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Potential of coconut oil and medium chain triglycerides in the prevention and treatment of Alzheimer's disease

Pratishtha Chatterjee[a,b,1], Malika Fernando[c,1], Binosha Fernando[b], Cintia B. Dias[a,d], Tejal Shah[a,b,j], Renuka Silva[c], Shehan Williams[e], Steve Pedrini[b], Heidi Hillebrandt[a], Kathryn Goozee[a,b,f,g,h], Edward Barin[i], Hamid R. Sohrabi[a,b,j], Manohar Garg[d], Stephen Cunnane[k], Ralph N. Martins[a,b,f,h,j,*]

[a] Department of Biomedical Sciences, Macquarie University, North Ryde, NSW, Australia
[b] School of Medical and Health Sciences, Edith Cowan University, Joondalup, WA, Australia
[c] Department of Applied Nutrition, Faculty of Livestock, Fisheries and Nutrition, Wayamba University of Sri Lanka, Sri Lanka
[d] Nutraceuticals Research Program, School of Biomedical Sciences and Pharmacy, University of Newcastle, Callaghan, NSW, Australia
[e] Department of Psychiatry, Faculty of Medicine, University of Kelaniya, Sri Lanka
[f] The Cooperative Research Centre (CRC) for Mental Health, Carlton South, VIC, Australia
[g] Clinical Research Department, Anglicare, Castle Hill, NSW, Australia
[h] KaRa Institute of Neurological Diseases, Macquarie Park, NSW, Australia
[i] Macquarie University Hospital, Macquarie University, North Ryde, NSW, Australia
[j] The Australian Alzheimer Research Foundation, Nedlands, WA, Australia
[k] Department of Medicine and Research Center on Aging, Université de Sherbrooke, Sherbrooke, Quebec, Canada

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ABSTRACT

Alzheimer's disease (AD) is the most common form of dementia. Currently, there is no effective medication for the prevention or treatment of AD. This has led to the search for alternative therapeutic strategies. Coconut oil (CO) has a unique fatty acid composition that is rich in medium chain fatty acids(MCFA), a major portion of which directly reaches the liver via the portal vein, thereby bypassing the lymphatic system. Given that brain glucose hypometabolism is a major early hallmark of AD, detectable well before the onset of symptoms, ketone bodies from MCFA metabolism can potentially serve as an alternative energy source to compensate for lack of glucose utilisation in the brain. Additionally, neuroprotective antioxidant properties of CO have been attributed to its polyphenolic content. This review discusses how the metabolism of CO and MCFA may aid in compensating the glucose hypometabolism observed in the AD brain. Furthermore, we present the current evidence of the neuroprotective properties of CO on cognition, amyloid-β pathogenicity, inflammation and oxidative stress. The current review addresses the influence of CO/MCFA on other chronic disorders that are risk factors for AD, and addresses existing gaps in the literature regarding the use of CO/MCFA as a potential treatment for AD.

1. Background

Alzheimer's disease (AD) is a progressive neurodegenerative disease and is the most common form of dementia (Patterson, 2018). Its major neuropathological hallmarks include senile plaques (SPs) and neurofibrillary tangles (NFTs), primarily comprising amyloid-beta (Aβ) and hyperphosphorylated-tau (p-tau), respectively (Asih et al., 2014).

Age, the ε4 allele of the apolipoprotein E (*APOE*) gene, certain genetic polymorphisms, hormonal changes and lifestyle factors influence the risk of the common, sporadic form of AD (Martins et al., 2018). Additionally, cardiovascular disease, dyslipidemia, hypertension, obesity, insulin resistance and type II diabetes (T2D) are all risk factors for AD. Interestingly, several risk factors mentioned above are mostly preventable conditions and are known to lead to chronic inflammation and increased oxidative stress, both believed to be central to AD pathogenesis. Modification of these risk factors, as well as lifelong learning or cognitive training have all been suggested to reduce the risk of cognitive decline (Baumgart et al., 2015). Moreover, physical activity and a diet high in fruits and vegetables have been reported to be inversely associated with AD-related neuropathology and cognitive

* Corresponding author at: School of Medical Science, Edith Cowan University, 270 Joondalup Drive, Joondalup, WA, 6027, Australia.
E-mail address: r.martins@ecu.edu.au (R.N. Martins).
[1] Authors contributed equally to the manuscript.

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decline, respectively (Brown et al., 2013; Gardener et al., 2015). Further, high adherence to the Mediterranean diet has been well recognized for its association with lower AD risk (Gardener et al., 2012; Gu et al., 2010; Martinez-Lapiscina et al., 2013; Psaltopoulou et al., 2013; Scarmeas et al., 2006; Valls-Pedret et al., 2015).

Currently, AD treatment consists mostly of acetylcholinesterase inhibitors, which temporarily ameliorate symptoms of the disease in some patients (Birks, 2006; Hansen et al., 2008; Wattmo et al., 2011). Despite considerable research targeting Aβ, there is still no medication for the prevention or effective treatment of AD, and there are no neurotherapeutics that block the progression of AD pathology. This has led to the search for alternative strategies for the prevention and treatment of AD.

