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.

Olive Oil

Evidence Summary

May provide protective benefits, especially for cardiovascular health and healthy aging when varieties containing high quantities of phenolic compounds are consumed as part of a Mediterranean diet.

Neuroprotective Benefit: May slightly improve cognition when extra virgin olive oil is consumed as part of a Mediterranean diet, but direct evidence for benefits of olive oil alone is limited.

Aging and related health concerns: Strong evidence from both observational and human clinical trials for benefits in longevity and across multiple aging-related diseases, but a direct role of olive oil may be confounded by other factors.

Safety: No adverse events reported in clinical trials; widely used in everyday life; possible risk if improperly heated during cooking.

What is it? Olive oil is a condiment made from grinding the fruits of *Olea europaea* (olive) trees and extracting the oils produced. It is most commonly consumed in salad dressings or used as a cooking oil. Olive oil is a staple of the Mediterranean diet where it serves as the main source of fat (Mayo Clinic) [1]. Some of the health benefits of the Mediterranean diet have been attributed to olive oil's high content of mono-unsaturated fats and phenolic compounds such as oleic acid, oleuropein, tyrosol, hydroxytyrosol and oleocanthal (Bendini et al., 2007) [2].

Olive oil comes in a variety of commercial grades and can have different levels of mono-unsaturated fat and phenolic compounds depending on many different factors such as olive variety, picking season and growing environment (Olive Oil Source). *Virgin* olive oil is produced only via mechanical extraction in contrast to other olive oils that undergo a refining process using solvents and heat to neutralize unpalatable tastes from generally poorer quality olives (International Olive Council, Trade Standards) [3]. *Extra virgin* olive oil (EVOO) is considered the highest quality, with more phenolic compounds and a required free fatty acid content of 0.8% or less (International Olive Council) [4].

Neuroprotective Benefit: May slightly improve cognition when extra virgin olive oil is consumed as part of a Mediterranean diet, but direct evidence for benefits of olive oil alone is limited.

Types of evidence:

For Neurodegeneration

- 1 meta-analysis with results based fully on the PREDIMED trial comparing the Mediterranean diet with extra-virgin olive oil vs nut supplementation vs control low-fat
- 4 trials using olive oil as a control (e.g. for fish oil intervention)
- 1 cohort study + 1 additional cross-sectional sub-study from PREDIMED trial
- Numerous laboratory studies *in vivo* and *in vitro*

Human research to suggest prevention of dementia and cognitive aging:

While there has been extensive review of the Mediterranean diet, few studies have investigated the impact of olive oil directly. To date, the PREDIMED trial remains the largest source of evidence. This 3-arm trial compared a Mediterranean (Med) diet with EVOO supplementation to a Med diet with nut supplementation and a control low fat diet in cognitively healthy individuals at high cardiovascular risk (average 67 years old). EVOO intake during the trial increased by 35.15 g/day in the Med + EVOO group, while the increase in Med + nuts and low-fat diet control groups was only 13.2 g/day and 10.6 g/day respectively (Valls-Pedret et al., 2015) [5]. This increase of EVOO in the Med + EVOO group was accompanied by a complete abstinence from refined olive oil whereas, in the nut or low fat control

groups, EVOO made up only about 62% of total olive oil intake (Valls-Pedret et al., 2015) [5]. This resulted in a significant increase in mono-unsaturated fatty acid levels in the Med + EVOO group and poly-unsaturated fatty acid levels in the Med + nuts group, both relative to control, while cholesterol, polyunsaturated fatty acid, saturated fatty acid and total calorie levels, including calories from fat, were not significantly different across all groups (Valls-Pedret et al., 2015) [5].

A meta-analysis concluded, based entirely on the PREDIMED trial, that a Med diet supplemented with olive oil may be one of the few factors to have small beneficial cognitive effects (Lehert et al., 2015) [6]. A small improvement of global cognition (0.22 mean difference, 95% CI: 0.16 to 0.27) and episodic memory (0.22 mean difference, 95% CI: 0.12 to 0.32) was reported with the Med + EVOO compared to the control low fat diet (Lehert et al., 2015) [6]. Whether EVOO contributed to this effect is uncertain. There were no significant differences, despite a trend, between the Med + EVOO and Med + nuts on composite scores for memory tests, frontal functions and global cognition (Valls-Pedret et al., 2015) [5]. However, another sub-study reported apparent differences between the EVOO and nut groups in 3 out of 16 cognitive measures (Martinez-Lapiscina et al., 2013-A) [7].

