The Effect of Nutrients on Alzheimer'S Disease Biomarkers: a Metabolomic Approach

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Abstract

A large number of plasma proteomic biomarkers have been discovered in the field of neurodegenerative diseases. Novel biomarker molecules in plasma and serum could significantly reduce the need for invasive methods in clinical practice such as the lumbar puncture for CSF collection and may be useful to specific patients. Furthermore, candidate biomarker proteins that have been identified and validated could be used to discriminate Alzheimer’s disease patients from MCI and healthy controls in clinical trials, before the onset of clinical symptoms as well as to improve personalized therapies. The development of new blood based biomarkers via proteomic technology offer a deep knowledge in the pathophysiology of neurodegenerative diseases and involves in the development of new therapeutic targets. This current report presents numerous dietary compounds that either promote or suppress the expression of biomarkers mainly in the blood of AD or MCI subjects.

I.Introduction

Different dietary patterns have been proposed for the delay of cognitive decline and the prevention of Alzheimer’s disease.In the majority of observational and clinical studies, the Mediterranean diet, the Dietary Approaches to Stop Hypertension (DASH) diet and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet was associated with reduced risk for AD (Cremonini et al., 2019). Other studies demonstrated a negative association between the ketogenic diet and the progress of neurodegerative diseases (Włodarek, 2019). However, there is little or insufficient evidence for the direct impact of nutrients and its metabolites upon the blood based biomarkers of Alzheimer’s disease.

II.Advanced glycation end products (AGEs) in AD

Advanced glycation end products (AGEs) also known as glycotoxins are abundant in highly processed foods in western diet and are also formed during high heat cooking methods. Several studies reveal that AGEs have been implicated in various chronic diseases such as diabetes chronic kidney disease, memory decline with age, cardiovascular pathology, polycystic ovary syndrome, increased cellular inflammatory and oxidative conditions, cancer, schizophrenia, aging and Alzheimer’s disease (Prasad et al., 2019). More precisely, advanced glycation end products that have been observed in intracellular neurofibrillary tangles (Sasaki et al., 1998), increase the ROS production, upregulate the expression of BACE, PS1M and SIRT1 and through these mechanisms they may contribute to the progression and neurotoxicity of AD (Ko et al., 2015).

Dietary intake of glucose and corn syrup with high concentration of fructose (HFCS) presented in processed foods (candy and cereal bars, confectionery products, specific brands of breakfast cereals, salad dressings, flavored yogurts, canned fruits, ice creams, ready to eat food) may lead to insulin resistance, type 2-diabetes and may induce the glycation process, presented by glycated Apo E (Han et al., 2014). Increased exposure of neurons and astrocytes to glucose and mainly to fructose may increase the risk of protein glycation leading to protein dysfunction and neuronal damage. On the other hand, studies have demonstrated a major protective role of n-3 fatty acids, a-lipoic acid, flavonoids such as quercetin and rutin (Li et al., 2014). Saffron (Samarghandian et al., 2014), green tea (Nakagawa et al., 2002) and garlic cloves and its constituent s-allylcysteine may all possess their neutraceutical effect by inhibiting the glycation process.

III.Apolipoproteins in AD

Apart from APOE ε4 allele that has been marked as a strongest genetic risk factor for AD, apolipoprotein B100 (Löffler et al., 2013), apolipoprotein J as well as apolipoprotein D (Bhatia et al., 2019) are associated with AD pathology. ApoJ, also known as clusterin could discriminate AD and MCI from healthy controls with an accuracy greater than 80% and greater than 75% respectively (Thambisetty et al., 2010; Gupta et al., 2016). Regular consumption of trans fatty acids upregulate the expression of ApoB-100 (Mitmesser & Carr., 2005).

IV.Amyloid precurson protein (APP) & BACE1 in AD

A type I transmembrane protein known as amyloid precurson protein (APP) with different isoforms is expressed in neurons and in astrocytes and has a crucial role in the pathogenesis of AD. Proteolysis of APP initially by the enzyme β-secretase or β-site APP cleaving enzyme 1 (BACE1)and consecutively by the enzyme γ- secretase gives rise to Abeta 1-40 and Abeta 1-42 peptides resulting in amyloidogenesis (Zhang et al., 2012). AD subjects have presented increased levels of BACE1 protein compared to age-matched non-demented subjects.Therefore peripheral APP and BACE1 can be used as both prognostic and therapeutic tool (Ashton et al., 2019; Decourt et al., 2011).

According to several studies, dietary intake of omega-3 fatty acids (Lukiw et al., 2005), selenium (Du et al., 2013), polyphenol-rich sesame lignans and cinnamon helps eliminate the APP activity (Katayama et al., 2016). Other dietary phenolic compounds such as (−)-Epicatechin, quercetin and myricetin found in tea, berries and herbs inhibit the activity of BACE1. Similar antiamyloidogenic properties are present in the flavonone nariturin found in citrus fruit and juices (Chakraborty, S., & Basu, S., 2017) and in the caffeic acid conjugated chitosan (Ouyang et al., 2017).

