*British Journal of Nutrition* (2015), **114**, 1–14
doi:10.1017/S0007114515001452


*Review Article*

# The role of dietary coconut for the prevention and treatment of Alzheimer's disease: potential mechanisms of action

W. M. A. D. B. Fernando[1,2], Ian J. Martins[1,2], K. G. Goozee[1,2,3,4], Charles S. Brennan[5], V. Jayasena[6] and R. N. Martins[1,2,3,4]*

[1]*Centre of Excellence in Alzheimer's Disease Research and Care, School of Medical Sciences, Edith Cowan University, 270 Joondalup Drive, Joondalup, WA 6027, Australia*
[2]*McCusker Alzheimer's Research Foundation, Hollywood Medical Centre, 85 Monash Avenue, Suite 22, Nedlands, WA 6009, Australia*
[3]*School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Nedlands, WA 6009, Australia*
[4]*McCusker KARVIAH Research Centre, ARV, 2 Alexander Avenue, Taren Point, NSW 2229, Australia*
[5]*Department of Wine, Food and Molecular Biosciences, Centre for Food Research and Innovation, Lincoln University, Lincoln, New Zealand*
[6]*Department of Nutrition, Dietetics and Food Technology, School of Public Health, Curtin University, WA, Australia*

*(Submitted 22 September 2014 – Final revision received 23 March 2015 – Accepted 2 April 2015 – First published online 22 May 2015)*

## Abstract

Coconut, *Cocos nucifera* L., is a tree that is cultivated to provide a large number of products, although it is mainly grown for its nutritional and medicinal values. Coconut oil, derived from the coconut fruit, has been recognised historically as containing high levels of saturated fat; however, closer scrutiny suggests that coconut should be regarded more favourably. Unlike most other dietary fats that are high in long-chain fatty acids, coconut oil comprises medium-chain fatty acids (MCFA). MCFA are unique in that they are easily absorbed and metabolised by the liver, and can be converted to ketones. Ketone bodies are an important alternative energy source in the brain, and may be beneficial to people developing or already with memory impairment, as in Alzheimer's disease (AD). Coconut is classified as a highly nutritious 'functional food'. It is rich in dietary fibre, vitamins and minerals; however, notably, evidence is mounting to support the concept that coconut may be beneficial in the treatment of obesity, dyslipidaemia, elevated LDL, insulin resistance and hypertension – these are the risk factors for CVD and type 2 diabetes, and also for AD. In addition, phenolic compounds and hormones (cytokinins) found in coconut may assist in preventing the aggregation of amyloid-β peptide, potentially inhibiting a key step in the pathogenesis of AD. The purpose of the present review was to explore the literature related to coconut, outlining the known mechanistic physiology, and to discuss the potential role of coconut supplementation as a therapeutic option in the prevention and management of AD.

**Key words: Coconut: Saturated fat: Amyloid: Alzheimer's: Diabetes**

In line with the global predictions for the prevalence of Alzheimer's disease (AD), Australia declared AD as the ninth National health priority in 2012. Alzheimer's is a complex disease that progresses over many years, such as diabetes, heart disease and other chronic conditions. The gradual accumulation of the pathology of cerebral extracellular AD known as amyloid, which is mostly composed of aggregated amyloid-β (Aβ) peptides[1], as well as the accumulation of intracellular neurofibrillary tangles, appears to start up to 17–20 years before a clinically observable disease[2]. A 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.

**Abbreviations:** 3HB, 3-β-hydroxybutyrate; Aβ, amyloid-β; AD, Alzheimer's disease; AcAc, acetoacetate; APP, amyloid precursor protein; BBB, blood–brain barrier; BP, blood pressure; EE, energy expenditure; IR, insulin resistance; KD, ketogenic diets; LCFA, long-chain fatty acids; LDL-C, LDL-cholesterol; MCFA, medium-chain fatty acids; MCT, medium-chain TAG; VCO, virgin coconut oil.

* **Corresponding author:** Professor R. N. Martins, fax +61 8 93474299, email r.martins@ecu.edu.au

Diet may play an important role in preventing AD. As many studies have linked AD risk to diet-modifiable conditions such as type 2 diabetes, hypertension and CVD, dietary approaches to AD prevention involving palatable, low risk, inexpensive substances are attracting great attention, as a method to ameliorating deficits concomitant with ageing and neurodegeneration. In particular, recent literature has suggested that the use of coconut oil (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. Coconut has also been identified as a potential cognitive strengthener[3,4] associated with AD. The present review reported the evidence for coconut oil consumption, with a particular emphasis on virgin coconut oil (VCO), outlining the potential risks and benefits in relation to AD prevention and/or management.

The scientific name for coconut is *Cocos nucifera*, and the plant is a member of the Arecaceae family[5–10]. Among the components of coconut, coconut oil is of the most interest related to human health. Of note, coconut oil is principally composed of SFA (about 92%), with 62–70% being medium-chain TAG (MCT)[4,11,12], making coconut oil unique among dietary fats. A few clinical trials and animal studies using a formulation of MCT have reported significant improvement of cognition in AD patients. While research on Alzheimer's and MCT is still in its infancy, the science behind MCT is that MCT can be rapidly metabolised to induce metabolic ketosis and ketogenic, which could be employed as a therapy for a variety of brain disorders, including epilepsy and neurodegeneration. Anecdotes via the media and word-of-mouth have promoted great interest in the action of ketones and, thus, coconut oil.

Recent studies have investigated the possibility of using *trans*-zeatin and phyto-oestrogen and other sex hormone-like substances present in coconut water and young coconut juice in reducing the risk of AD[13,14]. In contrast, experimental studies have suggested that coconut/coconut cream consumption can cause hyperlipidaemia and atherosclerosis, which are risk factors for AD. In contrast, several studies have reported that hyperlipidaemia and heart diseases are uncommon among high coconut consuming populations[15,16].

In view of the interest in the potential of coconut oil, coconut water and coconut cream as a dietary supplement that could ameliorate the symptoms of neurodegeneration, we analysed the literature to understand the influence of coconut on the pathology of AD and risk factors for AD. Adding complexity to this discussion is the various forms of coconut available, and also the method of extraction used to produce the end product.

## Coconut oil

Coconut oil is extracted by either hot or cold pressed techniques, and the method used is reported to influence the quality and grade of the oil, although agreement on which method is best has not been achieved. Both wet and dry methods are used, and some approaches also involve solvents for the final extraction, if using coconut expeller cake[4]. VCO, manufactured using controlled temperature (hot or cold) methods are thought to be the most effective methods if aiming to retain the highest levels of biologically active components such as tocotrienols, squalene (hydrocarbon, important for animal steroid formation), tocopherols and sterols (phytosterols)[3]. This is in contrast to copra oil (derived from the dried coconut meat or kernel) that is processed with no temperature control[3,17]. VCO is natural, chemically unrefined and considered safe for human consumption[4]. Thus, in addition to being used as a cooking oil, VCO can also be considered as a functional food supplement. The total phenolic content of VCO (7·78–29·18 mg gallic acid equivalents/100 g oil) is significantly higher than that of refined coconut oil (6·14 mg gallic acid equivalents/100 g oil)[4,18]. However, there is no significant difference in fatty acid content among VCO, Copra and refined coconut oil, all containing 92% SFA, 6% MUFA and 2% PUFA. However, VCO has shown greater beneficial effects than copra oil in lowering lipid levels in serum and tissues and in reducing LDL oxidation by physiological oxidants. This property of VCO may be attributed to the biologically active polyphenol components present in the oil[19].

Not surprisingly, the high levels of saturated fat have generally deterred those who are more health conscious from using coconut oils, 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[20,21]. Therefore, promoting coconut oil as a food would appear counter-intuitive. However, closer scrutiny of the chemical properties, digestion and uptake may suggest that this concern may not be well founded. Coconut oil is rich in medium-chain fatty acids (MCFA), which are metabolised differently to the long-chain fatty acids (LCFA) commonly found in human diets. In addition, coconut oil offers anti-ageing and anti-oxidant properties[22,23]. Coconut oil in food has a long history, and is very popular in South Asia and has a prominent place in Ayurvedic medicine.

## Coconut oil consists mostly of medium-chain fatty acids

Coconut oil is principally composed of SFA (about 92%), with 62–70% being MCFA[4,11,12] (Table 1), making coconut oil

**Table 1.** Fatty acid composition of coconut oil, showing percentage of total fat

| Name | % Total fat | Saturated/ unsaturated | MCFA/ LCFA |
|---|---|---|---|
| Caproic acid (6 : 0) | 0·6 | Saturated | MCFA |
| Caprylic (8 : 0) | 0·8 | Saturated | MCFA |
| Capric (10 : 0) | 6·4 | Saturated | MCFA |
| Lauric (12 : 0) | 48·5 | Saturated | MCFA |
| Myristic (14 : 0) | 17·6 | Saturated | MCFA |
| Palmitic acid (16 : 0) | 8·4 | Saturated | MCFA |
| Stearic acid (18 : 0) | 2·5 | Saturated | LCFA |
| Linoleic acid (18 : 1) | 6·5 | Unsaturated | LCFA |
| Linolenic (18 : 2) | 1·5 | Unsaturated | LCFA |

MCFA, medium-chain fatty acids; LCFA, long-chain fatty acids.

unique among dietary fats[3,11]. The difference between MCFA and LCFA is the length of the fatty acid carbon chain. MCFA have a chain length of six to twelve carbons[3,24] (Table 1), whereas LCFA contain fourteen or more carbons[11,24]. The length of the carbon chain determines the physical and chemical properties of the fats as well as their metabolism in the human body[24]. Soya oil contains 60 % PUFA, 24 % MUFA and 16 % SFA[25]. In contrast, palm oil contains 50 % MUFA and 50 % SFA. This high level of PUFA of soya oil can improve the blood lipid profile status[26]. In addition, with its high content of tocopherols, soya oil is known to exhibit various antioxidant actions against lipid peroxidation.

## Metabolism of medium-chain fatty acids

MCFA are broken down almost immediately by enzymes in the saliva and gastric juices, without the need for pancreatic fat-digesting enzymes[27]; furthermore, this process involves relatively moderate energy consumption. Therefore, the metabolism of coconut oil is significantly different from that of other fatty acids commonly found in the diet[18].

