Contents lists available at Science-Gate

International Journal of Advanced and Applied Sciences

Journal homepage: http://www.science-gate.com/IJAAS.html

Effects of coconut oil on Alzheimer disease

Tahani Ahmad Al-Matrafi *

Department of Anatomy, College of Medicine, King Saud University, Riyadh, Saudi Arabia

ARTICLE INFO

Article history:
Received 19 November 2020
Received in revised form
31 January 2021
Accepted 6 February 2021

Keywords:
Alzheimer's disease
Neurofibrillary tangles
Amyloid cascade hypothesis
Medium-chain triglycerides
Young coconut juice
Virgin coconut oil

ABSTRACT

Dementia is a general term for loss of memory, language, problem-solving, and other thinking abilities that are severe enough to interfere with daily life. Alzheimer's disease (AD) is the most common cause of dementia. Risk factors as age, genetics, environment, lifestyle, and metabolic disease. The etiology of AD remains not fully explained, but both genetic and environmental risk factors have been proposed to be involved. Microscopically, intraneuronal neurofibrillary tangles (NFTs) and extracellular senile plaques characterize the AD. The amyloid cascade hypothesis (ACH) suggests that the imbalance between the Amyloid-β generation and its clearance causes dysfunction and consequently cell death. Coconut oil may represent a cheap and natural treatment for AD. This is because coconut oil contains medium-chain triglycerides (MCTs), which are digested to ketones in the liver that are linked to mitochondrial function enhancement and oxidation-reduction. Recent studies have investigated the possibility of using trans-zeatin and phytoestrogen and other sex hormones like substances present in coconut water and a young coconut juice (YCJ) in reducing the chance of AD. Coconut is known as a 'functional food' that is extremely nutritious. Virgin coconut oil (VCO) differs from ordinary coconut oil as the former contains a lot more biologically active components. Phenolic compounds and hormones contained in coconut can help prevent amyloid b peptide aggregation, potentially inhibiting a key step in the pathogenesis of AD. Coconut can be useful in the treatment of obesity, dyslipidemia, elevated low-density lipoproteins, insulin resistance, and hypertension-these are the risk factors for chronic venous disease and type II diabetes, as well as for AD.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder related to the increase of age and it is the main cause of dementia in the world. AD affects cognitive functions, such as memory, with an intensity that leads to several functional losses (Solomon et al., 2014; Kumar and Singh, 2015).

It is estimated that the worldwide prevalence of AD will triple by 2050 (Langa, 2015). The World Alzheimer Report 2015 revealed that 46.8 million people worldwide were living with dementia in 2015, and the total global societal cost of dementia was estimated to be the US $818 billion. Alzheimer's disease AD is the most common dementia type and may account for 60–70% of dementia cases (Prince, 2015). AD is an extremely debilitating condition currently falling within the top 10 causes of death across the world. This causes a severe fiscal burden on health services since AD is an extremely financially costly neurological disease to manage (Nichols et al., 2019). Epidemiologic studies have been documented that women comprise two-thirds of people living with AD, regardless of age and ethnicity (Alzheimer's Association, 2016). The number of factors may increase or decrease an individual's chances of developing the disease. These risk factors include age, genetics, environment, lifestyle, and metabolic diseases (Fernando et al., 2015).

The etiology of AD remains not fully explained, but both genetic and environmental risk factors have been proposed to be involved. Thus, the etiopathogenesis of AD has been linked to hypometabolism (Kashiwaya et al., 2013), mitochondrial dysfunction (Johri and Beal, 2012; Rusek et al., 2019), inflammation (Takahashi et al., 2017; Rusek et al., 2019), and oxidative stress (Pinto et al., 2018).

* Corresponding Author.
Email Address: talmatrafi@ksu.edu.sa
https://doi.org/10.21833/ijaas.2021.05.013
Corresponding author's ORCID profile:
https://orcid.org/0000-0001-8098-2398

2. Neuropathology of AD

The gradual accumulation of the pathology of cerebral extracellular AD known as amyloid, which is mostly composed of aggregated amyloid-b (Ab) peptides, as well as the accumulation of intracellular neurofibrillary tangles, appears to start up to 17–20 years before a clinically observable disease (Villain et al., 2012).

Microscopically, intraneuronal neurofibrillary tangles (NFTs) and extracellular senile plaques (or amyloid plaques) characterize the AD. While senile plaques are constituted by extracellular deposits of β-amyloid (Aβ) peptide, the hyperphosphorylation and abnormal deposition of tau protein compose the NFTs (Selkoe and Hardy, 2016). Aβ derives from abnormal proteolysis of a larger protein called amyloid precursor protein (APP), an integral membrane protein that possesses the general properties of a cell surface receptor (Dawkins and Small, 2014), which passes through the neuronal membrane and gets accumulated outside the neurons, by the consecutive action of β- and γ-secretases (amyloidogenic pathway). However, this amyloidogenic pathway can be stopped by the competition of α-secretase with γ-secretase (non-amyloidogenic pathway) (Zhang et al., 2015). The amyloid cascade hypothesis (ACH) suggests that the imbalance between the Aβ generation and its clearance causes dysfunction and consequently cell death. Aβ polymerizes in a variety of structurally different forms including oligomeric, protofibrillar, and fibrils, forming the senile plaques (Mohamed et al., 2016). Several findings suggest that oligomers play an important role in the ACH (Sengupta et al., 2016). Nowadays, it is proved that Aβ oligomers, including protofibrils and prefibrils, are more toxic than fibrils (Verma et al., 2015). Tauopathy—characterized by hyperphosphorylated, filamentous tau aggregates prior to microtubule collapse—a major requisite for the formation of neurofibrillary tangles NFTs (Guo et al., 2016; Nilson et al., 2017). NFTs accumulate inside the neurons, resulting in their death. The ACH suggests that toxic concentrations of Aβ cause changes in tau protein and subsequent formation of NFTs, leading to synaptic and neuronal loss (Barage and Sonawane, 2015). Though a direct relationship between the degree of AD and the amount of Aβ aggregates and tau levels have been established, numerous other mechanisms of neurodegeneration have been suggested, such as neuroinflammation (Heneka et al., 2015), oxidative stress (Huang et al., 2016), genetic (Karch et al., 2014) and environmental factors (Chin-Chan et al., 2015).