Olive oil's ability to prevent progression to mild cognitive impairment (MCI) remains inconclusive. A lower risk of MCI was reported with a Med + EVOO diet versus low-fat control in one sub-study (Odds ratio (OR): 0.34, 95% CI: 0.12 to 0.97) (Martinez-Lapiscina et al., 2013-B) [8], but not another from a different PREDIMED site (Valls-Pedret et al., 2015) [5]. The null effect in the latter study may have been due to a shorter average follow-up time (4 versus 6.5 years) and a high withdrawal rate in the control group.

It is important to note that the PREDIMED population was restricted to those with high cardiovascular disease (CVD) risk and may not be generalizable to the entire population. There are, however, a few other encouraging studies. An analysis of baseline health in the PREDIMED trial found an association between virgin olive oil intake and improved performance in the delayed recall portion of the RAVLT (β=0.094, CI: 0.010 to 0.316, p=0.037) (Valls-Pedret et al., 2012) [9]. A cross-sectional study from Poland found similar benefits associated between olive oil consumption (grouped together with rapeseed oil, another oil high in mono-unsaturated fats) and executive memory performance in the Stroop test A (β=-0.021, $p<0.05$) and spatial span test (β=0.8, $p<0.05$) (Bajerska et al., 2014) [10]. A cohort study from the Three-City trial in France also saw that intensive use of olive oil (for both cooking and dressing) was significantly associated with lower odds of visual memory decline (OR:0.83, CI: 0.69 to 0.99, p=0.04) compared to non-users (Berr et al., 2009) [11]. Further studies with direct comparisons are needed.

Human research to suggest benefits to patients with dementia

There is no human research to suggest that olive oil can slow or reverse symptoms in people with dementia.

RCTs often use olive oil as a placebo in studies of other dietary supplements like fish oils (Chiu et al., 2008; Phillips et al., 2015) [12, 13] and fatty acids (Kotani et al., 2006) [14] for improving cognition in MCI and Alzheimer's disease (AD) populations but the (null) results are not relevant because the comparison arms were expected to promote brain health and they used extremely low levels (ranging from 0.24 – 1.8 g/day rather than the recommended daily dose of 28 g/day.

Mechanisms of action for neuroprotection identified from laboratory and clinical research

Despite the lack of concrete evidence from human trials, laboratory research focusing on the individual phenolic compounds in olive oil have developed promising mechanisms to explain how it may act to benefit the brain. Olive oil's phenolic components may interact with and reduce pathological tau and amyloid, possibly through disruption and inhibition of tau interaction, fibrillization and aggregation (Li et al., 2009; Monti et al., 2012, Daccache et al., 2011) [15-17], as well as inhibition of amyloid oligomers binding (Pitt et al., 2009) [18]. These phenolic components are also capable of reducing amyloid plaque deposition and rescuing impairments in cognitive tests with dietary supplementation in a transgenic amyloid mouse model (TgCRND8) (Grossi et al., 2013) [19]. The human equivalent doses to these animal studies are higher than what can be obtained through dietary olive oil but are not unfeasible for supplements.

APOE4 interactions: An analysis of APOE genotype in a PREDIMED sub-study that combined the nut and EVOO Med groups did not find any interaction between APOE4 status and dietary intervention on cognition, as the Mediterranean diet intervention benefited both carriers and non-carriers of APOE4 (Martinez-Lapiscina et al., 2014) [20].

Aging and related health concerns: Strong evidence from both observational and RCT human trials for benefits in longevity and across multiple aging-related diseases, but a direct role of olive oil may be confounded by other factors.

