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Dietary compounds and memory loss

Ke Dong[1], Warnakulasuriya M.A.D. Binosha Fernando[2], Vijay Jayasena[3*]
[1, 3] School of Science and Health, Western Sydney University, Locked Bag 1797, Penrith, New South Wales, Australia
[2] Centre of Excellence for Alzheimer's Disease Research and Care, School of Medical and Health Sciences, Edith Cowan University, Joondalup, Western Australia, Australia
[2] Australian Alzheimer's Research Foundation, Ralph and Patricia Sarich Neuroscience Research Institute, 8 Verdun Street, Nedlands, Western Australia, Australia

Abstract
Memory loss is a symptom of dementia while Alzheimer's disease (AD) is the most common cause of dementia. AD has been a social and economic burden worldwide. Unfortunately, there is no drug or treatment can cure or slow down the progression of AD so far. Evidence suggests that diets rich in protein, dietary fibre, vitamins, flavonoids or phenolics could enhance human's memory and reduce the risk of AD through direct effects on amyloid beta (Aβ, a hallmark of AD) and consequently influence AD pathogenesis. This paper has reviewed the pathology, mechanisms of Aβ mediated toxicity, contributing factors, diagnosis and therapeutics of AD. The diets which are beneficial to reduce AD risk have also been discussed in detail to provide a health advice.

Keywords: diet, memory loss, dementia, Alzheimer's disease

1. Introduction
Memory loss is a common and severe problem among adults. Nearly half of the people over 50 years in Australia have some extent of memory loss (Downey, 2014) [17]. An estimation made by Australian Institute of Health and Welfare in 2012 showed that there were 298,000 Australians living with dementia and this number is expected to increase to 400,000 by 2020 and around 900,000 by 2050 (Refshauge & Kalisch, 2012) [68]. Memory problems are usually one of the first signs of cognitive impairment related to AD. Certain diets have great influence on preventing or minimising memory loss (Chandola, Chaudhuri, Kumar, Ravishankar, & Samarakoon, 2011) [12]. A range of the phyto-chemical compounds have the potential to enhance human's memory and improve neuro-cognitive performance, such as vitamins, flavonoids, phenolic compounds (Spencer, 2008) [77]. There is a growing interest consuming specific diets to reduce the risk of AD. Thus, we have carried out a systematic review and try to reveal the link between certain diets and AD.

2. Memory loss
Memory loss is an abnormal degree of forgetfulness and/or inability to recall past events which is also referred to amnesia (Stöppler, 2017) [78]. It is a symptom which can be temporary or permanent and it disrupts people's daily work. The cause of memory loss varies, and may be due to disease, normal aging, abuse of drugs or alcohol, head injury, depression and stress, sleep deprivation, nutritional deficiency, etc. Nearly half of the people over 50 years in Australia have some extent of memory loss (Downey, 2014) [17]. Memory loss is often one of the common signs at the early stage of neuro-diseases such as dementia, Huntington's disease, Parkinson's disease and epilepsy (Jahn, 2013) [37].

3. Dementia
Dementia is a syndrome or group of diseases while AD is the most common form of dementia (Thies & Laura, 2011) [82]. It occurs due to a variety of brain disorders that affect memory, thinking, mood behaviour, communication and reasoning ability to perform everyday activities (Hoang, Crouch, Knifton, & Brayne, 2015) [31]. The number of people living with dementia worldwide is currently estimated at 47 million and it is projected to increase to 75 million by 2030 and almost triple by 2050 (Prince *et al.*, 2015) [64]. Dementia is a devastating problem not only for the people who have it, but also for their caregivers, families and communities. There is a lack of awareness and understanding of dementia in most countries leading to difficulty in diagnosis and care. There is no treatment to hold or prevent dementia so far.

4. Alzheimer's disease
AD is a progressive neurodegenerative disease of the central nervous system and comprises approximately 80% of all dementia cases in the elderly. The cost of AD is a major burden to current healthcare system due to recent increase of gross domestic product (GDP). The prevalence of AD upsurge is associated with increasing age and it is higher in women because of their increased longevity. The incidence of AD is common over the age of 65.
There are two types of AD. Early onset of AD (also called Familial AD) is usually linked with single gene mutations at one of the three loci, namely chromosomes 21, chromosomes 14 and chromosomes 1 which are linked with amyloid precursor protein (APP), presenilin 1 and presenilin 2 respectively (Bekris, Yu, Bird, & Tsuang, 2010) [5]. Late onset of AD (also called Sporadic AD) is the major type accounting for approximately 90% AD cases (Bekris *et al.*, 2010) [5]. Late onset of AD is highly associated with both

environmental and genetic factors (Piaceri, Nacmias, & Sorbi, 2013) [62].

4.1 Pathology

The pathological hallmarks of AD include β-amyloid (Aβ) plaques, neurofibrillary tangles (NFTs which are aggregates of hyper phosphorylated tau protein), dystrophic neurites and neuropil threads (J. Morris, Galvin, & Holtzman, 2006) [53]. All these hallmarks have abnormal insoluble protein aggregates which cause damage to normal cellular functioning. Major proteins associated with AD are summarised in Table 1.

Table 1: Main Protein relating to AD

Protein	Function	Association with AD
Aβ peptides	Form insoluble fibrils that aggregate in the extracellular space	Toxic to neurons; damage synapses; kill neurons (Gouras, Olsson, & Hansson, 2015) [23].
APP	Related to neuronal function	Mutations in APP increase Aβ levels (Tarditi, Caricasole, & Terstappen, 2009) [79]
Tau protein	Form NFTs inside neurons	Result in instability of microtubules or neuronal injury and death of cells (Grill & Cummings, 2010) [24]

Aβ is normal peptides of 36 to 43 amino acids generated throughout life. Aβ is the major component of the amyloid plaque diagnosed in AD patient brain. Particularly, accumulation of Aβ42 plays a significant role in AD pathogenesis which was selected as the target in this research. The image of normal brain and AD brain is shown in Figure 1.

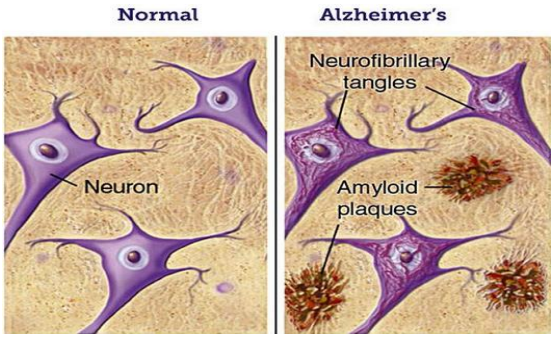

Figure 1: Normal brain and AD brain

(Amyloid plaques and neurofibrillary Tangles are major hallmarks of AD) (Mikulec & Bokulic, 2015) [48].