Molecular imaging studies such as those using amyloid positron emission tomography (PET) have shown that Aβ deposition reaches a plateau before brain atrophy can be identified from structural magnetic resonance imaging (MRI) and cognitive symptom. However, recent case series showing AD-diagnosed patients lacking Aβ deposits challenge the generalizability of the criteria, as well as the role of protein aggregates in the development and progression of AD (Crary, 2016). Nonetheless, the combined presence of Aβ aggregates, neurofibrillary tangles, which are associated with progressive dementia and neurodegeneration, is the most widely accepted view (Hardy and Selkoe, 2002; Crary, 2016). Another essential finding is brain atrophy, particularly in the hippocampus. In addition, a recent study by Laurent et al. (2017) showed that T-cells from the hippocampus mediate the inflammation process and promote cognitive decline (Laurent et al., 2017).

Antioxidants are substances of natural and synthetic origin that have a high potential to scavenge free radicals (Tepe et al., 2005). The development of AD has been linked to oxidative stress, and studies have suggested that antioxidant-rich natural diets may protect against AD. Although studies on the benefits for AD have not been conclusive (Park and Kim, 2002; Necula et al., 2007), many suggest that combinations of (rather than individual) antioxidants are beneficial (Shah, 2013).

Based on these mechanisms, different therapeutic molecules can act through different pathways (Loureiro et al., 2014; Karch and Goate, 2015). Nowadays, the study of these natural compounds revealed that they present neuroprotective effects, arousing an increasing interest in the scientific community and in the pharmaceutical industry (Dey et al., 2017; David et al., 2015). There have been many works on Virgin coconut oil (VCO) and its potential to salvage neurons from amyloid-induced degeneration, reduce inflammation, and provide ketone bodies for therapeutic effects and increased cognitive function (Nafar and Mearow, 2014). Since 2000, it has become increasingly evident that biophenols, plant phenolic compounds containing foods received extreme attention due to their vast occurrence and versatile actions including several cellular functions modulation, processes that go well beyond their first-described natural antioxidant capacities, and neuroprotection (Silva and Pogačnik, 2017). Vegetables, fruit, nuts, chocolate, and other types of foods and beverages, such as wine, coffee, and tea, are all rich sources of biophenols.

3. Origin of virgin coconut oil

The Scientific name for Coconut is Cocos nucifera and the plant is a member of Arecaceae (Janick and Paull, 2008) that is cultivated to provide a large number of products, although it is mainly grown for its nutritional and medicinal values.

4. Antioxidant effect of virgin coconut oil

Virgin Coconut oil (VCO) has captured a lot of interest because of its possible role in enhancing body defense against oxidative stress. VCO is different from ordinary coconut oil (CO) as the former contains a lot more biologically active components such as polyphenols, tocopherols, 2 Evidence-Based Complementary and Alternative

Medicine sterols, and squalene. It has been established that the antioxidant activity in VCO is higher than refined CO. VCO has been shown to enhance antioxidant enzyme activity and inhibit lipid peroxidation in rats (Abujazia et al., 2012).

VCO has a high percentage of phenolic acids, and these are phytochemicals, sometimes also referred to as polyphenols (Marina et al., 2009b). Phenolic acids are recognized for their antioxidant properties. p-Coumaric acid, ferulic acid, caffeic acid, and catechin acid are the major phenolic acids found in CO (Marina et al., 2009a). VCO is also rich in active polyphenol compounds, which are strong inhibitors of lipid peroxidation (Dosumu et al., 2010). Polyphenols are known for their neuroprotective actions, especially in preventing the neurotoxic effects of β-amyloid (Menard et al., 2013). The beneficial effects of VCO have been widely investigated. In fact, VCO has been reported for its excellent antioxidative, anti-inflammatory, and antistress properties (Yeap et al., 2015). VCO increased the production of antioxidants in the brain, namely SOD, CAT, GSH, and GPx. The up-regulated antioxidants served as protection against lipid peroxidation (MDA) by oxidative stress (NO). The collective effects of these two components would eventually prevent or delay neurodegeneration. The promising outcomes of this study strongly imply the possible use of VCO, not only as neuroprotective agents for those suffering from neurodegenerative diseases but also as brain food (supplements for the health populations) (Rahim et al., 2017). VCO is well-known as an antioxidant and anti-inflammatory natural compound, VCO has a potential prophylactic effect for memory enhancement, anti-excitotoxicity, and antioxidants in the AD model (Alghamdi, 2018).

Coconut oil (CO), derived from the coconut fruit, has been recognized historically as containing high levels of saturated fat; however, closer scrutiny suggests that coconut should be regarded more favorably. Unlike most other dietary fats that are high in long-chain fatty acids, CO comprises medium-chain fatty acids (MCFA). MCFA are unique in that they are easily absorbed and metabolized by the liver, and can be converted to ketones (Fernando et al., 2015). The difference between MCFA and LCFA is the length of the fatty acid carbon chain. LCFA contains fourteen or more carbons (Traul et al., 2000), whereas MCFA has a chain length of six to twelve carbons (Traul et al., 2000; Marina et al., 2009b). The length of the carbon chain determines the physical and chemical properties of the fats as well as their metabolism in the human body (Traul et al., 2000). MCT or MCFA can act as a non-carbohydrate fuel source by enhancing the formation of ketones or ketone bodies in the body which are AcAc, 3-b-hydroxybutyrate (3HB), and acetone (Traul et al., 2000). The first two molecules are used for energy production, whereas acetone is a breakdown product of AcAc. Fatty acids cannot pass the blood-brain barrier (BBB); thus, the human brain primarily depends on glucose. However, it can utilize alternative fuels such as monocarboxylic acids, lactate, and ketones to maintain energy homeostasis (Page et al., 2009), and ketone bodies are used extensively as an energy source during glucose deficiency (ketosis) (Sumithran et al., 2013) and may be beneficial to people developing or already with memory impairment, as in AD and epilepsy (Fernando et al., 2015). VCO improved hippocampus histological changes reduced Aβ plaques and phosphorylated tau. A high-fat diet has exacerbated the effects of Aβ, while VCO showed a potential neuroprotective effect (Mirzaei et al., 2018).