One clear feature of AD pathogenesis is the decrease in cerebral glucose metabolism, observed via ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET), approximately 10–15 years prior to the clinical manifestation of AD (Asih et al., 2014; Bateman et al., 2012; Mosconi et al., 2008). Dysregulation of glucose metabolism is a major feature of AD (discussed further below), and when the brain is unable to utilize enough glucose, which is its main fuel, it can utilize ketone bodies as an alternative. A dietary source rich in ketone body precursors is coconut oil (CO). Studies show that consumption of CO and medium chain triglyceride (MCT) supplements may have therapeutic properties relevant to AD pathogenesis, as well as in the treatment of obesity, dyslipidemia, insulin resistance and hypertension. In fact, a ketogenic diet (KD) comprising high fat, low carbohydrate and adequate protein intake, has been recognized to provide symptom- and disease-modifying effects in humans (Barañano and Hartman, 2008; Gasior et al., 2006; Krikorian et al., 2012; Taylor et al., 2018b). Increased ketone levels, obtained through a balanced healthy diet containing ketone precursors such as CO and MCT, may provide an alternative energy source in the disrupted glucose metabolism that features in AD and other neurodegenerative diseases (Augustin et al., 2018; Benlloch et al., 2019; De la Rubia Orti et al., 2017; Ota et al., 2019; Wlodarek, 2019).

1.1. Coconut extraction and uses

CO, extracted from the pulp of the fruit of the coconut tree (*Cocos nucifera* L.), has traditionally been used for nutritional, medicinal and cosmetic purposes for centuries. In the tropics, particularly in regions of India, Sri Lanka, Malaysia and the Philippines, CO is the most popular choice of cooking oil. CO extraction, chemistry, and applications have been reviewed in detail by Gopala Krishna and colleagues (Gopala Krishna et al., 2010). Production methods vary considerably. The wet processing extraction method involves collecting oil from freshly extracted coconut milk without using high heat ($\leq 60-80$ °C), chemicals or shear, while the conventional CO, i.e. refined, bleached and deodorised (RBD) CO, is extracted from dry copra and may be exposed to high temperatures and chemicals during the refining process (Gopala Krishna et al., 2010). Virgin coconut oil (VCO), extracted using the wet processing method, has been regarded to have superior properties such as improving serum lipid profiles (reducing total cholesterol, triglycerides, low density lipoprotein (LDL) and very low density lipoprotein (VLDL) and increasing high density lipoprotein (HDL)) and superior antioxidant properties, attributed to its high phenolic content, compared to RBD CO (Nevin and Rajamohan, 2004). The higher hydrogen peroxide levels in RBD CO compared to VCO (Dayrit et al., 2011, 2007) may also contribute to these differences. However, the fatty acid compositions of the two oil preparations are reportedly relatively similar (Dayrit et al., 2011, 2007; Marina et al., 2009b, c).

CO primarily comprises saturated fats (> 90 %) and small amounts of monounsaturated and polyunsaturated fatty acids (Table 1) (1999). Due to its high saturated fat level, several health organisations have cautioned against regular CO intake, given that diets rich in saturated fat have been associated with coronary heart disease (CHD), as well as dementia (Barnard et al., 2014; Morris and Tangney, 2014; Ulbricht and Southgate, 1991). However, the saturated fatty acids associated with disease are largely long chain fatty acids (LCFA), and not the MCFA found in CO. Since the major proportion of the saturated fatty acids in CO are MCFA (~60 %), which include C8 (caprylic acid), C10 (capric acid) and C12 (lauric acid), these concerns should be reconsidered (Khaw et al., 2018; Zhuang et al., 2019) (discussed further in the supplementary material).

1.2. Disturbances in brain energy metabolism are associated with AD: rationale for ketone body supplementation

Cerebral glucose hypometabolism is prevalent in AD and serves as an AD biomarker (Bateman et al., 2012; Mosconi et al., 2008). Recent evidence suggests that the overall decline in brain energy metabolism in individuals with mild cognitive impairment (MCI) and AD is mostly due to glucose hypometabolism, while brain ketone metabolism remains intact (Castellano et al., 2015; Croteau et al., 2017). Despite having normal cognition scores, regional deficit in brain glucose uptake is observed in elderly people over 65 years as well as in young adults (< 40 years) with a genetic predisposition for AD (carriage of an ADAD mutation or *APOE* ε4 allele(s)), mild insulin resistance or maternal family history of AD (Bateman et al., 2012; Cunnane et al., 2016a). Recently, AD brain investigations showed that higher brain tissue glucose concentration, reduced glycolytic flux, and lower levels of the GLUT3 glucose transporter correlate with AD pathology severity, indicating impaired glucose metabolism is intrinsic to AD pathogenesis, starting many years before clinical symptoms appear (An et al., 2018).

In a study of older human adults (mean age 74 years) compared to younger human adults (mean age 26 years), the older adults had lower glucose (K_{Glu}) and acetoacetate (K_{AcAc}) rate constants, and lower CMR_{glu} in frontal, temporal and subcortical regions, compared to the younger adults, yet there were no significant changes in CMR_{AcAc} in the older subjects (Nugent et al., 2014). More recently, a comparison of brain glucose and AcAc metabolism between MCI, early AD patients and cognitively healthy older adults found the CMR_{Glu} and the K_{Glu} were approximately 11 % and 15 % lower respectively, in the frontal, parietal, temporal lobes and in the cingulate gyrus of AD patients compared to controls, and 7 % glucose hypometabolism was observed in the cingulate gyrus of MCI individuals compared to controls (Croteau et al., 2017). However, no significant difference was observed in the CMR_{AcAc} or K_{AcAc} between controls and MCI or AD individuals (Croteau et al., 2017). Similarly, another study has reported a 13 % lower global CMR_{Glu} in mild AD patients compared to controls, yet no significant differences in CMR_{AcAc} or K_{AcAc} between groups (Castellano et al., 2015). Overall, these studies indicate glucose metabolism is affected in individuals at risk of AD or with AD, however, differences in ketone body metabolism (CMR_{AcAc}) are not apparent between control and AD individuals, therefore supporting ketone body supplementation as a potential therapeutic agent for AD.