V.Sirtuins in AD

The family of sirtuin deacetylases has been extensively studied for their implication in the development neurodegenerative diseases. The protein biomarkers Sirt1 and Sirt3 with suitable cut off points have been proposed and evaluated in the early stages of AD diagnosis. Sirt1 is a well known neuroprotective enzyme against AD through the autophagy process.Kumar et al. (2013) showed significant decline in blood SIRT1 concentrations in AD and MCI patients when compared to healthy controls. A high fibre, low fat diet upregulate the sirt1 expression (Martins, I. J., & Fernando, W. M., 2014).Cinnamon polyphenolic compounds cinnamtannin D1, B1, cassiatannin A and extra virgin olive oil constitute potential sirt1 activators (Vassallo, 2015).

Sirt3 in mitochondria promotes protein homeostasis and regulates a series of molecular and metabolic procedures such as cell signaling,oxidative phosphorylation, ATP production and apoptosis (Szegő et al., 2018) as well as protein folding and degradation (Yang et al., 2018). Therefore depletion of sirt3 has been related to mitochondrial dysfunction and AD pathology. Considering the nutritional impact, a calorie restricted ketogenic diet not only reduces the blood glucose levels but also promotes the sirt3 activity (Hirschey et al., 2011 ; Shimazu et al., 2010).

VI.Biomarkers of neuroinflammation in AD with respect to diet

Peripheral inflammatory mediators which reflect neuroinflammation are proposed as biomarker candidates, since they are associated with the pathogenesis of AD. Both APP and amyloid beta increased the production of cytokines and chemokines from microglia, neurons and astrocytes which in turn activates the amyloid accumulation (Solfrizzi et al., 2006). One of the well studied proinflammatory cytokines, is the IL-1 has been associated with ptau and with deposition of AB through the MAPK-P38 activation (Sheng et al., 2001). IL-1B is released due to mitochondrial dysfunction causing the cell death (Ramesh et al 2018). Other key mediators of the inflammation process is the tumor necrosis factor (TNF-a), IL-10, IL-12 (Baird et al., 2015; Leung et al., 2013) and the acute reactant protein c -CRP- (O'Bryant et al., 2011; Cheng et al., 2018; Kravitz et al., 2009; Ferrucci et al., 2006).

The n-3 fatty acids through the consumption of fatty fish (James et al., 2000) together with the polyphenols quercetin (Zhang et al., 2011), rutin, catechin, sesamol (Ren et al., 2018) and lycopene (Palozza et al., 2011) all have anti-inflammatory properties. In a practical manner, a diet rich in fruits and vegetables such as apple, red kidney bean, radish, onion, tomatoes, carrots and sesame oil might be considered as a novel anti-inflammatory therapy. Moreover, intake of both dietary fibres and probiotics through the consumption of fermented diary products, may suppress the CRP presentation (Akbari et al., 2016). Under other circumastances, dietary advanced glycation end products (d-AGEs), are key mediators of increased oxidant stress and inflammation by enhancing the activity of CRP.

VII.Other proteomic biomarkers for AD related to diet

Using a quantitative iTRAQ proteomics approach it has been discovered that the pancreatic peptide, known as amylin may cause reduction in mitochondrial respiration and mitochondrial complex IV activity, causing an overal mitochondrial dysfunction (Lim et al., 2010) and in addition, it has the capacity to misfold and aggregate under specific circumstances (Mietlicki-Baase, 2018). Therefore, the main target is to deactivate this peptide through diet in order to preserve mitochondrial function.Micronutrients such as folic acid and the polyphenols quercetin, rutin & oleuropein aglycon (in extra virgin olive oil) have the ability to inhibit the presentation of amylin (Aitken et al., 2017).

Other AD associated proteins, verified as biomarkers, included adiponectin (Teixeira et al., 2013), neuroprotectinD (NPD1) (Bazan et al., 2009), neurogenin2 (NGN2) (Ashton et al., 2019), peroxisome proliferator-activated receptor-γ coactivator (PGC-1α) (Sweeney et al., 2016), choline acytyltransferase (CHAT) (Greco et al., 2012), nuclear factor E2-related factor 2 (Nrf2) transcription factor (Bahn & Jo, 2019), brain-derived neurotrophic factor (BDNF) (Cheng et al., 2018) and transthyretin (TTR) (Velayudhan et al., 2012) all showing lower or insufficient levels in AD compared to controls.

