Clinical trials with high phenolic olive oil

1. Oleocanthal-rich extra virgin olive oil demonstrates acute anti-platelet effects in healthy men in a randomized trial

The phenolic profiles of extra virgin olive oils (EVOOs) may influence their cardiovascular benefits. In a randomized crossover of acute EVOO intake on platelet function, participants (n = 9) consumed 40 mL of EVOO weekly. EVOOs were matched for total phenolic content and were either tyrosol-poor with 1:2 oleacein/oleocanthal (D2i0.5), or 2:1 oleacein/ oleocanthal (D2i2), or predominantly tyrosol (D2i0). Ibuprofen provided a platelet inhibition control. Blood was collected pre- and 2 h post-EVOO intake. D2i0.5 and D2i2 reduced 1 mg/ mL collagen-stimulated maximum platelet aggregation (Pmax), with effects best correlated to oleocanthal intake (R = 0.56, P = 0.002). Total phenolic intake was independently correlated to eicosanoid production inhibition, suggesting that cyclooxygenase blockade was not responsible for the Pmax inhibition. Five participants exhibited >25% DPmax declines with D2i0.5 and D2i2 intake and plasma metabolomic profiles discriminated subjects by oil responsivity. Platelet responses to acute EVOO intake are associated with oil phenolic composition and may be influenced by diet.

Agrawal, Karan; Melliou, Eleni; Li, Xueqi; Pedersen, Theresa L; Wang, Selina C; Magiatis, Prokopios; Newman, John W; Holt, Roberta R; Oleocanthal-rich extra virgin olive oil demonstrates acute anti-platelet effects in healthy men in a randomized trial ***Journal of Functional Foods****,36, 84-93, 2017.*

2. A Randomized Clinical Trial of Greek High Phenolic Early Harvest Extra Virgin Olive Oil in Mild Cognitive Impairment: The MICOIL Pilot Study

Abstract

Background: Extra virgin olive oil (EVOO) constitutes a natural compound with high protection over cognitive function. **Objective**:To investigate for the first time the effect of Greek High Phenolic Early Harvest Extra Virgin Olive Oil (HP-EH-EVOO) versus Moderate Phenolic (MP-EVOO) and Mediterranean Diet (MeDi) in people with mild cognitive impairment (MCI). **Methods**:We conducted a randomized prospective study so as to examine the HP-EH-EVOO and MP-EVOO versus MeDi in MCI. Genetic predisposition (APOE ε4) to Alzheimer's disease (AD) was tested and an extensive neuropsychological battery was administered at baseline and after 12 months. Each participant was randomized and assigned one of three groups: 1) Group 1 received the HP-EH-EVOO (50 mL/day); 2) Group 2 received the MP-EVOO (50 mL/day), and 3) Group 3 received only the MeDi instructions. **Results**:Better follow-up performance was found in Group 1 compared to Group 2 and Group 3 in the almost all cognitive domains. Moreover, Group 2 showed also significant improvement compared to Group 3 in ADAS-cog (p = 0.001) and MMSE (p = 0.05), whereas Group 3 exhibited worse or similar to baseline performance in almost all domains. In

particular, Group 1 and Group 2 had better outcomes with regards to ADAS-cog (p = 0.003), Digit Span (p = 0.006), and Letter fluency (p = 0.003). Moreover, there was a significant difference (p = 0.001) in the presence of APOE ε4 between the Groups 1 and 2 versus Group 3. **Conclusion**: Long-term intervention with HP-EH-EVOO or MP-EVOO was associated with significant improvement in cognitive function compared to MeDi, independent of the presence of APOE ε4.

Tsolaki, M. Lazarou E., Kozori M., Petridou N., Tabakis I., Lazarou I., Karakota M., Saoulidis I., Melliou E., Magiatis P. (2020) . 'A Randomized Clinical Trial of Greek High Phenolic Early Harvest Extra Virgin Olive Oil in Mild Cognitive Impairment: The MICOIL Pilot Study'. (2020) ***Journal of Alzheimer's Disease****, vol. 78, no. 2, pp. 801-817. DOI: 10.3233/JAD-200405*

3. The pleiotropic beneficial intervention of olive oil intake on the Alzheimer's disease onset via fibrinolytic system

Abstract

The daily consumption of Extra Virgin Olive Oil (EVOO) in Mediterranean nutrition is tightly associated with lower frequency of many diseases' appearance, including Alzheimer's disease (AD). Fibrinolytic system is already assumed to be involved in AD pathophysiology through various factors, especially plasminogen activator inhibitor-1 (PAI-1), a2-antiplasmin (α2AP) and tissue plasminogen activator (tPA). We, here, present a biochemical study, as a continuation of a clinical trial of a cohort of 84 participants, focusing on the pleiotropic effect of the annual EVOO consumption on the fibrinolytic factors of Mild Cognitive Impairment (MCI) patients. The levels of all these fibrinolytic factors, measured by Enzyme-Linked Immunosorbent Assay (ELISA) method, were reduced in the serum of MCI patients annually administered with EVOO, versus not treated MCI patients, as well as AD patients. The well-established AD hallmarks (Aβ1–40 and Aβ1–42 species, tau, and p-tau) of MCI patients' group, annually administered with EVOO, were restored to levels equal to those of the cognitively-healthy group; in contrast to those patients not being administered, and their AD hallmarks levels increased at the end of the year. Moreover, one of the EVOO annual consumption multimodal effects on the MCI patients focused on the levels of an oxidative stress trademark, malondialdehyde (MDA), which displayed also a visible quenching; On the other hand, an increase exhibited in the MCI patients not consuming EVOO one year after, was attributed to the lack of the EVOO anti-oxidative properties. These outcomes are exploitable towards the establishment of natural products like EVOO, as a preventive remedy fighting this neurodegenerative disorder, AD.