2. Aspects of CO digestion and metabolism that may influence neuroprotection and AD pathogenesis

2.1. Digestion and metabolism of CO medium chain triglycerides

CO contains MCT that undergo hydrolysis by the enzyme lipase following ingestion, to give rise to MCFA. The fatty acid content in CO makes it unique, as most vegetable oils (except palm kernel oil) and animal fats primarily comprise LCFA (≥C14) (Clark et al., 2014; Orsavova et al., 2015; Pham et al., 1998). Furthermore, the unique structure of the CO triglycerides, where over 60 % of the MCFA are present in either the sn-1 or sn-3 positions of the triglyceride backbone, has been observed to favor quicker absorption compared to LCFA (Dayrit, 2015; Pham et al., 1998; Porsgaard and Hoy, 2000). Therefore, CO and palm kernel oil have markedly different triglyceride compositions, and different patterns of metabolism (Dayrit, 2015). The stereospecificity of the dominant triglyceride species reported in coconut oil

are C12-C12-C12, C10-C12-C12 and C10-C12-C14, whereas in palm kernel oil, they are C12-C12-C12, C14-C18-C12 and C18:1-C12-C18:1 (Karupaiah and Sundram, 2007).

Clinical studies have shown that about two-thirds of ingested MCFA are transported via the portal vein to the liver, while only one-third is incorporated into chylomicrons (whereas C14, C16 and C18 fatty acids were almost exclusively packaged into chylomicrons) (Bragdon and Karmen, 1960). However, it is important to note that the fraction of MCFA going into the lymphatic circulation also depends on the amount of MCT ingested, the rest of the diet, and the treatment length (Swift et al., 1990). Additionally, unlike LCFA which require carnitine assistance to cross the mitochondrial membrane, MCFA (including lauric acid) enter the mitochondria by passive diffusion (Aas, 1971; Bremer, 1983; Garland et al., 1970; Garlid et al., 1996; Scholte and Groot, 1975; van Tol and Hulsmann, 1970; Williamson et al., 1968).

While it has been argued that lauric acid (a major fraction of CO) does not carry MCFA-like properties, the digestion and metabolism of lauric acid resemble those of MCFA (such as capric acid) more closely than those of LCFA (such as palmitic acid) (Dayrit, 2015). A study investigating the portal venous transport route of different fatty acids in rats found that 72 % of lauric acid, 58 % of myristic acid, 41 % of palmitic acid and 28 % of stearic acid bypassed the lymphatic pathway, highlighting the increased propensity of LCFA to enter the lymphatic pathway compared to lauric acid (Bremer, 1983; Garlid et al., 1996; McDonald et al., 1980). Furthermore, lauric acid in the bloodstream in rats has been shown to be metabolised more rapidly than palmitic acid (Goransson, 1965).

Within liver mitochondria, MCFA are metabolised to produce ketone bodies: 3-β-hydroxybutyrate (βHB), acetoacetic acid (AcAc) and acetone (Ac) (Fernando et al., 2015). However, since the liver has little β-ketoacyl-CoA transferase to convert ketone bodies to Ac-CoA for energy production via the tricarboxylic acid (TCA/ Krebs) cycle, ketone bodies from the liver are transported to tissues such as the brain, heart and muscles, which do possess the enzyme (Fig. 1).

2.2. Ketone bodies as an alternative energy source for the glucose-deficient AD brain

To reach the brain, acetone readily crosses the BBB by simple diffusion, while AcAc and βHB cross the BBB via proton-linked monocarboxylic acid transporters (Conn et al., 1983; Henderson et al., 2009; Morris, 2005; Pan et al., 2002; Pierre and Pellerin, 2005; Vijay and Morris, 2013). Glucose crosses the BBB and enters neurons via the glucose transporters GLUT1 and GLUT3, respectively (Hashim and VanItallie, 2014; Puchowicz et al., 2007) and subsequently undergoes glycolysis, producing energy. The glycolysis product, pyruvate, enters the mitochondria, which is oxidised by pyruvate dehydrogenase (PDH) to produce Acetyl-CoA (Ac-CoA); this can then enter the TCA, to generate more energy. However, in AD pathogenesis, both insulin resistance and decreased PDH activity are observed (Craft et al., 2013; Hoshi et al., 1997, 1996; Li and Holscher, 2007; Sheu et al., 1985; Sorbi et al., 1983; Veech and King, 2017), lowering the concentrations of Ac-CoA available in the mitochondria to enter the TCA cycle. Therefore, AcAc and βHB synthesized in the liver and transported to the brain may serve as an alternative source of energy.

Studies of AD as well as Parkinson's disease, amyotrophic lateral sclerosis and some mitochondriopathies have shown that ketogenic diets can ameliorate the common pathogenic feature of focal brain hypometabolism, providing an efficient energy source (Augustin et al., 2018; Wlodarek, 2019). Ketones bypass the deficiencies in complex-1 activity of these conditions (Gasior et al., 2006; Paoli et al., 2014). A recent review cited a plethora of studies which have demonstrated neuroprotective and cognitive benefits of MCT- and ketone-rich diets, though cautioned against strict ketogenic diets (Wlodarek, 2019). The supplementation of a healthy balanced diet with CO or MCT (or the replacement of current unhealthy dietary fats with CO or MCT) would not influence appetite (suggested to occur on strict ketogenic diets, though some studies dispute this) (Paoli et al., 2015), and would be a cognition-enhancing treatment that would be more easily adopted and maintained.

