in Healthy Young Adults', *J Nutr*, 146: 1801--6.

Dementia, Alzheimer Disease İnternational The Global Voice on. 2015. "World Alzheimer Report " In.

Dias, I. H., M. C. Polidori, L. Li, D. Weber, W. Stahl, G. Nelles, T. Grune, and H. R. Griffiths. 2014. 'Plasma levels of HDL and carotenoids are lower in dementia patients with vascular comorbidities', *J Alzheimers Dis*, 40: 399--408.

Dixit, S., A. Bernardo, J. M. Walker, J. A. Kennard, G. Y. Kim, E. S. Kessler, and F. E. Harrison. 2015. 'Vitamin C deficiency in the brain impairs cognition, increases amyloid accumulation and deposition, and oxidative stress in APP/PSEN1 and normally aging mice', *ACS Chem Neurosci*, 6: 570--81.

Durk, M. R., K. Han, E. C. Chow, R. Ahrens, J. T. Henderson, P. E. Fraser, and K. S. Pang. 2014. '1alpha,25-Dihydroxyvitamin D3 reduces cerebral amyloid-beta accumulation and improves cognition in mouse models of Alzheimer's disease', *J Neurosci*, 34: 7091--101.

EFSA. 2010. 'Scientific Opinion on the re- evaluation of curcumin (E 100) as a food additive', *EFSA Journal*, 8.

———. 2013. 'Scientific Opinion on the re- evaluation of anthocyanins (E 163) as a food additive', *EFSA Journal*, 11.

———. 2016. 'Safety of synthetic trans- resveratrol as a novel food pursuant to Regulation (EC) No 258/97', *EFSA Journal*, 14.

Ferland, G. 2012. 'Vitamin K and the nervous system: an overview of its actions', *Adv Nutr*, 3: 204--12.

Ferreira-Vieira, T. H., I. M. Guimaraes, F. R. Silva, and F. M. Ribeiro. 2016. 'Alzheimer's disease: Targeting the Cholinergic System', *Curr Neuropharmacol*, 14: 101--15.

Foidl, B. M., P. Do-Dinh, B. Hutter-Schmid, H. R. Bliem, and C. Humpel. 2016. 'Cholinergic neurodegeneration in an Alzheimer mouse model overexpressing amyloid-precursor protein with the Swedish-Dutch-Iowa mutations', *Neurobiol Learn Mem*, 136: 86--96.

Fuso, A., V. Nicolia, A. Pasqualato, M. T. Fiorenza, R. A. Cavallaro, and S. Scarpa. 2011. 'Changes in Presenilin 1 gene methylation pattern in diet-induced B vitamin deficiency', *Neurobiol Aging*, 32: 187--99.

Gangwar, A. K., A. Rawat, S. Tiwari, S. C. Tiwari, J. Narayan, and S. Tiwari. 2015. 'Role of Vitamin-D in the prevention and treatment of Alzheimer's disease', *Indian J Physiol Pharmacol*, 59: 94--9.

Gezen-Ak, D., E. Dursun, B. Bilgic, H. Hanagasi, T. Ertan, H. Gurvit, M. Emre, E. Eker, T. Ulutin, O. Uysal, and S. Yilmazer. 2012. 'Vitamin D receptor gene haplotype is associated with late-onset Alzheimer's disease', *Tohoku J Exp Med*, 228: 189--96.

Gibson, G. E., J. A. Hirsch, R. T. Cirio, B. D. Jordan, P. Fonzetti, and J. Elder. 2013. 'Abnormal thiamine-dependent processes in Alzheimer's Disease. Lessons from diabetes', *Mol Cell Neurosci*, 55: 17--25.

Gibson, G. E., J. A. Hirsch, P. Fonzetti, B. D. Jordan, R. T. Cirio, and J. Elder. 2016. 'Vitamin B1 (thiamine) and dementia', *Ann N Y Acad Sci*, 1367: 21--30.

Grimm, M. O., J. Mett, and T. Hartmann. 2016. 'The Impact of Vitamin E and Other Fat-Soluble Vitamins on Alzheimer s Disease', *Int J Mol Sci*, 17.

Grimm, M. O., J. Mett, C. P. Stahlmann, V. J. Haupenthal, T. Blumel, H. Stotzel, H. S. Grimm, and T. Hartmann. 2016. 'Eicosapentaenoic acid and docosahexaenoic acid increase the degradation of amyloid-beta by affecting insulin-degrading enzyme', *Biochem Cell Biol*, 94: 534--42.

Grimm, M. O., L. Regner, J. Mett, C. P. Stahlmann, P. Schorr, C. Nelke, O. Streidenberger, H. Stoetzel, J. Winkler, S. R. Zaidan, A. Thiel, K. Endres, H. S. Grimm, D. A. Volmer, and T. Hartmann. 2016. 'Tocotrienol Affects Oxidative Stress, Cholesterol Homeostasis and the Amyloidogenic Pathway in Neuroblastoma Cells: Consequences for Alzheimer's Disease', *Int J Mol Sci*, 17.

Grossi, C., S. Rigacci, S. Ambrosini, T. Ed Dami, I. Luccarini, C. Traini, P. Failli, A. Berti, F. Casamenti, and M. Stefani. 2013. 'The polyphenol oleuropein aglycone protects TgCRND8 mice against Ass plaque pathology', *PLoS One*, 8: e71702.