## Medium-chain fatty acid absorption

In the case of most other fatty acids and cholesterol, the intestines play a major role in absorption[28]; yet unfortunately, pancreatic function declines with age, and therefore malabsorption problems can occur in patients who suffer from digestive and metabolic conditions. In other words, as the pancreatic output of digestive enzymes reduces, the efficiency of the small intestine in the absorption of nutrients diminishes[27–30]. This is important, as vitamin and mineral deficiencies are recognised as a global health issue[31], and age-related changes and select disease processes exacerbate this problem[29,32,33]. As weight loss and malnutrition are recognised as frequent companions and contributors to AD, dietary supplementation with coconut oil may help prevent weight loss and increase the intake of certain vitamins and minerals.

The concern that coconut oil may increase plasma lipid levels and adversely affect health is a point of contention. MCFA are partially hydrolysed from dietary TAG by lingual lipase in the stomach and completely digested by pancreatic lipase within the intestinal lumen[27]. Therefore, MCFA are absorbed directly from the intestines into the portal vein and sent straight to the liver[27,33]. 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[24,27,33,34]. These lipoproteins enter the bloodstream via the lymphatic system, thus mostly bypassing the liver[27,33]. As lipoproteins circulate in the blood, their fatty components are dispersed to tissues[35], therefore contributing to the accumulation of fat in such body tissues, as part of normal fat storage. However, in the process, some of these fats congeal within the artery walls, increasing the risk of hypertension and adding to the cardiovascular risk factors, and both known to increase AD risk[21]. In contrast to LCFA that are easily esterified and bind strongly to fatty acid binding proteins[36,37], MCFA are not easily esterified and resist binding. Thus, MCFA are less likely to contribute to such fat deposits, and thus have reduced impact on the cardiovascular system, including BP[34,35,38,39]. However, recent research with VCO has demonstrated that repeatedly heated VCO causes an elevation in BP. BP elevation has been associated with a significant increase in the inflammatory biomarkers (vascular cell adhesion molecule-1, intercellular adhesion molecule-1 and C-reactive protein), thromboxane $A_2$ and a significant reduction in the plasma $PGI_2$ level[40]. Repeatedly heated soya oil and palm oil also elevated BP[41,42].

## Medium-chain fatty acid breakdown

Similar to the absorption differences mentioned above, the human body metabolises MCFA and LCFA via different pathways[33,43]. SCFA are transported in the blood as NEFA, while longer-chain NEFA are combined with albumin[11]. The metabolism of fatty acids is initiated on the outer mitochondrial membrane and is catalysed by acyl-CoA synthetase[43] as shown in Fig. 1. This step is required partly to enable the transport of the fatty acids into the mitochondrial matrix. First, the fatty acid forms an acyl-adenylate; then while still tightly bound to the enzyme, acyl-adenylate is converted to acyl-CoA (medium-chain acyl-CoA or long-chain acyl-CoA) and AMP[43]. Acyl-CoA can then be transported into the mitochondria using different pathways depending on the fatty acid chain length[43]. Long-chain acyl-CoA molecules conjugate with carnitine (L-3-hydroxy-4-aminobutyrobetaine or L-3-hydroxy-4-*N*-trimethylaminobutanoic acid, and its acyl-esters (acylcarnitines)[43,44] to form acylcarnitine, and this reaction is catalysed by carnitine acyltransferase I[43]. In contrast, MCFA enter the mitochondria independently of the carnitine transport system[45], and therefore do not depend on the activity of the carnitine acyltransferase-1 enzyme, as with LCFA[43]. Medium-chain fatty acyl-CoA molecules easily transfer into the mitochondria and can then be converted into acetoacetate (AcAc) and β-hydroxybutyrate, mainly by medium-chain fatty acyl-CoA-dehydrogenase[45]. These two products can be metabolised further in the liver to produce $CO_2$, $H_2O$ and energy[29,33,45].

## Benefits of medium-chain fatty acids compared with long-chain fatty acids

The result of the quicker metabolic conversion of MCFA is that instead of being deposited as fat, the energy generated from MCFA is very competently converted into fuel for immediate use by organs and muscles. Furthermore, MCFA produce 34·7 kJ/g (8·3 kcal/g) ingested, whereas LCFA will produce 38·5 kJ/g (9·2 kcal/g) ingested[4]. Thus, MCFA provide about 10 % less energy than LCFA. Although the difference sounds insignificant, this is just one of the many advantages of

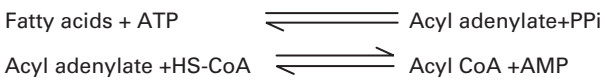


**Fig. 1.** Formation of acyl-CoA.

MCFA, as it will reduce obesity to some degree, and obesity is an independent risk factor for hypertension, hyperlipidaemia and diabetes, which are, in turn, the risk factors associated with AD[46].

Differences between LCFA and MCFA metabolism may also help in other more indirect ways in controlling obesity, and differences in the metabolism as well as the metabolic effects of LCFA and MCFA have been demonstrated in both animal and human studies[47–49]: for example, increases in post-prandial energy expenditure (EE) as well as the attenuation of weight accretion have been demonstrated, after short- or longer-term MCFA consumption, and these are discussed below.

In early clinical studies, Flatt *et al.*[50] compared diets rich in either MCFA, LCFA or low in fats, and found that low-fat diets were most efficient for weight loss; however, they also found that MCFA-rich diets may be better than LCFA-rich diets; this was supported by Hill *et al.*[51] who reported that higher EE was achieved through MCFA intake over 7 d when consumed in liquid formulation. This study demonstrated that excess dietary energy as MCFA motivated thermogenesis to a higher degree than did excess energy as LCFA. This higher EE induced by MCFA is most likely due to increased metabolic rates and thermogenesis. In a trial involving six participants, Scalfi *et al.*[52] introduced meals containing 30 % fat, in the form of maize oil and animal fat, or MCFA oil (56 % octanoate and 40 % decanoate), to evaluate EE. They found that EE after consumption of MCFA (compared with LCFA) was 48 % greater in lean individuals, and 65 % greater in obese individuals. Dulloo *et al.*[53] compared the effects of low-to-moderate amounts of MCFA and LCFA consumption in eight healthy adult men. Subjects were given MCFA and LCFA (30 g total) at (g:g) ratios of 0:30, 5:25, 15:15 and 30:0, and their EE were measured. Increases in EE of 45, 135 and 265 kJ were reported following 5, 15 and 30 g of MCFA in the diet, respectively, suggesting an approach to altering body fat composition and metabolism. White *et al.*[54], however, cautioned that the anti-obesity effect of MCFA results could be transient, as they found that short-term feeding of MCFA-enriched diets increased temporary EE, yet with longer intake, this benefit was reduced. Encouragingly, however, a double-blind controlled trial in men and women (*n* 78) over a 12-week period demonstrated a greater reduction in body weight and fat following the daily ingestion of 60 g/d of MCFA compared with 60 g/d LCFA[35], with other major dietary parameters not being significantly different. Furthermore, several studies have now shown that EE is higher when diets contain MCFA rather than LCFA; thus, MCFA are more conducive to weight loss[47,55–58]. The above studies are encouraging, yet may need to be repeated in larger cohorts to give the results further validation. However, a recent study in 2010 has concluded that there is no evidence that fatty acid chain length has an effect on the measures of appetite and food intake when assessed following a single high-fat test meal in lean participants. This study failed to observe any differences between SCFA (dairy fat), MCFA (coconut oil) and LCFA (beef tallow) when energy is held constant at a test meal[59]. Hamsi *et al.*[40] showed that heating of VCO repeatedly, which is a common practise in order to save the cost, could have detrimental effects on the body weight. This study demonstrated that rats fed with VCO, repeatedly heated one, five and ten times, resulted in higher weight gain than the non-heated oil-fed group. This finding is not unique to coconut oil, but is in line with earlier animal studies, which showed that heated palm oil and soya oil resulted in greater body weight gain compared with the control group[41,42].

PUFA play wide range of roles in cell metabolism, signalling and inflammation. Of the PUFA, very-long-chain EPA and DHA found principally in fish play key roles in metabolism and inflammation. Some studies have suggested that MCFA can enhance the positive effects of other dietary lipids such as PUFA. Conjugated linoleic acid, such as fish oil, is a popular dietary supplement marketed for its role in enhancing fat metabolism[60]. Conjugated linoleic acid is purported to have several physiological functions, including appetite suppression, increased fat mobilisation and increased fatty acid oxidation[61], and in one study[37] of mice fed conjugated linoleic acid, it has been found that the addition of MCFA (through dietary coconut oil)is associated with improved lipolysis (breakdown of TAG into glycerol and NEFA) compared with diets containing conjugated linoleic acid supplemented with soya oil. However, discrepancies exist across publications; for example, a number of studies have linked coconut oil to higher levels of LDL[13,18,19], higher risks for CVD[18,19] and impairments in memory[15,16,18,19] as well as in hippocampus morphology[16,18].

## Medium-chain fatty acids can be converted to ketone bodies

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-β-hydroxybutyrate (3HB) and acetone[24] (see Fig. 2). 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 utilise alternative fuels such as monocarboxylic acids, lactate and ketones to maintain energy homeostasis[62,63], and ketone bodies are used extensively as an energy source during glucose deficiency (ketosis)[64,65]. AcAc and 3HB are short-chain (four-carbon) organic acids (ketone bodies) that can cross cell membranes freely[64], and cross the BBB through proton-linked, monocarboxylic acid transporters[64].

Ketone bodies are absorbed by cells and converted back to acetyl-CoA, which enters the citric acid cycle (Krebs cycle) and is oxidised in the mitochondria to provide ATP[66] and also

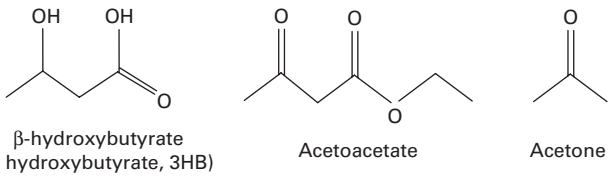


**Fig. 2.** Ketone bodies.

precursors of acetylcholine[62] in neurons. Alternatively, ketone bodies can be converted to acetyl-CoA in the brain for the purpose of synthesising LCFA[62,64,67].