Clinical studies have investigated dosages to achieve therapeutic levels of plasma ketones and CMR_{AcAc} by studying the effectiveness of oral ketogenic supplements such as MCT, ketone esters and high fat KDs (Cunnane et al., 2016a, b), and some are discussed in the supplementary material.

3. Neuroprotective potential of coconut oil and coconut oil components on cognition and AD related pathogenesis

3.1. Evidence of the neuroprotective properties of CO/VCO, MCT and MCT-derived compounds

Several studies have indicated CO or CO derivatives can improve cognition. For example, in mild-moderate AD patients, the oral intake of MCT (> 95 % C8 (Reger et al., 2004); C8 and C10 (Taylor et al., 2018b)) resulted in increased plasma ketone body (βHB) concentrations, postprandially (Reger et al., 2004) and chronically (3 months) (Taylor et al., 2018a), which was associated positively with cognitive performance. In another study, the adjunctive oral administration of VCO (20 g/d) to thirty-one moderate and severe AD patients positively influenced cognitive performance, as assessed using the AD Assessment Scale-Cognitive subscale (ADAS-cog) and the Clinicians Interview based Impression of Change Plus Caregivers input (CIBIC-Plus); however, this study did not have a placebo group and therefore requires further

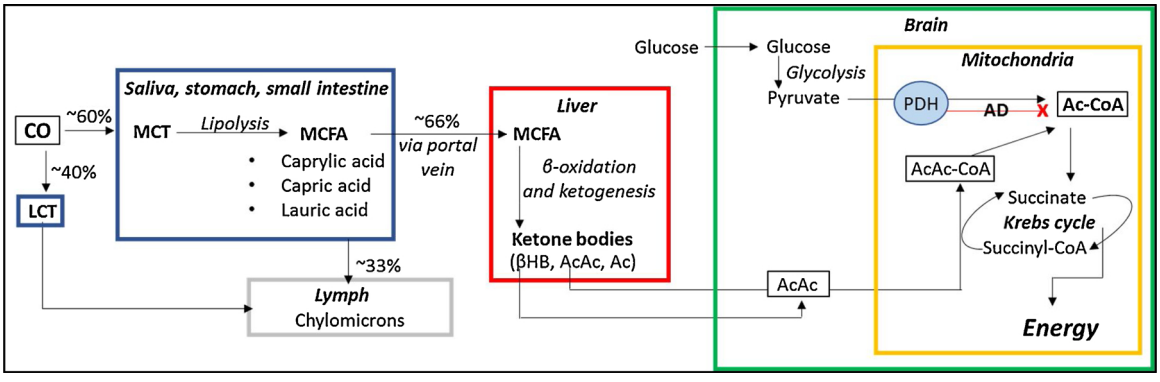

Fig. 1. Schematic of CO fatty acid digestion and metabolism, demonstrating how CO MCFA may supply energy to the brain. CO, coconut oil; LCT, long chain triglycerides; MCT, medium chain triglycerides; MCFA, medium chain fatty acids; βHB, beta-hydroxybutyrate; AcAc, acetoacetate; Ac, acetone; PDH, pyruvate dehydrogenase; AcAc-CoA, acetoacetate coenzyme A; AD, Alzheimer's disease; Ac-CoA, acetyl coenzyme A. In AD, disruptions in the glucose transporter and several TCA/Krebs cycle enzymes have been reported.

validation (Gandotra and Van der Waag, 2014). Additionally, hypoglycemic type I diabetic patients showed a significant improvement in verbal memory following oral administration of 40 g/day of MCT (67 % C8, 27 % C10 and 6 % other fatty acids) (Page et al., 2009). Further, a recent pilot study employing AD patients on an isocaloric, Mediterranean (n = 22) or CO enriched Mediterranean (n = 22) diet for 3 weeks reported improved semantic and episodic memory, and temporal orientation in those consuming CO (de la Rubia Orti et al., 2018). Furthermore, a 90 day randomised, placebo-controlled, double blind, parallel study in mild-moderate AD patients (n = 152) reported significantly elevated serum βHB concentrations following ingestion of MCT (> 95 % caprylic acid, from CO and palm kernel oil) in the treatment group compared to placebo (Henderson et al., 2009), and cognitive performance (ADAS-cog assessment), was significantly improved within the treatment group after 45 days, both when compared to baseline and when compared to the placebo group (Henderson et al., 2009). Interestingly, these observations were more pronounced in the *APOE* ε4 non-carriers (Henderson et al., 2009), and importantly, a significant positive association was observed between cognitive performance and serum βHB concentrations in the *APOE* ε4 non-carriers (Henderson et al., 2009). Additionally, decreased mitochondrial enzyme expression, including complex I–IV subunits of the electron transport chain in AD-susceptible human brain tissue (Liang et al., 2008), and the widespread dysregulation of energy metabolism observed earlier in the brain tissue samples of *APOE* ε4 versus non-*APOE* ε4-carriers is likely to have influenced the above results (Perkins et al., 2016).

The therapeutic efficacy of a βHB monoester (βHB-KET) has been investigated, as this can raise plasma ketone body levels to > 2 mM in humans (Hashim and VanItallie, 2014). It has been posited that βHB-KET generates higher energy per oxygen unit consumed, therefore having the potential to enhance therapeutic efficacy obtained from βHB (Hashim and VanItallie, 2014; Veech, 2004). One case study reported improved cognitive performance, execution of daily activities and behavior by oral administration of MCT, CO, and also βHB-KET (Newport et al., 2015), and in a triple transgenic AD mouse model, the dietary administration of βHB-KET significantly reduced anxiety and improved cognition (Kashiwaya et al., 2013). Interestingly, it also lowered levels of phospho-tau, in the hippocampus, amygdala and cortex, and decreased Aβ levels in the hippocampus and amygdala (Kashiwaya et al., 2013). Similar decreases in brain Aβ levels were first observed almost a decade earlier, on administration of a strict ketogenic diet to AD transgenic mice (Van der Auwera et al., 2005).