Aβ is formed by intra membrane proteolysis of APP and cleaved by the enzymes β and γ secretases (C. Zhang, 2007) [93]. The imbalance between Aβ production and defective clearance leads to Aβ aggregation which ultimately contributes to increased senile amyloid plaques (O'Brien & Wong, 2011) [58]. Aggregated Aβ initially form soluble oligomers and then further form larger insoluble fibre fragments due to polymerisation. The insoluble fibre fragments eventually precipitate as amyloid fibrils (Agamanolis, 2016 [1]; Gouras *et al*., 2015) [23]. The deposition of amyloid fibrils formulates Aβ plaques which initiate a cascade of reactions and contribute to apoptosis, cognitive dysfunction or even cell death relating to AD (Moneim, 2015) [51]. There is a close relationship between total amount of soluble Aβ and severity of AD in terms of neurological dysfunction (Eckman & Eckman, 2007) [19]. Experiments have indicated that some antibodies against Aβ lead to behavioural functioning improvement on transgenic mice with AD (Dodart *et al*., 2002) [16]. Factors affecting the clearance of Aβ in brain and plasma are summarised in Table 2.

Table 2: Main factors affecting the aggregation of Aβ

Factors	Function
Presence of Apolipoprotein E (APOE)	APOE alters transport and metabolism of Aβ (Bharadwaj, 2011) [6]
Insulin-degrading enzyme (IDE)	Decrease Aβ production through degradation (Yang, Sun, & Chen, 2012) [91]
Neprilysin (NEP)	Decrease Aβ production through degradation (Yang, Sun, & Chen, 2012) [91]
Endothelin converting enzymes (ECE-1,2);plasmin; matrix metal oproteinase (MMP-2, -3 and -9); angiotensin-converting enzyme (ACE)	Decrease Aβ production through degradation (Miners, Barua, Kehoe, Gill, & Love, 2011) [49]
Autophagy-lysosome pathway	Deteriorative autophagy-lysosome system accelerates Aβ production and aggregation. (Perluigi, Di Domenico, & Butterfield, 2015) [61]
Proteasome	Impaired proteasome activity results in accumulated Aβ. (Tseng, Green, Chan, Blurton-Jones, & LaFerla, 2008) [84]

Aggregation of Aβ is the primary event in AD pathogenesis as its deposition is specific to AD. Progressive accumulation of Aβ initialises AD progression and neurodegenerative pathology (Jiang, Zhi, Zhang, Pan, & Zhou, 2012) [38].

Aβ is considered as significant therapeutic target in AD prevention and treatment (Ohyagi, 2008) [59]. This is done mainly either modulating Aβ progression or reducing the effect of toxic Aβ plague, such as Aβ degradation and reduction of Aβ toxicity (Budson & Solomon, 2016) [9].

4.2 Potential mechanisms of Aβ mediated toxicity

4.2.1 Mitochondrial dysfunction

Neurons require high energy and are highly dependent on mitochondrial energy production, therefore mitochondrial dysfunction has fatal consequences for neuronal function (Bolisetty & Jaimes, 2013) [8]. Dysfunction of mitochondria appears regardless of Aβ plaques and NFTs deposition in the AD brain. This postulates that mitochondrial function is disrupted at early stage of AD and providing promise for Investigating mitochondrial dysfunction as an early therapeutic target for AD treatment.

The presence of dysfunctional mitochondria leads to the

impairment of energy metabolism in AD brain. The predominant role of mitochondria is producing adenosine triphosphate (ATP) through either aerobic respiration or anaerobic fermentation. One of the end products during this process is glucose which is the main energy source for brain. Dysfunctional mitochondria cause reduced glucose utilisation which is observed in AD patients (Sato & Morishita, 2015) [69]. During this process, mitochondria become smaller and more compact which means a reduction of energy provision to neurons (Gao *et al*., 2010) [22]. On the other hand, mitochondrial dysfunction results in reduced ATP generation and enhanced reactive oxygen species (ROS) production which are linked with cell degeneration and death (Bolisetty & Jaimes, 2013) [8].

4.2.2 Oxidative stress
Oxidative stress is an imbalance between free radicals and antioxidants which plays an important role in early pathology of AD. The free radicals in AD brain include Aβ and activated microglia (Agamanolis 2016) [1]. Oxidative stress takes place before the onset of AD symptoms and is accelerated by free radicals that may attack and damage lipids, proteins and deoxyribonucleic acid (DNA) in brain (Moreira, Carvalho, Zhu, Smith, & Perry, 2010 [52]; Tuppo & Forman, 2001) [85]. The brain damages caused by excessive oxidative stress consist of mutations of mitochondrial DNA, dysfunction of mitochondrial and further oxidative stress (Butterfield, Swomley, & Sultana, 2013) [10]. Research has also demonstrated that oxidative damage is associated with deposition of NFTs (Huang, Zhang, & Chen, 2016) [33]. On the other hand, oxidative stress leads to neurons disorder (Bhatti, Usman, Ali, & Satti, 2016) [7].

4.2.3 Synapse toxicity
A synapse is a structure that permits a neuron to pass an electrical or chemical signal to another neuron or target effector cell. Synaptic loss is one of the clinical symptoms of AD (Forner, Baglietto-Vargas, Martini, Trujillo-Estrada, & LaFerla, 2016) [21]. Aβ oligomers are harmful to synapse function and structure in terms of decreasing synaptic response. At the same time, Aβ and tau may have synergistic impairment to synaptic function while its mechanism remains unclear (Forner *et al*., 2016) [21].

4.2.4 Neurotrophic factors
Neurotrophic factors are a family of biomolecules and majority of neurotrophic factors are peptides or small proteins. The function of neurotrophic factors is to support or maintain survival and growth of neurons. AD is linked with abnormal distribution and dysregulation of neurotrophic factors. Research has indicated that neurotrophic factor is a critical molecule in AD due to involvement in cognition, learning and memory by modulating synaptic plasticity (Schindowski, Belarbi, & Buee, 2008) [71].

4.3 Contributing factors of AD
4.3.1 Age
Increasing age is a risk factor of AD. After age 65, the Prevalence of AD doubles every five years. After age of 85, nearly one third of people may have AD-related symptoms and signs (Qiu, Kivipelto, & Strauss, 2009) [65].

4.3.2 Gender
More women than men have AD. For example, almost two thirds of the AD patients in US are female (Thies & Laura, 2011) [82]. This could be explained by the fact that women live longer on average than men.

