Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Medium Chain Triglycerides (MCTs)

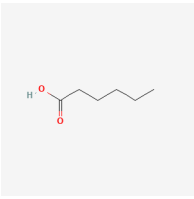
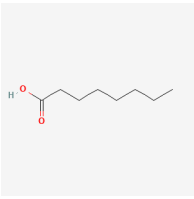
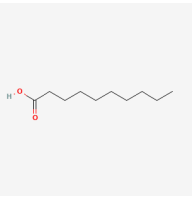
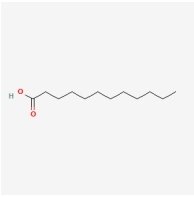
Evidence Summary

Preliminary clinical data hint at benefit for cognition in individuals with subjective or objective cognitive impairment. However, more robust and better characterized studies are needed.

Neuroprotective Benefit: Meta-analyses of clinical trials suggest MCTs might have some cognitive benefit in people with subjective cognitive decline or dementia, though not all trials were RCTs, and the largest Phase 3 trial of an MCT failed.

Aging and related health concerns: Some initial clinical evidence suggests that MCT supplementation may help improve frailty indices in older adults.

Safety: MCTs have gastrointestinal side effects that may be prohibitive to their long-term use. Few studies have investigated the long-term use of MCTs.

Availability: In foods like coconut oil or palm kernel oil, or as a supplement.	**Dose**: Studies have used a wide range of doses, from 6 to 56 grams a day in different formulations.	**Chemical formula and MW:** Caproic Acid $C_6H_{12}O_2$ 116.16 g/mol 
Half-life: 10 – 20 minutes	**BBB**: Penetrant	Caprylic Acid $C_8H_{16}O_2$ 144.21 g/mol 
Clinical trials: The largest meta-analysis identified included 848 total patients.	**Observational studies**: No observational studies of MCT supplementation were identified.	Capric Acid $C_{10}H_{20}O_2$ 172.26 g/mol 
		Lauric Acid $C_{12}H_{24}O_2$ 200.32 g/mol 
		Sources: PubChem

What is it?

As reviewed by Watanabe & Tsujino, 2022, medium-chain triglycerides (MCTs) are a kind of lipid that can be found in sources such as coconut oil and palm kernel oil. These sources can be refined to increase the concentration of MCTs, or MCTs can be synthesized. MCTs are composed of a glycerol backbone and medium chain fatty acids (MCFA) with 6-12 carbon atom tails. The main four kinds of MCTs are caproic or hexanoic acid; caprylic acid or octanoic acid; capric acid or decanoic acid; and lauric acid or dodecanoic acid. The metabolism of MCTs allows for quicker absorption and utilization as compared to long-chain triglycerides (LCTs). Upon ingestion, MCTs are digested into fatty acids; most are then

transported directly into the liver via the portal vein where they are readily metabolized into ketone bodies.

Ketone bodies such as β-hydroxybutyrate (BHB), acetoacetate (AcAc), and acetone, can be used by cells for energy metabolism. They enter the tricarboxylic acid (TCA) cycle directly, bypassing the glycolytic pathway, and mitochondria can use energy from their conversion to generate ATP. It is suggested that they may be an alternative energy source in situations of glucose hypometabolism, such as in Alzheimer's disease. Some groups are also exploring exogenous ketone supplementations such as ketone esters or ketone salts to achieve similar downstream effects to MCT supplementation (Avgerinos et al., 2022). While MCT supplementation is often studied as a monolith, there is developing appreciation for potential differences between different MCTs, like capric acid compared to dodecanoic acid (reviewed by Giannos et al., 2022 and Dunn et al., 2023), and how the ratios of the MCFAs can be impactful (Castro et al., 2023).

Plasma ketone levels are usually low (~0.2mM), and glucose supplies almost all of the brain's energy. In low carbohydrate conditions, like fasting or the ketogenic diet, plasma ketone levels can rise to 5 mM, and ketone bodies can supply nearly two-thirds of the brain's energy (Chourchesne-Loyer et al., 2013). Glucose metabolism decreases in the brains of patients with Alzheimer's disease but ketone metabolism remains to a certain extent, and raising plasma ketone levels might be an alternative strategy to supply energy to the brain of dementia patients (Castellano et al., 2015). Since fasting and ketogenic diets can be difficult and/or unpleasant to adhere to and can have negative health consequences (reviewed by Giannos et al., 2022 and Dunn et al., 2023), MCTs or exogenous ketones might be alternative strategies to raise plasma ketone levels and achieve concomitant benefits.