3.2. Evidence of the neuroprotective properties of phenolic compounds present in CO/VCO

VCO is a source of polyphenols (Illam et al., 2017), which have antioxidant properties, and is often added to other vegetable oils to improve their oxidative stability (Bhatnagar et al., 2009). As mentioned earlier, CO extraction methods influence phenolic content, with traditional extraction processes reported to yield approximately seven-fold more phenolic compounds compared to commercial extraction processes (Gopala Krishna et al., 2010).

Oxidative stress is known to play a key role in AD pathogenesis. Given that VCO is a rich source of phenolic compounds, such as caffeic acid, p-coumaric acid, ferulic acid, methyl catechin, dihydrokaempferol, gallic acid, quercetin and myricetin glycoside (Illam et al., 2017; Marina et al., 2009c), CO has also been proposed to have therapeutic value in AD pathogenesis by targeting oxidative stress. In cell culture studies (HCT-15 cells), VCO polyphenol pre-treatment was found to reduce oxidant-induced oxidative stress and cell death, restoring to near-normal the levels of glutathione, as well as glutathione reductase, glutathione peroxidase and catalase activities in the cells (Illam et al., 2017). Another *in vitro* study showed that CO had a protective effect on the survival of cortical neurons exposed to Aβ and supressed the mitochondrial alterations that were induced by Aβ in the control experiment (Nafar et al., 2017; Nafar and Mearow, 2014).

The addition of VCO to a high fat diet reduced oxidative stress and reduced the expression of the inflammasome-associated gene, NLRP3, which had been induced via Aβ and the high fat diet, in a rat model of AD (Mirzaei et al., 2018). VCO has also been reported to reduce ethyl phenyl-propiolate-induced ear edema, carrageenin- and arachidonic acid-induced paw edema and granuloma formation in male rats, further exhibiting anti-inflammatory properties (Intahphuak et al., 2010). Interestingly, a study on female Ossabaw mini-pigs on a high fat diet containing hydrogenated fats, fructose and coconut oil reported lower levels of inflammatory markers such as arachidonic acid and cytokines, IL-1β, TNF-α, IL-4, IL-10, when compared to mini-pigs fed a lean diet (Newell-Fugate et al., 2017). While CO in the high fat diet may have led to this response, the diets had many differences, and further studies are required (Newell-Fugate et al., 2017).

Maltolyl p-coumarate, an ester of p-coumaric acid (found in CO) and maltol, has been reported to decrease cognitive deficits in scopolamine-injected rats and in Aβ42-infused rats (Itoh et al., 1996; Peele and Baron, 1988; Shin et al., 2007); and in rats injected with Aβ42, the administration of p-coumarate reduced apoptosis levels (Shin et al., 2007). The CO-derived phenolic compound ferulic acid has been observed to lower cortical Aβ levels in an AD transgenic mouse model (Ji-Jing et al., 2013). Ferulic acid also possesses anti-inflammatory properties, given that mice injected with Aβ42 had reduced glial fibrillary acidic protein and IL-1β after chronic administration of ferulic acid (Sgarbossa et al., 2015; Yan et al., 2001). Other plant-derived phenolic compounds such as curcumin and grape-derived phenolics have also been reported to diminish Aβ toxicity by targeting Aβ aggregation in a transgenic AD mouse model and *in vitro* experiments (Ono et al., 2004; Porat et al., 2006; Wang et al., 2008); this may also apply to CO-derived phenolics, though the latter needs further research.

4. Influence of coconut oil and its derivatives on AD related risk factors

4.1. Therapeutic benefits of CO in obesity and CVD

Several studies have investigated this topic by examining changes in anthropometric measures, lipid profiles and blood pressure following CO supplementation/consumption. Adult male spontaneously hypertensive rats (SHR) (200 − 300 g) given VCO by gavage for 4 weeks had a lower weight gain compared to SHR on saline for the same period (Alves et al., 2015). Similarly, Sprague-Dawley rats exhibited significantly lower body weight increases following 16 weeks on a standard basal diet + VCO (1.42 mL/kg given as gavage) compared to those on a standard diet (Nurul-Iman et al., 2013).

Clinical studies have provided evidence that CO consumption can reduce waist circumference (WC) and body weight. For example, in a double blind, randomized, clinical trial involving 40 obese women aged between 20–40 years (WC > 88 cm), WC was observed to significantly decrease in the women taking CO (30 ml/day, for 12 weeks) as a dietary supplement, when compared to soy bean oil (Assuncao et al., 2009). Another clinical intervention study which involved administering VCO (30 mL/day) for 4 weeks reported significantly reduced WC in a cohort of generally healthy obese men, when compared to baseline (Liau et al., 2011), and a study conducted on moderately overweight type 2 diabetic Chinese subjects reported that moderate consumption of MCT (70 % C8 and 26 % C10, 18 g/day) reduced body weight and WC compared to consumption of long chain triglycerides (LCT) at the study endpoint of 90 days (Han et al., 2007). Additionally, a diet containing MCT (~65 % C8 and C10 derived from CO and palm kernel oil) and CO (~6 %) led to a significant decrease in upper body adiposity, and a trend towards a decrease in whole body subcutaneous adipose tissue when compared to a diet rich in LCT in humans (St-Onge et al., 2003).