Guo, Z., Z. Liao, L. Huang, D. Liu, D. Yin, and M. He. 2015. 'Kaempferol protects cardiomyocytes against anoxia/reoxygenation injury via mitochondrial pathway mediated by SIRT1', *Eur J Pharmacol*, 761: 245--53.

Hainsworth, A. H., N. E. Yeo, E. M. Weekman, and D. M. Wilcock. 2016. 'Homocysteine, hyperhomocysteinemia and vascular contributions to cognitive impairment and dementia (VCID)', *Biochim Biophys Acta*, 1862: 1008--17.

Haratake, M., S. Yoshida, M. Mandai, T. Fuchigami, and M. Nakayama. 2013. 'Elevated amyloid-beta plaque deposition in dietary selenium-deficient Tg2576 transgenic mice', *Metallomics*, 5: 479--83.

Harrison, F. E., G. L. Bowman, and M. C. Polidori. 2014. 'Ascorbic acid and the brain: rationale for the use against cognitive decline', *Nutrients*, 6: 1752--81.

Harrison, F. E., A. H. Hosseini, M. P. McDonald, and J. M. May. 2009. 'Vitamin C reduces spatial learning deficits in middle-aged and very old APP/PSEN1 transgenic and wild-type mice', *Pharmacol Biochem Behav*, 93: 443--50.

Heo, J. H., Lee Hyon, and K. M. Lee. 2013. 'The possible role of antioxidant vitamin C in Alzheimer's disease treatment and prevention', *Am J Alzheimers Dis Other Demen*, 28: 120--5.

Hickman, R. A., A. Faustin, and T. Wisniewski. 2016. 'Alzheimer Disease and Its Growing Epidemic: Risk Factors, Biomarkers, and the Urgent Need for Therapeutics', *Neurol Clin*, 34: 941--53.

Horigan, G., H. McNulty, M. Ward, J. J. Strain, J. Purvis, and J. M. Scott. 2010. 'Riboflavin lowers blood pressure in cardiovascular disease patients homozygous for the 677C-->T polymorphism in MTHFR', *J Hypertens*, 28: 478--86.

Huang, T. C., K. T. Lu, Y. Y. Wo, Y. J. Wu, and Y. L. Yang. 2011. 'Resveratrol protects rats from Abeta-induced neurotoxicity by the reduction of iNOS expression and lipid peroxidation', *PLoS One,* 6: e29102.

Huang, Z., Q. Huang, L. Ji, Y. Wang, X. Qi, L. Liu, Z. Liu, and L. Lu. 2016. 'Epigenetic regulation of active Chinese herbal components for cancer prevention and treatment: A follow-up review', *Pharmacol Res,* 114: 1--12.

Huy, P. D., Y. C. Yu, S. T. Ngo, T. V. Thao, C. P. Chen, M. S. Li, and Y. C. Chen. 2013. 'In silico and in vitro characterization of anti-amyloidogenic activity of vitamin K3 analogues for Alzheimer's disease', *Biochim Biophys Acta,* 1830: 2960--9.

Jan, Y. H., J. R. Richardson, A. A. Baker, V. Mishin, D. E. Heck, D. L. Laskin, and J. D. Laskin. 2015. 'Vitamin K3 (menadione) redox cycling inhibits cytochrome P450-mediated metabolism and inhibits parathion intoxication', *Toxicol Appl Pharmacol,* 288: 114--20.

Jia, S., C. Mou, Y. Ma, R. Han, and X. Li. 2016. 'Magnesium regulates neural stem cell proliferation in the mouse hippocampus by altering mitochondrial function', *Cell Biol Int,* 40: 465--71.

Jin, Y., A. Amaral, A. McCann, and L. Brennan. 2011. 'Homocysteine levels impact directly on epigenetic reprogramming in astrocytes', *Neurochem Int,* 58: 833--8.

Jollant, F., S. Richard-Devantoy, Y. Ding, G. Turecki, A. Bechara, and J. Near. 2016. 'Prefrontal inositol levels and implicit decision-making in healthy individuals and depressed patients', *Eur Neuropsychopharmacol,* 26: 1255--63.

Joven, J., V. Micol, A. Segura-Carretero, C. Alonso-Villaverde, and J. A. Menendez. 2014. 'Polyphenols and the modulation of gene expression pathways: can we eat our way out of the danger of chronic disease?', *Crit Rev Food Sci Nutr*, 54: 985--1001.

Karuppagounder, S. S., H. Xu, Q. Shi, L. H. Chen, S. Pedrini, D. Pechman, H. Baker, M. F. Beal, S. E. Gandy, and G. E. Gibson. 2009. 'Thiamine deficiency induces oxidative stress and exacerbates the plaque pathology in Alzheimer's mouse model', *Neurobiol Aging*, 30: 1587--600.

Kennedy, D. O. 2016. 'B Vitamins and the Brain: Mechanisms, Dose and Efficacy--A Review', *Nutrients*, 8: 68.

Kent, K., K. Charlton, S. Roodenrys, M. Batterham, J. Potter, V. Traynor, H. Gilbert, O. Morgan, and R. Richards. 2015. 'Consumption of anthocyanin-rich cherry juice for 12 weeks improves memory and cognition in older adults with mild-to-moderate dementia', *Eur J Nutr*.

Kim, H., G. Kim, W. Jang, S. Y. Kim, and N. Chang. 2014. 'Association between intake of B vitamins and cognitive function in elderly Koreans with cognitive impairment', *Nutr J*, 13: 118.