Neuroprotective Benefit: Meta-analyses of clinical trials suggest MCTs might have some cognitive benefit in people with subjective cognitive decline or dementia, though not all trials were RCTs, and the largest Phase 3 trial of an MCT failed.

Types of evidence:

- 3 meta-analyses and systematic reviews
- 1 systematic review
- 6 clinical trials
- 2 case studies

- 1 study protocol
- 4 reviews
- Multiple animal studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

A 2020 systematic review examined whether MCT oil may have cognitive benefits in individuals who do not have dementia. They identified 6 randomized controlled trials for review, comprising a total of 238 participants. The shortest study was a single MCT-containing meal, and the longest study was 3 months in duration. Doses ranged from 6 grams to 40 grams daily of MCT oil or matching placebo. The authors were not able to perform a meta-analysis given the different cognitive measures used, different dose, composition, and duration of MCT exposure, and lack of information on APOE status. They did find that 4 of the 6 studies reported cognitive benefits, and that this effect might be more robust in individuals with lower baseline cognitive function. Benefits were reported even from short-term use, but effects disappeared at the end of dosing. It is worth noting some of the potential shortfalls of some of the included studies that yielded positive results, including repeated testing over the course of 3 hours that might lead to practice effects and partly blinded design. In the latter case, statistically significant differences between groups were reported from the cognitive measurement performed by unblinded investigators, whereas the assessment performed by blinded investigators was not significantly different; however, as scales can have different sensitivities and test different aspects of function, it's impossible to say whether these results are from bias or an underlying biological truth (Giannos et al., 2022).

Human research to suggest benefits to patients with dementia:

Sun et al., 2023 published a systematic review and meta-analysis on the effects of MCT for AD related cognitive impairment, reviewing literature up until December 2022. They included a total of 10 total clinical trials; 8 testing the effects of MCT, and 2 testing the effects of coconut oil, comprising a total of 848 patients with MCI or AD. Three of the trials were open-label, and two were single-arm designs. Meta-analysis was complicated by the fact that not all studies were controlled or reported the pre-post change in function, and many of the studies were deemed to be of poor methodological quality. Nevertheless, in the four studies available for meta-analysis of general cognitive function, the authors found a significantly greater improvement in patients receiving MCT compared to those receiving

placebo (standard mean difference (SMD)=0.64; 95% CI 0.05 to 1.24). There was significant heterogeneity between studies. Trends towards benefit in the cognitive domains of memory, language, and attention were observed, but these trends did not reach statistical significance. The authors conclude that there may be some evidence towards benefit of MCT supplementation, but more robust studies are needed.

Three of the studies included in the above meta-analysis examined the effects of an MCT solution developed by Accera, Inc. In 2018, Accera changed their name to Cerecin after receiving new investments (AlzForum).

- In a double-blind cross-over trial, Reger et al., 2004 reported that in 20 patients (15 probable AD, 9=ApoE4; 5 aMCI, 1=ApoE4) MCTs increased plasma beta-hydroxybutyrate (BHB) levels in all patients and improved ADAS-Cog scores in ApoE4(-) patients (p=0.04) but not in ApoE4(+) patients. No groups scored better in the Stroop test and MMSE scores were not reported.
- In a double-blind randomized controlled phase II study (NCT00142805) of 152 patients with mild-to-moderate Alzheimer's disease (MMSE avg. 19.5), Henderson et al., 2009 reported that daily MCT treatment (Accera, Inc's AC-1202, classified as a medical food and known as Axona and Ketasyn) in dosage compliant ApoE4(-) subjects improved ADAS-Cog scores over placebo (day 45, 6.26 points; p=0.001; day 90, 5.33 points; p=0.006). These improvements disappeared after a 14-day washout period. There was no improvement in ApoE4(+) patients. The increase in ApoE4(-) group might be slightly exaggerated since ApoE4(-) placebo patients scored worse on the ADAS-Cog at day 45 and 90 while ApoE4(+) placebo patients remained at baseline. Also, there was a high dropout rate in MCT patients (MCT dropout = 23.3%; placebo = 6.1%). This is likely due to gastrointestinal effects commonly caused by MCT supplementation, but if non-responders dropped out, the results could be further skewed. In 2013, Accera was issued a warning letter by the FDA which stated that Ketasyn does not meet their statutory definition of a medical food but was instead an unapproved drug.
- Henderson et al., 2020 describes the double-blind randomized placebo-controlled Phase 3 trial from Accera on AC-1204 (Tricaprilin), a new formulation follow-up to Axona (AlzForum). The double blinded Phase 3 trial of AC-1204 enrolled 413 patients with mild to moderate probable AD and randomized them to either placebo or AC-1204. Participants received study medication for 26 weeks. The primary and secondary outcomes were measures of cognitive function. The trial failed to detect any differences in cognition between the AC-1204 group and the placebo group; the authors hypothesized that this was because the different formulation of AC-1204