These observations mentioned above support the therapeutic

Table 1
Major fatty acids present in coconut oil (FAO, 1999).

Fatty Acid	Carbon atoms: double bonds	Saturation	Percent of total FA content	MCFA/ LCFA
Caprylic acid	C8:0	Saturated	4.6–10.0	MCFA
Capric acid	C10:0	Saturated	5.0–8.0	MCFA
Lauric acid	C12:0	Saturated	45.1–53.2	MCFA
Myristic acid	C14:0	Saturated	16.8–21.0	LCFA
Palmitic acid	C16:0	Saturated	7.5–10.2	LCFA
Stearic acid	C18:0	Saturated	2.0–4.0	LCFA
Oleic acid	C18:1	Unsaturated	5.0–10.0	LCFA

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

potential of CO/MCT for the treatment of obesity, a CVD risk factor. Interestingly, there is also evidence CO moderates other CVD risk factors such as dyslipidemia and uncontrolled blood pressure (Eyres et al., 2016; Famurewa et al., 2018; Smith et al., 2011). A study of 114 coronary artery disease (CAD) participants on a standardized diet who either supplemented this diet with VCO (13 ml/day) for 3 months, or did not (control group), reported significantly decreased WC and increased high density lipoprotein cholesterol (HDL-C) in those who had consumed the VCO compared to those patients on the standardized diet alone, while no significant differences in low density lipoprotein cholesterol (LDL-C), triglycerides or blood pressure were observed (Cardoso et al., 2015). Further, in a study of women with abdominal obesity, CO supplementation (30 ml/d) for a 12-week period resulted in more favorable lipid profiles, as significantly increased HDL-C and decreased ratios of LDL-C to HDL-C were observed, when compared to soy bean oil supplementation (Assuncao et al., 2009). A study of 1839 Filipino women aged 35–69 years reported that higher dietary CO consumption was associated with higher plasma HDL-C, particularly in premenopausal women (Feranil et al., 2011). Similarly, lauric acid (the major fatty constituent of CO), has been reported to elevate both total cholesterol and HDL-C, while decreasing the ratio of total-C to HDL-C, in healthy individuals (German and Dillard, 2004).

Epidemiological studies have indicated that vascular disease is uncommon in the inhabitants of Polynesian atolls Pukapuka and Tokelau, despite coconut (mainly coconut flesh) being their main source of dietary energy (Prior et al., 1981). However, it must be noted that the lower vascular disease incidence in these individuals could also be attributed to other dietary and lifestyle factors, such as high fish consumption, and low sugar intake. Further, although there is inadequate data on dietary fibre intake in the Pukapuka population, a moderate fibre intake has been reported in the Tokelau population, which may also have influenced the above observation. Additionally, no significant difference in coconut consumption in terms of CO, coconut milk and flesh was found between CHD patients and healthy controls in independent epidemiological studies carried out in India and Indonesia (Kumar, 1997; Lipoeto et al., 2004).

Additionally, human consumption of grated coconut flesh or milk/ cream in the context of traditional dietary patterns has been reported not to lead to adverse CVD outcomes (Eyres et al., 2016; Lindeberg and Lundh, 1993; Lindeberg et al., 1996). Furthermore, a 2-year comparison of CO versus (polyunsaturated) sunflower oil for cooking media did not result in differences in the occurrence of CVD events in an Indian cohort with stable coronary artery disease, implying that CVD events are not due to CO, often maligned for its high saturated fat content (Vijayakumar et al., 2016). Additionally, both CO and lauric acid have been reported to reduce oxidative stress and lower blood pressure in spontaneously hypertensive rats (Alves et al., 2017, 2015), which are protective measures against both CVD and AD.

In studies of CO, MCT, or MCFA, it is important to understand which fatty acids have been tested – in particular, whether C12 is included. The definition of MCFA and MCT as C8 and C10 (only) has been described as having its origin in commerce, while its definition as "C6 to C12″ is based on its metabolic and physiological properties (Dayrit, 2014), though evidence suggests C12 does have some properties of both C8 and C10, as well as some properties of the longer fatty acids (Dayrit, 2014). Therefore another study which investigated saturated LCFA, and regarded them as atherogenic and thrombogenic, included C12 as well as C14, C16 and C18 in their study (Ulbricht and Southgate, 1991). The literature is also still unclear on the effect of coconut oil on blood lipids, with several animal and human studies showing an increase in total cholesterol, LDL-C and triglycerides when coconut oil consumption is compared to the consumption of other oils rich in unsaturated fats (Cox et al., 1995, 1998; Fisher et al., 1983; Heber et al., 1992; Mendis and Kumarasundaram, 1990; Mendis et al., 2001; Voon et al., 2011; Wall-Medrano et al., 2017). A summary of the clinical trials comparing CO (or VCO) with other saturated and unsaturated oils is listed in Supplementary Table 1. Interestingly, the two studies employing VCO reported significantly elevated HDL-C and no significant changes in LDL-C between participants taking VCO compared to those on a virgin olive oil/ butter/ standard diet (Cardoso et al., 2015; Khaw et al., 2018) while all other clinical trials reported increased LDL following CO intake compared to other saturated and unsaturated oils. Whether the superior properties of VCO compared to CO account for these observations is yet to be investigated, but these findings collectively indicate that the manner of CO preparation may be an important factor to consider. Wet or dry processing of the oil, and whether the oil undergoes RBD (refining, bleaching and deodorizing) processing, determines the nature of the oil and the levels of polyphenolic compounds retained in the oil (Marina et al., 2009a).