Types of evidence:

- 6 meta-analyses (1 each for mortality (cohort), cancer (case control), depression (cohort), inflammation (cohort), osteoporosis, CVD (mostly cohort with some case control & RCT)
- 15 other RCT & 9 prospective cohorts on various age-related conditions.

- Multiple laboratory studies *in vivo*

More extensive work has been done to investigate the beneficial impact of olive oil on aging biology and diseases. A 2014 meta-analysis of cohort studies found that individuals in the highest tertile for olive oil intake had a reduced risk for death from all causes (Risk Ratio (RR): 0.77, 95% CI: 0.71 to 0.84, p<0.00001) compared to the lowest (Schwingshackl et al., 2014) [21].

This trend for longevity is likely, in part, due to olive oil's strong cardio-protective role. Multiple meta-analyses of cohort, case control and RCTs found a significantly reduced risk for **cardiovascular disease (CVD)** with olive oil consumption (RR: 0.72, 95% CI 0.57 to 0.91, p = 0.007 (Schwingshackl et al., 2014) [21], RR: 0.83; 95% CI: 0.77 to 0. 89; I^2 = 0% (Grosso et al., 2015) [22]). Analyses of typical risk factors for CVD such as **obesity** and **diabetes** (Ros et al., 2014) [23] have also found protective associations, making this the strongest case for a beneficial role of olive oil. As such, both the American Heart Association [24] and American Diabetes Association [25] encourage the use of olive oil as a good source of healthy mono-unsaturated fats. Replacing products with high levels of saturated and trans fats like butter, margarine and coconut oil with olive oil may also have a prevention of harm effect and protect against increases in LDL cholesterol levels and CVD risks (AHA) [26].

Olive oil intake has also been associated (less robustly) with benefits for **cancer** (0.66-times lower odds, logOR: -0.41; 95% CI -0.53 to -0.29; p<0.001), especially breast and digestive-system related types (Psaltopoulou et al., 2011) [27]. Likewise, olive oil consumption has been associated with potential protective effects against **depression** (Sanhueza et al., 2013) [28], **osteoporosis** (Garcia-Martinez et al., 2014) [29], and **inflammation** (Dell'Agli et al., 2013; Urpi-Sarda et al., 2012) [30, 31].

Safety: No adverse events reported in clinical trials; widely used in everyday life; possible risk if improperly heated during cooking.

Types of evidence:

- No meta-analyses
- 2 RCT (for stability and bioavailability)
- Multiple biochemistry studies (for stability, toxicity)

Generally, olive oil is considered a safe, natural substance for normal consumption and no significant adverse effects have been highlighted across human supplement trials. Consuming excessive olive oil can result in mild temporary diarrhea (Drugs.com) [32].

The greatest potential safety concern with olive oil is that, when heated for cooking past its smoke point, it can release volatile organic compounds (aldehydes, hydrocarbons, alcohols and ketones) and lose some of its phenolic content (Allouche et al., 2007, Katragadda et al., 2010) [33, 34]. However, it remains one of the safer alternatives for use in cooking.

When used for pan-frying, virgin olive oil emits significantly fewer potentially mutagenic higher aldehydes compared to margarine (Sjaastad et al., 2008) [35]. Refined olive oil is also more stable than many other oils (corn, soybean, sunflower) in tests with deep-frying: showing the least deterioration and fatty acid hydrolysis (Zribi et al., 2014) [36]. Lower emission rates of toxins were also seen in deep-frying tests with EVOO compared to other oils (canola, sunflower, vegetable) (Fullana et al., 2004; Guillen et al, 2013; Casal et al., 2010) [37-39].

The few studies investigating the safety of olive oil outside of the context of heating also support its safety. Olive oil phenolics have been shown to be non-mutagenic in multiple robust Ames tests *in vitro*, and any genotoxic potentials *in vivo* are thought to be negligible (Kirkland et al., 2015) [40].

A minor cautionary note has been proposed for those intending to combine olive oil (or its phenolic compounds) with other drugs, due to the potential escalation of their "beneficial" effects (Memorial Sloan Kettering Integrative Medicine) [41]. For example, the hypoglycemic (Gonzalez et al., 1992) [42] or hypotensive (Somova et al., 2003) [43] impact of olive oil combined with prescribed drugs with similar mechanisms could potentially result in unsafe changes, but these effects have not been clinically confirmed.