Kim, Y., J. S. Goo, I. Y. Kim, J. E. Kim, M. H. Kwak, J. Go, S. Shim, J. T. Hong, D. Y. Hwang, and J. K. Seong. 2014. 'Identification of the responsible proteins for increased selenium bioavailability in the brain of transgenic rats overexpressing selenoprotein M', *Int J Mol Med*, 34: 1688--98.

Koc, E. R., A. Ilhan, Ayturk Zubeyde, B. Acar, M. Gurler, A. Altuntas, M. Karapirli, and A. S. Bodur. 2015. 'A comparison of hair and serum trace elements in patients with Alzheimer disease and healthy participants', *Turk J Med Sci*, 45: 1034--9.

Kook, S. Y., K. M. Lee, Y. Kim, M. Y. Cha, S. Kang, S. H. Baik, H. Lee, R. Park, and I. Mook-Jung. 2014. 'High-dose of vitamin C supplementation reduces amyloid plaque burden and ameliorates pathological changes in the brain of 5XFAD mice', *Cell Death Dis*, 5: e1083.

Kunjara, S., P. McLean, L. Rademacher, T. W. Rademacher, F. Fascilla, S. Bettocchi, and M. Scioscia. 2016. 'Putative Key Role of Inositol Messengers in Endothelial Cells in Preeclampsia', *Int J Endocrinol*, 2016: 7695648.

Laczmanski, L., M. Jakubik, G. Bednarek-Tupikowska, J. Rymaszewska, N. Sloka, and F. Lwow. 2015. 'Vitamin D receptor gene polymorphisms in Alzheimer's disease patients', *Exp Gerontol*, 69: 142--7.

Lakshmi, B. V., M. Sudhakar, and K. S. Prakash. 2015. 'Protective effect of selenium against aluminum chloride-induced Alzheimer's disease: behavioral and biochemical alterations in rats', *Biol Trace Elem Res*, 165: 67--74.

Lee, M., E. G. McGeer, and P. L. McGeer. 2016. 'Quercetin, not caffeine, is a major neuroprotective component in coffee', *Neurobiol Aging*, 46: 113--23.

Lehmann, D. J., H. Refsum, D. R. Warden, C. Medway, G. K. Wilcock, and A. D. Smith. 2011. 'The vitamin D receptor gene is associated with Alzheimer's disease', *Neurosci Lett*, 504: 79--82.

Lerner, A. J., K. Gustaw-Rothenberg, S. Smyth, and G. Casadesus. 2012. 'Retinoids for treatment of Alzheimer's disease', *Biofactors*, 38: 84--9.

Li, D., Y. J. Tian, J. Guo, W. P. Sun, Y. Z. Lun, M. Guo, N. Luo, Y. Cao, J. M. Cao, X. J. Gong, and S. S. Zhou. 2013. 'Nicotinamide supplementation induces detrimental metabolic and epigenetic changes in developing rats', *Br J Nutr*, 110: 2156--64.

Li, W., J. Yu, Y. Liu, X. Huang, N. Abumaria, Y. Zhu, X. Huang, W. Xiong, C. Ren, X. G. Liu, D. Chui, and G. Liu. 2014. 'Elevation of brain magnesium prevents synaptic loss and reverses cognitive deficits in Alzheimer's disease mouse model', *Mol Brain*, 7: 65.

Lim, T. S., Y. H. Hong, H. Y. Lee, J. Y. Choi, H. S. Kim, and S. Y. Moon. 2012. 'Metabolite investigation in both anterior and posterior cingulate gyri in Alzheimer's disease spectrum using 3-tesla MR spectroscopy', *Dement Geriatr Cogn Disord*, 33: 149--55.

Littlejohns, T. J., W. E. Henley, I. A. Lang, C. Annweiler, O. Beauchet, P. H. Chaves, L. Fried, B. R. Kestenbaum, L. H. Kuller, K. M. Langa, O. L. Lopez, K. Kos, M. Soni, and D. J. Llewellyn. 2014. 'Vitamin D and the risk of dementia and Alzheimer disease', *Neurology*, 83: 920--8.

Liu, J., J. Zhou, Z. Wu, X. Wang, L. Liu, and C. Yao. 2016. 'Cyanidin 3-O-beta-Glucoside Ameliorates Ethanol-Induced Acute Liver Injury by Attenuating Oxidative Stress and Apoptosis: The Role of SIRT1/FOXO1 Signaling', *Alcohol Clin Exp Res*, 40: 457--66.

Liu, Z. J., Z. H. Li, L. Liu, W. X. Tang, Y. Wang, M. R. Dong, and C. Xiao. 2016. 'Curcumin Attenuates Beta-Amyloid-Induced Neuroinflammation via Activation of Peroxisome Proliferator-Activated Receptor-Gamma Function in a Rat Model of Alzheimer's Disease', *Front Pharmacol*, 7: 261.

Luccarini, I., C. Grossi, S. Rigacci, E. Coppi, A. M. Pugliese, D. Pantano, G. la Marca, T. Ed Dami, A. Berti, M. Stefani, and F. Casamenti. 2015. 'Oleuropein aglycone protects against pyroglutamylated-3 amyloid-ss toxicity: biochemical, epigenetic and functional correlates', *Neurobiol Aging*, 36: 648--63.

Mach, R. H. 2014. 'New targets for the development of PET tracers for imaging neurodegeneration in Alzheimer disease', *J Nucl Med*, 55: 1221--4.

Madsen, S. K., P. Rajagopalan, S. H. Joshi, A. W. Toga, and P. M. Thompson. 2015. 'Higher homocysteine associated with thinner cortical gray matter in 803 participants from the Alzheimer's Disease Neuroimaging Initiative', *Neurobiol Aging*, 36 Suppl 1: S203-10.