4.3.3 Genes
Three genes are identified for early onset of AD, they are APP, presenilin 1, and presenilin 2 genes (Bekris *et al*., 2010) [5]. In late onset of AD, apolipoprotein E (APOE) ε4 allele is the key genetic risk. There are three forms of APOE gene (APOE ε2, ε3 and ε4) and their combination determines APOE "genotype". The function of APOE ε4 is to provide a protein the blueprint for carrying cholesterol in the bloodstream (Thies & Laura, 2011) [82]. People who inherit APOE ε4 gene have increased risk of developing AD at early stage compared to those inherit APOE ε2 or ε3 gene. In addition, heritage of two APOE ε4 genes has 4-6 times higher risk of AD than that has one APOE ε4 gene (Dacks, 2016) [14]. However, APOE ε4 does not always lead to AD (Gureje et al., 2010) [26]. On the contrary, some AD patients do not have APOE ε4 alleles (Thies & Laura, 2011) [82].

4.3.4 Neuroin flammation
One of the hallmarks of AD is deposition of Aβ plaque and its related neuroin flammation (Ray & Lahiri, 2009) [67]. Several genes are associated with sporadic AD encoding factors through regulation of inflammatory reaction and mis folded proteins clearance in glial (Heneka *et al*., 2015) [29]. For example, APP is encoded by transcriptional regulation of the genes and producing Aβ peptides through cleavage in AD brain (Bekris *et al*., 2010) [5]. On the other hand, immunological processes are also impacted by environmental factors which further accelerate AD progression, such as systemic inflammation (Heneka *et al*., 2015) [29]. The effects of neuroin flammation are mediated by activated microglial cells which are a source of cytokines and a potent generator of free radicals. At the same time, multiple aberrations in the microglial which cause brain damage and accelerate Aβ and tau deposition take place during neuroin flammation (Agamanolis, 2016) [1].

4.3.5 Disease
People with some vascular diseases are more vulnerable to AD. This includes but not limited to heart disease, stroke and high blood pressure. Brain impairment due to vascular conditions includes inability of cerebral arterioles, damage of brain capillary network and leukoencephalopathy (Agamanolis 2016) [1]. At the same time, some metabolic diseases are also an increased risk of AD. For example, diabetes, particularly type 2 diabetes which is associated with abnormal glucose metabolism and high levels of plasma cholesterol increases individual's risk of developing AD (L. Li & Hölscher, 2007) [43]. Obesity is another disease which is a risk factor of developing AD (Thies & Laura, 2011) [82].

4.3.6 Traumatic brain injury
A lot of evidence has indicated that traumatic brain injury promotes Aβ production and tau hyper phosphorylation which lead to increased risk of AD. Research has further stated that cerebrovascular dysfunction is a key element regarding traumatic brain injury relating to AD (Ramos-

Cejudo *et al*., 2018) [66].

4.3.7 Environmental and Lifestyle

Research has indicated that approximately 30% of AD risk is due to environmental factors and human lifestyle patterns (Manivannan, Manivannan, Beach, & Halden, 2015) [46]. Environmental factors include but not limited to inorganic and organic hazards, toxic metals, pesticides, industrial chemicals and air pollution. Exposures to these environmental factors along with individual's unhealthy lifestyle over time potentially contribute to neuroin flammation and neuropathology paving the way to development of AD (Manivannan *et al*., 2015) [46].

4.4 Diagnosis of AD

There are no specific clinical findings in AD. However, evaluation of biomarkers in plasma and cerebrospinal fluid (CSF) is one of the effective diagnosis methods. Investigation of proteins in plasma is based on pathophysiologic process which indicates biomarker attribute of AD (Irizarry, 2004) [35]. CSF could not only indicate presence of Aβ in brain but also predict the rate of AD progression from mild to severe brain impairment (Holtzman, 2011) [32]. Definitive diagnosis can only be made by pathological examination of brain tissues. The main biomarkers of AD are shown in Table 3.

Table 3: Main Biomarkers of AD

Biomarker	Evaluation	Technique
Amyloid beta	Blood and CSF	Plasma- blood test; enzyme linked immuno sorbent assay (ELISA)
Tau protein	CSF	ELISA; imaging
APOEε4 allele	Blood; CSF	ELISA; genotyping
APP	CSF	ELISA
DNA	Blood	Polymerase chain reaction (PCR)

(Humpel, 2011[34]; Tarditi *et al*., 2009) [79]

4.5 Some of the therapeutics of AD

There is currently no therapy which could neither cure nor modify AD progression. Current treatments only provide a temporary and slight symptomatic improvement. There are some potential effective therapeutics of AD.

4.5.1 Drugs

Approved drugs are an important approach for AD treatment including single or combined drugs targeting different mechanisms (C. Zhang, 2017) [94]. These drugs not only maintain or even improve AD patients' current cognitive abilities but also potentially decrease their associated behavioural problems. For example, Donepezil, Rivastigmine and Galantamine are widely used as cholinesterase inhibitors which target mild to moderate AD. Another drug called Memantine, acts as N-methyl-D-aspartate receptor antagonist is for moderate to severe AD patients. Memantine is often used with Donepezil for a synergistic effect (Kim & Factora, 2018) [40].

4.5.2 Physical exercise

Physical exercise is well recognised which is beneficial to brain. Physical exercise not only benefits on maintaining brain size but also prevents some AD risks, such as obesity and stroke (Chen, Zhang, & Huang, 2016) [33]. Research also has unravelled that physical exercise may postpone the onset of AD and reduce the mortality (Cendoroglo, Thiessen, Blake, Forbes, & Forbes, 2014) [11]. An example of common physical exercises is walking which is proved to benefit cognition of AD patients (Venturelli, Scarsini, & Schena, 2011) [87].

4.5.3 Diet

Certain diets have great influence on increasing or decreasing AD risk which is supported by a lot of studies (Luchsinger, Noble, & Scarmeas, 2007) [45]. For example, one investigation has indicated that healthy diet is in favour of maintaining or improving cognitive function (Ngandu et al., 2015) [56]. The link between diet and AD was discussed in detail below.

5. Diet and AD

5.1 Dietary patterns

Dietary patterns refer to the habit how people eat their diets, this mainly includes quantities, proportions, and combination of all food consumed including drink and supplement (Krebs-Smith, 2014) [41]. A summary of major dietary patterns which could reduce the risk of AD is listed in Table 4.