Coconut oil comprises medium-chain fatty acids (MCFAs) with a high amount of medium-chain triglycerides. Coconut oil downregulates the expression of ADP-ribosylation factor 1, thereby inhibiting the secretion and aggregation of Aβ and restraining the expression of APP (Pinto et al., 2018). MCFAs could be converted into ketone bodies, which are related to the improvement of mitochondrial function and reduction of oxidation (Yuan et al., 2017). Coconut oil can resist oxidation and neuroprotection.

5. Effect of hormone in reducing the chance of AD

A phase 3 clinical trial to investigate the effect of coconut oil in mild to moderate AD was initiated in June 2013. However, it was terminated in February 2017. The reasons for the termination were funding limitations and a low enrollment rate (Huang et al., 2020).

The Aβ-plaques are increased in andropausal human brains (Vickers et al., 2000) and in the brains of aging male mice (Rosario et al., 2010). With advancing age, a significant decrease in sex steroid hormones occurs in men and women leading to the development of AD (AD) (Şöhretoğlu and Arroo, 2018). In males, the depletion of testosterone level affects different organs that are dependent on androgen, especially the brain. It was reported that the level of testosterone in the brain is inversely correlated with the brain levels of β-amyloid1-42 (Aβ), which is well known as one of the AD hallmark pathologies (Rosario and Pike, 2008). Although estrogen supplements could reduce AD pathologies in human brains, they could also cause gynecomastia and induce benign prostatic hyperplasia and prostatic cancer (Chen et al., 2015). Therefore, plant-derived phytoestrogens may be a better choice than estrogens. Similar to 17β estradiol (E2), phytoestrogens canal so bind to α andβ estrogen receptors (ERα and ERβ) (Ososki and Kennelly, 2003).

Recent studies have investigated the possibility of using trans-zeatin and phytoestrogen and other sex hormones like substances present in coconut water and a young coconut juice (YCJ) in reducing the risk of AD (Karch et al., 2014; Huang et al., 2016). In contrast, experimental studies have suggested that coconut/coconut cream consumption can cause hyperlipidemia and atherosclerosis, which are risk factors for AD. In contrast, several studies have reported that hyperlipidemia and heart diseases are

uncommon among high coconut-consuming populations (Chin-Chan et al., 2015).

Radenahmad et al. (2009) reported that giving YCJ to ovariectomized rats could increase NF200- and PV-reactive cells in the brain and reduce the accumulation of Aβ. The active ingredient(s) of YCJ was found to be β-sitosterol (Rattanaburee et al., 2014). YCJ was found to prevent osteoporosis (Yusuh et al., 2010; Suwanpal et al., 2011), preserve cells involved in motility of the gastrointestinal tract (Radenahmad et al., 2014), accelerate wound healing, and improve skin complexion (Radenahmad et al., 2012). It was also found that YCJ at a dose of40 ml/kgb.w./day was the best to reduce AD pathologies in ovariectomized rats within 10-weeks (Balit et al., 2019). However, a high dose of YCJ supplement had caused unfavorable side effects, such as glycogen deposition in the liver.

Recent literature has suggested that the use of CO (extra virgin/virgin), coconut water, and coconut cream may have significant positive effects on the lowering of plasma cholesterol, blood pressure (BP) control, and blood glucose levels, all of which are risk factors associated with AD.

6. Effect of coconut in treatment of diabetes and hypertension

Coconut is classified as a highly nutritious 'functional food'. It is rich in dietary fiber, vitamins, and minerals; however, notably, the evidence is mounting to support the concept that coconut may be beneficial in the treatment of obesity, dyslipidemia, elevated LDL, insulin resistance, and hypertension–these are the risk factors for CVD and type II diabetes, and also for AD. In addition, phenolic compounds and hormones (cytokinins) found in coconut may assist in preventing the aggregation of the amyloid-b peptide, potentially inhibiting a key step in the pathogenesis of A (Fernando et al., 2015).

The high levels of saturated fat have generally deterred those who are more health-conscious from using CO, cream, or milk. Furthermore, low-fat diets have been considered to be the best approach to reduce the risk of AD, in particular the Mediterranean diet (Gu et al., 2010). CO is rich in medium-chain fatty acids (MCFA), which are metabolized differently from the long-chain fatty acids (LCFA) commonly found in human diets. In addition, CO offers anti-aging and antioxidant properties (Marina et al., 2009a).

The major components in CO are fatty acids (such as lauric acid (45–50%) and capric acid) and phenolic compounds (such as ferulic acid and p-coumaric acid) (Nomura et al., 2003). Levels of the beneficial components are believed to be higher in VCO, which, as mentioned earlier, is prepared via a cold or low-heat-based extraction method. This oil contains higher levels of phenolic acids than copra or refined CO.

There is literature that indicates that the circulating D-b-3hydroxybutyrate ketone body, which is formed out of MCFA, crosses the BBB and enters the mitochondria where it is metabolized to AcAc and converted to acetyl-CoA, which enters into the Krebs cycle. One in vivo study with mice has identified the capacity of caprylic acid, a constituent of CO, to cross the BBB. This study indicates that as a result of crossing the BBB, caprylic acid demonstrated anti-convulsant and a neuroprotective effect (Wlaź et al., 2012). Medium-chain fatty acyl-CoA molecules easily transfer into the mitochondria and can then be converted into acetoacetate (AcAc) and b-hydroxybutyrate, mainly by medium-chain fatty acyl-CoA-dehydrogenase (Rosario and Pike, 2008). These two products can be metabolized further in the liver to produce CO2, H2O, and energy (Tepe et al., 2005).