Other the other hand, overexpression of the plasma neurofilament light (NFL) (Ashton et al., 2019), peptidyl-prolyl cis–trans isomerase (pin1) (Pastorino et al., 2006), 3-nitrotyrosine (3-NT) (Swomley et al., 2014), glycogen synthase kinase-3 (GSK3B) (King et al., 2014), carcinoembryonic antigen (CEA) (Martins et al., 2018), brain natruiretic peptide (Llano et al., 2013), homocysteine (Doecke et al., 2012), are detectable in AD subjects.

A low calorie/low - carbohydrate diet may be involved in the regulation of adiponectin levels (Martins et al., 2014) and dietary intake of DHA (Heras-Sandoval et al., 2016) EPA and AA (Irizarry, 2004) increase the neuroprotectinD (NPD1) and the neurogenin2 presentation (Katakura et al., 2009). Furthermore, choosing food items rich in resveratrol such as grapes, berries, cocoa, peanuts (Kim et al., 2007), and foods rich in quercetin such as apples, onions, cherries, citrus fruits, broccoli, green tea (Davis et al., 2009) combined with and a daily consumption of olives & extra virgin olive oil rich in hydroxytyrosol may contribute to restore the plasma level of peroxisome proliferator-activated receptor-γ coactivator (PGC-1α) and thus regulate mitochondrial biogenesis (Zhu et al., 2010). Dietary choline found abundant in whole eggs, meat, fish and whole grains (Marriott, 1994) together with medium chain triglyceride (MCT) and fatty acids considered as activators of choline acytyltransferase via the acetyl coenzyme activity (Reger et al., 2004).

The restoration of the Nrf2 transcription factor in the blood of AD subjects can be achieved through sufficient intake of specific nutrients and phenolic compounds such as carnosinic acid which is highly found in rosemary *(Rosmarinus officinalis)* (Satoh et al., 2008), cinnamon (Momtaz et al., 2018), hesperidin (a citus bioflavonoid), resveratrol, lycopene, glucosinolates (brassica vegetables) (Angeloni et al., 2016), n-3 fatty acids (fatty fish, flaxseeds) (Zhang et al., 2014), pterostilbene (blueberries) (Saw et al., 2014). Additionaly, several studies highlightened a beneficial role of olive oil via hydroxytyrosol oleuropein oleacein (Martinez-Huelamo et al., 2017), sesame oil (Ren et al., 2018) and butyrate (butter) coupled with β-hydroxybutyrate (Cavaleri et al., 2018).

Caloric restriction and intermittent fasting have been proposed as a lifestyle way to slow down the progression of Alzheimer's disease by increasing the circulating BDNF levels promoting neuronal survival, neurogenesis and synaptic plasticity (Baik et al., 2020). Dietary intake of lycopene and carotenoids-rich foods (Elango & Asmathulla, 2017), palmitoylethanolamide (PEA) in egg yolk, peanut oil, bovine milk, legumes, corn, tomatoes with luteolin found in celery, chamomile, olive oil, carrots, spinach, oregano, rosemary elevate the expression and the activity of BDNF (Paterniti et al., 2014). Vitamin D (Gezen-Ak et al., 2014), grape seed polyphenol extract (GSPE), and concord grape juice (CGJ) showed similar properties (Jiang et al., 2019). Blood concentration of TTR are declined by AGEs (Salahuddi et al., 2014), while curcumin modulates TTR abnormal aggregation (Ferreira et al., 2019).

A diet regimen supplemented with n-3 fatty acids and particularly with DHA, has the potential to downregulate the increased blood levels of plasma neurofilament light (NFL)(Oliver et al 2016).Moreover, tannic acid (herbal teas), caffeic acid (cereals, fruitsseeds, herbs, spices), epigallocatechin gallate (EGCG) are well-known neuroprotective compounds that inhibit the overexpression of peptidyl-prolyl cis–trans isomerase (pin1) in AD (Hidaka et al., 2018).

The excessive presentation of 3-nitrotyrosine (3-NT) is further increased by the presence of acrylamide in the foods, the alcohol (Szumska et al., 2012) and the iron consumption in the diet (Bian et al., 2003). Interestingly, the flavonoids rosmarinic acid (Paudel et al., 2018) and resveratrol (Simão et al., 2012) reduce the activity of the biomarker glycogen synthase kinase-3 (GSK3B). Regarding the hyperhomocysteinemia, vitamin B_{12}, B_6 and methyltetrahydrofolate can optimize the high blood levels (Tanaka et al., 2009). Finally, dietary salt intake(Lang et al., 1991) and alcohol consumption (Sun et al., 2016) further increase the activity of the brain natruiretic peptide and the carcinoembryonic antigen (CEA) biomarker respectively.