Table 4: Major dietary patterns associated with AD prevention

Dietary pattern	Characteristics of the diets	Link to AD
Prudent pattern diet	-Higher consumption of vegetables, fruit, legumes, and whole grains --Higher consumption of fish and poultry	Relating to prevention of cognitive impairment and dementia (Shakersain *et al*., 2016) [75].
Calorie restricted diet	--Minimised energy intake --Sufficient vitamins, minerals and other important nutrients	Beneficial effects on brain aging and AD (Van Cauwenberghe, Vandendriessche, Libert, & Vandenbroucke, 2016) [86].
The Mediterranean diet	--High consumption of olive oil, legumes, unrefined cereals, fruits, and vegetables, --Moderate to high consumption of fish --Moderate consumption of dairy products (mainly cheese and yogurt) --Moderate wine consumption --Low consumption of meat and meat products	Associated with a reduction of AD risk (Scarmeas, Stern, Mayeux, & Luchsinger, 2006) [70].
Dietary approaches to stop	--Rich in fruits, vegetables, whole grains	--Improved neurocognitive function

hypertension (DASH) diet	--Low-fat dairy foods --Some meat, fish, poultry, nuts and beans --Limited sugar-sweetened foods and beverages, red meat, and added fats computation	--Reduction of blood pressure may also be beneficial to AD prevention (P. J. Smith *et al*., 2010) [74].
Vegetarian diet	--No meat --Higher consumption of vegetables, fruit, legumes, whole grains --Some eat eggs and dairy products	--Link with AD is disputable. --Lower blood pressure and improve blood lipid profile which are positive to AD prevention. --On the contrary, vegetarian diet is a risk of some nutrients deficiency which cause cognitive problems, such B_{12}, homocysteine (Osimani, Berger, Friedman, Porat-Katz, & Abarbanel, 2005 [60]; Williams & O'Connell, 2002) [88].

5.2 Nutrients

5.2.1 Protein

Diet with high protein content seems to reduce the risk of AD. In a clinical trial carried out in Australia indicated significantly reduced chance of higher level of Aβ in brain on participants served with high protein diet daily compared to those with lower protein consumption (Fernando *et al*., 2018) [20]. However, the clear relationship between dietary protein and AD is still unclear. The possible cause is high protein diet may lower blood pressure while high blood pressure is a known risk factor of AD.

5.2.2 Carbohydrate

High carbohydrate diet generally could increase the risk of AD. High carbohydrate diet contributes to obesity. One study has demonstrated that diet containing high carbohydrate could influence lipid metabolism and damage brain cells through excessive insulin/ IGF signalling in nervous system (Henderson, 2004) [28]. However, carbohydrate include sugar, fibre and they have different effects on AD.

5.2.2.1 Sugar

Researchers from UK have indicated that people eating diets with high sugar are at a greater risk of AD. High sugar uptake is harmful to a vital enzyme called macrophage migration inhibitory factor (MIF) which is involved in a series of AD events, such as oxidative stress, immune response, hyperglycaemia (Kassaar *et al*., 2017) [39]. High-sugar diets may also lead to an increased blood sugar (glucose) level or hyperglycaemia which is a known risk factor of AD.

5.2.2.2 Fibre

Dietary fibre assists in production of short chain fatty acids (e.g. butyrate) through gut Bacteria while short chain fatty acids Inhibit the production of certain toxins to brains (e.g. interleukin-1β) (Matt *et al*., 2018) [47]. On the other hand, high fibre diet helps to prevent diabetes and obesity (U. Smith, 1987) [75]. A higher fibre diet is recommended to prevent AD.

5.2.2.3 Polysaccharide

Polysaccharide has shown the great potential on anti-AD effect. The polysaccharides from traditional Chinese medicine prevent AD progression with different targets or pathways, such as free radical metabolism, anti-apoptosis, APP and Aβ expression (Liu, Wang, & Ding, 2017) [44]. One study has demonstrated that polysaccharide extracted from flammulina velutipes could enhance rat's cognitive function against AD (Y. Zhang, Li, Yang, Jin, & Zhang, 2018) [95].

5.2.3 Fat

High fat diet could contribute to cognitive decline in AD due to blood-brain barrier dysfunction and modulated immune response (Thériault, Elali, & Rivest, 2016) [81]. One animal trial feeding wild rabbits with high fat diet indicated an increased Aβ accumulation in brain (Sparks *et al*., 1994) [76]. High fat diet may also result in obesity and hypertension which are risk factors of AD. In addition to fat content, the composition of dietary fat is also associated with AD (M. C. Morris & Tangney, 2014) [55]. High consumption of saturated and trans fatty acids could double the risk of AD while lower intake of mono saturated and polysaturated fatty acids reduces the risk of developing AD (M. C. Morris, 2004) [54].

5.2.4 Vitamins

Diet rich in vitamins are beneficial to AD prevention and treatment. Vitamins could attenuate oxidative stress which potentially inhibits AD progression (Bhatti *et al*., 2016) [7]. A summary of vitamins with their links to AD is shown in Table 5.

Table 5: Different vitamins and their links to AD

Name	Link to AD
Vitamin A including β-Carotene	Influence multiple aspects of neurodegenerative disorders; enhance cognitive function (Bhatti *et al*., 2016) [7].
B vitamins	Deficiency of B_6, B_9, and B_{12} could lead to decreased level of homocysteine which is AD risk factor. (Bhatti *et al*., 2016 [7]; Osimani *et al*., 2005) [60].
Vitamin C	Alters progression of AD by preventing the oligomerization of Aβ peptides; decrease oxidative stress (Bhatti *et al*., 2016) [7].
Vitamin D	Beneficial to AD prevention and treatment (Annweiler, Llewellyn, & Beauchet, 2013) [2].
Vitamin E	Protection against AD (Devore *et al*., 2010) [15].
Vitamin K	Prevent oxidative stress and reduce AD risk (J. Li, Wang, & Rosenberg, 2009) [42].

5.2.5 Flavonoid
Flavonoid has protective effect against AD. Research has indicated that flavonoid could prevent specific enzymes during the phosphorylation of tau protein, such as β-secretases (Bakhtiari *et al*. 2017) [4]. At the same time, flavonoid is beneficial to improve cognitive function (Bakhtiari, Panahi, Ameli, & Darvishi, 2017) [4]. Examples include but not limited to quercetin, kaempferol, luteolin and rutin.

5.2.6 Phenolic compounds
Certain phenolic compounds could reduce the risk of AD development. Some examples include curcumin, ferulic acid, myricetin, tannic acid in which those compounds have shown the ability to prevent Aβ aggregation (Hamaguchi, Ono, Murase, & Yamada, 2009) [27]. Commonly consumed fruits, such as sweet orange, grapefruit and lemon contain high phenolic compounds.