The safety of olive oil as a supplement may require more studies, especially for concentrated extracts using large qualities of olive oil or containing levels of phenolics higher than naturally occurring in olive oil.

Sources and dosing: Olive oil is readily available in supermarkets in the United States, with varying grades and qualities. Phenolic components (oleuropein, oleocanthal) are also available in supplement form.

As the levels of phenolic components in olive oil can vary across different trials using different brands/types of olive oil, the exact dose of olive oil that may have benefits for the brain is not known and a clear mechanistic understanding of olive oil's benefits requires more investigation.

Some RCTs have compared olive oils with high and low phenolic contents, suggesting relative health benefits regarding LDL particle levels (Hernaez et al., 2015) [44], oxidative and inflammatory markers (Ruano et al., 2005) [45], systolic blood pressure (Fito et al, 2005) [46], and vascular damage caused by

high cholesterol (Ruano et al., 2005) [45]. As EVOOs have significantly higher phenolic content compared to refined olive oils (232 vs 62 mg/kg, p<0.0001) (Owen et al., 2000) [47], selecting higher quality olive oils for use and supplementation may provide the most advantages while controlling fat intake. However, EVOO has a lower smoke point (165 - 204°C) than refined olive oil (REF) (240°C) so while sautéing vegetables or potatoes at lower temperatures (130 - 145°C) with EVOO may be acceptable, REFs may be more appropriate for cooking with high heat (155 - 190°C) for short periods of time like deep-frying or batter frying (Achitoff-Gray, N., 2014, Olive Oil Source) [48, 49].

Some concern has also been raised in the false marketing of "extra virgin olive oils" in the United States that do not meet international standards. In Europe, olive oil must have a concentration of at least 5 mg of hydroxytyrosol (and derivatives) per 20 g (assuming a daily intake of 20 g) to be able to claim to have health benefits (EFSA Panel on Dietetic Products) [50]. Out of 110 EVOOs sampled in California, only about half could qualify for this health claim (Magiatis et al., 2013) [51]. Another investigation of EVOOs from California highlighted that 73% of samples from the top selling imported brands failed at least one biochemical or sensory standard due to oxidation from inappropriate storage, adulteration with cheaper refined olive oil, or poor quality oils as a starting material (Frankel et al., 2011) [52]. A member of the UC Davis Olive Oil Taste Panel suggests that, when picking quality EVOO, look for a seal of approval from a reputable source and a harvest date that is not beyond two years (Corn, E., 2013) [53].

Olive oil is still a pure fat and as such, should not be taken in excess. The current suggested dosage for olive oil in dietary use is 14% of total daily calories (which equates to approximately 2 tablespoons (28g)/day or 239 kcal) (WebMD) [54], however individuals from the PREDIMED trials were consuming nearly twice that amount (Valls-Pedret et al., 2015) [5].

Until more research can be done on the specific beneficial components of olive oil, it will be difficult to pinpoint an exact, effective dose as olive oil constituents, including the putative bioactive polyphenols, vary greatly by region, manufacturing process and grade.

Research underway: No ongoing clinical trials publicly registered could be found for olive oil on cognition/dementia.

Search terms:

Pubmed:

- Olive oil, oleocanthal or oleuropein separately with dementia, Alzheimer's, cognition, cognitive, aging, mortality, osteoporosis, telomere length, lifespan, CVD, APOE4, diabetes

Google or other

- Olive oil, oleocanthal or oleruopein separately with Alzheimer's, overdose, side effect, fake, standard

Clinicaltrials.gov, clinicaltrialsregister.eu, NIH reporter

- Olive oil spearately with Alzheimer's, cognition, dementia, cognitive
- Oleocanthal
- Oleuropein

References:

1. Clinic, M. *Choose healthier fats.* Healthy Lifestyle: Nutrition and Healthy eating 2013 [cited 2016 02/17/16]; Available from: http://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/mediterranean-diet/art-20047801?pg=2.