CO is principally composed of SFA (about 92%), with 62–70% being MCFA (Chandrashekar et al., 2010), making CO unique among dietary fats (Marina et al., 2009b). The concern that CO may increase plasma lipid levels and adversely affect health is a point of contention. MCFA are partially hydrolyzed from dietary TAG by lingual lipase in the stomach and completely digested by pancreatic lipase within the intestinal lumen (Ruppin and Middleton, 1980). Therefore, MCFA is absorbed directly from the intestines into the portal vein and sent straight to the liver (Ruppin and Middleton, 1980). Unlike MCFA, other fats such as cholesterol, as well as saturated fat, monounsaturated fat, and polyunsaturated fat-containing LCFA, combine with proteins and form lipoproteins (Hardy and Selkoe, 2002; Tepe et al., 2005; Necula et al., 2007; Guo et al., 2016). These lipoproteins enter the bloodstream via the lymphatic system, thus mostly bypassing the liver (Ruppin and Middleton, 1980).

Apart from the benefits already mentioned above, both lauric acid, the main fatty acid in coconut, and phenolic compounds have anti-microbial or anti-bacterial properties. Thus, these compounds are considered to be protective against low-grade infections often associated with IR (Yan et al., 2013).

Nafar et al.'s (2017) study showed treatment with octanoic or lauric acid also provided protection against Aβ but was not as effective as the complete oil. Treatment with CO, as well as octanoic, decanoic and lauric acids resulted in a modest increase in ketone bodies compared to controls. The biochemical data suggest that Akt and ERK activation may contribute to the survival-promoting influence of CO. This was supported by observations that a PI3-Kinase inhibitor blocked the rescue effect of CO on Aβ amyloid toxicity, pretreatment with CO prior to Aβ exposure showed the best outcomes.

Interestingly, specific fractions of CO, extracted under hot conditions, have been shown to reduce blood glucose, cholesterol, and lipid peroxidation, and some polyphenolic compounds appear to reduce liver lipid peroxidation (Seneviratne et al., 2009). Coconut water has also been shown to have beneficial effects on serum and tissue lipid parameters when given to rats concurrently fed a high-cholesterol containing diet (Sandhya and

Rajamohan, 2006). Another study has investigated the positive effect of regular consumption of two tropical food drinks, coconut (C. Nucifera) water and mauby (Colubrina arborescens), on the control of hypertension (Alleyne et al., 2005). The combined products were found to be almost twice as effective as the products in isolation. CO and exercise during lactation can ameliorate the effects of stress on anxiety-like behavior and episodic-like memory in young rats through evaluation cognitive test Mini-Mental State Examination for changes (da Silva et al., 2018).

Several studies consistently showed consumption of CO increases low-density lipoprotein cholesterol (LDL-C) (Sankararaman and Sferra, 2018) and hyperglycemia, hyperinsulinemia, hyperleptinemia, and hypertriglyceridemia. These metabolic consequences may contribute to hippocampal-dependent memory impairment, accompanied by a lower central leptin level, and a higher SCD1 gene expression in the brain (Lin et al., 2017), and thereby could increase adverse cardiovascular health. Even though CO has a relatively high MCT concentration, the clinical benefits of commercial MCT oils cannot be generalized to CO. Until the long-term effects of CO on cardiovascular health are clearly established, CO should be considered as a saturated fat and its consumption should not exceed the USDA's daily recommendation (less than 10% of total calorie intake) (Sankararaman and Sferra, 2018).

7. Conclusion

The effect of coconut oil on Alzheimer's disease is unclear and more research is required before drawing any firm conclusions. But the interest in coconut oil reinforces the value we place on research. It's our best hope of finding effective treatments for Alzheimer's disease and other dementias and improving the quality of life and care for those affected. The consumption and use of coconut in its various forms have a long and established history in medicinal, scientific, and nutritional arenas. Coconut is, however, widely available, inexpensive, non-toxic, and highly palatable that may be shown in the future to prophylactically reduce the risk of AD. The molecular and clinical events, including amyloid accumulation, tau accumulation, oxidative stress, neuroinflammation, cognitive decline, and occurrence of behavioral psychological symptoms, develop along with AD progression. The lipid content of coconut, being mostly MCFA, offers an energy source that bypasses the usual glucose pathway, in the form of ketone bodies, and without the associated fat deposition often caused by LCFA. Coconut oil appears to improve the cognitive abilities of Alzheimer's patients, with different intensities depending on the cognitive area, but as CO should be considered as saturated fat and its consumption should not exceed the USDA's daily recommendation (less than 10% of total calorie intake). Observational studies must also be interpreted in context with their susceptibility to bias. In this example, people who consume coconut oil may differ from those who do not in various ways. These differences could explain why dementia is (or is not) more common in one group. For this reason, to obtain stronger evidence of "cause and effect" researchers conduct randomized controlled trials (RCTs). With RCTs, study participants are randomly assigned to receive an intervention such as a drug, diet, or lifestyle program, or not. This random assignment is meant to make the groups as similar as possible, except for having received the intervention being studied. The study participants are followed over time and their health outcomes are compared. Furthermore, research needs to be conducted to quantify the yield of and support the ability of various coconut as milk or powder to prevent or delay AD.