Therefore, it is important to highlight that the observed health effects of dietary CO and its derived products may be influenced by differences in processing methods, as demonstrated in comparisons of CO and VCO, as well as the form it is consumed in (oil, milk or flesh) (Eyres et al., 2016; Kumar, 1997; Lindeberg and Lundh, 1993; Lindeberg et al., 1996; Lipoeto et al., 2004; Nevin and Rajamohan, 2004, 2009). Additionally, the many variations in study design as well as population, dose and intervention length may contribute to the heterogeneity of the outcomes in CVD risk factors. Sex, for example, has been shown to modulate cholesterol homeostasis, as well as fat metabolism and deposition, thus is highly likely to influence the effects of different dietary fats on blood lipid levels and other CVD biomarkers (Koutsari et al., 2004; Marinis et al., 2008; Power and Schulkin, 2008). Together, these reports indicate that while there may be other oils that result in desirable lipid profiles for cardiovascular health, VCO and nutritional compounds derived from CO may also have therapeutic potential. However, given the inconsistency in the literature, more controlled and isocaloric clinical studies are required to evaluate the intake of VCO, RBD CO and polyunsaturated fatty acid (PUFA)-rich oils on CVD risk factors.

Furthermore in the context of CVD and T2D (which is discussed further in the next section), the sodium–glucose linked transporter 2 (SGLT-2) inhibitor treatment administered to type 2 diabetic patients, lowers glucose levels in the plasma (by lowering glucose reabsorption from glomerular filtrate) and increases plasma ketone body concentrations (Ferrannini et al., 2016a, b). Interestingly, the elevation in ketone levels has been posited to be one of the contributing factors to the 38 % plummet reported in cardiovascular related mortality in type 2 diabetic patients treated with SGLT-2 inhibitors (Ferrannini et al., 2016b; Gormsen et al., 2017). Circulating ketone bodies are readily taken up by organs, including the heart, by the monocarboxylate transporter via a saturable transport mechanism that is independent of insulin levels. The ketones are oxidized to produce energy within the TCA cycle, with a relatively lower oxygen cost, thus lowering mitochondrial oxidative stress and improving cardiac efficiency, due to inhibition of histone deacetylases (Ferrannini et al., 2016b; Shimazu et al., 2013). Concomitantly, the mitochondrial cell membrane potential is stabilized by ketone bodies, suggesting antiarrhythmic potential (Cotter et al., 2013), as mitochondrial dysfunction is central in heart

failure (Zhou and Tian, 2018). Further, PET studies of healthy people with hyperketonemia (induced by Na-3-hydroxybutyrate) demonstrated a 75 % increment in myocardial blood flow, and a concomitant reduction in myocardial glucose uptake by 50 %, without any significant change in fatty acid metabolism (Gormsen et al., 2017). The above observations reflect the potential therapeutic benefits of ketone bodies as a vasodilator, as well as a preferential fuel source in cardiac muscle cells in humans.

4.2. Therapeutic benefits of CO in insulin resistance and T2D

Strong evidence supports the associations between impaired insulin signaling and AD (Blázquez et al., 2014; Derakhshan and Toth, 2013). Impaired insulin action leads to central insulin resistance and T2D, which doubles the risk of AD (Blázquez et al., 2014). Dietary fatty acids, specifically the lauric acid present in CO, has been shown to protect against T2D (in rats), by improving glucose tolerance and insulin sensitivity (Kochikuzhyil et al., 2010). Insulin resistance, correlating with triglyceride accumulation in skeletal muscle, can be induced (in rats) by a diet high in saturated fatty acids (Storlien et al., 1991). In contrast, MCFA intake was observed to significantly stimulate basal insulin secretion and insulin sensitivity in rats and a mouse islet model, which could be due to improved ATP production via mitochondrial β-oxidation, and greater signal transduction for the exocytosis of insulin (Garfinkel et al., 1992; Wein et al., 2009).

In other studies, diabetic rats demonstrated improved levels of antioxidant enzymes and glucose tolerance when fed CO (mostly C12), compared to those fed palm oil and groundnut oil (Kochikuzhyil et al., 2010). Further, MCFA, compared to LCFA, have been reported to be beneficial in the prevention of peripheral insulin resistance and adiposity in mice (Turner et al., 2009). In studies of total parenteral infusion formulations, C6 and C8 fatty acids produced no effects and minimal effects, respectively, while C10 and C12 (and also C18 linoleic acid) stimulated insulin secretion, demonstrating the importance of the MCFA chain length (Garfinkel and Lee, 1992).

Sun and colleagues compared the effects of MCFA (CO), LCFA (lard), n-6 PUFA (sunflower oil) and n-3 PUFA (fish oil) on insulin resistance in rats, measuring the changes in liver X receptor α (LXRα), carbohydrate response element binding protein (ChREBP) and LCFA elongase 6 (Elovl6) expression in liver and white adipose tissue (WAT) after 8 weeks of supplementation. An increase in LXRα, ChREBP and Elovl6 expression and hepatic insulin resistance were noted in LCFA and n-6 PUFA groups, while the MCFA and n-3 PUFA groups demonstrated decreased expression and improved insulin signaling and decreased insulin resistance (Sun et al., 2013). Moreover, in contrast to the claims concerning heart-friendly long-chain unsaturated oils, an epidemiological study in the Indian subcontinent concluded that the traditional cooking fats including CO have a protective effect against T2D and atherosclerotic heart disease, compared to the sole or excessive use of vegetable oils rich in PUFA (Sircar and Kansra, 1998). In addition to CO, other coconut products such as coconut flesh, milk and water have also been demonstrated to have protective effects against T2D in rats (Bhagya et al., 2012; Nwangwa and Aloamaka, 2011; Salil et al., 2012).