5.3 Some fruits, grains and spice which reduce the risk of AD
5.3.1 Sea buckthorn
A study on feeding rat by sea buckthorn extract has illustrated sea buckthorn could improve cognitive ability by stimulating cholinergic system or increase neurotransmitters level (Shivakumar, Ilango, Agrawal, & Dubey, 2014) [73]. A similar study carried out on cognitive impaired mouse by scopolamine induction implied that sea buckthorn could be helpful on cognitive disorder by promoting antioxidant system (Attrey, Singh, Naved, & Roy, 2012) [3]. A number of elderly individuals who suffered from dementia were supplied with sea buckthorn juice for six months in which sea buckthorn appeared to be an effective remedial measure for age related memory loss and other cognitive deficits (Dubey & Agrawal, 2003) [18].
Flavonoid is one of the major bioactive compounds which is rich in sea buckthorn. Research has indicated that sea buckthorn's flavonoid can improve cognitive impairment by decreasing oxidative stress (Attrey *et al*., 2012) [3]. At the same time, sea buckthorn's flavonoid is capable of activating the extra-cellular signal-regulated kinase and protein kinase B signalling pathways (a signal transduction pathway) which could improve long-term memory (Spencer, 2008) [77]. Quercetin is the key flavonoid in sea buckthorn enhancing cognitive function due to strong free radical scavenging ability (Terdthai, Panakaporn, Jintanaporn, & Wathita, 2010) [80]. Sea buckthorn is rich in antioxidants and its major antioxidants include but not limited to vitamins (C, B_1, B_2, B_6, E), SOD, and flavonoids (Xu, Sun, & Qiu, 1999) [90]. In China, researchers undertook a series of study regarding sea buckthorn's benefit on cognitive function. The memory improvement was attributed to sea buckthorn's strong antioxidant property which could not only prevent lead accumulation but also alleviate lead's toxicity. On the other hand, sea buckthorn could reduce lead-increased monoamine oxidase activity which was associated to nervous disorder (Xu, Han, & Yu, 2005) [89]. In a similar trial using mice with lead-induced deficit of learning, oral administration of sea buckthorn juice improved mice's memory (Xu *et al*., 1999) [90].

At the same time, sea buckthorn's beneficial effect on Cardiovascular disease also reduces the risk of AD.

5.3.2 Goji berry
Goji berry is rich in polysaccharide which is beneficial to cognitive function and reduce AD risk. Goji berry's polysaccharide exhibits neuro protective effect and ameliorate neurological dysfunction. The polysaccharide derived from goji berry could protect protein kinase from being phosphorylated by Aβ (Ho, So, & Chang, 2010) [28]. The polysaccharide also reduces Aβ toxicity through decreased level of lactate dehydrogenase (Yu *et al*. 2005) [92]. In addition, goji berry polysaccharide reduces tau phosphorylation. Betaine is another goji berry bioactive compound which could enhance memory. Research has indicated that betaine has positive effect against lipopolysaccharide-included memory impairment (Miwa *et al*., 2011) [50].

5.3.3 Lupin
No work has been done on the linkage between lupin and AD. However, lupin is high in protein and fibre which has shown great potential in reduction of AD risk.

5.3.4 Carob
Carob is abundant in phenolic compounds which could not only protect but also ameliorate neurogenerative disease. For example, carob cinnamon could improve monosodium glutamate-induced AD through reduction of cognition and hippocampus neuronal cells loss (Jackson, O'Donnell, Takano, Coulter, & Robinson, 2014) [36]. Ferulic acid in carob could reduce Aβ (Tosetti, Noonan, & Albini, 2009) [83]. Chlorogenic acid protects neuros against oxidative stress (Oboh, Agunloye, Akinyemi, Ademiluyi, & Adefegha, 2013) [57].

5.3.5 Turmeric
Turmeric can reduce memory and cognitive decline. Research has demonstrated that curcumin extracted from turmeric can enhance clearance of Aβ (Downey, 2014) [17]. Both curcumin and curcuminoid in turmeric have numerous effects ameliorating symptoms of AD. One of the major concerns in curcumin application is poor absorption and bioavailability (Prasad, Tyagi, & Aggarwal, 2014) [63]. One study suggested that the formulated form of curcumin showed better bioavailability than that of unformulated form (Prasad *et al*., 2014) [63]. Incorporation of curcumin into food formulations could not only increase end product nutritional value but also improve the bioavailability of curcumin. At the same time, curcumin can boost the levels of brain-derived neurotrophic factor (BDNF) by assisting new neurons growth and resisting various degenerative processes in brain (Gunnars, 2016) [25].

6. Conclusion
AD has been a growing concern while memory loss is one of the first symptoms of AD. This review explains the difference among memory loss, dementia and AD. In particular, the pathology, potential mechanism of Aβ mediated toxicity, contributing factors, diagnosis and some therapeutics of AD have been discussed. Since there is no confirmed treatment which can effectively cure or stop the progression of AD, certain diet has been a preventative way to reduce the risk of AD. In this paper, the role of certain nutrients (e.g. protein, carbohydrate, fat, vitamin, flavonoid, phenolics) on AD has been reviewed. In addition, the link between AD and some fruit or grain or spice has also

explored. This review article can provide some advisory information to help people improve memory and reduce the risk of AD from a diet perspective.