Compliance with ethical standards

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

Abujazia MA, Muhammad N, Shuid AN, and Soelaiman IN (2012). The effects of virgin coconut oil on bone oxidative status in ovariectomised rat. Evidence-Based Complementary and Alternative Medicine, 2012: 525079. https://doi.org/10.1155/2012/525079 **PMid:22927879 PMCid:PMC3426286**

Alghamdi BSA (2018). Possible prophylactic anti-excitotoxic and anti-oxidant effects of virgin coconut oil on aluminium chloride-induced Alzheimer's in rat models. Journal of Integrative Neuroscience, 17(3-4): 593-607. https://doi.org/10.3233/JIN-180089 **PMid:30010139**

Alleyne T, Roache S, Thomas C, and Shirley A (2005). The control of hypertension by use of coconut water and mauby: Two tropical food drinks. West Indian Medical Journal, 54(1): 3-8. https://doi.org/10.1590/S0043-31442005000100002 **PMid:15892382**

Alzheimer's Association (2016). 2016 Alzheimer's disease facts and figures. Alzheimer's and Dementia, 12(4): 459-509. https://doi.org/10.1016/j.jalz.2016.03.001 **PMid:27570871**

Balit T, Abdel-Wahhab MA, and Radenahmad N (2019). Young coconut juice reduces some histopathological changes associated with Alzheimer's disease through the modulation of estrogen receptors in orchidectomized rat brains. Journal of Aging Research, 2019: 7416419. https://doi.org/10.1155/2019/7416419 **PMid:31885921 PMCid:PMC6914913**

Barage SH and Sonawane KD (2015). Amyloid cascade hypothesis: Pathogenesis and therapeutic strategies in Alzheimer's disease. Neuropeptides, 52: 1-18. https://doi.org/10.1016/j.npep.2015.06.008 **PMid:26149638**

Chandrashekar P, Lokesh BR, and Krishna AG (2010). Hypolipidemic effect of blends of coconut oil with soybean oil or sunflower oil in experimental rats. Food Chemistry, 123(3): 728-733. https://doi.org/10.1016/j.foodchem.2010.05.042

Chen Z, Wang O, Nie M, Elison K, Zhou D, Li M, and Xing X (2015). Aromatase deficiency in a Chinese adult man caused by novel

compound heterozygous CYP19A1 mutations: Effects of estrogen replacement therapy on the bone, lipid, liver and glucose metabolism. Molecular and Cellular Endocrinology, 399: 32-42.
https://doi.org/10.1016/j.mce.2014.09.016
PMid:25301327 PMCid:PMC4457386

Chin-Chan M, Navarro-Yepes J, and Quintanilla-Vega B (2015). Environmental pollutants as risk factors for neurodegenerative disorders: Alzheimer and Parkinson diseases. Frontiers in Cellular Neuroscience, 9: 124.
https://doi.org/10.3389/fncel.2015.00124
PMid:25914621 PMCid:PMC4392704

Crary JF (2016). Primary age-related tauopathy and the amyloid cascade hypothesis: The exception that proves the rule? Journal of Neurology and Neuromedicine, 1(6): 53-57.
https://doi.org/10.29245/2572.942X/2016/6.1059
PMid:27819070

da Silva DDC, Tavares MG, do Nascimento CKB, Lira EC, dos Santos ÂA, de Seixas Maia LMS, and Hornsby MBDO (2018). Can coconut oil and treadmill exercise during the critical period of brain development ameliorate stress-related effects on anxiety-like behavior and episodic-like memory in young rats? Food and Function, 9(3): 1492-1499.
https://doi.org/10.1039/C7FO01516J **PMid:29517774**

David B, Wolfender JL, and Dias DA (2015). The pharmaceutical industry and natural products: Historical status and new trends. Phytochemistry Reviews, 14(2): 299-315.
https://doi.org/10.1007/s11101-014-9367-z

Dawkins E and Small DH (2014). Insights into the physiological function of the β-amyloid precursor protein: Beyond Alzheimer's disease. Journal of Neurochemistry, 129(5): 756-769.
https://doi.org/10.1111/jnc.12675
PMid:24517464 PMCid:PMC4314671

Dey A, Bhattacharya R, Mukherjee A, and Pandey DK (2017). Natural products against Alzheimer's disease: Pharmaco-therapeutics and biotechnological interventions. Biotechnology Advances, 35(2): 178-216.
https://doi.org/10.1016/j.biotechadv.2016.12.005
PMid:28043897

Dosumu OO, Duru FIO, Osinubi AA, Oremosu AA, and Noronha CC (2010). Influence of virgin coconut oil (VCNO) on oxidative stress, serum testosterone and gonadotropic hormones (FSH, LH) in chronic ethanol ingestion. Agriculture and Biology Journal of North America, 6: 1126-1132.
https://doi.org/10.5251/abjna.2010.1.6.1126.1132

Fernando WMADB, Martins IJ, Goozee KG, Brennan CS, Jayasena V, and Martins RN (2015). The role of dietary coconut for the prevention and treatment of Alzheimer's disease: Potential mechanisms of action. British Journal of Nutrition, 114(1): 1-14.
https://doi.org/10.1017/S0007114515001452
PMid:25997382

Gu Y, Luchsinger JA, Stern Y, and Scarmeas N (2010). Mediterranean diet, inflammatory and metabolic biomarkers, and risk of Alzheimer's disease. Journal of Alzheimer's Disease, 22(2): 483-492.
https://doi.org/10.3233/JAD-2010-100897
PMid:20847399 PMCid:PMC3022949

Guo JL, Narasimhan S, Changolkar L, He Z, Stieber A, Zhang B, and Lee VM (2016). Unique pathological tau conformers from Alzheimer's brains transmit tau pathology in nontransgenic mice. Journal of Experimental Medicine, 213(12): 2635-2654.
https://doi.org/10.1084/jem.20160833
PMid:27810929 PMCid:PMC5110027

Hardy J and Selkoe DJ (2002). The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. Science, 297(5580): 353-356.
https://doi.org/10.1126/science.1072994 **PMid:12130773**

Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, and Herrup K (2015). Neuroinflammation in Alzheimer's disease. The Lancet Neurology, 14(4): 388-405.
https://doi.org/10.1016/S1474-4422(15)70016-5

Huang LK, Chao SP, and Hu CJ (2020). Clinical trials of new drugs for Alzheimer disease. Journal of Biomedical Science, 27(1): 1-13.
https://doi.org/10.36255/exonpublications.alzheimersdisease.2020 **PMid:33400453**

Huang WJ, Zhang XIA, and Chen WW (2016). Role of oxidative stress in Alzheimer's disease. Biomedical Reports, 4(5): 519-522.
https://doi.org/10.3892/br.2016.630
PMid:27123241 PMCid:PMC4840676