Conclusion

The effect of nutrients and dietary regimens on the blood based biomarkers using the proteomic data analysis technology generates promising results for the prevention and the treatment of AD. Personalised nutritional interventions could be a promising tool for the delay of the AD progression. A low carbohydrate diet with an optimal dietary intake of n-3 fatty acids, MCT, polyphenols (resveratol, quercetin, rosmarinic acid, carnosinic acid, epigallocatechin gallate) and extra virgin olive oil exert neuroprotective action through activation or inactivation of serum/plasma biomarkers of AD and MCI patients. However, further clinical studies are needed to be conducted taking into account the metabolomic area for the achievement of better outcomes in Alzheimer's disease tharapy.

References

Aitken, J. F., Loomes, K. M., Riba-Garcia, I., Unwin, R. D., Prijic, G., Phillips, A. S., ... & Barran, P. E. (2017). Rutin suppresses human-amylin/hIAPP misfolding and oligomer formation in-vitro, and ameliorates diabetes and its impacts in human-amylin/hIAPP transgenic mice. *Biochemical and biophysical research communications*, *482*(4), 625-631.

Akbari, E., Asemi, Z., Daneshvar Kakhaki, R., Bahmani, F., Kouchaki, E., Tamtaji, O. R., ... & Salami, M. (2016). Effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: a randomized, double-blind and controlled trial. *Frontiers in aging neuroscience*, *8*, 256.

Angeloni, C., Hrelia, S., & Malaguti, M. (2016). Neuroprotective effects of Glucosinolates. *Glucosinolates*, 1-25.

Ashton, N. J., Nevado-Holgado, A. J., Barber, I. S., Lynham, S., Gupta, V., Chatterjee, P., ... & Schöll, M. (2019). A plasma protein classifier for predicting amyloid burden for preclinical Alzheimer's disease. *Science advances*, *5*(2), eaau7220.

Bahn, G., & Jo, D. G. (2019). Therapeutic approaches to Alzheimer's disease through modulation of NRF2. *Neuromolecular medicine*, *21*(1), 1-11.

Baik, S. H., Rajeev, V., Fann, D. Y. W., Jo, D. G., & Arumugam, T. V. (2020). Intermittent fasting increases adult hippocampal neurogenesis. Brain and Behavior, 10(1), e01444.

Baird, A. L., Westwood, S., & Lovestone, S. (2015). Blood-based proteomic biomarkers of Alzheimer's disease pathology. *Frontiers in neurology*, *6*, 236.

Bazan, N. G. (2009). Neuroprotectin D1-mediated anti-inflammatory and survival signaling in stroke, retinal degenerations, and Alzheimer's disease. Journal of lipid research, 50(Supplement), S400-S405.

Bhatia, S., Kim, W. S., Shepherd, C. E., & Halliday, G. M. (2019). Apolipoprotein D Upregulation in Alzheimer's Disease but Not Frontotemporal Dementia. *Journal of Molecular Neuroscience*, *67*(1), 125-132.

Bian, K., Gao, Z., Weisbrodt, N., & Murad, F. (2003). The nature of heme/iron-induced protein tyrosine nitration. *Proceedings of the National Academy of Sciences*, *100*(10), 5712-5717.

Cavaleri, F., & Bashar, E. (2018). Potential synergies of β-hydroxybutyrate and butyrate on the modulation of metabolism, inflammation, cognition, and general health. *Journal of nutrition and metabolism*, *2018*.

Chakraborty, S., & Basu, S. (2017). Multi-functional activities of citrus flavonoid narirutin in Alzheimer's disease therapeutics: An integrated screening approach and in vitro validation. *International journal of biological macromolecules*, *103*, 733-743.

Cheng, Z., Yin, J., Yuan, H., Jin, C., Zhang, F., Wang, Z., ... & Xiao, S. (2018). Blood-derived plasma protein biomarkers for Alzheimer's disease in Han Chinese. *Frontiers in aging neuroscience*, *10*.

Cremonini, A. L., Caffa, I., Cea, M., Nencioni, A., Odetti, P., & Monacelli, F. (2019). Nutrients in the Prevention of Alzheimer's Disease. Oxidative medicine and cellular longevity, 2019.

Davis, J. M., Murphy, E. A., Carmichael, M. D., & Davis, B. (2009). Quercetin increases brain and muscle mitochondrial biogenesis and exercise tolerance. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *296*(4), R1071-R1077.

Decourt, B., & Sabbagh, M. N. (2011). BACE1 as a potential biomarker for Alzheimer's disease. *Journal of Alzheimer's Disease*, *24*(s2), 53-59.

Doecke, J. D., Laws, S. M., Faux, N. G., Wilson, W., Burnham, S. C., Lam, C. P., ... & De Ruyck, K. (2012). Blood-based protein biomarkers for diagnosis of Alzheimer disease. *Archives of neurology*, *69*(10), 1318-1325.

Du, X., Li, H., Wang, Z., Qiu, S., Liu, Q., & Ni, J. (2013). Selenoprotein P and selenoprotein M block Zn 2+-mediated Aβ 42 aggregation and toxicity. *Metallomics*, *5*(7), 861-870.