## Ketogenic diets

Diets that comprise very low carbohydrate levels, substantial amounts of protein and high fat levels have a capacity to result in the production of high levels of ketone bodies (3HB, AcAc and acetone) and are often known as ketogenic diets (KD)[68]. A KD has been found to be one of the most effective therapies for drug-resistant epilepsy; it has also provided specific benefits in conditions such as GLUT protein I (GLUT-I) deficiency, pyruvate dehydrogenase deficiency, myoclonic astatic epilepsy (Doose syndrome), tuberous sclerosis complex, Rett syndrome and severe myoclonic epilepsy in infancy (Dravet syndrome)[69–74]. Despite being used for many decades, the mechanism whereby a KD can reduce epilepsy is not understood. Recent research has suggested ketosis, reduced glucose, elevated fatty acid levels and enhanced bioenergetics reserves, as well as neuron-specific effects such as modulation of ATP-sensitive potassium channels, enhanced neurotransmission, increased brain-derived neurotrophic factor expression due to glycolytic restriction and reduced neuroinflammation may be involved.

Rats maintained on a KD display an altered influx of nutrients to the brain, due to the up-regulation of both ketone transporters and GLUT type 1[75–77]. However, in early studies, it has also been found that the classic KD leads to a higher risk of atherosclerosis[78], a condition known to increase the risk of AD. More recent studies have indicated that the fatty acid content of the KD influences this risk of atherosclerosis: the classic KD contains a 4:1 or 3:1 ratio (by weight) of fat to combined protein and carbohydrate[79], with most of this fat being LCFA. Later studies have found that altered KD that are rich in MCFA, sometimes known as the MCT-KD, are more nutritionally adequate than classic KD, and are still effective in treating epilepsy disorders yet reduce cardiac risk[80,81]. The MCT-KD countenances more fruits and vegetables, more food choices and causes lesser incidence of kidney stones, hypoglycaemia, constipation, low bone density and growth retardation[81].

The MCT-KD contains less fat overall, as it includes MCFA (from coconut oil) that can provide a greater amount of ketone bodies per gram of fat and thus allows more carbohydrate and protein in the diet, making the diet more palatable than the classic KD. KD rich in MCFA have significant effects on lowering the cholesterol:HDL ratio compared with the classic KD[80].

The use of glucose for energy is vital in the brain; yet, this system is impaired in AD, partly due to disruption of the insulin signalling mechanism[82]. Low glucose utilisation has been demonstrated in many studies by fluoro-2-deoxy-D-glucose positron emission tomography imaging in AD subjects. Importantly, this has also been detected in elderly people who later develop AD[83]. In fact, the strikingly reduced expression in the central nervous system of genes encoding insulin, insulin like growth factor I (*IGF-I*) and insulin like growth factor II (*IGF-II*), as well as the insulin and IGF-I receptors, suggests that AD may represent a neuroendocrine disorder, which has been termed 'Type 3 diabetes'. Since energy provision via glucose appears to be inadequate in emergent (pre-clinical) AD as well as established AD, it has been suggested that an enhanced supply of ketone bodies may be beneficial due to the resultant enhanced ATP output of mitochondria[69,76,84]. In type 1 diabetic patients, who would also benefit considerably from sources of energy other than glucose to maintain brain energy homeostasis, an elevation in 3HB levels in plasma[63] has been observed when coconut oil has been consumed.

The effectiveness of KD diets in raising ketone body levels is measurable in plasma, as has been shown, for example, by measuring increased 3HB levels in rat plasma[75]. Significantly, some clinical studies of AD or mild cognitive impairment patients[63,75,85,86] have reported positive effects on cognitive performance after consuming MCFA-rich foods, while also observing significant increases in blood 3HB levels after treatment ($P = 0{\cdot}007$)[85]. However, in this last study, the cognitive improvement has not been seen in ApoE-ε4 allele carriers (carriage of ApoE-ε4 alleles increases AD risk). Later studies investigating KD diets in AD patients have shown that KD diets raised mean serum 3HB levels from about 0·1 mmol/l to about 0·4 mmol/l in these patients[87]. In this trial, AD patients have demonstrated improvement in cognition when measured at 45 and 90 d post ketone supplementation. However, the benefits were seen only in ApoE4-ε4 allele-negative patients and resulted in adverse events including diarrhoea, flatulence and dyspepsia. Additional research is important to determine the therapeutic benefits of MCT for patients with AD and how ApoE-ε4 status may mediate β-OHB efficacy.

Barañano & Hartman[84] supported the concept that KD can enhance the mitochondrial production of ATP, and prevent the development of AD via numerous other pathways. Together with ATP production, mechanisms proposed include altered brain pH affecting neuronal excitability, direct inhibitory effects on ion channels, increasing levels of both ketone transporters and GLUT-1, increasing capillary density or improving the regulation of sirtuins, a family of proteins that play a major role in mediating anti-ageing effects of energy restriction.

In AD, the deposition of aggregated Aβ peptides in the brain is recognised as a hallmark feature of AD, and while it is known that Aβ is formed by proteolytic cleavage of the amyloid precursor protein (APP) by various proteases, the mechanisms that cause the peptide to accumulate in the brain, aggregate and cause neuronal toxicity are not fully understood[88]. By providing an alternative energy source to glucose, ketones may be able to sustain neuronal viability. In support of this, a dual-tracer positron emission tomography imaging study of rats on a KD showed that the diet caused increases in brain uptake of the two tracers $^{11}$C-AcAc and $^{18}$F-fluorodeoxyglucose S[89]. Later studies by the same group have shown that a 14-d KD could increase the cerebral metabolic rate of AcAc and glucose by 28 and 44 %, respectively, in aged (24-month) rats[90]. Another recent pilot study[91], which investigated the effects of coconut oil supplementation directly on cortical neurons treated with

amyloid-(A) peptide *in vitro*, has indicated that neuron survival in cultures co-treated with coconut oil and Aβ is rescued compared with cultures exposed only to Aβ. Coconut oil co-treatment also attenuated Aβ-induced mitochondrial alterations. The results of this pilot study have provided a basis for further investigation of the effects of coconut oil, or its constituents, on neuronal survival, focusing on the mechanisms that may be involved[91]. There are some contrasting results among the Animal studies. Van der Auwera *et al.*[92] reported a decrease of Aβ in the brain of young transgenic AD mice over expressing the London APP mutation fed with KD for 1·5 months, while study with aged dogs that has reported the effect of KD on Aβ is restricted to the parietal lobe of the brain[93]. Kashiwaya *et al.*[94] observed that long-term (8 months) feeding of a ketone ester in middle-aged mice (8·5 months old) improved cognition and reduced Aβ and τ pathology. Another study[95] has demonstrated that AD mice model fed with a high-fat, low-carbohydrate KD shows improved motor function but without changes in Aβ. Providing further support for the benefits of high dietary MCFA levels against AD, an *in vitro* study demonstrated that the addition of ketone bodies (β-hydroxybutyrate) protects the hippocampal neurons from Aβ toxicity, thus suggesting possible therapeutic roles for KD on mitochondrial defects related to AD[69]. Few studies have demonstrated that KD could significantly improve glucose homeostasis, reducing metabolic dysregulation and insulin resistance (IR), which is important to reduce the pathology of AD[96–98].

Morris *et al.*[99] suggested that a high intake of unsaturated, unhydrogenated fats may be protective against AD, proposing that coconut oil may also be protective against AD. Despite the positive effect of KD, how the KD affects β-amyloid levels and whether this effect could be disease modifying in AD requires further study.

## Adverse effects of ketones

There is a paucity of data on the adverse effects of ketone administration in the literature. A study has reported significant rise in the mean blood cholesterol level to over 2500 mg/l following a prolonged intake of a KD[100]. This effect, in turn, may be atherogenic, leading to lipid deposition in blood vessels. Some researchers have observed dilated cardiomyopathy in patients on the KD, due to the toxic effects of elevated plasma NEFA. Further, an increased incidence in nephrolithiasis as well as increases in serum uric acid levels has been reported[101,102]. Some side effects are common following administration of ketone bodies, such as dehydration and hypoglycaemia. However, growth retardation, obesity, nutrient deficiency, decreased bone density, hepatic failure and immune dysfunction are also observed, but not frequently[81,87].

Hiraide *et al.*[103] reported a significant increase in pH and Na concentrations following the administration of a 20 % solution of Na β-hydroxyl butyrate (BHB) to severe trauma patients. Also, reduction in glucose cerebral metabolism and the increase in cerebral blood flow were observed by Hasselbalch *et al.*[104] during the administration of intravenous BHB. The long-term consequences of these deviations are not yet known.

KD with high-protein diets may cause possible kidney damage due to high levels of N excretion during protein metabolism[105]. However, several researches have reported that even high levels of protein in the diet do not damage renal function[106]. KD with very low carbohydrate can cause a regression of diabetic nephropathy due to acidosis[107]. As the concentration of ketone bodies never rises above 8 mmol/l, this risk is minimum with normal insulin function subjects[108].

## Coconut oil as a source of antioxidants

Antioxidants are substances of natural and synthetic origin that have a high potential to scavenge free radicals[109–111]. 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[109,110,112], many suggest that combinations of (rather than individual) antioxidants are beneficial[113]. Coconut oil has a high percentage of phenolic acids, and these are phytochemicals, sometimes also referred to as a polyphenols. Phenolic acids are recognised for their antioxidant properties. *p*-Coumaric acid, ferulic acid, caffeic acid and catechin acid are the major phenolic acids found in coconut oil[22]. The hydroxyl group of phenolic compounds may be able to reduce the toxicity of the Alzheimer's Aβ peptide[114–118]. *In vitro* studies that have investigated flavonoids indicate that the hydroxyl groups could trap hydrogen bonds of Aβ, which is important as this may reduce Aβ aggregation[114]. It has also been shown that phenolic compounds can bind Aβ fibrils with their long axis parallel to the long axis of Aβ fibrils[119]. Several other phenolic compounds have been shown to prevent Aβ aggregation and/or toxicity such as resveratrol, catechin and curcumin[120,121]. However, despite the encouraging studies mentioned above, the exact mechanisms by which the phenolic group affects Aβ toxicity is not currently clear. While data from AD studies[80–83] have suggested the beneficial effects of phenolic compounds on Aβ-related pathology, some discrepancies still exist. For example, recent work has demonstrated a significant inhibition of Aβ oligomers as well as higher growth of Aβ fibrils[122] by phenolic compounds. These controversial results should be investigated further[123].