7. References

1. Agamanolis DP. Neuropathology Degenerative Disease, 2016. Retrieved from http://neuropathology-web.org/
2. Annweiler C, Llewellyn DJ, Beauchet O. Low Serum Vitamin D Concentrations in Alzheimer's Disease: A Systematic Review and Meta-Analysis. Journal of Alzheimer's Disease. 2013; 33(3):659-674.
3. Attrey D, Singh A, Naved T, Roy B. Effect of seabuckthorn extract on scopolamine induced cognitive impairment. Indian Journal of Experimental Biology. 2012; 50(10):690- 695.
4. Bakhtiari M, Panahi Y, Ameli J, Darvishi B. (2017). Protective Effects of Flavonoids Against Alzheimer's Disease-Related Neural Dysfunctions. Biomedicine & Pharmacotherapy. 2017; 93:218-229.
5. Bekris LM, Yu C, Bird TD, Tsuang DW. Genetics of Alzheimer Disease. Journal of Geriatric Psychiatry and Neurology. 2010; 23(4):213-222.
6. Bharadwaj, P. R. (2011). *Yeast as A Model for Studying Aβ Aggregation, Toxicity and Clearance.* (Doctor). Edith Cowan University, Perth.
7. Bhatti AB, Usman M, Ali F, Satti SA. Vitamin Supplementation as an Adjuvant Treatment for Alzheimer's disease. Journal of Clinical and Diagnostic Research. 2016; 10(8):OE07-OE11.
8. Bolisetty S, Jaimes EA. Mitochondria and Reactive Oxygen Species: Physiology and Pathophysiology. International Journal of Molecular Sciences. 2013; 4(3):6306-6344.
9. Budson AE, Solomon PR. Memory Loss, Alzheimer's disease, and Dementia (Second Edition) - A Practical Guide for Clinicians. London: Elsevier Health Sciences, 2016, 18.
10. Butterfield DA, Swomley AM, Sultana R. Amyloid β-Peptide (1-42)-Induced Oxidative Stress in Alzheimer Disease: Importance in Disease Pathogenesis and Progression. Antioxidants & Redox Signaling. 2013; 19(8):823-835.
11. Cendoroglo MS, Thiessen EJ, Blake CM, Forbes SS, Forbes S. Exercise Programs for People with Dementia. Sao Paulo Medical Journal. 2014; 132:195‑196.
12. Chandola H, Chaudhuri K, Kumar R, Ravishankar B, Samarakoon SMS. Evaluation of Diet and Life Style in Etiopathogenesis of Senile Dementia: A Survey Study. An International Quarterly Journal of Research in Ayurveda. 2011; 32(2):171.
13. Chen W, Zhang X, Huang W. Role of Physical Exercise in Alzheimer's disease. Biomedical Reports. 2016; 4(4):403-407.
14. Dacks P. What APOE Means for Your Health, 2016. Retrieved from https://www.alzdiscovery.org/cognitive-vitality/blog/what-apoe-means-for-your-health
15. Devore EE, Grodstein F, van Rooij FJ, Hofman A, Stampfer MJ, Witteman JC, *et al*. Dietary Antioxidants and Long-Term Risk of Dementia. Archives of Neurology. 2010; 67(7):819-825. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/20625087
16. Dodart JC, Bales KR, Gannon KS, Greene SJ, DeMattos RB, Mathis C, *et al*. Immunization Reverses Memory Deficits Without Reducing Brain Aβ Burden in Alzheimer's Disease Model. Nature Neuroscience. 2002; 5(5):452-457.
17. Downey M. Bio-enhanced Turmeric Compounds Block Multiple Inflammatory Pathways. Life Extension, 2014, (66)11.
18. Dubey GP, Agrawal A. Memory enhancing potentials of Seabuckthorn (Hippophae rhamnoide) - A placebo controlled study. Paper presented at the 1st Congress of the ISA - International Seabuckthorn Association, Berlin, 2003
19. Eckman CB, Eckman EA. An Update on the Amyloid Hypothesis. Neurologic Clinics. 2007; 25(3):669-680.
20. Fernando WMADB, Rainey-Smith SR, Gardener SL, Villemagne VL, Burnham SC, Macaulay SL, *et al*. Associations of Dietary Protein and Fiber Intake with Brain and Blood Amyloid-β Journal of Alzheimer's Disease. 2018; 61(4):1589-1598.
21. Forner S, Baglietto-Vargas D, Martini AC, Trujillo-Estrada L, LaFerla FM. Synaptic Impairment in Alzheimer's Disease: A Dysregulated Symphony. Trends in Neurosciences, 2016, 40(6).
22. Gao C, Zhu C, Zhao Y, Chen X, Ji C, Zhang C,*et al*. Mitochondrial Dysfunction is Induced by High Levels of Glucose and Free Fatty Acids in 3T3-L1 Adipocytes. Molecular and Cellular Endocrinology. 2010; 1-2(320):25-33.
23. Gouras GK, Olsson TT, Hansson O. β-amyloid Peptides and Amyloid Plaques in Alzheimer's disease. Neuro therapeutics. 2015; 12(1):3-11.
24. Grill JD, Cummings JL. Novel Targets for Alzheimer's disease Treatment. Expert Review of Neuro therapeutics. 2010; 10(5):711–728.
25. Gunnars K. 10 Proven Health Benefits of Turmeric and Curcumin, 2016. Retrieved from https://authoritynutrition.com/top-10-evidence-based-health-benefits-of-turmeric/
26. Gureje, O., Ogunniyi, A., Baiyewu, O., Price, B., Unverzagt, F. W., Evans, R. W., . . . Murrell, J. R. (2010). APOE ε4 Is Not Associated with Alzheimer's Disease in Elderly Nigerians. *Annals of Neurology, 59*(1), 182-185.
27. Hamaguchi T, Ono K, Murase A, Yamada M. Phenolic Compounds Prevent Alzheimer's Pathology through Different Effects on the Amyloid-β Aggregation Pathway. The American Journal of Pathology. 2009; 175(6):2557-2565.
28. Henderson ST. High Carbohydrate Diets and Alzheimer's disease. Medical Hypotheses. 2004; 62(5):689-700.
29. Heneka MT, Carson MJ, Khoury EIJ, Landreth GE, Brosseron F, Feinstein DL, *et al*. Neuroinflammation in Alzheimer's Disease. The Lancet Neurology. 2015; 14(4):388-405.
30. Ho, Y., So, K., & Chang, R. (2010). Wolfberry (Lycium Barbarum) Protects Primary Cortical Neurons against Alzheimer's Disease-Related Pathological Damages. *International Journal of Neuropsychopharmacology*, *13*(Suppl 1), 136.
31. Hoang U, Crouch SEM, Knifton L, Brayne C. Dementia: A Public Mental Health Priority. Journal of Public Mental Health. 2015; 14(1):1-2.