Elango, P., & Asmathulla, S. (2017). A Systematic Review on Lycopene and its Beneficial Effects". *Biomedical and Pharmacology Journal*, *10*(4), 2113-2120.

Ferreira, N., Saraiva, M. J., & Almeida, M. R. (2019). Uncovering the Neuroprotective Mechanisms of Curcumin on Transthyretin Amyloidosis. *International journal of molecular sciences*, *20*(6), 1287.

Ferrucci, L., Cherubini, A., Bandinelli, S., Bartali, B., Corsi, A., Lauretani, F., ... & Guralnik, J. M. (2006). Relationship of plasma polyunsaturated fatty acids to circulating inflammatory markers. *The Journal of Clinical Endocrinology & Metabolism*, *91*(2), 439-446.

Gezen-Ak, D., Yılmazer, S., & Dursun, E. (2014). Why vitamin D in Alzheimer's disease? The hypothesis. *Journal of Alzheimer's Disease*, *40*(2), 257-269.

Greco, I., Day, N., Riddoch-Contreras, J., Reed, J., Soininen, H., Kłoszewska, I., ... & Wahlund, L. O. (2012). Alzheimer's disease biomarker discovery using in silico literature mining and clinical validation. Journal of translational medicine, 10(1), 217.

Gupta, V. B., Doecke, J. D., Hone, E., Pedrini, S., Laws, S. M., Thambisetty, M., ... & Masters, C. L. (2016). Plasma apolipoprotein J as a potential biomarker for Alzheimer's disease: Australian Imaging, Biomarkers and Lifestyle study of aging. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, *3*, 18-26.

Han, S. H., Kim, J. S., Lee, Y., Choi, H., Kim, J. W., Na, D. L., ... & Mook-Jung, I. (2014). Both targeted mass spectrometry and flow sorting analysis methods detected the decreased serum apolipoprotein E level in Alzheimer's disease patients. *Molecular & Cellular Proteomics*, *13*(2), 407-419.

Heras-Sandoval, D., Pedraza-Chaverri, J., & Pérez-Rojas, J. M. (2016). Role of docosahexaenoic acid in the modulation of glial cells in Alzheimer's disease. *Journal of neuroinflammation*, *13*(1), 61.

Hidaka, M., Kosaka, K., Tsushima, S., Uchida, C., Takahashi, K., Takahashi, N., ... & Uchida, T. (2018). Food polyphenols targeting peptidyl prolyl cis/trans isomerase pin1. *Biochemical and biophysical research communications*, *499*(3), 681-687.

Hirschey, M. D., Shimazu, T., Huang, J. Y., Schwer, B., & Verdin, E. (2011, January). SIRT3 regulates mitochondrial protein acetylation and intermediary metabolism. In *Cold Spring Harbor symposia on quantitative biology* (Vol. 76, pp. 267-277). Cold Spring Harbor Laboratory Press.

Irizarry, M. C. (2004). Biomarkers of Alzheimer disease in plasma. *NeuroRx*, *1*(2), 226-234.

James, M. J., Gibson, R. A., & Cleland, L. G. (2000). Dietary polyunsaturated fatty acids and inflammatory mediator production. *The American journal of clinical nutrition*, *71*(1), 343s-348s.

Jiang, C., Sakakibara, E., Lin, W. J., Wang, J., Pasinetti, G. M., & Salton, S. R. (2019). Grape-derived polyphenols produce antidepressant effects via VGF-and BDNF-dependent mechanisms. Annals of the New York Academy of Sciences, 1455(1), 196.

Katakura, M., Hashimoto, M., Shahdat, H. M., Gamoh, S., Okui, T., Matsuzaki, K., & Shido, O. (2009). Docosahexaenoic acid promotes neuronal differentiation by regulating basic helix–loop–helix transcription factors and cell cycle in neural stem cells. *Neuroscience*, *160*(3), 651-660.

Katayama, S., Sugiyama, H., Kushimoto, S., Uchiyama, Y., Hirano, M., & Nakamura, S. (2016). Effects of sesaminol feeding on brain Aβ accumulation in a senescence-accelerated mouse-prone 8. *Journal of agricultural and food chemistry*, *64*(24), 4908-4913.

Kim, D., Nguyen, M. D., Dobbin, M. M., Fischer, A., Sananbenesi, F., Rodgers, J. T., ... & Puigserver, P. (2007). SIRT1 deacetylase protects against neurodegeneration in models for Alzheimer's disease and amyotrophic lateral sclerosis. *The EMBO journal*, *26*(13), 3169-3179.

King, M. K., Pardo, M., Cheng, Y., Downey, K., Jope, R. S., & Beurel, E. (2014). Glycogen synthase kinase-3 inhibitors: rescuers of cognitive impairments. *Pharmacology & therapeutics*, *141*(1), 1-12.