Ferulic acid (4-hydroxy-3-methoxycinnamic acid) is a phenolic compound that has potent antioxidant and anti-inflammatory activities[124,125]. Ferulic acid, in particular, is one of the phenolic compounds demonstrated to have strong anti-Aβ aggregation properties[126]. Researchers have found that the chronic administration of ferulic acid can reduce cortical levels of Aβ1-40 and Aβ1-42 as well as IL-1β levels in APP/PSI AD-model transgenic mice[127]. Ferulic acid has also been shown to inhibit Aβ deposition in the brain[127]. However, another study has found that ferulic acid could not prevent the formation of Aβ fibrils, but could reduce the length of the fibrils[128]. It appears that ferulic acid may be able to interrupt the elongation process

by binding to the Aβ fibrils[129]. In other mouse studies, the long-term administration of ferulic acids could suppress the increase in glial fibrillary acidic protein and IL-1β immunoreactivity in the hippocampus that is induced by Aβ 1–42 treatment[130].

*p*-Coumaric acid is another compound found in coconut oil that has high antioxidant capacity[131]. Maltolyl *p*-coumarate had been found to attenuate cognitive deficits in rat models and to cause a reduction in apoptotic cell death in the hippocampus of Aβ1–42-infused rats. All these studies have suggested that coconut oil contains many antioxidants with the potential to reduce the development of AD pathology.

## Coconut oil in insulin resistance and control of plasma lipids

There are currently no effective AD treatments, and there is currently no cure on the immediate horizon. As mentioned earlier in this review, health issues, such as IR and obesity, similar to CVD, disrupted cholesterol metabolism, type 2 diabetes and hypertension, are all risk factors for AD[132,133]. Recent studies, many of which have already been mentioned, have shown that including coconut oil in the diet can reduce the risk of these factors, and due to the major disruption in insulin function that appears to happen early in the pathogenesis of AD, this aspect has gained particular attention.

IR is a condition where cells fail to respond to the normal actions of the hormone insulin[134]. This results in hyperinsulinaemia that can eventually be diagnosed as type 2 diabetes. Insulin and insulin receptors have been reported to be enriched in brain areas where memory functions take place[134]. Therefore, impaired insulin regulation results in cognitive and memory shortfalls, such as those observed in AD patients as well as people with mild cognitive impairment[135]. Insulin is also an important regulator of proteins involved in the pathology of AD, namely the APP, and τ[136]. Poor insulin action leads to poor regulation of brain glucose levels, which, in turn, can lead to an acceleration of neurodegeneration, due to oxidative stress and increased Aβ production from APP, both of which are key steps in the pathogenesis of AD[88].

A higher rate of diabetes has developed in India and South Pacific Islands following dietary changes from traditional fats such as ghee and coconut oil to polyunsaturated fats such as sunflower or safflower oils[137]. Conversely, researchers have observed that a diet rich in coconut oil shields against IR in diabetic rats[138]. Furthermore, a more recent study has found that rats fed with LCFA and *n*-6 PUFA for 8 weeks induce IR, and increased the expression of liver X-receptors (LXRα), carbohydrate response element binding protein and LCFA elongase-6 in the liver and white adipose tissue[139]. In contrast, the rats fed MCFA (from coconut oil) had reduced LXRα, carbohydrate response element binding protein and LCFA elongase-6 expression as well as improved insulin signalling and less IR. In an *in vitro* study that compared LCFA and MCFA effects in myotubes, it has been found that MCFA-treated cells displayed less lipid accumulation, and MCFA increased the intrinsic respiratory capacity of mitochondria without increasing oxidative stress (less reactive oxygen species generation)[140]. Furthermore, in studies of thiazolidinediones, ligands that increase insulin sensitivity in type 2 diabetes via the PPARγ, it has been found that certain MCFA such as those in coconut oil (C8–C10) are low-potency agonists, yet without the deleterious side effects[141]. Such studies are beginning to characterise the mechanisms involved in the insulin signalling-protective effects of MCFA-containing diets. However, not all studies agree; for example, one study of male rats on a MCFA-rich diet has found that the diet causes increases in body adiposity and hyperinsulinaemia and reduces insulin-mediated glucose uptake in the skeletal muscle[142], indicating that further research is required to understand the metabolism and effects of different MCFA.

The major components in coconut oil that are believed to be involved in reducing IR are fatty acids (such as lauric acid (45–50 %) and capric acid) and phenolic compounds (such as ferulic acid and *p*-coumaric acid)[143,144]. 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 coconut oil[4].

## Coconut oil and lipid metabolism

The addition of VCO to the diet has also been associated with a decrease in plasma LDL-cholesterol (LDL-C) and TAG levels and an increase in HDL-cholesterol levels[19]. In this rat study, Nevin & Rajamohan[19] demonstrated that VCO has a higher capacity to reduce serum LDL levels than copra oil, and to reduce LDL oxidation by physiological oxidants. Another study has concluded that coconut oil can lower cholesterol synthesis in human subjects, possibly due to lower production rates of apoB-containing lipoproteins[145].

Abnormal metabolism of lipoproteins such as lipoprotein (a)/Lp(a) and their variants has been associated with peripheral artery disease, stroke, atherosclerosis, cerebrovascular disease as well as AD[146,147]. Coconut oil has been shown to help reduce Lp (a) levels, and the addition of coconut oil to the diet may improve cholesterol metabolism. In a study of twenty-five women, it has been observed that lipoprotein(a) levels are 13 % lower after the women had consumed a high-fat diet containing coconut oil (38·4 % of energy from fat)[23]. The same study has found that the postprandial plasma concentration of tissue plasminogen activator antigen (tPA antigen, often abnormally high in diabetes/IR)[148], has dwindled when the women consumed the high-fat coconut diet, when compared with women who had consumed a diet high in unsaturated fat. Another study of women has noted that dietary coconut oil intake has been positively associated with HDL-cholesterol levels, especially among pre-menopausal women; the study has also found that coconut oil consumption did not cause a significant increase in LDL-C or TAG levels[149]. A meta-analysis[150] of prospective epidemiological studies has demonstrated that dietary saturated fat is not associated with an increased risk of CHD or CVD. In contrast to these positive studies, Tsai *et al.*[151] reported that both MCT and lauric acid raised serum LDL-C concentrations compared with the more polyunsaturated

baseline diet. Cater *et al.*[152] also showed that MCT have one-half the potency that palmitic acid has at raising total and LDL-C concentrations. Interestingly, in 2004, Tholstrup *et al.*[34] observed that MCFA had a hypercholesterolaemic effect. One study has noted that soya oil reduces cholesterol to a greater degree than coconut oil with no influence on HDL-cholesterol[153], and addition of Psyllium fibre supplementation lowers serum cholesterol regardless of saturation level of dietary fat[153]. As cholesterol metabolism and AD pathology have been shown to be linked[147], further clinical research is required to understand the contribution of coconut oil to cholesterol metabolism and AD. Nevertheless, due to the many likely benefits of VCO, most researchers would recommend the inclusion of coconut oil in the diet; however, researchers are yet to decide how much coconut oil is required for optimal health. Two studies have recommended a daily intake of 3·5 tablespoons of VCO for a 72 kg man[154,155]. This was based on the quantity of MCFA present in human breast milk. Interestingly, VCO and human breast milk have more saturated fats than mono- or poly-unsaturated fats, and in both cases, the main fat is lauric acid, with VCO containing the most, at about 50 %[155]. However, coconut dosage to enhance the memory of impaired people has not been concluded.

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[127,130]. Interestingly, specific fractions of coconut oil, 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[156,157].

## Coconut oil and blood–brain barrier

The blood–brain barrier (BBB) is a brain endothelial structure of the fully differentiated neurovascular system[158] that protects the brain from foreign substances. It is noted that more than 98 % of all small-molecule drugs, and approximately 100 % of all large-molecule drugs or genes, do not cross the BBB[159]. Thus, it is very difficult to develop effective new neurotherapeutics for AD that permeate the BBB. However, there is literature that indicates that circulating D-β-3hydroxybutyrate ketone body, which is formed out of MCFA, crosses the BBB and enters the mitochondria where it is metabolised to AcAc and converted to acetyl-CoA, which enters into the Krebs cycle[160]. One *in vivo* study with mice has identified the capacity of caprylic acid, a constituent of coconut oil, to cross the BBB. This study indicates that as a result of crossing the BBB, caprylic acid demonstrated anti-convulsant and a neuroprotective effect[161].

## Coconut water

In countries where coconuts are a primary produce, coconut water is a common beverage. Coconut water contains a range of beneficial ingredients, including vitamins, minerals, antioxidants, amino acids, enzymes, growth factors and other nutrients[162]. Cytokinins, a class of plant growth hormones (phytohormones) present in coconut water, influence plant cell division, and are considered to have anti-ageing properties[163,164]. There are two types of cytokinins: adenine-type cytokinins (kinetin, zeatin and 6-benzylaminopurine) and phenylurea-type cytokinins (diphenylurea and thidiazuron). Recent studies have investigated the possibility of using *trans*-zeatin as a treatment drug for neuronal diseases including AD. Zeatin has demonstrated antioxidant and cell protective effects against Aβ-induced neurotoxicity in cultures of neuronal PC12 cells, and in experiments of mice treated with scopolamine to induce amnesia, pretreatment of the mice with zeatin caused a reduction in the level of induced amnesia, according to the passive avoidance test and Y maze test[165]. Interestingly, another study has found that *trans*-zeatin could inhibit acetylcholinesterase[166,167]. This indicates that cytokinin could have therapeutic value, as levels of the neurotransmitter acetylcholine are reduced in AD, and acetylcholinesterase inhibitors are currently used to ameliorate the symptoms of AD.

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[168]. 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[169]. The combined products were found to be almost twice as effective as the products in isolation.