5. Apolipoprotein E (APOE) and MCT ingestion

APOE ε4 carriage is the major genetic risk factor for AD and has been shown to be associated with decreased parietal cerebral glucose metabolism and increased parietal asymmetry in non-demented relatives of AD subjects, compared to *APOE* ε4-free relatives (Small et al., 1995). Similarly, while cognitive performance remained stable, cerebral glucose metabolism was observed to decrease in non-demented middle-aged individuals carrying an *APOE* ε4 allele, at a 2-year follow-up (Small et al., 2000). In a study with AD and MCI individuals, plasma βHB levels increased in the *APOE* ε4 non-carriers and carriers 90 min following ingestion of MCT. Interestingly, while the plasma βHB levels remained constant in the non-*APOE* ε4 carriers, they continued to rise in the *APOE* ε4 carriers in the 90 − 120 min interval (Reger et al., 2004). Additionally, on testing cognition at 90 min in these subjects, Reger and colleagues observed that MCT intake facilitated cognitive performance on the ADAS-cog in *APOE* ε4 non-carriers, but not in the *APOE* ε4 carriers (Reger et al., 2004). These observations suggest that the improved cognitive performance in the non- *APOE* ε4 carriers is not due to ketone availability, but may be the ability of the non- *APOE* ε4 carriers to more effectively use the generated ketone bodies, given that the *APOE* ε4 carriers did not show improvement in cognitive performance despite significant increases in plasma βHB levels (Reger et al., 2004). Therefore, similar to previous reports by Henderson and colleagues (Henderson et al., 2009), these *APOE* genotype-specific observations are supported by the observation of earlier and greater deficiency in cerebral glucose metabolism in *APOE* ε4 carriers compared to non-carriers, possibly due to earlier decreased mitochondrial enzyme expression and function, observed in AD brain tissue samples (Liang et al., 2008). In this case, supplementing *APOE* ε4 carriers with CO/MCT prior to the onset of cerebral glucose hypometabolism may need to be considered.

6. Conclusions and future directions

PET imaging has revealed a decrease in cerebral glucose metabolism 10–15 years prior to AD symptom manifestation (Bateman et al., 2012). Therefore, given that the deterioration of regional brain glucose metabolism is an early stage of pathogenesis (Courchesne-Loyer et al., 2017), future longitudinal clinical trials investigating the therapeutic potential of CO should include healthy older adults with normal global cognition, both with and without preclinical biomarkers of AD, as well as MCI and AD participants. Prevention, or the slowing of AD pathogenesis, should be implemented as early as possible. Whether as a supplement to a balanced healthy diet, or as part of a ketogenic diet, there is much epidemiological and intervention study evidence to warrant further CO investigations (McDonald and Cervenka, 2018). Additionally, potential epigenetic effects of CO/MCT consumption need to be investigated (Garcia-Escobar et al., 2017; Gonzalez-Becerra et al., 2019).

Additionally, it is important to acknowledge the differences between employing CO (or VCO) versus MCT oil (derived from coconut) in clinical trials, given their different constituents. VCO is rich in polyphenols; however, it also contains undesirable saturated LCFA (fatty acids with chain length > 12, ~40 %). In contrast, MCT oil only constitutes MCFA but may contain low polyphenolic concentration. The anti-inflammatory, anti-oxidative and anti-amyloidogenic properties of the phenolic compounds need further investigation, to help determine their therapeutic value. The digestion, absorption, and conversion of CO/MCT also need to be considered, as CO (compared to MCT) was found in a small clinical study to increase the plasma AcAc:βHB ratio, whereas MCT resulted in a higher overall level of ketones compared to CO, but lower plasma AcAc:βHB ratio (Vandenberghe et al., 2017). Given that βHB requires conversion to AcAc for ATP production, higher plasma AcAc:βHB ratios observed with CO intake could potentially increase the efficiency of the availability of energy from ketones (Cotter et al., 2013; Vandenberghe et al., 2017).

Further, the palatability and practicability of the KD was questioned with regard to its low carbohydrate and protein content, however, the incorporation of MCT in the KD has made it more palatable and practicable. In the classic KD, 90 % of the dietary calories were derived from fat (Wheless, 1995), whereas in the modified versions of the classic KD, MCTs (preferably from CO) contribute to 30–60 % of the calories, wherein, MCT oil provides 60 % of the total calories in the traditional MCT oil diet and 30 % of the total calories in the modified MCT diet.

It is acknowledged that there are several limitations on reviewing the literature and therefore considered, in the current review. These

include the lack of investigating and factoring in the differential effects MCT, VCO, RBD CO or PUFA-rich oils may have on lipid profiles and CVD risk. Further, there was a paucity of studies using controlled and isocaloric study designs in the current literature. Additionally, while studies on the Polynesian Pukapuka and Tokelau populations that have coconut as their main source of dietary energy report low incidence of CVD, these studies do not account for other dietary components (for example high fish consumption) and lifestyle factors, that may have also contributed to a lower incidence of CVD.

To conclude, for the treatment of preclinical AD, MCI and symptomatic AD, VCO and MCT oil extracted from CO are promising avenues that should be explored further for the management of brain glucose hypometabolism. There is also increasing evidence that VCO contains phenolic compounds that can help combat inflammation, oxidative stress and other AD-associated risk factors. However, additional studies are required to determine MCFA effects on blood lipid profiles accounting for confounding factors such as physical activity and dietary patterns, and to determine an appropriate dosage for optimal benefits to brain health.

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Appendix A. Supplementary data

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