Ko, S. Y., Ko, H. A., Chu, K. H., Shieh, T. M., Chi, T. C., Chen, H. I., ... & Chang, S. S. (2015). The possible mechanism of advanced glycation end products (AGEs) for Alzheimer's disease. PLoS One, 10(11), e0143345.

Kravitz, B. A., Corrada, M. M., & Kawas, C. H. (2009). Elevated C-reactive protein levels are associated with prevalent dementia in the oldest-old. *Alzheimer's & Dementia*, *5*(4), 318-323.

Kumar, R., Chaterjee, P., Sharma, P. K., Singh, A. K., Gupta, A., Gill, K., ... & Dey, S. (2013). Sirtuin1: a promising serum protein marker for early detection of Alzheimer's disease. *PloS one*, *8*(4), e61560.

Lang, C. C., Coutie, W. J., Khong, T. K., Choy, A. M., & Struthers, A. D. (1991). Dietary sodium loading increases plasma brain natriuretic peptide levels in man. *Journal of hypertension*, *9*(9), 779-782.

Leung, R., Proitsi, P., Simmons, A., Lunnon, K., Güntert, A., Kronenberg, D., ... & Vellas, B. (2013). Inflammatory proteins in plasma are associated with severity of Alzheimer's disease. *PloS one*, *8*(6), e64971.

Lim, Y. A., Rhein, V., Baysang, G., Meier, F., Poljak, A., J. Raftery, M., ... & Götz, J. (2010). Abeta and human amylin share a common toxicity pathway via mitochondrial dysfunction. *Proteomics*, *10*(8), 1621-1633.

Llano, D. A., Devanarayan, V., Simon, A. J., & Alzheimer's Disease Neuroimaging Initiative (ADNI. (2013). Evaluation of plasma proteomic data for Alzheimer disease state classification and for the prediction of progression from mild cognitive impairment to Alzheimer disease. *Alzheimer Disease & Associated Disorders*, *27*(3), 233-243.

Löffler, T., Flunkert, S., Havas, D., Sántha, M., Hutter-Paier, B., Steyrer, E., & Windisch, M. (2013). Impact of ApoB-100 expression on cognition and brain pathology in wild-type and hAPPsl mice. Neurobiology of aging, 34(10), 2379-2388.

Lukiw, W. J., Cui, J. G., Marcheselli, V. L., Bodker, M., Botkjaer, A., Gotlinger, K., ... & Bazan, N. G. (2005). A role for docosahexaenoic acid–derived neuroprotectin D1 in neural cell survival and Alzheimer disease. *The Journal of clinical investigation*, *115*(10), 2774-2783.

Marriott, B. M. (1994). Choline: Human Requirements and Effects on Human Performance. In *Food Components to Enhance Performance: An Evaluation of Potential Performance-Enhancing Food Components for Operational Rations*. National Academies Press (US).

Martinez-Huelamo, M., Rodriguez-Morato, J., Boronat, A., & De la Torre, R. (2017). Modulation of Nrf2 by olive oil and wine polyphenols and neuroprotection. *Antioxidants*, *6*(4), 73.

Martins, I. J. (2014). The global obesity epidemic is related to stroke, dementia and Alzheimer's disease.

Martins, I. J., & Fernando, W. M. (2014). High fibre diets and Alzheimer's disease.

Martins, R. N., Villemagne, V., Sohrabi, H. R., Chatterjee, P., Shah, T. M., Verdile, G., ... & Hone, E. (2018). Alzheimer’s disease: a journey from amyloid peptides and oxidative stress, to biomarker technologies and disease prevention strategies—gains from AIBL and DIAN cohort studies. *Journal of Alzheimer's Disease*, *62*(3), 965-992.

Mietlicki-Baase, E. G. (2018). Amylin in Alzheimer's disease: Pathological peptide or potential treatment?. Neuropharmacology, 136, 287-297.

Mitmesser, S. H., & Carr, T. P. (2005). Trans fatty acids alter the lipid composition and size of apoB-100-containing lipoproteins secreted by HepG2 cells. The Journal of nutritional biochemistry, 16(3), 178-183.

Momtaz, S., Hassani, S., Khan, F., Ziaee, M., & Abdollahi, M. (2018). Cinnamon, a promising prospect towards Alzheimer’s disease. *Pharmacological research*, *130*, 241-258.

Nakagawa, T., Yokozawa, T., Terasawa, K., Shu, S., & Juneja, L. R. (2002). Protective activity of green tea against free radical-and glucose-mediated protein damage. *Journal of agricultural and food chemistry*, *50*(8), 2418-2422.

O’Bryant, S. E., Xiao, G., Barber, R., Reisch, J., Hall, J., Cullum, C. M., ... & Diaz-Arrastia, R. (2011). A blood-based algorithm for the detection of Alzheimer’s disease. *Dementia and geriatric cognitive disorders*, *32*(1), 55-62.