## Other coconut food products

Apart from coconut water and extracted coconut oil, the coconut has a number of other culinary uses. The fleshy part of the seed, the coconut meat, can be used fresh or dried in cooking. Coconut cream and coconut milk are made by pressing the flesh to extract fluid, and these are used in many countries in cooking; for example, coconut milk is a component of many curries in India, Sri Lanka and other Asian countries. Desiccated coconut and coconut flour are also used in cooking and baking. Other products include coconut chips and flakes. Each of these products has a lipid (MCFA) component, and may also contain high levels of both soluble and insoluble fibre, as well as varying levels of the antioxidants and other beneficial components already mentioned above. Research has shown that many of these coconut products can improve lipid profiles as well as provide other benefits. For example, one study[170] has shown that the consumption of coconut milk does not elevate serum lipid levels, and another study[171] has found that a coconut milk porridge fed to sixty healthy people 5 d a week for 8 weeks caused a decrease in LDL levels and an increase in HDL levels. Further studies should be carried out to help validate these significant benefits of consuming coconut milk and cream, and to determine whether such benefits are counteracted by any unfavourable changes to serum lipid profiles. In another study[172], coconut flakes have been shown to reduce total cholesterol as well as LDL-C and serum TAG levels. Coconut residue after fluid extraction has a high percentage of soluble (3·41 g/100 g)

and insoluble (34·0 g/100 g) dietary fibre[173], and such high fibre content has been suggested to contribute to many of coconut's health benefits as in the coconut flake study mentioned above.

Salil *et al.*[174] demonstrated an improvement in diabetic indicators following the consumption of coconut flesh; in this case, it is believed to be due to the protein content of coconut[175]. The coconut kernel protein is rich in arginine, and the observed anti-diabetic activity of coconut flesh has been suggested to be due to the provision of arginine, which has been shown to influence pancreatic β cell regeneration[174,175]. Similarly, another study has found that coconut water has a blood glucose-lowering effect and that coconut milk has a regenerative effect on the pancreatic cells damaged by diabetes[87]. Arginine is a precursor of NO, produced by the endothelial isoform of NO synthase, and NO is a signalling molecule that has a direct influence on insulin sensitivity. Maintaining NO production is also thought to be important in reducing cardiovascular complications of diabetes: arginine availability impacts on NO production, which can expand the blood vessels, allowing for the BP in the patients to be reduced[176].

## Conclusions

The consumption and use of coconut in its various forms has a long and established history in medicinal, scientific and nutritional arenas. While consumed prolifically in regions engaged in coconut primary production, Western cultures have tended to highlight the fatty acid content, particularly the saturated fat, and therefore limited its culinary usage.

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. Despite the positive effect of a KD, whether the KD influences β-amyloid levels and protects against AD requires further study. The dosage of ketones and the duration relevant to the AD also needs to be investigated. At this time, it is not clear whether ketone bodies produced from coconut oil has a direct effect on AD, specifically in relation to slowing or clearance of Aβ and τ pathologies – and if so, under what conditions. Furthermore, research needs to be conducted to quantify the yield of ketones from VCO, and support the ability of coconut derivatives to cross the BBB, to establish likely efficacy.

However, evidence to suggest that coconut may lower total and LDL-C, reduce systolic BP and ameliorate IR is of particular interest, in relation to AD risk reduction. A small number of clinical trials and animal studies using a formulation of MCT have reported significant improvement of cognition in AD patients. At the same time, studies in which the diet has been supplemented with SFA, particularly hydrogenated coconut oil, have reported deleterious effects on hippocampal morphology and behaviour, and increased plasma LDL levels.

Evidence suggests that despite coconut being a saturated fat, it may not pose the usual negative effects on lipid profiles; however, the influence on neuronal function and survival, as well as cardiovascular effects remains unknown. While the nutritional components of coconut are well accepted, inconsistencies in the data, it is suggested that further research needs to be undertaken before broadly advocating the use of coconut oil in addition to existing fat consumption or in substitution.

Coconut is, however, widely available, inexpensive, non-toxic and highly palatable, and consuming a regular intake of good quality coconut oil or another coconut product may become a simple yet important dietary change that may be shown in the future to reduce the risk of AD. However, research has suggested that the extraction method used to obtain VCO appears to affect the quality of coconut oil and may directly affect the efficacy. If specific extraction methods are essential to achieve efficacy, only particular preparations may confer benefit. Once this is known, further analysis needs to be undertaken regarding the absorption process, recommended dose, and whether it should be taken in combination with other food groups or in isolation.

It must be emphasised that the use of coconut oil to treat or prevent AD is not supported by any peer-reviewed large cohort clinical data; any positive findings are based on small clinical trials and on anecdotal evidence; however, coconut remains a compound of interest requiring further investigation.

## Acknowledgements

The authors gratefully acknowledge the support from the McCusker Alzheimer's Research Foundation and Edith Cowan University. W. M. A. D. B. F. is supported by the McCusker Alzheimer's Research Foundation and a grant from the CSIRO for the AIBL (The Australian Imaging, Biomarkers and Lifestyle) study. K. G. G. is supported by a grant from the Anglican Retirement Villages, Foundation for Aged Care and a grant from the CRC-Mental Health Limited. All authors contributed to the literature search, analysis of the data published, manuscript writing and revisions of the article. The authors declare no conflicts of interest arising from the conclusions of this research.

## References

1. Chetelat G, Villemagne VL, Bourgeat P, *et al.* (2010) Relationship between atrophy and β-amyloid deposition in Alzheimer disease. *Ann Neurol* **67**, 317–324.
2. Villain N, Chetelat G, Grassiot B, *et al.* (2012) Regional dynamics of amyloid-β deposition in healthy elderly, mild cognitive impairment and Alzheimer's disease: a voxelwise PiB-PET longitudinal study. *Brain Res Bull* **135**, 2126–2139.
3. Marina AM, Che Man YB & Nazimah AH (2009) Chemical properties of virgin coconut oil. *J Am Oil Chem Soc* **86**, 301–307.
4. Gopala KAG, Gaurav R, Ajit SB, *et al.* (2010) Coconut oil: chemistry, production and its applications – a review. *Indian Coconut J* **73**, 15–27.
5. Lopes MA & Larkins BA (1993) Endosperm origin, development and function. *Plant cell* **5**, 1383–1399.
6. Hahn WJ (1997) Arecanae: the palms. In Tree of Life Web Project Website. http://tolweb.org/Arecanae/21337

7. Pearsall J (1999) *Coconut Oxford Dictionary*, 10th ed. Oxford: Clarendon Press.
8. Patrick JW & Offler CE (2001) Compartmentation of transport and transfer events in developing seeds. *J Exp Bot* **52**, 551–564.
9. Janick J and Paull RE (editors) (2008) *The Encyclopedia of Fruit & Nuts*. Wallingford: CAB International.
10. Royal Botanic Gardens (2014) *Cocos nucifera* L. In *World Checklist of Selected Plant Families* [Royal Botanic Gardens, editor]. Kew: Royal Botanic Gardens.
11. Bach AC & Babayan VK (1982) Medium chain triglycerides: an update. *Am J Clin Nutr* **36**, 950–962.
12. Chandrashekar P, Lokesh BR & Gopala KAG (2010) Hypolipidemic effect of blends of coconut oil with soybean oil or sunflower oil in experimental rats. *Food Chem* **123**, 728–733.
13. Radenahmad N, Vongvatcharanon U, Withyachumnarnkul B, *et al.* (2006) Serum levels of 17β-estradiol in ovariectomized rats fed young-coconut-juice and its effect on wound healing. *Songklanagarind J Sci Technol* **28**, 897–910.
14. Radenahmad N, Saleh F, Sawangjaroen K, *et al.* (2011) Young coconut juice, a potential therapeutic agent that could significantly reduce some pathologies associated with Alzheimer's disease: novel findings. *Br J Nutr* **105**, 738–746.
15. Kumar PD (1997) The role of coconut and coconut oil in coronary heart disease in Kerala, south India. *Trop Doct* **27**, 215–217.
16. Lindeberg S & Lundh B (1993) Apparent absence of stroke and ischaemic heart disease in a traditional Melanesian island: a clinical study in Kitava. *J Intern Med* **233**, 269–275.
17. Villarino BJ, Dy LM & Lizada CC (2007) Descriptive sensory evaluation of virgin coconut oil and refined, bleached and deodorized coconut oil. *LWT Food Sci Technol* **40**, 193–199.
18. Dauqan EMA, Sani HA, Abdullah A, *et al.* (2011) Fatty acids composition of four different vegetable oils (red palm olein, palm olein, corn oil and coconut oil) by gas chromatography. In *2nd International Conference on Chemistry and Chemical Engineering,* 29–31 July 2011, Chengdu, China, pp. 31–34.
19. Nevin KG & Rajamohan T (2004) Beneficial effects of virgin coconut oil on lipid parameters and *in vitro* LDL oxidation. *Clin Biochem* **37**, 830–835.
20. Scarmeas N, Stern Y, Tang MX, *et al.* (2006) Mediterranean diet and risk for Alzheimer's disease. *Ann Neurol* **59**, 912–921.
21. Gu Y, Luchsinger JA, Stern Y, *et al.* (2010) Mediterranean diet, inflammatory and metabolic biomarkers, and risk of Alzheimer's disease. *J Alzheimers Dis* **22**, 483–492.
22. Marina AM, Man YB, Nazimah SA, *et al.* (2009) Antioxidant capacity and phenolic acids of virgin coconut oil. *Int J Food Sci Nutr* **60**, 114–123.
23. Müller H, Lindman AS, Blomfeldt A, *et al.* (2003) A diet rich in coconut oil reduces diurnal postprandial variations in circulating plasminogen activator antigen and fasting lipoprotein (a) compared with a diet rich in unsaturated fat in women. *J Nutr* **133**, 3422–3427.
24. Traul KA, Driedger A, Ingle DL, *et al.* (2000) Review of the toxicologic properties of medium-chain triglycerides. *Food Chem Toxicol* **38**, 79–98.
25. Warner K (2005) Effects on the flavor and oxidative stability of stripped soybean and sunflower oils with added pure tocopherols. *J Agric Food Chem* **53**, 9906–9910.
26. Adam SK, Das S, Faizah O, *et al.* (2009) Fresh soy oil protects against vascular changes in an estrogen-deficient rat model: an electron microscopy study. *Clinics* **64**, 1113–1119.
27. Ruppin DC & Middleton WRJ (1980) Clinical use of medium chain triglycerides. *Drugs* **20**, 216–224.
28. Masson CJ, Plat J, Mensink RP, *et al.* (2010) Fatty acid- and cholesterol transporter protein expression along the human intestinal tract. *PLoS ONE* **5**, 1–10.
29. Mishkin S, Stein L, Gatmaitan Z, *et al.* (1972) The binding of fatty acids to cytoplasmic proteins: binding to Z protein in liver and other tissues of the rat. *Biochem Biophys Res Commun* **47**, 997–1003.
30. Holt PR (2007) Intestinal malabsorption in the elderly. *Digest Dis* **25**, 144–150.
31. Mandelbaum-Schmid J (2004) Vitamin and mineral deficiencies harm one-third of the world's population. *Bull World Health Organ* **82**, 230–231.
32. McCann JC & Ames BN (2011) Adaptive dysfunction of selenoproteins from the perspective of the triage theory: why modest selenium deficiency may increase risk of diseases of aging. *FASEB J* **25**, 1793–1814.
33. Ockner RK, Manning JA, Poppenhausen RB, *et al.* (1972) A binding protein for fatty acids in cytosol of intestinal mucosa, liver, myocardium and other tissues. *Science* **177**, 56–58.
34. Tholstrup T, Ehnholm C, Jauhiainen M, *et al.* (2004) Effects of medium-chain fatty acids and oleic acid on blood lipids, lipoproteins, glucose, insulin, and lipid transfer protein activities. *Am J Clin Nutr* **79**, 564–569.
35. Tsuji H, Kasai M, Takeuchi H, *et al.* (2001) Dietary medium-chain triacylglycerols suppress accumulation of body fat in a double-blind, controlled trial in healthy men and women. *J Nutr* **131**, 2853–2859.
36. Valdivieso V (1972) Absorption of medium-chain triglycerides in animals with pancreatic atrophy. *Am J Dig Dis* **17**, 129–136.
37. Ippagunta S, Hadenfeldt TJ, Miner JL, *et al.* (2011) Dietary conjugated linoleic acid induces lipolysis in adipose tissue of coconut oil-fed mice but not soy oil-fed mice. *Lipids* **46**, 821–830.
38. Agnew IE & Holdsworth CD (1971) The effect of fat on calcium absorption from a mixed meal in normal subjects, patients with malabsorptive disease, and patients with a partial gastrectomy. *Gut* **12**, 973–980.
39. Tantibhedhyangkul P & Hashim SA (1978) Medium-chain triglyceride feeding in premature infants: effects on calcium and magnesium absorption. *Pediatrics* **61**, 537–545.
40. Hamsi MA, Othman F, Das S, *et al.* (2014) Effect of consumption of fresh and heated virgin coconut oil on the blood pressure and inflammatory biomarkers: an experimental study in Sprague Dawley rats. *Alexandria J Med* **51**, 53–63.
41. Leong XF, Najib MNM, Das S, *et al.* (2009) Intake of repeatedly heated palm oil causes elevation in blood pressure with impaired vasorelaxation in rats. *Tohoku J Exp Med* **219**, 71–78.
42. Adam SK, Das S, Soelaiman IN, *et al.* (2008) Consumption of repeatedly heated soy oil increases the serum parameters related to atherosclerosis in ovariectomized rats. *Tohoku J Exp Med* **215**, 219–226.
43. Paul NB & Concetta CD (2003) Transmembrane movement of exogenous long-chain fatty acids: proteins, enzymes, and vectorial esterification. *Microbiol Mol Biol Rev* **67**, 454–472.
44. Hoppel C (2003) The role of carnitine in normal and altered fatty acid metabolism. *AM J Kidney Dis* **41**, S4–S12.