Janick J and Paull RE (2008). The encyclopedia of fruit and nuts. Centre for Agriculture and Bioscience International, Wallingford, UK.
https://doi.org/10.1079/9780851996387.0000

Johri A and Beal MF (2012). Mitochondrial dysfunction in neurodegenerative diseases. Journal of Pharmacology and Experimental Therapeutics, 342(3): 619-630.
https://doi.org/10.1124/jpet.112.192138
PMid:22700435 PMCid:PMC3422529

Karch CM and Goate AM (2015). Alzheimer's disease risk genes and mechanisms of disease pathogenesis. Biological Psychiatry, 77(1): 43-51.
https://doi.org/10.1016/j.biopsych.2014.05.006
PMid:24951455 PMCid:PMC4234692

Karch CM, Cruchaga C, and Goate AM (2014). Alzheimer's disease genetics: From the bench to the clinic. Neuron, 83(1): 11-26.
https://doi.org/10.1016/j.neuron.2014.05.041
PMid:24991952 PMCid:PMC4120741

Kashiwaya Y, Bergman C, Lee JH, Wan R, King MT, Mughal MR, and Veech RL (2013). A ketone ester diet exhibits anxiolytic and cognition-sparing properties, and lessens amyloid and tau pathologies in a mouse model of Alzheimer's disease. Neurobiology of Aging, 34(6): 1530-1539.
https://doi.org/10.1016/j.neurobiolaging.2012.11.023
PMid:23276384 PMCid:PMC3619192

Kumar A and Singh A (2015). A review on Alzheimer's disease pathophysiology and its management: An update. Pharmacological Reports, 67(2): 195-203.
https://doi.org/10.1016/j.pharep.2014.09.004
PMid:25712639

Langa KM (2015). Is the risk of Alzheimer's disease and dementia declining? Alzheimer's Research and Therapy, 7: 34.
https://doi.org/10.1186/s13195-015-0118-1
PMid:25815064 PMCid:PMC4374373

Laurent C, Dorothée G, Hunot S, Martin E, Monnet Y, Duchamp M, and Faivre E (2017). Hippocampal T cell infiltration promotes neuroinflammation and cognitive decline in a mouse model of tauopathy. Brain, 140(1): 184-200.
https://doi.org/10.1093/brain/aww270
PMid:27818384 PMCid:PMC5382942

Lin CI, Shen CF, Hsu TH, and Lin SH (2017). A high-fructose-high-coconut oil diet induces dysregulating expressions of hippocampal leptin and stearoyl-CoA desaturase, and spatial memory deficits in rats. Nutrients, 9(6): 619.
https://doi.org/10.3390/nu9060619
PMid:28621759 PMCid:PMC5490598

Loureiro JA, Crespo R, Börner H, Martins PM, Rocha FA, Coelho M, and Rocha S (2014). Fluorinated beta-sheet breaker peptides. Journal of Materials Chemistry B, 2(16): 2259-2264.
https://doi.org/10.1039/C3TB21483D **PMid:32261713**

Marina AM, Che Man YB, Nazimah SAH, and Amin I (2009a). Antioxidant capacity and phenolic acids of virgin coconut oil. International Journal of Food Sciences and Nutrition, 60(sup2): 114-123.
https://doi.org/10.1080/09637480802549127
PMid:19115123

Marina AM, Man YC, Nazimah SAH, and Amin I (2009b). Chemical properties of virgin coconut oil. Journal of the American Oil Chemists' Society, 86(4): 301-307. https://doi.org/10.1007/s11746-009-1351-1

Menard C, Bastianetto S, and Quirion R (2013). Neuroprotective effects of resveratrol and epigallocatechin gallate polyphenols are mediated by the activation of protein kinase C gamma. Frontiers in Cellular Neuroscience, 7: 281. https://doi.org/10.3389/fncel.2013.00281 **PMid:24421757 PMCid:PMC3872731**

Mirzaei F, Khazaei M, Komaki A, Amiri I, and Jalili C (2018). Virgin coconut oil (VCO) by normalizing NLRP3 inflammasome showed potential neuroprotective effects in Amyloid-β induced toxicity and high-fat diet fed rat. Food and Chemical Toxicology, 118: 68-83. https://doi.org/10.1016/j.fct.2018.04.064 **PMid:29729307**

Mohamed T, Shakeri A, and Rao PP (2016). Amyloid cascade in Alzheimer's disease: Recent advances in medicinal chemistry. European Journal of Medicinal Chemistry, 113: 258-272. https://doi.org/10.1016/j.ejmech.2016.02.049 **PMid:26945113**

Nafar F and Mearow KM (2014). Coconut oil attenuates the effects of amyloid-β on cortical neurons in vitro. Journal of Alzheimer's Disease, 39(2); 233-237. https://doi.org/10.3233/JAD-131436 **PMid:24150106**

Nafar F, Clarke JP, and Mearow KM (2017). Coconut oil protects cortical neurons from amyloid beta toxicity by enhancing signaling of cell survival pathways. Neurochemistry International, 105: 64-79. https://doi.org/10.1016/j.neuint.2017.01.008 **PMid:28126466**

Necula M, Kayed R, Milton S, and Glabe CG (2007). Small molecule inhibitors of aggregation indicate that amyloid β oligomerization and fibrillization pathways are independent and distinct. Journal of Biological Chemistry, 282(14): 10311-10324. https://doi.org/10.1074/jbc.M608207200 **PMid:17284452**

Nichols E, Szoeke CE, Vollset SE, Abbasi N, Abd-Allah F, Abdela J, and Awasthi A (2019). Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: A systematic analysis for the global burden of disease study 2016. The Lancet Neurology, 18(1): 88-106. https://doi.org/10.1016/S1474-4422(18)30403-4

Nilson AN, English KC, Gerson JE, Barton Whittle T, Nicolas Crain C, Xue J, and Kayed R (2017). Tau oligomers associate with inflammation in the brain and retina of tauopathy mice and in neurodegenerative diseases. Journal of Alzheimer's Disease, 55(3): 1083-1099. https://doi.org/10.3233/JAD-160912 **PMid:27716675 PMCid:PMC5147514**