Oliver, J. M., Jones, M. T., Kirk, K. M., Gable, D. A., Repshas, J. T., Johnson, T. A., ... & Zetterberg, H. (2016). Effect of docosahexaenoic acid on a biomarker of head trauma in American football. *Medicine & Science in Sports & Exercise*, *48*(6), 974-982.

Ouyang, Q. Q., Zhao, S., Li, S. D., & Song, C. (2017). Application of chitosan, chitooligosaccharide, and their derivatives in the treatment of Alzheimer’s disease. *Marine drugs*, *15*(11), 322.

Palozza, P., Simone, R., Catalano, A., Monego, G., Barini, A., Mele, M. C., ... & Ranelletti, F. O. (2011). Lycopene prevention of oxysterol-induced proinflammatory cytokine cascade in human macrophages: inhibition of NF-κB nuclear binding and increase in PPARγ expression. *The Journal of nutritional biochemistry*, *22*(3), 259-268.

Pastorino, L., Sun, A., Lu, P. J., Zhou, X. Z., Balastik, M., Finn, G., ... & Xia, W. (2006). The prolyl isomerase Pin1 regulates amyloid precursor protein processing and amyloid-β production. *Nature*, *440*(7083), 528.

Paudel, P., Seong, S., Zhou, Y., Park, C., Yokozawa, T., Jung, H., & Choi, J. (2018). Rosmarinic acid derivatives’ inhibition of glycogen synthase kinase-3β is the pharmacological basis of Kangen-Karyu in Alzheimer’s disease. *Molecules*, *23*(11), 2919.

Prasad, C., Davis, K. E., Imrhan, V., Juma, S., & Vijayagopal, P. (2019). Advanced glycation end products and risks for chronic diseases: intervening through lifestyle modification. American Journal of Lifestyle Medicine, 13(4), 384-404.

Ramesh, S., Govindarajulu, M., Jones, E., Knowlton, S., Weeks, L., Suppiramaniam, V.& Dhanasekaran, M. (2018). Current and Novel Biomarkers for Alzheimer’s disease.

Reger, M. A., Henderson, S. T., Hale, C., Cholerton, B., Baker, L. D., Watson, G. S., ... & Craft, S. (2004). Effects of β-hydroxybutyrate on cognition in memory-impaired adults. *Neurobiology of aging*, *25*(3), 311-314

Ren, B., Yuan, T., Diao, Z., Zhang, C., Liu, Z., & Liu, X. (2018). Protective effects of sesamol on systemic oxidative stress-induced cognitive impairments via regulation of Nrf2/Keap1 pathway. *Food & function*, *9*(11), 5912-5924.

Salahuddin, P., Rabbani, G., & Khan, R. H. (2014). The role of advanced glycation end products in various types of neurodegenerative disease: a therapeutic approach. Cellular & molecular biology letters, 19(3), 407-437.

Samarghandian, S., Azimi-Nezhad, M., & Samini, F. (2014). Ameliorative effect of saffron aqueous extract on hyperglycemia, hyperlipidemia, and oxidative stress on diabetic encephalopathy in streptozotocin induced experimental diabetes mellitus. *BioMed research international*, *2014*

Sasaki, N., Fukatsu, R., Tsuzuki, K., Hayashi, Y., Yoshida, T., Fujii, N., ... & Amano, N. (1998). Advanced glycation end products in Alzheimer's disease and other neurodegenerative diseases. *The American journal of pathology*, *153*(4), 1149-1155.

Satoh, T., Kosaka, K., Itoh, K., Kobayashi, A., Yamamoto, M., Shimojo, Y., ... & Izumi, M. (2008). Carnosic acid, a catechol‐ type electrophilic compound, protects neurons both in vitro and in vivo through activation of the Keap1/Nrf2 pathway via S‐ alkylation of targeted cysteines on Keap1. *Journal of neurochemistry*, *104*(4), 1116-1131.

Sheng, J. G., Jones, R. A., Zhou, X. Q., McGinness, J. M., Van Eldik, L. J., Mrak, R. E., & Griffin, W. S. T. (2001). Interleukin-1 promotion of MAPK-p38 overexpression in experimental animals and in Alzheimer's disease: potential significance for tau protein phosphorylation. Neurochemistry international, 39(5-6), 341-348.

Shimazu, T., Hirschey, M. D., Hua, L., Dittenhafer-Reed, K. E., Schwer, B., Lombard, D. B., ... & Jacobson, M. P. (2010). SIRT3 deacetylates mitochondrial 3-hydroxy-3-methylglutaryl CoA synthase 2 and regulates ketone body production. *Cell metabolism*, *12*(6), 654-661.