45. Papamandjaris AA, Macdougall DE & Jones PJH (1998) Medium chain fatty acid metabolism and energy expenditure: obesity treatment implications. *Life Sci* **62**, 1203–1221.
46. Dara LD, Jessica W, Hannah B, *et al.* (2010) Role of vascular risk factors and vascular dysfunction in Alzheimer's disease. *Mt Sinai J Med* **77**, 82–102.
47. St-Onge MP & Jones PJ (2002) Physiological effects of medium-chain triglycerides: potential agents in the prevention of obesity. *J Nutr* **132**, 329–332.
48. Assuncao ML, Ferreira HS, dos Santos AF, *et al.* (2009) Effects of dietary coconut oil on the biochemical and anthropometric profiles of women presenting abdominal obesity. *Lipids* **44**, 593–601.
49. Xue C, Liu Y, Wang J, *et al.* (2009) Consumption of medium- and long-chain triacylglycerols decreases body fat and blood triglyceride in Chinese hypertriglyceridemic subjects. *Eur J Clin Nutr* **63**, 879–886.
50. Flatt JP, Ravussin E & Acheson KJ (1985) Effects of dietary fat on postprandial substrate oxidation and on carbohydrate and fat balances. *J Clin Invest* **76**, 1019–1024.
51. Hill JO, Peters JC, Yang D, *et al.* (1989) Thermogenesis in humans during overfeeding with medium-chain triglycerides. *Metabolism* **38**, 641–648.
52. Scalfi L, Coltorti A & Contaldo F (1991) Postprandial thermogenesis in lean and obese subjects after meals supplemented with medium-chain and long-chain triglycerides. *Am J Clin Nutr* **53**, 1130–1133.
53. Dulloo AG, Fathi M, Mensi N, *et al.* (1996) Twenty-four-hour energy expenditure and urinary catecholamines of humans consuming low-to-moderate amounts of medium-chain triglycerides: a dose–response study in human respiratory chamber. *Eur J Clin Nutr* **50**, 152–158.
54. White MD, Papamandjaris AA & Jones PJH (1999) Enhanced postprandial energy expenditure with medium-chain fatty acid feeding is attenuated after 14 d in premenopausal women. *Am J Clin Nutr* **69**, 883–889.
55. Noguchi O, Takeuchi H, Kubota F, *et al.* (2002) Larger diet-induced thermogenesis and less body fat accumulation in rats fed medium-chain triacylglycerols than in those fed long-chain triacylglycerols. *J Nutr Sci Vitaminol* **48**, 524–529.
56. Kasai M, Nosaka N, Maki H, *et al.* (2002) Comparison of diet-induced thermogenesis of foods containing medium versus long-chain triacylglycerols. *J Nutr Sci Vitaminol* **48**, 536–540.
57. Krotkiewski M (2001) Value of VLCD supplementation with medium chain triglycerides. *Int J Obes Relat Metab Disord* **25**, 1393–1400.
58. Baba N, Bracco EF & Hashim SA (1982) Enhanced thermogenesis and diminished deposition of fat in response to overfeeding with diet containing medium chain triglyceride. *Am J Clin Nutr* **35**, 678–682.
59. Poppitt SD, Strik CM, MacGibbon AKH, *et al.* (2010) Fatty acid chain length, postprandial satiety and food intake in lean men. *Physiol Behav* **101**, 161–167.
60. Li JJ, Huang CJ & Xie D (2008) Anti-obesity effects of conjugated linoleic acid, docosahexaenoic acid, and eicosapentaenoic acid. *Mol Nutr Food Res* **52**, 631–645.
61. Vemuri M, Kelley DS, Mackey BE, *et al.* (2007) Docosahexaenoic acid (DHA) but not eicosapentaenoic acid (EPA) prevents *trans*-10, *cis*-12 conjugated linoleic acid (CLA)-induced insulin resistance in mice. *Metab Syndr Relat Disord* **5**, 315–322.
62. Hasselbalch SG, Knudsen GM, Jakobsen J, *et al.* (1994) Brain metabolism during short-term starvation in humans. *J Cereb Blood Flow Metab* **14**, 125–131.
63. Page K, Williamson A, Yu N, *et al.* (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**, 1237–1244.
64. Morris AA (2005) Cerebral ketone body metabolism. *J Inherit Metab Dis* **28**, 109–121.
65. Sumithran P, Prendergas LA, Delbridge E, *et al.* (2013) Ketosis and appetite-mediating nutrients and hormones after weight loss. *Eur J Clin Nutr* **67**, 759–764.
66. Sato K, Yoshihiro K, Keon CA, *et al.* (1995) Insulin, ketone bodies, and mitochondrial energy transduction. *FASEB J* **9**, 651–658.
67. Serra D, Casals N, Asins G, *et al.* (1993) Regulation of mitochondrial 3-hydroxy-3-methylglutaryl-coenzyme A synthase protein by starvation, fat feeding, and diabetes. *Arch Biochem Biophys* **307**, 40–45.
68. Freeman JM & Kossoff EH (2010) Ketosis and the ketogenic diet, 2010: advances in treating epilepsy and other disorders. *Adv Pediatr* **57**, 315–329.
69. Kashiwaya Y, Takeshima T, Mori N, *et al.* (2000) D-β-Hydroxybutyrate protects neurons in models of Alzheimer's and Parkinson's disease. *Proc Natl Acad Sci U S A* **97**, 5440–5444.
70. Rho JM, Anderson GD, Donevan SD, *et al.* (2002) Acetoacetate, acetone, and dibenzylamine (a contaminant in L-(+)-β-hydroxybutyrate) exhibit direct anticonvulsant actions *in vivo*. *Epilepsia* **43**, 358–361.
71. Likhodii SS, Serbanescu I, Cortez MA, *et al.* (2003) Anticonvulsant properties of acetone, a brain ketone elevated by the ketogenic diet. *Ann Neurol* **54**, 219–226.
72. Tieu K, Perier C, Caspersen C, *et al.* (2003) D-β-Hydroxybutyrate rescues mitochondrial respiration and mitigates features of Parkinson disease. *J Clin Invest* **112**, 892–901.
73. Freeman J, Veggiotti P, Lanzi G, *et al.* (2006) The ketogenic diet: from molecular mechanisms to clinical effects. *Epilepsy Res* **68**, 145–180.
74. Imamura K, Takeshima T, Kashiwaya Y, *et al.* (2006) d-β-Hydroxybutyrate protects dopaminergic SH-SY5Y cells in a rotenone model of Parkinson's disease. *J Neurosci Res* **84**, 1376–1384.
75. Puchowicz MA, Xu K, Sun X, *et al.* (2007) Diet-induced ketosis increases capillary density without altered blood flow in rat brain. *Am J Physiol Endocrinol Metab* **292**, E1607–E1615.
76. Kwiterovich PO Jr, Vining EP, Pyzik P, *et al.* (2003) Effect of a high-fat ketogenic diet on plasma levels of lipids, lipoproteins, and apolipoproteins in children. *JAMA* **290**, 912–920.
77. Patel A, Pyzik PL, Turner Z, *et al.* (2010) Long-term outcomes of children treated with the ketogenic diet in the past. *Epilepsia* **51**, 1277–1282.
78. Klag MJ, Ford DE, Mead LA, *et al.* (1993) Serum cholesterol in young men and subsequent cardiovascular disease. *N Engl J Med* **328**, 313–318.
79. Alexander L, Rogovik MD & Ran DG (2010) Ketogenic diet for treatment of epilepsy. *Can Fam Physician* **56**, 540–542.
80. Liu YM, Williams S, Basualdo-Hammond C, *et al.* (2003) A prospective study: growth and nutritional status of children treated with the ketogenic diet. *J Am Diet Assoc* **103**, 707–712.
81. Liu YM (2008) Medium-chain triglyceride (MCT) ketogenic therapy. *Epilepsia* **49**, 33–36.
82. Steen E, Terry BM, Rivera EJ, *et al.* (2005) Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease – is this type 3 diabetes? *J Alzheimers Dis* **7**, 63–80.