Nomura E, Kashiwada A, Hosoda A, Nakamura K, Morishita H, Tsuno T, and Taniguchi H (2003). Synthesis of amide compounds of ferulic acid, and their stimulatory effects on insulin secretion in vitro. Bioorganic and Medicinal Chemistry, 11(17): 3807-3813. https://doi.org/10.1016/S0968-0896(03)00280-3

Ososki AL and Kennelly EJ (2003). Phytoestrogens: A review of the present state of research. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives, 17(8): 845-869. https://doi.org/10.1002/ptr.1364 **PMid:13680814**

Page KA, Williamson A, Yu N, McNay EC, Dzuira J, McCrimmon RJ, and Sherwin RS (2009). Medium-chain fatty acids improve cognitive function in intensively treated type 1 diabetic patients and support in vitro synaptic transmission during acute hypoglycemia. Diabetes, 58(5): 1237-1244. https://doi.org/10.2337/db08-1557 **PMid:19223595 PMCid:PMC2671041**

Park SY and Kim DS (2002). Discovery of natural products from Curcuma l onga that protect cells from beta-amyloid insult: A drug discovery effort against Alzheimer's disease. Journal of Natural Products, 65(9): 1227-1231. https://doi.org/10.1021/np010039x **PMid:12350137**

Pinto A, Bonucci A, Maggi E, Corsi M, and Businaro R (2018). Anti-oxidant and anti-inflammatory activity of ketogenic diet: New perspectives for neuroprotection in Alzheimer's disease. Antioxidants, 7(5): 63. https://doi.org/10.3390/antiox7050063 **PMid:29710809 PMCid:PMC5981249**

Prince MJ (2015). World Alzheimer report 2015: The global impact of dementia: An analysis of prevalence, incidence, cost and trends. Alzheimer's Disease International, London, UK.

Radenahmad N, Boonyoung P, Kamkaew K, Chanchula K, and Kirirat P (2014). Effects of young coconut juice on the numbers of argyrophil endocrine cells in the gastrointestinal tract of male rats: Novel preliminary findings. Songklanakarin Journal of Science and Technology, 36(6): 599-606.

Radenahmad N, Saleh F, Sawangjaroen K, Rundorn W, Withyachumnarnkul B, and Connor JR (2009). Young coconut juice significantly reduces histopathological changes in the brain that is induced by hormonal imbalance: A possible implication to postmenopausal women. Histology and Histopathology, 24(6): 667-674.

Radenahmad N, Saleh F, Sayoh I, Sawangjaroen K, Subhadhirasakul P, Boonyoung P, and Mitranun W (2012). Young coconut juice can accelerate the healing process of cutaneous wounds. BMC Complementary and Alternative Medicine, 12: 252. https://doi.org/10.1186/1472-6882-12-252 **PMid:23234369 PMCid:PMC3538627**

Rahim NS, Lim SM, Mani V, Abdul Majeed AB, and Ramasamy K (2017). Enhanced memory in Wistar rats by virgin coconut oil is associated with increased antioxidative, cholinergic activities and reduced oxidative stress. Pharmaceutical Biology, 55(1): 825-832. https://doi.org/10.1080/13880209.2017.1280688 **PMid:28118770 PMCid:PMC6130622**

Rattanaburee P, Amnuaikit T, Radenahmad N, and Puripattanavong J (2014). Phytochemical study and its quantity and quality of fresh and freeze-dried young coconut juice (Cocos nucifera L.). In: Zhang Y (Ed.), Advanced materials research: 490-493. Volume 884, Trans Tech Publications Ltd., Stafa-Zurich, Switzerland. https://doi.org/10.4028/www.scientific.net/AMR.884-885.490

Rosario ER and Pike CJ (2008). Androgen regulation of β-amyloid protein and the risk of Alzheimer's disease. Brain Research Reviews, 57(2): 444-453. https://doi.org/10.1016/j.brainresrev.2007.04.012 **PMid:17658612 PMCid:PMC2390933**

Rosario ER, Carroll J, and Pike CJ (2010). Testosterone regulation of Alzheimer-like neuropathology in male 3xTg-AD mice involves both estrogen and androgen pathways. Brain Research, 1359: 281-290. https://doi.org/10.1016/j.brainres.2010.08.068 **PMid:20807511 PMCid:PMC2965035**

Ruppin DC and Middleton WRJ (1980). Clinical use of medium chain triglycerides. Drugs, 20(3): 216-224. https://doi.org/10.2165/00003495-198020030-00005 **PMid:7428670**

Rusek M, Pluta R, Ułamek-Kozioł M, and Czuczwar SJ (2019). Ketogenic diet in Alzheimer's disease. International Journal of Molecular Sciences, 20(16): 3892. https://doi.org/10.3390/ijms20163892 **PMid:31405021 PMCid:PMC6720297**

Sandhya VG and Rajamohan T (2006). Beneficial effects of coconut water feeding on lipid metabolism in cholesterol-fed rats. Journal of Medicinal Food, 9(3): 400-407. https://doi.org/10.1089/jmf.2006.9.400 **PMid:17004906**

Sankararaman S and Sferra TJ (2018). Are we going nuts on coconut oil? Current Nutrition Reports, 7(3): 107-115. https://doi.org/10.1007/s13668-018-0230-5 **PMid:29974400**

Selkoe DJ and Hardy J (2016). The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Molecular Medicine, 8(6): 595-608. https://doi.org/10.15252/emmm.201606210 **PMid:27025652 PMCid:PMC4888851**

Seneviratne KN, HapuarachchI CD, and Ekanayake S (2009). Comparison of the phenolic-dependent antioxidant properties of coconut oil extracted under cold and hot conditions. Food Chemistry, 114(4): 1444-1449. https://doi.org/10.1016/j.foodchem.2008.11.038