Markova, N., N. Bazhenova, D. C. Anthony, J. Vignisse, A. Svistunov, K. P. Lesch, L. Bettendorff, and T. Strekalova. 2016. 'Thiamine and benfotiamine improve cognition and ameliorate GSK-3beta-associated stress-induced behaviours in mice', *Prog Neuropsychopharmacol Biol Psychiatry*.

Marti-Carvajal, A. J., I. Sola, and D. Lathyris. 2015. 'Homocysteine-lowering interventions for preventing cardiovascular events', *Cochrane Database Syst Rev*, 1: Cd006612.

Masci, A., R. Mattioli, P. Costantino, S. Baima, G. Morelli, P. Punzi, C. Giordano, A. Pinto, L. M. Donini, M. d'Erme, and L. Mosca. 2015. 'Neuroprotective Effect of Brassica oleracea Sprouts Crude Juice in a Cellular Model of Alzheimer's Disease', *Oxid Med Cell Longev*, 2015: 781938.

Mazzanti, G., and S. Di Giacomo. 2016. 'Curcumin and Resveratrol in the Management of Cognitive Disorders: What is the Clinical Evidence?', *Molecules*, 21.

Mehedint, M. G., M. D. Niculescu, C. N. Craciunescu, and S. H. Zeisel. 2010. 'Choline deficiency alters global histone methylation and epigenetic marking at the Re1 site of the calbindin 1 gene', *Faseb j*, 24: 184--95.

Min, J. Y., and K. B. Min. 2014. 'Serum lycopene, lutein and zeaxanthin, and the risk of Alzheimer's disease mortality in older adults', *Dement Geriatr Cogn Disord*, 37: 246--56.

Mitchell, E. S., N. Conus, and J. Kaput. 2014. 'B vitamin polymorphisms and behavior: evidence of associations with neurodevelopment, depression, schizophrenia, bipolar disorder and cognitive decline', *Neurosci Biobehav Rev*, 47: 307--20.

Mohammadzadeh Honarvar, N., A. Saedisomeolia, M. Abdolahi, A. Shayeganrad, G. Taheri Sangsari, B. Hassanzadeh Rad, and G. Muench. 2016. 'Molecular Anti-inflammatory Mechanisms of Retinoids and Carotenoids in Alzheimer's Disease: a Review of Current Evidence', *J Mol Neurosci*.

Mohebali, N., S. A. Shahzadeh Fazeli, H. Ghafoori, Z. Farahmand, E. MohammadKhani, F. Vakhshiteh, A. Ghamarian, M. Farhangniya, and M. H. Sanati. 2016. 'Effect of flavonoids rich extract of Capparis spinosa on inflammatory involved genes in amyloid-beta peptide injected rat model of Alzheimer's disease', *Nutr Neurosci*: 1--8.

Molina-Lopez, J., D. Florea, B. Quintero-Osso, A. P. de la Cruz, M. Rodriguez-Elvira, and E. P. Del Pozo. 2016. 'Pyridoxal-5'-phosphate deficiency is associated with hyperhomocysteinemia regardless of antioxidant, thiamine, riboflavin, cobalamine, and folate status in critically ill patients', *Clin Nutr*, 35: 706--12.

Morris, M. C., D. A. Evans, J. L. Bienias, P. A. Scherr, C. C. Tangney, L. E. Hebert, D. A. Bennett, R. S. Wilson, and N. Aggarwal. 2004. 'Dietary niacin and the risk of incident Alzheimer's disease and of cognitive decline', *J Neurol Neurosurg Psychiatry*, 75: 1093--9.

Nishihira, J., T. Tokashiki, Y. Higashiuesato, D. C. Willcox, N. Mattek, L. Shinto, Y. Ohya, and H. H. Dodge. 2016. 'Associations between Serum Omega-3 Fatty Acid Levels and Cognitive Functions among Community-Dwelling Octogenarians in Okinawa, Japan: The KOCOA Study', *J Alzheimers Dis*, 51: 857--66.

Nolan, J. M., E. Loskutova, A. Howard, R. Mulcahy, R. Moran, J. Stack, M. Bolger, R. F. Coen, J. Dennison, K. O. Akuffo, N. Owens, R. Power, D. Thurnham, and S. Beatty. 2015. 'The impact of supplemental macular carotenoids in Alzheimer's disease: a randomized clinical trial', *J Alzheimers Dis*, 44: 1157--69.

Oulhaj, A., F. Jerneren, H. Refsum, A. D. Smith, and C. A. de Jager. 2016. 'Omega-3 Fatty Acid Status Enhances the Prevention of Cognitive Decline by B Vitamins in Mild Cognitive Impairment', *J Alzheimers Dis*, 50: 547--57.

Pan, X., G. Fei, J. Lu, L. Jin, S. Pan, Z. Chen, C. Wang, S. Sang, H. Liu, W. Hu, H. Zhang, H. Wang, Z. Wang, Q. Tan, Y. Qin, Q. Zhang, X. Xie, Y. Ji, D. Cui, X. Gu, J. Xu, Y. Yu, and C. Zhong. 2016. 'Measurement of Blood Thiamine Metabolites for Alzheimer's Disease Diagnosis', *EBioMedicine*, 3: 155--62.

Pantano, D., I. Luccarini, P. Nardiello, M. Servili, M. Stefani, and F. Casamenti. 2016. 'Oleuropein aglycone and polyphenols from olive mill wastewater ameliorate cognitive deficits and neuropathology', *Br J Clin Pharmacol*.