2. Bendini, A., et al., *Phenolic molecules in virgin olive oils: a survey of their sensory properties, health effects, antioxidant activity and analytical methods. An overview of the last decade.* Molecules, 2007. 12(8): p. 1679-719.

3. Council, I.O., *Trade Standard Applying to Olive Oils and Olive-Pomace Oils.* 2012.

4. Council, I.O. *Designations and Definitions of Olive Oils.* [cited 2016 02/16/16]; Available from: http://www.internationaloliveoil.org/estaticos/view/83-designations-and-definitions-of-olive-oils.

5. Valls-Pedret, C., et al., *Mediterranean Diet and Age-Related Cognitive Decline: A Randomized Clinical Trial.* JAMA Intern Med, 2015. 175(7): p. 1094-103.

6. Lehert, P., et al., *Individually modifiable risk factors to ameliorate cognitive aging: a systematic review and meta-analysis.* Climacteric, 2015. 18(5): p. 678-89.

7. Martinez-Lapiscina, E.H., et al., *Virgin olive oil supplementation and long-term cognition: the PREDIMED-NAVARRA randomized, trial.* J Nutr Health Aging, 2013. 17(6): p. 544-52.

8. Martinez-Lapiscina, E.H., et al., *Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial.* J Neurol Neurosurg Psychiatry, 2013. 84(12): p. 1318-25.

9. Valls-Pedret, C., et al., *Polyphenol-rich foods in the Mediterranean diet are associated with better cognitive function in elderly subjects at high cardiovascular risk.* J Alzheimers Dis, 2012. 29(4): p. 773-82.

10. Bajerska, J., et al., *Eating patterns are associated with cognitive function in the elderly at risk of metabolic syndrome from rural areas.* Eur Rev Med Pharmacol Sci, 2014. 18(21): p. 3234-45.

11. Berr, C., et al., *Olive oil and cognition: results from the three-city study.* Dement Geriatr Cogn Disord, 2009. 28(4): p. 357-64.

12. Chiu, C.C., et al., *The effects of omega-3 fatty acids monotherapy in Alzheimer's disease and mild cognitive impairment: a preliminary randomized double-blind placebo-controlled study.* Prog Neuropsychopharmacol Biol Psychiatry, 2008. 32(6): p. 1538-44.

13. Phillips, M.A., et al., *No Effect of Omega-3 Fatty Acid Supplementation on Cognition and Mood in Individuals with Cognitive Impairment and Probable Alzheimer's Disease: A Randomised Controlled Trial.* Int J Mol Sci, 2015. 16(10): p. 24600-13.

14. Kotani, S., et al., *Dietary supplementation of arachidonic and docosahexaenoic acids improves cognitive dysfunction.* Neurosci Res, 2006. 56(2): p. 159-64.

15. Daccache, A., et al., *Oleuropein and derivatives from olives as Tau aggregation inhibitors.* Neurochem Int, 2011. 58(6): p. 700-7.

16. Li, W., et al., *Inhibition of tau fibrillization by oleocanthal via reaction with the amino groups of tau.* J Neurochem, 2009. 110(4): p. 1339-51.

17. Monti, M.C., et al., *Modulation of tau protein fibrillization by oleocanthal.* J Nat Prod, 2012. 75(9): p. 1584-8.

18. Pitt, J., et al., *Alzheimer's-associated Abeta oligomers show altered structure, immunoreactivity and synaptotoxicity with low doses of oleocanthal.* Toxicol Appl Pharmacol, 2009. 240(2): p. 189-97.

19. Grossi, C., et al., *The polyphenol oleuropein aglycone protects TgCRND8 mice against Ass plaque pathology.* PLoS One, 2013. 8(8): p. e71702.

20. Martinez-Lapiscina, E.H., et al., *Genotype patterns at CLU, CR1, PICALM and APOE, cognition and Mediterranean diet: the PREDIMED-NAVARRA trial.* Genes Nutr, 2014. 9(3): p. 393.

21. Schwingshackl, L. and G. Hoffmann, *Monounsaturated fatty acids, olive oil and health status: a systematic review and meta-analysis of cohort studies.* Lipids Health Dis, 2014. 13: p. 154.