compared to AC-1202 lead to lower drug exposure than predicted (see also a news article on the study results as well as the Cognitive Vitality blog post on this trial).

A second meta-analysis examining the effects of MCTs on the prevention and treatment of dementia was published in 2023, including literature until January 2021. This paper included studies of individuals with subjective cognitive decline, MCI, and AD, and included 16 publications and 17 studies. The authors report that all of the studies that assessed levels of blood ketone levels detected an increase after MCT supplementation (n=12). They saw more variability in change in cognition, with 4 trials reporting no differences in cognitive function, 8 studies reporting improvement in cognitive function, and 2 trials reporting improvement in cognitive function only in individuals without an APOE4 allele. When they performed a meta-analysis of the three placebo-controlled studies using ADAS-Cog as an assessment, they did not find any statistically significant differences between placebo and MCT treated groups. They report that BHB levels were significantly increased following MCT supplementation compared to control (MD=72.59 mmol/L; 95%CI 12.45 to 132.73 mmol/L; p=0.02), but that there was heterogeneity in the data (Castro et al., 2023).

A third meta-analysis and systematic review on the effects of MCT on cognition in dementia was published in 2021, including literature through March 2019. The main difference in this analysis was that the authors included pilot studies, case reports, and observational studies, which Sun et al., 2023 did not. They also included at least one paper that involved a ketogenic diet intervention. The 2021 paper also assessed the effects of MCTs on peripheral ketone levels. A total of 12 publications representing 13 studies were included; 7 were RCTs, 3 were single arm, and 3 were case studies. When examining the RCTs, the authors found a significant change in peripheral ketone levels as measured by levels of plasma BHB (mean difference [MD]=0.355; 95% CI 0.286 to 0.424), and a significant difference in cognition when they combined the standard mean differences (SMD) from different cognitive measures (SMD= −0.289; 95% CI −0.551 to −0.027) (Avgerinos et al., 2020).

MCTs might provide acute benefits in patients with Alzheimer's disease/dementia, but plasma BHB levels soon drop back to baseline and the positive benefits seem to disappear soon after MCT supplementation is suspended. In addition, since no long-term MCT study has been conducted, it is unclear whether patients taking MCTs will see sustained, long-term benefits.

Two case studies (Newport et al., 2015, Chu & Jiao, 2015) reported beneficial effects of a ketone ester in a total of three ApoE4(+) Alzheimer's disease patients. Unfortunately, Newport et al., 2015 reported no

objective cognition measures after ketone ester treatment (it was reported "the patients could remember better", etc.). In addition, Newport et al., 2015 reported an incredibly high improvement in MMSE score (8 points) after a 75 day MCT treatment (prior to the ketone ester treatment) accompanied by an impairment of ADAS-Cog score. The reason for this discrepancy is unknown. In January 2016 the patient passed away (he was diagnosed in 2008). The second publication came out soon after the first and reported suspiciously similar findings. The quality of data and validity of these studies is questionable.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Brain glucose hypometabolism is a feature and early indicator of Alzheimer's disease. In individuals with presenilin 1 mutations, APOE4, a maternal history of Alzheimer's disease, and type II diabetes, regional brain glucose hypometabolism precedes cognitive dysfunction (Cunnane et al., 2011, Cunnane et al., 2016). Since imaging studies show that brain ketone metabolism is directly related to plasma ketone concentration, even in early Alzheimer's patients (Chourchesne-Loyer et al., 2013; Castellano et al., 2015), and MCTs and ketone esters raise plasma BHB levels (Reger et al., 2004; Henderson et al., 2009; Clarke et al., 2012), the brains of pre- or early-Alzheimer's patients may be able to use ketones, even in the face of glucose hypometabolism. Treatment with MCT supplementation was reported to increase total brain energy metabolism in patients with mild to moderate AD (Croteau et al., 2018).