Porquet, D., C. Grinan-Ferre, I. Ferrer, A. Camins, C. Sanfeliu, J. Del Valle, and M. Pallas. 2014. 'Neuroprotective role of trans-resveratrol in a murine model of familial Alzheimer's disease', *J Alzheimers Dis*, 42: 1209--20.

Presse, N., S. Belleville, P. Gaudreau, C. E. Greenwood, M. J. Kergoat, J. A. Morais, H. Payette, B. Shatenstein, and G. Ferland. 2013. 'Vitamin K status and cognitive function in healthy older adults', *Neurobiol Aging*, 34: 2777--83.

Priyadarsini, R. V., and S. Nagini. 2012. 'Quercetin suppresses cytochrome P450 mediated ROS generation and NFkappaB activation to inhibit the development of 7,12-dimethylbenz[a]anthracene (DMBA) induced hamster buccal pouch carcinomas', *Free Radic Res*, 46: 41--9.

Qiang, X., Z. Sang, W. Yuan, Y. Li, Q. Liu, P. Bai, Y. Shi, W. Ang, Z. Tan, and Y. Deng. 2014. 'Design, synthesis and evaluation of genistein-O-alkylbenzylamines as potential multifunctional agents for the treatment of Alzheimer's disease', *Eur J Med Chem*, 76: 314--31.

Raha, S., H. J. Lee, S. Yumnam, G. E. Hong, V. Venkatarame Gowda Saralamma, Y. L. Ha, J. O. Kim, Y. S. Kim, J. D. Heo, S. J. Lee, E. H. Kim, and G. S. Kim. 2016. 'Vitamin D2 suppresses amyloid-beta 25--35 induced microglial activation in BV2 cells by blocking the NF-kappaB inflammatory signaling pathway', *Life Sci*, 161: 37--44.

Rashid, M. A., M. Haque, and M. Akbar. 2016. 'Role of Polyunsaturated Fatty Acids and Their Metabolites on Stem Cell Proliferation and Differentiation', *Adv Neurobiol*, 12: 367--80.

Rehman, S. U., S. A. Shah, T. Ali, J. I. Chung, and M. O. Kim. 2016. 'Anthocyanins Reversed D-Galactose-Induced Oxidative Stress and Neuroinflammation Mediated Cognitive Impairment in Adult Rats', *Mol Neurobiol*.

Rey, C., A. Nadjar, B. Buaud, C. Vaysse, A. Aubert, V. Pallet, S. Laye, and C. Joffre. 2016. 'Resolvin D1 and E1 promote resolution of inflammation in microglial cells in vitro', *Brain Behav Immun*, 55: 249--59.

Ribeiro, M. L., L. M. Moreira, D. P. Arcari, L. F. Dos Santos, A. C. Marques, J. Pedrazzoli, Jr., and S. M. Cerutti. 2016. 'Protective effects of chronic treatment with a standardized extract of Ginkgo biloba L. in the prefrontal cortex and dorsal hippocampus of middle-aged rats', *Behav Brain Res*, 313: 144--50.

Rijpma, A., O. Meulenbroek, A. M. van Hees, J. W. Sijben, B. Vellas, R. C. Shah, D. A. Bennett, P. Scheltens, and M. G. Olde Rikkert. 2015. 'Effects of Souvenaid on plasma micronutrient levels and fatty acid profiles in mild and mild-to-moderate Alzheimer's disease', *Alzheimers Res Ther*, 7: 51.

Rita Cardoso, Bárbara, Verônica Silva Bandeira, Wilson Jacob-Filho, and Silvia Maria Franciscato Cozzolino. 2014. 'Selenium status in elderly: Relation to cognitive decline', *Journal of Trace Elements in Medicine and Biology*, 28: 422--26.

Sezgin, Z., and Y. Dincer. 2014. 'Alzheimer's disease and epigenetic diet', *Neurochem Int*, 78: 105--16.

Shen, L., and H. F. Ji. 2015. 'Vitamin D deficiency is associated with increased risk of Alzheimer's disease and dementia: evidence from meta-analysis', *Nutr J*, 14: 76.

Shu, L., W. Sun, L. Li, Z. Xu, L. Lin, P. Xie, H. Shen, L. Huang, Q. Xu, P. Jin, and X. Li. 2016. 'Genome-wide alteration of 5-hydroxymenthylcytosine in a mouse model of Alzheimer's disease', *BMC Genomics*, 17: 381.

Siahmard, Z., H. Alaei, P. Reisi, and A. A. Pilehvarian. 2012. 'The effect of red grape juice on Alzheimer's disease in rats', *Adv Biomed Res*, 1: 63.

Sontag, J. M., B. Wasek, G. Taleski, J. Smith, E. Arning, E. Sontag, and T. Bottiglieri. 2014. 'Altered protein phosphatase 2A methylation and Tau phosphorylation in the young and aged brain of methylenetetrahydrofolate reductase (MTHFR) deficient mice', *Front Aging Neurosci*, 6: 214.

Soutif-Veillon, Anne, Guylaine Ferland, Yves Rolland, Nancy Presse, Kariane Boucher, Catherine Féart, and Cedric Annweiler. 2016. 'Increased dietary vitamin K intake is associated with less severe subjective memory complaint among older adults', *Maturitas*, 93: 131--36.

Speckmann, B., and T. Grune. 2015. 'Epigenetic effects of selenium and their implications for health', *Epigenetics*, 10: 179--90.