83. Mosconi L (2005) Brain glucose metabolism in the early and specific diagnosis of Alzheimer's disease. FDG-PET studies in MCI and AD. *Eur J Nucl Med Mol Imaging* **32**, 486–510.
84. Barañano KW & Hartman AL (2008) The ketogenic diet: uses in epilepsy and other neurologic illnesses. *Curr Treat Options Neurol* **10**, 410–419.
85. Reger MA, Henderson ST, Hale C, *et al.* (2004) Effects of β-hydroxybutyrate on cognition in memory-impaired adults. *Neurobiol Aging* **25**, 311–314.
86. Newport MT (2010) Caregiver reports following dietary intervention with medium chain fatty acids in 60 persons with dementia. In *International Symposium of Dietary Interventions for Epilepsy and other Neurological Diseases,* October 2010, Edinburgh, Scotland.
87. Henderson ST, Vogel JL, Barr LJ, *et al.* (2009) Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled, multicenter trial. *Nutr Metab (Lond)* **6**, 31.
88. Castellani RJ, Lee HG, Zhu X, *et al.* (2008) Alzheimer disease pathology as a host response. *J Neuropathol Exp Neurol* **67**, 523–531.
89. Pifferi F, Tremblay S, Croteau E, *et al.* (2011) Mild experimental ketosis increases brain uptake of $^{11}$C-acetoacetate and $^{18}$F-fluorodeoxyglucose: a dual-tracer PET imaging study in rats. *Nutr Neurosci* **14**, 51–58.
90. Roy M, Nugent S, Tremblay-Mercier J, *et al.* (2012) The ketogenic diet increases brain glucose and ketone uptake in aged rats: a dual tracer PET and volumetric MRI study. *Brain Res* **1488**, 14–23.
91. Nafar F & Mearow KM (2014) Coconut oil attenuates the effects of amyloid-β on cortical neurons *in vitro*. *J Alzheimers Dis* **39**, 233–237.
92. Van Der Auwera I, Wera S, Van Leuven F, *et al.* (2005) A ketogenic diet reduces amyloid β 40 and 42 in a mouse model of Alzheimer's disease. *Nutr Metab* **2**, 28.
93. Studzinski CM, MacKay WA, Beckett TL, *et al.* (2008) Induction of ketosis may improve mitochondrial function and decrease steady-state amyloid-β precursor protein (APP) levels in the aged dog. *Brain Res Bull* **1226**, 209–217.
94. Kashiwaya Y, Bergman C, Lee JH, *et al.* (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. *Neurobiol Aging* **34**, 1530–1539.
95. Beckett TL, Studzinski CM, Keller JN, *et al.* (2013) A ketogenic diet improves motor performance but does not affect β-amyloid levels in a mouse model of Alzheimer's disease. *Brain Res* **1505**, 61–67.
96. Dashti HM, Mathew TC, Khadada M, *et al.* (2007) Beneficial effects of ketogenic diet in obese diabetic subjects. *Mol Cell Biochem* **302**, 249–256.
97. Westman EC, Yancy WS Jr, Mavropoulos JC, *et al.* (2008) The effect of a low-carbohydrate, ketogenic diet versus a low-glycemic index diet on glycemic control in type 2 diabetes mellitus. *Nutr Metab (Lond)* **5**, 36.
98. Paoli A, Bianco A, Grimaldi KA, *et al.* (2013) Long term successful weight loss with a combination biphasic ketogenic Mediterranean diet and Mediterranean diet maintenance protocol. *Nutrients* **5**, 5205–5217.
99. Morris MC, Evans DA, Bienias JL, *et al.* (2003) Dietary fats and the risk of incident Alzheimer disease. *Arch Neurol* **60**, 194–200.
100. Freeman JM, Vining EPG, Pillas DJ, *et al.* (1998) The efficacy of the ketogenic diet – 1998: a prospective evaluation of intervention in 150 children. *Pediatrics* **102**, 1358–1363.
101. Hall ED, Andrus PK & Yonkers PA (1993) Brain hydroxyl radical generation in acute experimental head injury. *J Neurochem* **60**, 588–594.
102. Kielb S, Koo HP, Bloom DA, *et al.* (2000) Nephrolithiasis associated with the ketogenic diet. *J Urol* **164**, 464–466.
103. Hiraide A, Katayama M, Sugimoto H, *et al.* (1991) Effect of 3-hydroxybutyrate on posttraumatic metabolism in man. *Surgery* **109**, 176–181.
104. Hasselbalch SG, Madsen PL, Hageman LP, *et al.* (1996) Changes in cerebral blood flow and carbohydrate metabolism during acute hyperketonemia. *Am J Physiol* **270**, E746–E751.
105. Westerterp-Plantenga MS, Nieuwenhuizen A, Tome D, *et al.* (2009) Dietary protein, weight loss, and weight maintenance. *Ann Rev Nutr* **29**, 21–41.
106. Skov AR, Haulrik N, Toubro S, *et al.* (2002) Effect of protein intake on bone mineralization during weight loss: a 6-month trial. *Obes Res* **10**, 432–438.
107. Poplawski MM, Mastaitis JW, Isoda F, *et al.* (2011) Reversal of diabetic nephropathy by a ketogenic diet. *PLoS ONE* **6**, e18604.
108. Cahill GF Jr (2006) Fuel metabolism in starvation. *Ann Rev Nutr* **26**, 1–22.
109. Kim DS, Park SY & Kim JY (2001) Curcuminoids from *Curcuma longa* L. (Zingiberaceae) that protect PC12 rat pheochromocytoma and normal human umbilical vein endothelial cells from βA (1–42) insult. *Neurosci Lett* **303**, 57–61.
110. Park YS & Kim DS (2002) Discovery of natural products from *Curcuma longa* that protect cells from β-amyloid insult: a drug discovery effort against Alzheimer's disease. *J Nat Prod* **65**, 1227–1231.
111. Tepe B, Sokmen M, Sokmen A, *et al.* (2005) Antimicrobial and antioxidative activity of the essential oil and various extracts of *Cyclotrichium origanifolium* (Labill.) Manden. & Scheng. *J Food Eng* **69**, 335–342.
112. Necula M, Kayed R, Milton S, *et al.* (2007) Small molecule inhibitors of aggregation indicate that amyloid β oligomerization and fibrillization pathways are independent and distinct. *J Biol Chem* **282**, 10311–10324.
113. Shah R (2013) The role of nutrition and diet in Alzheimer disease: a systematic review. *J Am Med Dir Assoc* **14**, 398–402.
114. Hirohata M, Hasegawa K, Tsutsumi-Yasuhara S, *et al.* (2007) The anti-amyloidogenic effect is exerted against Alzheimer's β-amyloid fibrils *in vitro* by preferential and reversible binding of flavonoids to the amyloid fibril structure. *Biochemistry* **46**, 1888–1889.
115. Murray NJ, Williamson MP, Lilley TH, *et al.* (1994) Study of the interaction between salivary proline-rich proteins and a polyphenol by $^{1}$H-NMR spectroscopy. *Eur J Biochem* **219**, 923–935.
116. Richard T, Verge S, Berke B, *et al.* (2001) NMR and simulated annealing investigations of bradykinin in presence of polyphenols. *J Biomol Struct Dyn* **18**, 627–637.
117. Savaskan E, Olivieri G, Meier F, *et al.* (2003) Red wine ingredient resveratrol protects from β-amyloid neurotoxicity. *Gerontology* **49**, 380–383.
118. Bastianetto S & Quirion R (2004) Natural antioxidants and neurodegenerative diseases. *Front Biosci* **9**, 3447–3452.
119. Krebs MRH, Bromley EHC & Donald AMT (2005) The binding of thioflavin-T to amyloid fibrils: localization and implications. *J Struct Biol* **149**, 30–37.
120. Ono K, Hasegawa K, Naiki H, *et al.* (2004) Curcumin has potent anti-amyloidogenic effects for Alzheimer's β-amyloid fibrils *in vitro*. *J Neurosci Res* **75**, 742–750.