Animal studies suggest that a shift from glucose metabolism to ketone metabolism is an early event in Alzheimer's disease and aging (Yao et al., 2009; Yao et al., 2011; Ding et al., 2013; Yin et al., 2016) and that glucose hypometabolism might accelerate the progression of Alzheimer's disease (Velliquette et al., 2005). In addition, there is evidence from animal studies that ketones might compensate for glucose hypometabolism in aging and Alzheimer's disease. In the parietal cortex of aged beagles (~9 years), short-term (2 months, 2g/kg/day) MCT treatment increased mitochondrial respiration, the ability to drive electrons through mitochondrial complex 1, decreased protein oxidation and nitration, decreased APP levels, and increased non-sterol lipids, phospholipids, saturated fatty acids, and n-3 polyunsaturated fatty acids. There were no differences in BACE1 levels or mitochondria uncoupling proteins (Studzinski et al., 2008; Taha et al., 2009). Long-term treatment in aged beagles (8 months, 5.5%) improved visuospatial functions, learning ability, and attention – improvements that were more pronounced with increased difficulty (Pan et al., 2010).

Additional animal and cell culture studies support the notion that ketones might be beneficial in Alzheimer's disease. In cultured cells, raising plasma ketone levels acted as an HDAC 1 inhibitor, raised antioxidant capability possibly through induction of Nrf2, protected neurons from Aß42 toxicity and prevented the entry of oligomeric Aß42 into cultured cells (Kashiwaya et al., 2000; Yin et al., 2016, Shimazu et al., 2013, Xie et al., 2015). In healthy male rats, ketone esters decreased plasma glucose and insulin levels and increased levels of mitochondrial uncoupling proteins 4 and 5; these proteins are thought to reduce oxidative stress (Kashigawa et al., 2010; Ramsden et al., 2012). In Alzheimer's disease mouse models, raising plasma ketone levels had an anxiolytic effect, improved some measures of memory (but not others), decreased apoptosis and lipid peroxidation levels, decreased reactive oxygen species, enhanced mitochondrial complex 1 activity, restored mitochondrial membrane potential, decreased amyloid beta and phosphorylated tau levels, and increased soluble APPα levels (Kashigawa et al., 2013; Zhang et al., 2013; Van der Auwera et al., 2005; Yin et al., 2016). There are other more novel or less explored hypotheses in the field as to how MCTs could mediate beneficial effects. For instance, MCTs might have some form of antimicrobial and/or infection prevention activity in animals, and might otherwise modulate immunity, particularly intestinal immunity (Watanabe & Tsujino, 2022).

There are also more direct hypotheses for how MCT supplementation might be neuroprotective. While significant attention has been paid to the beneficial role that ketones may play in dementia, MCFAs themselves can also cross the blood-brain barrier (BBB) and exert local influence. Certain MCFAs like decanoic acid are thought to activate peroxisome proliferator-activated receptor gamma (PPARγ), which may increase mitochondrial biogenesis and reduce oxidative stress. MCFAs may modulate AMPA receptor activity (Watanabe & Tsujino, 2022, Dunn et al., 2023).

This evidence supports a role for MCT/ketone supplementation for patients with early Alzheimer's disease/dementia. However, a number of questions still remain. First, some studies suggest that enzymes downstream of ketone metabolism decrease in the later stages of Alzheimer's disease at which point ketone supplementation might not be useful (Yao et al., 2009; Correia et al., 2012). Also, although ketones seem to have a protective role against Aβ toxicity, the mechanism of action for this protection is still unclear. For instance, in some of the experiments described above, weight loss or a reduction in caloric intake that occur as a side effect of MCT/ketone ester supplementation might be the cause of the benefit rather than increased ketones, per se (Clark et al., 2012).