Steinbrenner, H., and H. Sies. 2013. 'Selenium homeostasis and antioxidant selenoproteins in brain: implications for disorders in the central nervous system', *Arch Biochem Biophys*, 536: 152--7.

Suantawee, T., H. Cheng, and S. Adisakwattana. 2016. 'Protective effect of cyanidin against glucose- and methylglyoxal-induced protein glycation and oxidative DNA damage', *Int J Biol Macromol*, 93: 814--21.

Sun, Q., J. G. Weinger, F. Mao, and G. Liu. 2016. 'Regulation of structural and functional synapse density by L-threonate through modulation of intraneuronal magnesium concentration', *Neuropharmacology*, 108: 426--39.

Sundaram, K. S., J. H. Fan, J. A. Engelke, A. L. Foley, J. W. Suttie, and M. Lev. 1996. 'Vitamin K status influences brain sulfatide metabolism in young mice and rats', *J Nutr*, 126: 2746--51.

Takada, S. H., J. M. Ikebara, E. de Sousa, D. S. Cardoso, R. R. Resende, H. Ulrich, M. Ruckl, S. Rudiger, and A. H. Kihara. 2016. 'Determining the Roles of Inositol Trisphosphate Receptors in Neurodegeneration: Interdisciplinary Perspectives on a Complex Topic', *Mol Neurobiol*.

Teng, E., K. Taylor, T. Bilousova, D. Weiland, T. Pham, X. Zuo, F. Yang, P. P. Chen, C. G. Glabe, A. Takacs, D. R. Hoffman, S. A. Frautschy, and G. M. Cole. 2015. 'Dietary DHA supplementation in an APP/PS1 transgenic rat model of AD reduces behavioral and Abeta pathology and modulates Abeta oligomerization', *Neurobiol Dis*, 82: 552--60.

Thomas, M. H., S. Pelleieux, N. Vitale, and J. L. Olivier. 2016. 'Dietary arachidonic acid as a risk factor for age-associated neurodegenerative diseases: Potential mechanisms', *Biochimie*, 130: 168--77.

Torres, M., S. L. Price, M. A. Fiol-Deroque, A. Marcilla-Etxenike, H. Ahyayauch, G. Barcelo-Coblijn, S. Teres, L. Katsouri, M. Ordinas, D. J. Lopez, M. Ibarguren, F. M. Goni, X. Busquets, J. Vitorica, M. Sastre, and P. V. Escriba. 2014. 'Membrane lipid modifications and therapeutic effects mediated by hydroxydocosahexaenoic acid on Alzheimer's disease', *Biochim Biophys Acta*, 1838: 1680--92.

Ueland, P. M., A. McCann, O. Midttun, and A. Ulvik. 2016. 'Inflammation, vitamin B6 and related pathways', *Mol Aspects Med*.

Uguz, A. C., M. Naziroglu, J. Espino, I. Bejarano, D. Gonzalez, A. B. Rodriguez, and J. A. Pariente. 2009. 'Selenium modulates oxidative stress-induced cell apoptosis in human myeloid HL-60 cells through regulation of calcium release and caspase-3 and -9 activities', *J Membr Biol*, 232: 15--23.

Vahid, F., H. Zand, E. Nosrat-Mirshekarlou, R. Najafi, and A. Hekmatdoost. 2015. 'The role dietary of bioactive compounds on the regulation of histone acetylases and deacetylases: a review', *Gene*, 562: 8--15.

van Eersel, J., Y. D. Ke, X. Liu, F. Delerue, J. J. Kril, J. Gotz, and L. M. Ittner. 2010. 'Sodium selenate mitigates tau pathology, neurodegeneration, and functional deficits in Alzheimer's disease models', *Proc Natl Acad Sci U S A*, 107: 13888--93.

Venigalla, M., E. Gyengesi, and G. Munch. 2015. 'Curcumin and Apigenin – novel and promising therapeutics against chronic neuroinflammation in Alzheimer's disease', *Neural Regen Res*, 10: 1181--5.

Voevodskaya, O., P. C. Sundgren, O. Strandberg, H. Zetterberg, L. Minthon, K. Blennow, L. O. Wahlund, E. Westman, and O. Hansson. 2016. 'Myo-inositol changes precede amyloid pathology and relate to APOE genotype in Alzheimer disease', *Neurology*, 86: 1754--61.

Wan, W., C. Zhang, M. Danielsen, Q. Li, W. Chen, Y. Chan, and Y. Li. 2016. 'EGb761 improves cognitive function and regulates inflammatory responses in the APP/PS1 mouse', *Exp Gerontol*, 81: 92--100.

Wang, L. S., C. T. Kuo, S. J. Cho, C. Seguin, J. Siddiqui, K. Stoner, Y. I. Weng, T. H. Huang, J. Tichelaar, M. Yearsley, G. D. Stoner, and Y. W. Huang. 2013. 'Black raspberry-derived anthocyanins demethylate tumor suppressor genes through the inhibition of DNMT1 and DNMT3B in colon cancer cells', *Nutr Cancer*, 65: 118--25.

Wang, R., S. Chen, Y. Liu, S. Diao, Y. Xue, X. You, E. A. Park, and F. F. Liao. 2015. 'All-trans-retinoic acid reduces BACE1 expression under inflammatory conditions via modulation of nuclear factor kappaB (NFkappaB) signaling', *J Biol Chem*, 290: 22532--42.