32. Holtzman, D. M. (2011). CSF Biomarkers for Alzheimer's Disease: Current Utility and Potential Future Use. *Neurobiology of Aging, 32*(Suppl 1), S4-S9.
33. Huang W, Zhang X, Chen W. Role of Oxidative Stress in Alzheimer's disease. Biomedical Reports. 2016; 4(5):519-522.
34. Humpel C. Identifying and Validating Biomarkers for Alzheimer's disease. Trends in Biotechnology. 2011; 29(1):26-32.
35. Irizarry, M. C. (2004). Biomarkers of Alzheimer Disease in Plasma. *he Journal of the American Society for Experimental NeuroTherapeutics, 1*(2), 226-234.
36. Jackson, J. G., O'Donnell, J. C., Takano, H., Coulter, D. A., & Robinson, M. B. (2014). Neuronal Activity and Glutamate Uptake Decrease Mitochondrial Mobility in Astrocytes and Position Mitochondria Near Glutamate Transporters. *The Journal of Neuroscience, 34*(5), 1613–1624.
37. Jahn H. Memory Loss in Alzheimer's disease. Dialogues in Clinical Neuroscience. 2013; 15(4):445-454.
38. Jiang J, Zhi X, Zhang X, Pan L, Zhou P. Inhibitory Effect of Curcumin on The Al (Iii)-Induced Aβ 42 Aggregation and Neurotoxicity in Vitro. Bio chimical et Bio physical Acta-Molecular Basis of Disease. 2012; 1822(8):1207- 1215.
39. Kassaar O, Morais MP, Xu S, Adam EL, Chamberlain RC, Jenkins B, *et al*. Macrophage Migration Inhibitory Factor Is Subjected to Glucose Modification and Oxidation in Alzheimer's Disease. Scientific Reports. 2017; 7(42874):1-11.
40. Kim L, Factora RM. Alzheimer Dementia: Starting, Stopping Drug Therapy. Cleveland Clinic Journal of Medicine. 2018; 85(3):209-214.
41. Krebs-Smith SM. Approaches to Dietary Pattern Analyses: Potential to Inform Guidance Retrieved, 2014. from https://health.gov/dietary guidelines/2015-BINDER/meeting2/docs/work GroupPresentations/DGAC_Patttern_Sue_Krebs_Smith_2-27-14.pdf
42. Li J, Wang H, Rosenberg PA. Vitamin K Prevents Oxidative Cell Death by Inhibiting Activation of 12-Lipoxygenase in Developing Oligo dendrocytes. Journal of Neuroscience Research. 2009; 87(9):1997-2005.
43. Li L, Hölscher C. Common Pathological Processes in Alzheimer Disease and Type 2 Diabetes A Review. Brain Research Reviews. 2017; 56(2):384-402.
44. Liu Q, Wang S, Ding K. Research Advances in The Treatment of Alzheimer's Disease with Polysaccharides from Traditional Chinese Medicine. Chinese Journal of Natural Medicines. 2017; 15(9):641-652.
45. Luchsinger, J. A., Noble, J. M., & Scarmeas, N. (2007). Diet and Alzheimer's disease. *Current Neurology and Neuroscience Reports, 7*(5), 366-372.
46. Manivannan Y, Manivannan B, Beach TG, Halden RU. Role of Environmental Contaminants in the Etiology of Alzheimer's disease: A Review. Current Alzheimer Research. 2015; 12(2):116-146.
47. Matt SM, Allen JM, Lawson MA, Mailing LJ, Woods JA, Johnson RW, *et al*. Butyrate and Dietary Soluble Fiber Improve Neuroinflammation Associated with Aging in Mice. Retrieved, 2018.
48. Mikulec S, Bokulic E. The Influence of Immune Processes on Neurogenesis, Learning and Memory. Gyrus Journal. 2015; 3(2):66-71.
49. Miners JS, Barua N, Kehoe PG, Gill S, Love S. Aβ-degrading Enzymes: Potential for Treatment of Alzheimer Disease. Journal of Neuropathology & Experimental Neurology. 2011; 70(11):944-959.
50. Miwa M, Tsuboi M, Noguchi Y, Enokishima A, Nabeshima T, Hiramatsu M, *et al*. Effects of betaine on lipopolysaccharide-induced memory impairment in mice and the involvement of GABA transporter 2. Journal of Neuroin flammation. 2011; (8):153.
51. Moneim AEA. Oxidant/Antioxidant Imbalance and the Risk of Alzheimer's disease. Current Alzheimer Research. 2015; 12(4):335-349.
52. Moreira PI, Carvalho C, Zhu X, Smith MA, Perry G. Mitochondrial Dysfunction Is A Trigger of Alzheimer's Disease Pathophysiology. Bio chimical et Bio physical Acta. 2010; 1802(1):2-10.
53. Morris J, Galvin JE, Holtzman DM. Handbook of Dementing Illnesses. Boca Raton: CRC Press, 2006.
54. Morris MC. Diet and Alzheimer's Disease: What the Evidence Shows. Medscape General Medicine. 2004; 6(1):48.
55. Morris MC, Tangney CC. Dietary Fat Composition and Dementia Risk. Neurobiology of Aging. 2014; 35(2):S59-S64.
56. Ngandu T, Lehtisalo J, Solomon A, Levälahti E, Ahtiluoto S, Antikainen R, *et al*. A 2 Year Multidomain Intervention of Diet, Exercise, Cognitive Training, and Vascular Risk Monitoring Versus Control to Prevent Cognitive Decline in At-Risk Elderly People (Finger): A Randomised Controlled Trial. The Lancet. 2015; 385(9984):2255-2263.
57. Oboh, G., Agunloye, O. M., Akinyemi, A. J., Ademiluyi, A. O., & Adefegha, S. A. (2013). Comparative Study on The Inhibitory Effect of Caffeic And Chlorogenic Acids on Key Enzymes Linked to Alzheimer's Disease and Some Pro-Oxidant Induced Oxidative Stress in Rats' Brain-In Vitro. *Neurochemical Research, 38*(2), 413-419.
58. O'Brien RJ, Wong PC. Amyloid Precursor Protein Processing and Alzheimer's disease. Annual review of neuroscience. 2011; 34:185-204.
59. Ohyagi Y. Intracellular Amyloid β-Protein as a Therapeutic Target for Treating Alzheimer's Disease Current Alzheimer Research. 2008; 5(6):555-561.
60. Osimani A, Berger A, Friedman J, Porat-Katz BS, Abarbanel JM. Neuropsychology of Vitamin B12 Deficiency in Elderly Dementia Patients and Control Subjects. Journal of Geriatric Psychiatry and Neurology. 2005; 18(1):33-38.
61. Perluigi M, Di Domenico F, Butterfield DA. mTOR Signaling in Aging and Neuro degeneration: at The Crossroad between Metabolism Dysfunction and Impairment of Autophagy. Neurobiology of Disease. 2015; 84:39-49.
62. Piaceri I, Nacmias B, Sorbi S. Genetics of Familial and Sporadic Alzheimer's disease. Frontiers in Bioscience. 2013; 1(5):167-177.
63. Prasad S, Tyagi AK, Aggarwal BB. Recent Developments in Delivery, Bioavailability, Absorption and Metabolism of Curcumin: the Golden Pigment from Golden Spice. Cancer Res Treat. 2014; 46(1):2-