It should be noted that the mechanism of action is affected by the specific type(s) of MCT, and this both confounds results and also provides the possibility of different mechanisms of action by different MCTs.

For instance, octanoic acid appears to be more ketogenic than decanoic acid or dodecanoic acid. Octanoic acid is β-oxidized at a faster rate than decanoic acid, and this may result in decanoic acid being more available to interact with other cellular components like PPARγ (St-Pierre et al., 2019; Khabbush et al., 2017; Giannos et al., 2022; Dunn et al., 2023). Castro et al., 2023, found that the ratio of included MCFAs might have some impact, with a mix of MCFAs potentially providing a benefit over octanoic acid alone. More research is needed to more fully characterize the human response to MCTs overall and also to specific MCFAs.

APOE4 interactions:

The data thus far indicate that APOE status may affect response to MCT supplementation. The meta-analysis from Sun et al., 2023 explored the influence of APOE4 status in the effects of MCTs on cognitive function. Four of their included studies assessed the impact of APOE allele, and all used the same cognitive scale (ADAS-Cog), allowing for an analysis of the mean difference (MD) in change from baseline in the APOE4(-) group compared to the APOE4(+) group. The meta-analysis identified a large effect size (MD = 1.87; 95% CI 0.35 to 3.40; p=0.02). There was some heterogeneity between studies (Sun et al., 2023). Other meta-analyses and systematic reviews, such as that by Giannos et al., 2022, note lack of APOE information as a potential confounding factor.

The patients in the ketone ester case studies were ApoE4(+) (Newport et al., 2015, Chu & Jiao, 2015). Overall, more information is needed to fully understand the interaction of APOE allele and effects of MCT supplementation.

Aging and related health concerns: Some initial clinical evidence suggests that MCT supplementation may help improve frailty indices in older adults.

Types of evidence:

- 2 meta-analyses and systematic reviews
- 1 meta-analysis
- 5 clinical trials
- 1 analysis of several of the above clinical trials
- 2 reviews
- 1 C. elegans study

Lifespan: Preclinical study suggests potential for benefit

BHB supplementation (20mM) increased *C. elegans* lifespan by 26% (Edwards et al., 2014). Lifespan extension did not occur in conjunction with dietary restriction, suggesting that BHB acted as a dietary restriction mimetic. Like the mouse studies above, BHB acted as an HDAC 1 inhibitor and increased the expression of the *C. elegans* homolog of Nrf2 (Skn-1). Nrf2 is a transcription factor that increases the expression of antioxidant proteins. Two caveats to consider: first, there is evidence that prolonged activation of Nrf2 may increase the chances of cancer metastasis (Wang et al., 2016); second, higher levels of BHB in the *C. elegans* study, 50 mM and 100 mM, *decreased* lifespan by ~20% and 30%, respectively.

Frailty: Potential for benefit

There are some studies exploring the utility of MCTs in treating sarcopenia, which is age related involuntary loss of skeletal muscle mass and strength. Several small studies, largely from the same group, report potential benefits of MCT usage, sometimes in conjunction with exercise, in older patients on measures of muscle mass and function (Abe et al., 2016; Abe et al., 2019; Abe et al., 2022; Ezaki & Abe, 2023 analyzed the previous 3 trials together with additional post-hoc tests; Kojima et al., 2023). Another randomized controlled trial also hinted at improved balance in those treated with MCT (Mutoh et al., 2022). Larger studies would be needed to better understand and characterize the potential effects of MCT on frailty.

Safety: MCTs have gastrointestinal side effects that may be prohibitive to their long-term use. Few studies have investigated the long-term use of MCTs.

Types of evidence:

- 5 meta-analyses and systematic reviews
- 3 clinical trials
- Multiple animal studies

MCT supplements are generally safe with the most common side effects being gastrointestinal effects.

A 2023 systemic review and meta-analysis including 10 trials and 848 patients, lasting up to 6 months in duration, reports that adverse events that 'could have contributed to dropouts during the clinical trial' were noted in six studies. Diarrhea was a commonly reported adverse event that made MCT intolerable for some patients. Other gastrointestinal effects included such as abdominal or stomach discomfort, nausea, vomiting, indigestion, and/or constipation (Sun et al., 2023). Another systematic review and meta-analysis also notes that gastrointestinal side effects were reported in their included papers (Avgerinos et al., 2020).