121. Porat Y, Abramowitz A & Gazit E (2006) Inhibition of amyloid fibril formation by polyphenols: structural similarity and aromatic interactions as a common inhibition mechanism. *Chem Biol Drug Des* **67**, 27–37.
122. Wang J, Ho L, Zhao W, *et al.* (2008) Grape-derived polyphenolics prevent Aβ oligomerization and attenuate cognitive deterioration in a mouse model of Alzheimer's disease. *J Neurosci* **28**, 6388–6392.
123. Singh M, Arseneault M, Sanderson T, *et al.* (2008) Challenges for research on polyphenols from foods in Alzheimer's disease: bioavailability, metabolism, and cellular and molecular mechanisms. *J Agr Food Chem* **56**, 4855–4873.
124. Ono K, Hirohata M & Yamada M (2005) Ferulic acid destabilizes preformed β-amyloid fibrils *in vitro*. *Biochem Biophys Res Commun* **336**, 444–449.
125. Zhao ZH & Moghadasian MH (2008) Chemistry, natural sources, dietary intake and pharmacokinetic properties of ferulic acid. *Food Chem* **109**, 691–702.
126. Ono K, Condron MM, Ho L, *et al.* (2008) Effects of grape seed-derived polyphenols on amyloid β-protein self-assembly and cytotoxicity. *J Biol Chem* **283**, 32176–32187.
127. Ji-Jing Y, Jun-Sub J, Taek-Keun KM, *et al.* (2013) Protective effects of ferulic acid in amyloid precursor protein plus presenilin-1 transgenic mouse model of Alzheimer disease. *Biol Pharm Bull* **36**, 140–143.
128. Seema J & Jayakumar R (2012) Effect of phenolic compounds against Aβ aggregation and Aβ-induced toxicity in transgenic *C. elegans*. *Neurochem Res* **37**, 40–48.
129. McLaurin J, Kierstead ME, Brown ME, *et al.* (2006) Cyclohexanehexol inhibitors of Aβ aggregation prevent and reverse Alzheimer. *Nat Med* **12**, 801–808.
130. Ji-Jing Y, Jae-Young C, Hee-Sung K, *et al.* (2001) Protection against β-amyloid peptide toxicity *in vivo* with long-term administration of ferulic acid. *Br J Pharmacol* **133**, 89–96.
131. Konishi Y, Hitomi Y & Yoshioka E (2004) Intestinal absorption of *p*-coumaric and gallic acids in rats after oral administration. *J Agric Food Chem* **52**, 2527–2532.
132. Martins IJ, Hone E, Foster JK, *et al.* (2006) Apolipoprotein E, cholesterol metabolism, diabetes and the convergence of risk factors for Alzheimer's disease and cardiovascular disease. *Mol Psychiatr* **11**, 721–736.
133. Martins IJ, Berger T, Sharman MJ, *et al.* (2009) Cholesterol metabolism and transport in the pathogenesis of Alzheimer's disease. *J Neurochem* **111**, 1275–1308.
134. Ali AT, Ferris WF, Naran NH, *et al.* (2011) Insulin resistance in the control of body fat distribution: a new hypothesis. *Horm Metab Res* **43**, 77–80.
135. Fernández-Real JM, López-Bermejo A, Vendrell J, *et al.* (2006) Burden of infection and insulin resistance in healthy middle-aged men. *Diabetes Care* **29**, 1058–1064.
136. Behl C, Davis JB, Klier FG, *et al.* (1994) Amyloid β peptide induces necrosis rather than apoptosis. *Brain Res Bull* **645**, 253–264.
137. Sircar S & Kansra U (1998) Choice of cooking oils – myths and realities. *J Indian Med Assoc* **96**, 304–307.
138. Kochikuzhyil BM, Devi K & Fattepur SR (2010) Effect of saturated fatty acid-rich dietary vegetable oils on lipid profile, antioxidant enzymes and glucose tolerance in diabetic rats. *Indian J Pharmacol* **42**, 142–145.
139. Sun H, Jiang T, Wang S, *et al.* (2013) The effect of LXRα, ChREBP and Elovl6 in liver and white adipose tissue on medium- and long-chain fatty acid diet-induced insulin resistance. *Diabetes Res Clin Pract* **102**, 183–192.
140. Montgomery MK, Osborne B, Brown SH, *et al.* (2013) Contrasting metabolic effects of medium- versus long-chain fatty acids in skeletal muscle. *J Lipid Res* **54**, 3322–3333.
141. Liberato MV, Nascimento AS, Ayers SD, *et al.* (2012) Medium chain fatty acids are selective peroxisome proliferator activated receptor (PPAR) γ activators and pan-PPAR partial agonists. *PLOS ONE* **7**, e36297.
142. Marçal AC, Camporez JP, Lima-Salgado TM, *et al.* (2013) Changes in food intake, metabolic parameters and insulin resistance are induced by an isoenergetic, medium-chain fatty acid diet and are associated with modifications in insulin signalling in isolated rat pancreatic islets. *Br J Nutr* **28**, 2154–2165.
143. Sykes G & Margaret CH (1954) Phenol as the preservative in insulin injections. *J Pharm Pharmacol* **6**, 552–557.
144. Nomura E, Kashiwada A, Hosoda A, *et al.* (2003) Synthesis of amide compounds of ferulic acid, and their stimulatory effects on insulin secretion *in vitro*. *Bioorg Med Chem* **11**, 3807–3813.
145. Cox C, Sutherland W, Mann J, *et al.* (1998) Effects of dietary coconut oil, butter and safflower oil on plasma lipids, lipoproteins and lathosterol levels. *Eur J Clin Nutr* **52**, 650–654.
146. Iwamoto T, Watanabe D, Umahara T, *et al.* (2004) Dual inverse effects of lipoprotein(a) on the dementia process in Japanese late-onset Alzheimer's disease. *Psychogeriatrics* **4**, 64–71.
147. Matsuzaki T, Sasaki K, Hata J, *et al.* (2011) Association of Alzheimer disease pathology with abnormal lipid metabolism: the Hisayama Study. *Neurology* **77**, 1068–1075.
148. Eliasson MC, Jansson JH, Lindahl B, *et al.* (2003) High levels of tissue plasminogen activator (tPA) antigen precede the development of type 2 diabetes in a longitudinal population study. The Northern Sweden MONICA Study. *Cardiovasc Diabetol* **22**, 19.
149. Feranil AB, Duazo PL, Kuzawa CW, *et al.* (2011) Coconut oil is associated with a beneficial lipid profile in pre-menopausal women in the Philippines. *Asia Pac J Clin Nutr* **20**, 190–195.
150. Siri-Tarino PW, Sun Q, Hu FB, *et al.* (2010) Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. *Am J Clin Nutr* **91**, 535–546.
151. Tsai Y-H, Park S, Kovacic J, *et al.* (1999) Mechanisms mediating lipoprotein responses to diets with medium-chain triglyceride and lauric acid. *Lipids* **34**, 895–905.
152. Cater NB, Heller HJ & Denke MA (1997) Comparison of the effects of medium-chain triacylglycerols, palm oil, and high oleic acid sunflower oil on plasma triacylglycerol fatty acids and lipid and lipoprotein concentrations in humans. *Am J Clin Nutr* **65**, 41–45.
153. Ganji V & Kies CV (1996) Psyllium husk fiber supplementation to the diets rich in soybean or coconut oil: hypocholesterolemic effect in healthy humans. *Int J Food Sci Nutr* **47**, 103–110.
154. Hayatullina Z, Norliza M, Norazlina M, *et al.* (2012) Virgin coconut oil supplementation prevents bone loss in osteoporosis rat model. *Evid Based Complement Alternat Med* **2012**, 237236.
155. Isaacs CE & Thormar H (1990) *Human Milk Lipids Inactivated Enveloped Viruses, Breastfeeding, Nutrition, Infection and Infant Growth in Developed and Emerging Countries*. St John's Newfoundland: Arts Biomedical.
156. Seneviratnea KN, HapuarachchIa CD & Ekanayake S (2009) Comparison of the phenolic-dependent antioxidant properties of coconut oil extracted under cold and hot conditions. *Food Chem* **114**, 1444–1449.
157. Mahadevappa S, Arunchand R & Farhath K (2011) Antidiabetic effects of cold and hot extracted virgin coconut oil. *J Diabetes Mellit* **1**, 118–123.

158. Zlokovic BV (2008) The blood–brain barrier in health and chronic neurodegenerative disorders. *Neuron* **57**, 178–201.
159. Pardridge WM (2005) The blood–brain barrier and neurotherapeutics. *NeuroRx* **2**, 1–2.
160. Laffel L (1999) Ketone bodies: a review of physiology, pathophysiology and application of monitoring to diabetes. *Diabetes Metab Res Rev* **15**, 412–426.
161. Wlaź P, Socała K, Nieoczym D, *et al.* (2012) Anticonvulsant profile of caprylic acid, a main constituent of the medium-chain triglyceride (MCT) ketogenic diet, in mice. *Neuropharmacology* **62**, 1882–1889.
162. Adams W & Bralt DE (1992) Young coconut water for home rehydration in children with mild gastroenteritis. *Trop Geogr Med* **44**, 149–153.
163. Letham DS (1974) Regulators of cell division in plant tissues. XX. The cytokinins of coconut milk. *Physiol Plant* **32**, 66–70.
164. Huan L, Takamura T & Tanaka M (2004) Callus formation and plant regeneration from callus through somatic embryo structures in *Cymbidium* orchid. *Plant Sci* **166**, 1443–1449.
165. Choi SJ, Jeong CH, Choi SG, *et al.* (2009) Zeatin prevents amyloid β-induced neurotoxicity and scopolamine-induced cognitive deficits. *J Med Food* **12**, 271–277.
166. Heo HJ, Hong SC, Cho HY, *et al.* (2002) Inhibitory effect of zeatin, isolated from *Fatoua villosa*, on acetylcholinesterase activity from PC12 cells. *Mol Cells* **13**, 113–117.
167. Mirjana BČ, Danijela ZK & Tamara DL (2013) Acetylcholinesterase inhibitors: pharmacology and toxicology. *Curr Neuropharmacol* **11**, 315–335.
168. Sandhya VG & Rajamohan T (2006) Beneficial effects of coconut water feeding on lipid metabolism in cholesterol-fed rats. *J Med Food* **9**, 400–407.
169. Alleyne T, Roache S, Thomas C, *et al.* (2005) The control of hypertension by use of coconut water and mauby: two tropical food drinks. *West Indian Med J* **54**, 3–8.
170. Chukwunonso ECCE, Obioma ON & Ifeoma II (2010) Consumption of coconut milk did not increase cardiovascular disease risk in mice. *Int J Curr Res* **6**, 063–064.
171. Ekanayaka RA, Ekanayaka NK, Perera B, *et al.* (2013) Impact of a traditional dietary supplement with coconut milk and soya milk on the lipid profile in normal free living subjects. *J Nutr Metab* **2013**, 481068.
172. Trinidad PT, Anacleta SL, Aida CM, *et al.* (2004) The cholesterol-lowering effect of coconut flakes in humans with moderately raised serum cholesterol. *J Medi Food* **7**, 136–140.
173. Ng SP, Tan CP, Lai OM, *et al.* (2010) Extraction and characterization of dietary fiber from coconut residue. *J Food Agric Environ* **8**, 172–177.
174. Salil G, Nevin KG & Rajamohan T (2011) Arginine rich coconut kernel protein modulates diabetes in alloxan treated rats. *Chem Biol Interact* **189**, 107–111.
175. Nwangwa EK & Chukwuemeka PA (2011) Regenerative effects of coconut water and coconut milk on the pancreatic β-cells and cyto architecture in alloxan induced diabetic Wistar Albino rat. *Am J Trop Med Public Health* **1**, 137–146.
176. Hoang HH, Padgham SV & Meininger CJ (2013) L-Arginine, tetrahydrobiopterin, nitric oxide and diabetes. *Curr Opin Clin Nutr Metab Care* **16**, 76–82.

British Journal of Nutrition