Simão, F., Matté, A., Pagnussat, A. S., Netto, C. A., & Salbego, C. G. (2012). Resveratrol prevents CA1 neurons against ischemic injury by parallel modulation of both GSK-3β and CREB through PI3-K/Akt pathways. European Journal of Neuroscience, 36(7), 2899-2905.

Solfrizzi, V., D'Introno, A., Colacicco, A. M., Capurso, C., Todarello, O., Pellicani, V., ... & Panza, F. (2006). Circulating biomarkers of cognitive decline and dementia. Clinica Chimica Acta, 364(1-2), 91-112

Sun, L., MingjieXu, M., Wang, L., Wang, Y., & Wang, Y. (2016). Increase of carcinoembryonic antigen level in serum is associated with metabolic factors and lifestyle. *International Journal of New Technology and Research*, *2*(4).

Sweeney, G., & Song, J. (2016). The association between PGC-1α and Alzheimer's disease. *Anatomy & cell biology*, *49*(1), 1-6.

Swomley, A. M., Förster, S., Keeney, J. T., Triplett, J., Zhang, Z., Sultana, R., & Butterfield, D. A. (2014). Abeta, oxidative stress in Alzheimer disease: evidence based on proteomics studies. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, *1842*(8), 1248-1257.

Szegő, É. M., Outeiro, T. F., & Kazantsev, A. G. (2018). Sirtuins in brain and neurodegenerative disease. In Introductory Review on Sirtuins in Biology, Aging, and Disease (pp. 175-195). Academic Press.

Szumska, M., Wielkoszyński, T., & Tyrpień, K. (2012). 3-nitrotyrosine determination as nitrosative stress marker and health attitudes of medical students considering exposure to environmental tobacco smoke. *Przeglad lekarski*, *69*(10), 798-802.

Tanaka, T., Scheet, P., Giusti, B., Bandinelli, S., Piras, M. G., Usala, G., ... & Sofi, F. (2009). Genome-wide association study of vitamin B6, vitamin B12, folate, and homocysteine blood concentrations. The American Journal of Human Genetics, 84(4), 477-482.

Teixeira, A. L., Diniz, B. S., Campos, A. C., Miranda, A. S., Rocha, N. P., Talib, L. L., ... & Forlenza, O. V. (2013). Decreased levels of circulating adiponectin in mild cognitive impairment and Alzheimer's disease. *Neuromolecular medicine*, *15*(1), 115-121.

Thambisetty, M., Simmons, A., Velayudhan, L., Hye, A., Campbell, J., Zhang, Y., ... & Proitsi, P. (2010). Association of plasma clusterin concentration with severity, pathology, and progression in Alzheimer disease. *Archives of general psychiatry*, *67*(7), 739-748.

Vassallo, N. (Ed.). (2015). Natural compounds as therapeutic agents for amyloidogenic diseases (Vol. 863). Springer.

Velayudhan, L., Killick, R., Hye, A., Kinsey, A., Güntert, A., Lynham, S., ... & Powell, J. (2012). Plasma transthyretin as a candidate marker for Alzheimer's disease. *Journal of Alzheimer's Disease*, *28*(2), 369-375.

Włodarek, D. (2019). Role of ketogenic diets in neurodegenerative diseases (Alzheimer's disease and Parkinson's disease). Nutrients, 11(1), 169.

Yang, W., van de Ven, R. A., & Haigis, M. C. (2018). Mitochondrial Sirtuins: Coordinating Stress Responses Through Regulation of Mitochondrial Enzyme Networks. In Introductory Review on Sirtuins in Biology, Aging, and Disease (pp. 95-115). Academic Press.

Zhang, H., Ma, Q., Zhang, Y. W., & Xu, H. (2012). Proteolytic processing of Alzheimer's β-amyloid precursor protein. Journal of Neurochemistry: REVIEW, 120, 9-21.

Zhang, M., Wang, S., Mao, L., Leak, R. K., Shi, Y., Zhang, W., ... & Xu, Y. (2014). Omega-3 fatty acids protect the brain against ischemic injury by activating Nrf2 and upregulating heme oxygenase 1. *Journal of Neuroscience*, *34*(5), 1903-1915.

Zhang, Z. J., Cheang, L. C. V., Wang, M. W., & Lee, S. M. Y. (2011). Quercetin exerts a neuroprotective effect through inhibition of the iNOS/NO system and pro-inflammation gene expression in PC12 cells and in zebrafish. *International journal of molecular medicine*, *27*(2), 195-203.

Zhu, L., Liu, Z., Feng, Z., Hao, J., Shen, W., Li, X., ... & Weber, P. (2010). Hydroxytyrosol protects against oxidative damage by simultaneous activation of mitochondrial biogenesis and phase II detoxifying enzyme systems in retinal pigment epithelial cells. *The Journal of nutritional biochemistry*, *21*(11), 1089-1098.