A randomized placebo-controlled crossover trial testing GSK2981710, a pharmaceutical MCT, enrolled 8 people in a dose-finding stage and 96 people in the crossover study portion, 80 of whom completed the trial; all participants were older participants with age-related cognitive decline, but not MCI or dementia. All participants in the dose-finding portion of the trial and 75% of the participants in the crossover study reported diarrhea. Most adverse events were mild to moderate; 11% of participants were withdrawn due to one or more adverse events (O'Neill et al., 2019).

Henderson et al., 2009 and Clark et al., 2012 also report gastrointestinal side effects but no severe side effects. Animal studies using up to ~8 months of MCTs/ketone esters (Pan et al., 2010; Kashiwaya et al., 2013) reported no adverse effects. That said, coconut oil (an effective MCT supplement) is widely used, and MCTs are listed by the FDA as Generally Recognized as Safe.

Diabetic ketoacidosis is a life-threatening condition where low levels of insulin lead to an uncontrolled increase in blood ketone levels (and subsequent decrease in blood pH). Although the use of MCTs and ketone esters has not been shown to raise plasma ketones near dangerous levels, those at risk for elevated blood ketone levels (e.g. diabetics) should consult with their doctor before considering supplementation. Individuals with liver disease should also speak with their doctor before supplementing with MCTs (Drugs.com).

There is some debate as to if and how MCT supplementation affects blood lipids. A 2021 systematic review and meta-analysis of randomized trials found that MCT oil supplementation did not affect total, LDL, or HDL cholesterol levels, but it does cause a 'small increase' in triglycerides (McKenzie et al., 2021). Prior systematic reviews and meta-analyses have found some discrepant results, potentially due to different comparisons. For instance, a 2018 paper reported that diets enriched with MCFA were associated with changes in HDL levels compared to diets enriched with long-chain saturated fatty acids (LCFAs) (Panth et al., 2018), and a 2015 meta-analysis found no difference in blood lipids between

groups given MCTs vs LCTs (Mumme & Stonehouse, 2015). Individuals can discuss their specific medical situation with their doctor.

Drug interactions:

Information on drug interactions of MCTs is not yet available.

Research underway:

There are approximately 45 trials registered on clinicaltrials.gov that involve MCTs; many of them involve dietary interventions for different populations, such as preterm infants. While the search does yield studies of ketogenic diet alone, these studies were not included in this report as ketogenic diets have confounders that affect evaluation of administration of MCT itself. Three of the registered trials involve MCT supplementation and neurodegenerative disease in some way.

NCT04322461 is an ongoing open-label study of 20 individuals with AD or Parkinson's disease (PD). Participants will receive 50 g/day of a commercial MCT supplement, along with supervised exercise three times a week, for 2 months. The daily MCT dose will be divided into 3 dosing sessions along with breakfast, lunch, and dinner. Outcome measures include assessments of cognition and ketone concentrations.

NCT03860792 is a three month long randomized trial of therapeutic diets for AD. The trial seeks to enroll a total of 80 individuals. Participants will be randomized to either a ketogenic diet with an MCT supplement, or a therapeutic lifestyle changes diet low in fat and cholesterol, and high in fruits, vegetables and whole grains, and moderate in protein. The primary outcome measures will include various measures of cognition.

NCT05469997 is a randomized crossover study that will compare the effects of a Mediterranean ketogenic diet to a Mediterranean diet supplemented with MCTs on the microbiome in patients with PD. The trial aims to enroll a total of 50 patients, and will consist of an 8 week period on one diet, an 8 week washout period, and then an 8 week period on the other trial arm. Primary outcomes include measures of the health of the gut and gut microbiome. Other outcome measures will include assessments of disease progression and psychiatric symptoms.

Search terms:

Pubmed, Google: medium chain triglycerides, MCT

- Dementia, AD, aging, diabetes, liver disease, neurodegeneration, aging

Websites visited for MCT:

- Clinicaltrials.gov
- Examine.com
- Drugs.com
- WebMD.com
- PubChem: Caproic Acid, Caprylic Acid, Capric Acid, Lauric Acid
- DrugBank.ca
- ConsumerLab.com