22. Grosso, G., et al., *A Comprehensive Meta-analysis on Evidence of Mediterranean Diet and Cardiovascular Disease: Are Individual Components Equal?* Crit Rev Food Sci Nutr, 2015: p. 0.

23. Ros, E., et al., *Mediterranean diet and cardiovascular health: Teachings of the PREDIMED study.* Adv Nutr, 2014. 5(3): p. 330S-6S.

24. Association, A.H. *Use Olive, Canola, Corn or Safflower Oil as Your Main Kitchen Fats.* 2015 [cited 2016 02/26/16]; Available from: http://www.heart.org/HEARTORG/HealthyLiving/HealthyEating/Nutrition/Use-Olive-Canola-Corn-or-Safflower-Oil-as-Your-Main-Kitchen-Fats_UCM_320268_Article.jsp#.VtC61ZwrIdU.

25. Assocation, A.D. *Making Healthy Food Choices.* 2015 [cited 2016 02/26/16]; Available from: http://www.diabetes.org/food-and-fitness/food/what-can-i-eat/making-healthy-food-choices/fats-and-diabetes.html?referrer=https://www.google.com/.

26. Association, A.H. *Saturated Fats.* 2016; Available from: http://www.heart.org/HEARTORG/HealthyLiving/HealthyEating/Nutrition/Saturated-Fats_UCM_301110_Article.jsp#.VtTBzpwrIdU.

27. Psaltopoulou, T., et al., *Olive oil intake is inversely related to cancer prevalence: a systematic review and a meta-analysis of 13,800 patients and 23,340 controls in 19 observational studies.* Lipids Health Dis, 2011. 10: p. 127.

28. Sanhueza, C., L. Ryan, and D.R. Foxcroft, *Diet and the risk of unipolar depression in adults: systematic review of cohort studies.* J Hum Nutr Diet, 2013. 26(1): p. 56-70.

29. Garcia-Martinez, O., et al., *The effect of olive oil on osteoporosis prevention.* Int J Food Sci Nutr, 2014. 65(7): p. 834-40.

30. Dell'Agli, M., et al., *Plant food supplements with anti-inflammatory properties: a systematic review (I).* Crit Rev Food Sci Nutr, 2013. 53(4): p. 403-13.

31. Urpi-Sarda, M., et al., *Virgin olive oil and nuts as key foods of the Mediterranean diet effects on inflammatory biomakers related to atherosclerosis.* Pharmacol Res, 2012. 65(6): p. 577-83.

32. Drugs.com. *Olive Oil.* 2009 [cited 2016 02/21/16]; Available from: http://www.drugs.com/npp/olive-oil.html.

33. Allouche, Y., et al., *How heating affects extra virgin olive oil quality indexes and chemical composition.* J Agric Food Chem, 2007. 55(23): p. 9646-54.

34. Katragadda, H.R.F., Andres; Sidhu, Sukh; Carbonell-Barrachina, Angel A, *Emissions of volatile aldehydes from heated cooking oils.* Food Chemistry, 2010. 120(1): p. 59-65.

35. Sjaastad, A.K. and K. Svendsen, *Exposure to mutagenic aldehydes and particulate matter during panfrying of beefsteak with margarine, rapeseed oil, olive oil or soybean oil.* Ann Occup Hyg, 2008. 52(8): p. 739-45.

36. Zribi, A., et al., *Monitoring of quality and stability characteristics and fatty acid compositions of refined olive and seed oils during repeated pan- and deep-frying using GC, FT-NIRS, and chemometrics.* J Agric Food Chem, 2014. 62(42): p. 10357-67.

37. Fullana, A., A.A. Carbonell-Barrachina, and S. Sidhu, *Comparison of volatile aldehydes present in the cooking fumes of extra virgin olive, olive, and canola oils.* J Agric Food Chem, 2004. 52(16): p. 5207-14.

38. Guillen, M.D. and P.S. Uriarte, *Relationships between the evolution of the percentage in weight of polar compounds and that of the molar percentage of acyl groups of edible oils submitted to frying temperature.* Food Chem, 2013. 138(2-3): p. 1351-4.