Tzekaki E.E., Tsolaki M., Pantazaki A.A, Geromichalos G., Lazarou E., Kozori M., Sinakos Z., (2021) The pleiotropic beneficial intervention of olive oil intake on the Alzheimer's disease onset via fibrinolytic system, ***Experimental Gerontology,*** *150, 111344,* https://doi.org/10.1016/j.exger.2021.111344.

4. Post-prandial effects of high-polyphenolic extra virgin olive oil on endothelial function in adults at risk for type 2 diabetes: A randomized controlled crossover trial

Abstract

Effects of olive oil on cardiovascular risk have been controversial. We compared the effects of high-polyphenolic extra virgin olive oil (EVOO) and refined olive oil without polyphenols on endothelial function (EF) in adults at risk for Type 2 diabetes mellitus (T2DM).

Randomized, controlled, double-blind, crossover trial of 20 adults (mean age 56.1 years; 10 women, 10 men) at risk for T2DM (i.e., as defined by either prediabetes or metabolic syndrome) assigned to one of two possible sequence permutations of two different single dose treatments (50 mL of high-polyphenolic EVOO or 50 mL of refined olive oil without polyphenols), with 1-week washout. Participants received their olive oils in a smoothie consisting of ½ cup frozen blueberries and 1 cup (8 oz) low-fat vanilla yogurt blended together. Primary outcome measure was EF measured as flow-mediated dilatation. Participants were evaluated before and 2 h after ingestion of their assigned olive oil treatment

EVOO acutely improved EF as compared to refined olive oil (1.2 ± 6.5% versus −3.6 ± 3.8%; p = 0.0086). No significant effects on systolic or diastolic blood pressure were observed.

High-polyphenolic EVOO acutely enhanced EF in the study cohort, whereas refined olive oil did not. Blood pressure effects were not observed. Reports on the vascular effects of olive oil ingestion should specify the characteristics of the oil.

Njike V.Y., Ayettey R., Treu J.A., Doughty K.N., Katz D.L.,. (2021) Post-prandial effects of high-polyphenolic extra virgin olive oil on endothelial function in adults at risk for type 2 diabetes: A randomized controlled crossover trial, ***International Journal of Cardiology****, 330, 171-176.*

https://doi.org/10.1016/j.ijcard.2021.01.062.

5. Effect of polyphenol-rich extra-virgin olive oil on lipid profile and inflammatory biomarkers in patients undergoing coronary angiography: a randomised, controlled, clinical trial

Abstract

The present study was conducted to compare the effects of high polyphenol extra-virgin olive oil (EVOO) with low polyphenol refined olive oil (ROO) on some cardiovascular risk factors in patients undergoing coronary angiography. In a randomized, controlled, parallel-arm, clinical trial, 40 patients with at least one classic cardiovascular risk factor who referred to coronary angiography were randomly allocated to two groups and received 25 mL EVOO or ROO daily for 6 weeks. Plasma LDL-cholesterol significantly reduced in EVOO group (–9.52 ± 20.44 vs 8.68 ± 18.77 mg/dL, p = .007 for EVOO and ROO respectively). EVOO resulted in a significant reduction in plasma CRP (–0.40 ± 0.52 vs 0.007 ± 0.42 mg/L, p = .01 for EVOO and ROO respectively) and increased ex-vivo whole blood LPS-stimulated IL-10 production (12.13 ± 33.64 vs −17.47 ± 49.04 pg/mL, p = .035 for EVOO and ROO respectively). Daily consumption of polyphenol-rich EVOO in subjects who have been under medical treatment with risk-reducing agents could additionally improve LDL-C and selected inflammatory markers.

Khandouzi, N., Zahedmehr, A., & Nasrollahzadeh, J. (2021). Effect of polyphenol-rich extra-virgin olive oil on lipid profile and inflammatory biomarkers in patients undergoing coronary angiography: A randomised, controlled, clinical trial. ***International Journal of Food Sciences and Nutrition****, 72(4), 548–558.* https://doi.org/10.1080/09637486.2020.1841123

6. The Effect of High Polyphenol Extra Virgin Olive Oil on Blood Pressure and Arterial Stiffness in Healthy Australian Adults: A Randomized, Controlled, Cross-Over Study