Sengupta U, Nilson AN, and Kayed R (2016). The role of amyloid-β oligomers in toxicity, propagation, and immunotherapy. EBioMedicine, 6: 42-49. https://doi.org/10.1016/j.ebiom.2016.03.035 **PMid:27211547 PMCid:PMC4856795**

Shah R (2013). The role of nutrition and diet in Alzheimer disease: A systematic review. Journal of the American Medical Directors Association, 14(6): 398-402. https://doi.org/10.1016/j.jamda.2013.01.014 **PMid:23419980**

Silva RF and Pogačnik L (2017). Food, polyphenols and neuroprotection. Neural Regeneration Research, 12(4): 582-583. https://doi.org/10.4103/1673-5374.205096 **PMid:28553336 PMCid:PMC5436354**

Şöhretoğlu D and Arroo R (2018). Plant-derived antiinflammatory steroid analogs for neuroprotection: A recent update. In: Brahmachari G (Ed.), Discovery and development of neuroprotective agents from natural products: 321-358. Elsevier, Amsterdam, Netherlands. https://doi.org/10.1016/B978-0-12-809593-5.00007-0

Solomon A, Mangialasche F, Richard E, Andrieu S, Bennett DA, Breteler M, and Skoog I (2014). Advances in the prevention of Alzheimer's disease and dementia. Journal of Internal Medicine, 275(3): 229-250. https://doi.org/10.1111/joim.12178 **PMid:24605807 PMCid:PMC4390027**

Sumithran P, Prendergast LA, Delbridge E, Purcell K, Shulkes A, Kriketos A, and Proietto J (2013). Ketosis and appetite-mediating nutrients and hormones after weight loss. European Journal of Clinical Nutrition, 67(7): 759-764. https://doi.org/10.1038/ejcn.2013.90 **PMid:23632752**

Suwanpal P, Radenahmad N, Yusuh M, Eksomtramate M, Ruangsri P, and Chantanasuksilpa A (2011). Effects of young-coconut juice on increasing mandibular cancellous bone in orchidectomized rats: Preliminary novel findings. Songklanakarin Journal of Science and Technology, 33(6): 617-623.

Takahashi RH, Nagao T, and Gouras GK (2017). Plaque formation and the intraneuronal accumulation of β-amyloid in Alzheimer's disease. Pathology International, 67(4): 185-193. https://doi.org/10.1111/pin.12520 **PMid:28261941**

Tepe B, Sokmen M, Sokmen A, Daferera D, and Polissiou M (2005). Antimicrobial and antioxidative activity of the essential oil and various extracts of Cyclotrichium origanifolium (Labill.) Manden and Scheng. Journal of Food Engineering, 69(3): 335-342. https://doi.org/10.1016/j.jfoodeng.2004.08.024

Traul KA, Driedger A, Ingle DL, and Nakhasi D (2000). Review of the toxicologic properties of medium-chain triglycerides. Food and Chemical Toxicology, 38(1): 79-98. https://doi.org/10.1016/S0278-6915(99)00106-4

Verma M, Vats A, and Taneja V (2015). Toxic species in amyloid disorders: Oligomers or mature fibrils. Annals of Indian Academy of Neurology, 18(2): 138-145. https://doi.org/10.4103/0972-2327.144284 **PMid:26019408 PMCid:PMC4445186**

Vickers JC, Dickson TC, Adlard PA, Saunders HL, King CE, and McCormack G (2000). The cause of neuronal degeneration in Alzheimer's disease. Progress in Neurobiology, 60(2): 139-165. https://doi.org/10.1016/S0301-0082(99)00023-4

Villain N, Chételat G, Grassiot B, Bourgeat P, Jones G, Ellis KA, and Masters CL (2012). Regional dynamics of amyloid-β deposition in healthy elderly, mild cognitive impairment and Alzheimer's disease: A voxelwise PiB–PET longitudinal study. Brain, 135(7): 2126-2139. https://doi.org/10.1093/brain/aws125 **PMid:22628162**

Wlaź P, Socała K, Nieoczym D, Łuszczki JJ, Żarnowska I, Żarnowski T, and Gasior M (2012). Anticonvulsant profile of caprylic acid, a main constituent of the medium-chain triglyceride (MCT) ketogenic diet, in mice. Neuropharmacology, 62(4): 1882-1889. https://doi.org/10.1016/j.neuropharm.2011.12.015 **PMid:22210332**

Yan JJ, Jung JS, Kim TK, Hasan MA, Hong CW, Nam JS, and Song DK (2013). Protective effects of ferulic acid in amyloid precursor protein plus presenilin-1 transgenic mouse model of Alzheimer disease. Biological and Pharmaceutical Bulletin, 36(1): 140-143. https://doi.org/10.1248/bpb.b12-00798 **PMid:23075678**

Yeap SK, Beh BK, Ali NM, Yusof HM, Ho WY, Koh SP, and Long K (2015). Antistress and antioxidant effects of virgin coconut oil in vivo. Experimental and Therapeutic Medicine, 9(1): 39-42. https://doi.org/10.3892/etm.2014.2045 **PMid:25452773 PMCid:PMC4247320**

Yuan Q, Wang CW, Shi J, and Lin ZX (2017). Effects of Ginkgo biloba on dementia: An overview of systematic reviews. Journal of Ethnopharmacology, 195: 1-9. https://doi.org/10.1016/j.jep.2016.12.005 **PMid:27940086**

Yusuh M, Phochanukoon N, Radenahmad N, Eksomtramate M, Ruangsri P, Chantanasuksilpa A, and Nitiruangjaras A (2010). Changes of condyle cartilage in orchidectomized rats fed with young coconut juice: Novel preliminary findings. Songklanakarin Journal of Science and Technology, 32(4): 333-339.

Zhang Z, Song M, Liu X, Kang SS, Duong DM, Seyfried NT, and Jia J (2015). Delta-secretase cleaves amyloid precursor protein and regulates the pathogenesis in Alzheimer's disease. Nature Communications, 6(1): 1-16. https://doi.org/10.1038/ncomms9762 **PMid:26549211 PMCid:PMC4659940**