Wang, S. W., S. G. Yang, W. Liu, Y. X. Zhang, P. X. Xu, T. Wang, T. J. Ling, and R. T. Liu. 2016. 'Alpha-tocopherol quinine ameliorates spatial memory deficits by reducing beta-amyloid oligomers, neuroinflammation and oxidative stress in transgenic mice with Alzheimer's disease', *Behav Brain Res*, 296: 109--17.

Wang, X., X. Hu, Y. Yang, T. Takata, and T. Sakurai. 2016. 'Nicotinamide mononucleotide protects against beta-amyloid oligomer-induced cognitive impairment and neuronal death', *Brain Res*, 1643: 1--9.

Wang, Y., B. Cai, J. Shao, T. T. Wang, R. Z. Cai, C. J. Ma, T. Han, and J. Du. 2016. 'Genistein suppresses the mitochondrial apoptotic pathway in hippocampal neurons in rats with Alzheimer's disease', *Neural Regen Res*, 11: 1153--8.

Wang, Z., Y. Wang, W. Li, F. Mao, Y. Sun, L. Huang, and X. Li. 2014. 'Design, synthesis, and evaluation of multitarget-directed selenium-containing clioquinol derivatives for the treatment of Alzheimer's disease', *ACS Chem Neurosci*, 5: 952--62.

Watamura, N., J. Toba, A. Yoshii, M. Nikkuni, and T. Ohshima. 2016. 'Colocalization of phosphorylated forms of WAVE1, CRMP2, and tau in Alzheimer's disease model mice:

Involvement of Cdk5 phosphorylation and the effect of ATRA treatment', *J Neurosci Res*, 94: 15--26.

Witte, A. V., L. Kerti, D. S. Margulies, and A. Floel. 2014. 'Effects of resveratrol on memory performance, hippocampal functional connectivity, and glucose metabolism in healthy older adults', *J Neurosci*, 34: 7862--70.

Xia, W., and H. Mo. 2016. 'Potential of tocotrienols in the prevention and therapy of Alzheimer's disease', *J Nutr Biochem*, 31: 1--9.

Xie, Q., Q. Bai, L. Y. Zou, Q. Y. Zhang, Y. Zhou, H. Chang, L. Yi, J. D. Zhu, and M. T. Mi. 2014. 'Genistein inhibits DNA methylation and increases expression of tumor suppressor genes in human breast cancer cells', *Genes Chromosomes Cancer*, 53: 422--31.

Xu, Z. P., L. Li, J. Bao, Z. H. Wang, J. Zeng, E. J. Liu, X. G. Li, R. X. Huang, D. Gao, M. Z. Li, Y. Zhang, G. P. Liu, and J. Z. Wang. 2014. 'Magnesium protects cognitive functions and synaptic plasticity in streptozotocin-induced sporadic Alzheimer's model', *PLoS One*, 9: e108645.

Yamakawa, M. Y., K. Uchino, Y. Watanabe, T. Adachi, M. Nakanishi, H. Ichino, K. Hongo, T. Mizobata, S. Kobayashi, K. Nakashima, and Y. Kawata. 2016. 'Anthocyanin suppresses the toxicity of Abeta deposits through diversion of molecular forms in in vitro and in vivo models of Alzheimer's disease', *Nutr Neurosci*, 19: 32--42.

Yang, S. J., J. M. Choi, L. Kim, S. E. Park, E. J. Rhee, W. Y. Lee, K. W. Oh, S. W. Park, and C. Y. Park. 2014. 'Nicotinamide improves glucose metabolism and affects the hepatic NAD-sirtuin pathway in a rodent model of obesity and type 2 diabetes', *J Nutr Biochem*, 25: 66--72.

Yao, Y., J. Li, Y. Niu, J. Q. Yu, L. Yan, Z. H. Miao, X. X. Zhao, Y. J. Li, W. X. Yao, P. Zheng, and W. Q. Li. 2015. 'Resveratrol inhibits oligomeric Abeta-induced microglial activation via NADPH oxidase', *Mol Med Rep*, 12: 6133--9.

Youn, K., and M. Jun. 2013. 'In vitro BACE1 inhibitory activity of geraniin and corilagin from Geranium thunbergii', *Planta Med*, 79: 1038--42.

Yuan, T., H. Ma, W. Liu, D. B. Niesen, N. Shah, R. Crews, K. N. Rose, D. A. Vattem, and N. P. Seeram. 2016. 'Pomegranate's Neuroprotective Effects against Alzheimer's Disease Are Mediated by Urolithins, Its Ellagitannin-Gut Microbial Derived Metabolites', *ACS Chem Neurosci*, 7: 26--33.

Zhang, P., K. Tsuchiya, T. Kinoshita, H. Kushiyama, S. Suidasari, M. Hatakeyama, H. Imura, N. Kato, and T. Suda. 2016. 'Vitamin B6 Prevents IL-1beta Protein Production by Inhibiting NLRP3 Inflammasome Activation', *J Biol Chem*, 291: 24517--27.

Zhang, Q., G. Yang, W. Li, Z. Fan, A. Sun, J. Luo, and Z. J. Ke. 2011. 'Thiamine deficiency increases beta-secretase activity and accumulation of beta-amyloid peptides', *Neurobiol Aging*, 32: 42--53.

Zhang, R., J. Zhang, L. Fang, X. Li, Y. Zhao, W. Shi, and L. An. 2014. 'Neuroprotective effects of sulforaphane on cholinergic neurons in mice with Alzheimer's disease-like lesions', *Int J Mol Sci*, 15: 14396--410.