28.
64. Prince M, Wimo A, Guerchet M, Ali G, Wu Y, Prina M. The Global Impact of Dementia. Retrieved from London, 2015.
65. Qiu C, Kivipelto M, Strauss E. Epidemiology of Alzheimer's disease: Occurrence, Determinants, and Strategies Toward Intervention. Dialogues in Clinical Neuroscience. 2009; 11(2):111-128.
66. Ramos-Cejudo J, Wisniewski T, Marmar C, Zetterberg H, Blennow K, de Leon MJ, *et al*. Traumatic Brain Injury and Alzheimer's Disease: The Cerebrovascular Link. E Bio Medicine. 2018; 28:21-30.
67. Ray B, Lahiri DK. Neuroinflammation in Alzheimer's disease: Different Molecular Targets and Potential Therapeutic Agents Including Curcumin. Current Opinion in Pharmacology. 2009; 9(4):434-444.
68. Refshauge A, Kalisch D. Dementia in Australia [Press release]. Retrieved, 2012. From https://www.aihw.gov.au/getmedia/199796bc-34bf-4c49-a046-7e83c24968f1/ 13995. pdf.aspx? inline=true
69. Sato N, Morishita R. The Roles of Lipid and Glucose Metabolism in Modulation of B-Amyloid, Tau, and Neuro degeneration in The Pathogenesis of Alzheimer Disease. Front Aging Neurosci. 2015; 7(199):1-9.
70. Scarmeas N, Stern Y, Mayeux R, Luchsinger JA. Mediterranean Diet, Alzheimer Disease, and Vascular Mediation. Archives of Neurology. 2006; 63(12):1709-1717.
71. Schindowski K, Belarbi K, Buee L. Neurotrophic Factors in Alzheimer ’s disease: Role of Axonal Transport. Genes Brain and Behavior. 2008; 7(1):43-56.
72. Shakersain B, Santoni G, Larsson SC, Faxen-Irving G, Fastbom J, Fratiglioni L, *et al*. Prudent Diet May Attenuate The Adverse Effects of Western Diet on Cognitive Decline. Alzheimer’s & Dementia. 2016; 12(2):100-109.
73. Shivakumar S, Ilango K, Agrawal A, Dubey GP. Effect of Hippophae rhamnoides on cognitive enhancement via neurochemical modulation in scopolamine induced Sprague Dawely rats. International Journal of Pharmaceutical Sciences and Research. 2014; 5(10):4153.
74. Smith PJ, Blumenthal JA, Babyak MA, Craighead L, Welsh-Bohmer KA, Browndyke JN, *et al*. Effects of the Dietary Approaches to Stop Hypertension Diet, Exercise, and Caloric Restriction on Neurocognition in Overweight Adults with High Blood Pressure. Hypertension. 2010; 55(6):1331-1338.
75. Smith U. Dietary Fibre, Diabetes and Obesity. International Journal of Obesity. 1987; 11(1):27-31.
76. Sparks DL, Scheff SW, Hunsaker JC, Liu H, Landers T, Gross DR, *et al*. Induction of Alzheimer-Like β-Amyloid Immuno reactivity in The Brains of Rabbits with Dietary Cholesterol. Experimental Neurology. 1994; 126(1):88-94.
77. Spencer JPE. Food for Thought the Role of Dietary Flavonoids in Enhancing Human Memory, Learning and Neuro-Cognitive Performance. Paper presented at the The Summer Meeting of the Nutrition Society, Coleraine, 2008.
78. Stöppler MC. Memory Loss: Symptoms & Signs. Retrieved, 2017. From https://www.medicinenet. com/memory_loss/symptoms.htm
79. Tarditi A, Caricasole A, Terstappen GC. Therapeutic Targets for Alzheimer's Disease. Expert Opinion on Therapeutic Targets. 2009; 13(5):551-567.
80. Terdthai T, Panakaporn W, Jintanaporn W, Wathita P. Quercetin liposomes via nasal administration reduce anxiety and depression-like behaviors and enhance cognitive performances in rats. American Journal of Pharmacology and Toxicology. 2010; 5(2):80-88.
81. Thériault P, Elali A, Rivest S. High Fat Diet Exacerbates Alzheimer's Disease-related Pathology in APPswe/PS1 Mice. Oncotarget. 2016; 7(42):67808-67827.
82. Thies W, Laura L. Alzheimer's Disease Facts and Figures. Alzheimer's & Dementia. 2011; 7(2):208-244.
83. Tosetti, F., Noonan, D. M., & Albini, A. (2009). Metabolic Regulation and Redox Activity as Mechanisms for Angioprevention by Dietary Phytochemicals. *International Journal of Cancer*, *125*(9), 1997-2003.
84. Tseng, B. P., Green, K. N., Chan, J. L., Blurton-Jones, M., & LaFerla, F. M. (2008). Aβ Inhibits The Proteasome and Enhances Amyloid and Tau Accumulation. *Neurobiology of Aging*, *29*(11), 1607–1618.
85. Tuppo EE, Forman LJ. Free Radical Oxidative Damage and Alzheimer's disease. The Journal of the American Osteopathic Association. 2001; 101(12-1):S11-15.
86. Van Cauwenberghe C, Vandendriessche C, Libert C, Vandenbroucke RE. Caloric Restriction: Beneficial Effects on Brain Aging and Alzheimer's disease. 2016; 27(7-8):300-319.
87. Venturelli M, Scarsini R, Schena F. Six‐month Walking Program Changes Cognitive and ADL Performance in Patients with Alzheimer. American Journal of Alzheimer's disease & Other Dementias. 2011; 26:381-388. Retrieved from https://www.ncbi.nlm.nih. gov/pubmed/21852281
88. Williams JH, O'Connell TC. Differential Relations between Cognition and 15n Isotopic Content of Hair in Elderly People with Dementia and Controls. Journals of Gerontology. Series A: Biological Sciences & Medical Sciences. 2002; 57(12):M797-802.
89. Xu Y, Han C, Yu X. Effect of Hippophae Rhamnoides L. Juice on Monoamine Oxidase-A and Monoamine Oxidase-B Activities by Lead in Mice Brain. Journal of Medical Science Yanbian University. 2005; 28(2):97-99.
90. Xu Y, Sun L, Qiu D. The Effects of Hippophae Rhamnoides L.Juice on Lead-Induced Deficit of Learning and Memory of Mice. Journal of Medical Sciecnce Yanbian University. 1999; 22(4):278-280.
91. Yang H, Sun Z, Chen S. Current Advances in The Treatment of Alzheimer's disease: Focused on Considerations Targeting Aβ and Tau. Translational Neuro degeneration. 2012; 1(1):21-21.
92. Yu, M., Leung, S., Lai, S., Che, C., Zee, S., So, K., Chang, R. (2005). Neuroprotective Effects of Anti-Aging Oriental Medicine Lycium Barbarum against B-Amyloid Peptide Neurotoxicity. *Experimental Gerontology*, *40*(8- 9), 716- 727.
93. Zhang C. Therapeutic Targeting of the Alpha-Secretase Pathway to Treat Alzheimer’s disease. Discovery Medicine. 2007; 7(39):113-117.
94. Zhang C. Developing Effective Therapeutics for

Alzheimer's disease- Emerging Mechanisms and Actions in Translational Medicine. Discovery Medicine. 2017; 23(125):105-111.
95. Zhang Y, Li H, Yang X, Jin G, Zhang Y. Cognitive-Enhancing Effect of Polysaccharides from Flammulina Velutipes on Alzheimer's Disease by Compatibilizing with Ginsenosides. International Journal of Biological Macromolecules. 2018; 112: 788-795.