39. Casal, S., et al., *Olive oil stability under deep-frying conditions.* Food Chem Toxicol, 2010. 48(10): p. 2972-9.

40. Kirkland, D., et al., *Investigations into the genotoxic potential of olive extracts.* Mutat Res Genet Toxicol Environ Mutagen, 2015. 777: p. 17-28.

41. Center, M.S.K.C. *Olive Leaf.* About Herbs, Botanicals & Other Products 2013 [cited 2016 02/17/16]; Available from: https://www.mskcc.org/cancer-care/integrative-medicine/herbs/olive-leaf.

42. Gonzalez, M., et al., *Hypoglycemic activity of olive leaf.* Planta Med, 1992. 58(6): p. 513-5.

43. Somova, L.I., et al., *Antihypertensive, antiatherosclerotic and antioxidant activity of triterpenoids isolated from Olea europaea, subspecies africana leaves.* J Ethnopharmacol, 2003. 84(2-3): p. 299-305.

44. Hernaez, A., et al., *Olive Oil Polyphenols Decrease LDL Concentrations and LDL Atherogenicity in Men in a Randomized Controlled Trial.* J Nutr, 2015. 145(8): p. 1692-7.

45. Ruano, J., et al., *Phenolic content of virgin olive oil improves ischemic reactive hyperemia in hypercholesterolemic patients.* J Am Coll Cardiol, 2005. 46(10): p. 1864-8.

46. Fito, M., et al., *Antioxidant effect of virgin olive oil in patients with stable coronary heart disease: a randomized, crossover, controlled, clinical trial.* Atherosclerosis, 2005. 181(1): p. 149-58.

47. Owen, R.W., et al., *Phenolic compounds and squalene in olive oils: the concentration and antioxidant potential of total phenols, simple phenols, secoiridoids, lignansand squalene.* Food Chem Toxicol, 2000. 38(8): p. 647-59.

48. Achitoff-Gray, N. *Cooking Fats 101: What's a Smoke Point and Why Does it Matter?* 2014; Available from: http://www.seriouseats.com/2014/05/cooking-fats-101-whats-a-smoke-point-and-why-does-it-matter.html.

49. Miksa, M., et al., *Fractalkine-induced MFG-E8 leads to enhanced apoptotic cell clearance by macrophages.* Molecular medicine (Cambridge, Mass.), 2007. 13(11-12): p. 553-560.

50. EFSA Panel on Dietetic Products, N.a.A.N., *Scientific Opinion on the substantiation of health claims related to polyphenols in olive and protection of LDL particles from oxidative damage (ID 1333, 1638, 1639, 1696, 2865), maintenance of normal blood HDL-cholesterol concentrations (ID 1639), maintenance of normal blood pressure (ID 3781), "anti-inflammatory properties" (ID 1882), "contributes to the upper respiratory tract health" (ID 3468), "can help to maintain a normal function of gastrointestinal tract" (3779), and "contributes to body defences against external agents" (ID 3467) pursuant to Article 13(1) of Regulation (EC) No 1924/20061.* 2011.

51. Magiatis, P.M., Eleni; Killday; Brian, *Quantities of Phenolic Compounds in Olive Oils Bought in California*, in *FOODMR*. 2013: Cesena, Italy.

52. Frankel, E.N.M., R.J.; Wang, S.C.; Shoemaker, C.F.; Guinard, J.-X; FLynn, J.D.; Sturzenberger, N.D., *Evaluation of Extra-Virgin Olive Oil.* 2011, University of Caliornia - Davis.

53. Corn, E. *Consumers Still In The Dark: 6 Tips To Buying Better Olive Oil.* 2013 [cited 2016 02/26/16]; Available from: http://zesterdaily.com/cooking/uc-davis-olive-oil-report-and-buying-tips/.

54. WebMD. Olive Side Effects and Safety 2009 [cited 2016 02/18/16]; Available from: http://www.webmd.com/vitamins-supplements/ingredientmono-233-olive.aspx?activeingredientid=233&activeingredientname=olive.

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