Zhao, L., J. L. Wang, R. Liu, X. X. Li, J. F. Li, and L. Zhang. 2013. 'Neuroprotective, anti-amyloidogenic and neurotrophic effects of apigenin in an Alzheimer's disease mouse model', *Molecules*, 18: 9949--65.

Table 1. The relationship between some bioactive nutrient components and formation, progression, epigenetics of AD

Bioactive nutrient components	Formation and progression effect	Epigenetic effects
Curcumin (Turmeric)	Rats supplemented with curcumin 150 mg / kg for 8 weeks, suppressed NF-kβ pathway, reduced proinflammatory cytokines such as IL-1β, TNFα, NO and protect cholinergic neurons (Liu, Li, et al. 2016). Curcumin may also binds Fe and Cu to reduce Aβ aggregation and may protects against Aβ-induced ROS damage (Baum and Ng 2004). NOAEL→250-320 mg/kg/day ADI → 3 mg/kg/day (EFSA 2010).	It may suppresses DNMT, especially DNMT1 and DNMT3B, HAT, H3K227me3 in the Neurog 1 promotor region and HDAC 1,4,5 (Huang et al. 2016; Mazzanti and Di Giacomo 2016).
Kaempferol-Ginkgo Bilabo	Ginkgo bilabo supplementation at 0.5 mg / kg and 1 mg / kg for 30 days protected DNA against H_2O_2-induced damage and improved short-term memory (Ribeiro et al. 2016). Ginkgo bilabo supplementation at 50 mg / kg for 6 months decreased proinflammatory cytokines by decreasing iNOS, reduced ROS to antioxidant activity, and reduced insoluble Aβ (Wan et al. 2016). 240 mg / day Ginkgo biloba developed cognitive function (Beck et al. 2016) .	The epigenetic effect of kaempferol is shown by decreasing HDAC (2,4,7,8) activity, increasing BCI-2 gene expression, and regulating SIRT1 (Guo et al. 2015; Berger et al. 2013).
Oleriopein **(olive etc.)**	Aβ aggregation decreases, plaque accumulation is inhibited, cognitive function develops at 12.5 mg / kg and 50 mg / kg 8 week supplementation of oleriopein (Grossi et al. 2013; Pantano et al. 2016).	Oleriopein increases Histone 3 and histone 4 acetylation, decreases histone 2 deacetylase 2 enzyme expression and improves synaptic function (Luccarini et al. 2015).
Quarsetin **(Citrus fruits, apples, etc.)**	Quercetin protected against DNA damage, lipid and protein oxidation by reducing ROS production and NF-kβ from cytochrome p450 (Priyadarsini and Nagini 2012). In addition, quercetin supplements at 100 ng / mL and higher dose have been shown to reduce the release of proinflammatory cytokines such as TNF-α and IL-6 and protect against neuronal damage by affecting the	It may reduces the regulation of BACE-1, APP, PSEN1, PSEN2. At the same time, It may inhibits SIRT1, NAD-dependent acetylase, HDAC and DNMT1 (Mohebali et al. 2016; Vahid et al. 2015).

	NF-kβ pathway (Lee, McGeer, and McGeer 2016).	
İsoflavonlar **(Soy products etc.) (genistein)**	In particular 25d derivative of gensistein reduces Aβ 1-42 aggregation by 35%, Cu + 2 -induced Aβ 1-42 aggregation by 77.8%, AChE (by inhibiting choline esterase) -induced Aβ 1-42 aggregation by 36.2% (Qiang et al. 2014) . 10, 30 and 90 mg / kg / day Supplements of Genisteine reduced mitochondrial apoptosis and neuronal loss and improved learning and memory (Wang, Cai, et al. 2016).	It is effective in DNA methylation, histone modification and gene expression. In particular, It suppresses DNMT, in particular DNMT1 activity and regulates HAT and miRNA activity (Vahid et al. 2015; Xie et al. 2014).
İsosiyonatlar **(Broccoli, cabbage etc.)**	Cabbage juice protects against Aβ cytotoxicity and apoptotic cell death. Cabbage juice increased antioxidant enzyme activity, reduced oxidative stress induced neuronal damage and prevented cognitive damage (Masci et al. 2015). The amount of brain aluminum was found to be low in the group receiving sulforaphane than non-sulforaphane group. At the same time, sulphorophane prevented the cholinergic cell damage (Zhang et al. 2014).	It affects ıntracellular glutathione concentration and mRNA activity, HSP70 gene transcription and expression, mitochondrial function. It reduces PSEN1, increases histone acetylation by inhibiting HDAC activity in DNA methylation (Masci et al. 2015; Athanasopoulos, Karagiannis, and Tsolaki 2016; Sezgin and Dincer 2014).
Apigenin **(Daisy, celery, parsley, grapefruit, etc.)**	Apigenin has anti-inflammatory and antioxidant effect (Huang et al. 2016). Apigenin supplementation 40 mg / kg orally for 3 months in APP / PSEN1 mice; - ımproved learning and memory, - prevented the worsening of A by regulating the path of APP and decreasing BACE1 levels, - reduced ıncomplete Aβ the levels of 1-40 (20%) and Aβ 1-42 (19,8%), - Reduced oxidative stress by improving superoxide dismutase and glutathione peroxidase (Zhao et al. 2013). No toxic effects were observed and high doses were considered safe (Venigalla, Gyengesi, and Munch 2015).	It was indicated as a newly emerging plant-derived HDAC inhibitor (Huang et al. 2016).