Abstract

Extra virgin olive oil (EVOO) is suggested to be cardioprotective, partly due to its high phenolic content. We investigated the effect of extra virgin high polyphenol olive oil (HPOO) versus low polyphenol olive oil (LPOO) on blood pressure (BP) and arterial stiffness in healthy Australian adults. In a double-blind, randomized, controlled cross-over trial, 50 participants (age 38.5 ± 13.9 years, 66% female) were randomized to consume 60 mL/day of either HPOO (360 mg/kg polyphenols) or LPOO (86 mg/kg polyphenols) for three weeks. Following a two-week washout period, participants crossed over to consume the alternate oil. Anthropometric data, peripheral BP, central BP and arterial stiffness were measured at baseline and follow up. No significant differences were observed in the changes from baseline to follow up between the two treatments. However, a significant decrease in peripheral and central systolic BP (SBP) by 2.5 mmHg (95% CI: −4.7 to −0.3) and 2.7 mmHg (95% CI: −4.7 to −0.6), respectively, was observed after HPOO consumption. Neither olive oil changed diastolic BP (DBP) or measures of arterial stiffness. The reductions in SBP after HPOO consumption provide evidence for a potentially widely accessible dietary intervention to prevent cardiovascular disease in a multiethnic population. Longer intervention studies and/or higher doses of EVOO polyphenols are warranted to elucidate the potential effect on DBP and arterial stiffness.

Sarapis, K.; Thomas, C.J.; Hoskin, J.; George, E.S.; Marx, W.; Mayr, H.L.; Kennedy, G.; Pipingas, A.; Willcox, J.C.; Prendergast, L.A.; Itsiopoulos, C.; Moschonis, G. The Effect of High Polyphenol Extra Virgin Olive Oil on Blood Pressure and Arterial Stiffness in Healthy Australian Adults: A Randomized, Controlled, Cross-Over Study. ***Nutrients 2020****, 12, 2272.*
https://doi.org/10.3390/nu12082272

7. Olive oil polyphenols decrease blood pressure and improve endothelial function in young women with mild hypertension

Abstract

Background: Olive oil polyphenols have been associated with several cardiovascular health benefits. This study aims to examine the influence of a polyphenol-rich olive oil on blood pressure (BP) and endothelial function in 24 young women with high-normal BP or stage 1 essential hypertension.

Methods: We conducted a double-blind, randomized, crossover dietary-intervention study. After a run-in period of 4 months (baseline values), two diets were used, one with polyphenol-rich olive oil (~30 mg/day), the other with polyphenol-free olive oil. Each dietary

period lasted 2 months with a 4-week washout between diets. Systolic and diastolic BP, serum or plasma biomarkers of endothelial function, oxidative stress, and inflammation, and ischemia-induced hyperemia in the forearm were measured.

Results: When compared to baseline values, only the polyphenol-rich olive oil diet led to a significant ($P < 0.01$) decrease of 7.91 mm Hg in systolic and 6.65 mm Hg of diastolic BP. A similar finding was found for serum asymmetric dimethylarginine (ADMA) (-0.09 ± 0.01 µmol/l, $P < 0.01$), oxidized low-density lipoprotein (ox-LDL) (-28.2 ± 28.5 µg/l, $P < 0.01$), and plasma C-reactive protein (CRP) (-1.9 ± 1.3 mg/l, $P < 0.001$). The polyphenol-rich olive oil diet also elicited an increase in plasma nitrites/nitrates (+4.7 ± 6.6 µmol/l, $P < 0.001$) and hyperemic area after ischemia (+345 ± 386 perfusion units (PU)/sec, $P < 0.001$).

Conclusions: We concluded that the consumption of a diet containing polyphenol-rich olive oil can decrease BP and improve endothelial function in young women with high-normal BP or stage 1 essential hypertension.

Rafael Moreno-Luna 1, Rocio Muñoz-Hernandez, Maria L Miranda, Alzenira F Costa, Luis Jimenez-Jimenez, Antonio J Vallejo-Vaz, Francisco J G Muriana, Jose Villar, Pablo Stiefel. Olive oil polyphenols decrease blood pressure and improve endothelial function in young women with mild hypertension. ***Am J Hypertens*** *2012 Dec;25(12):1299-304. doi: 10.1038/ajh.2012.128. Epub 2012 Aug 23.*

8. Anti-inflammatory effect of virgin olive oil in stable coronary disease patients: a randomized, crossover, controlled trial

Abstract

Objectives: To assess the effect of two similar olive oils, but with differences in their phenolic compounds (powerful antioxidant compounds), on inflammatory markers in stable coronary heart disease patients.

Design: Placebo-controlled, crossover, randomized trial.

Setting: Cardiology Department of Hospital del Mar and Institut Municipal d'Investigació Mèdica (Barcelona).

Subjects: Twenty-eight stable coronary heart disease patients.

Interventions: A raw daily dose of 50 ml of virgin and refined olive oil (ROO) was sequentially administered over two periods of 3-weeks, preceded by 2-week washout periods in which ROO was used.

Results: Interleukin-6 ($P<0.002$) and C-reactive protein ($P=0.024$) decreased after virgin olive oil intervention. No changes were observed in soluble intercellular and vascular adhesion molecules, glucose and lipid profile.

Conclusions: Consumption of virgin olive oil, could provide beneficial effects in stable coronary heart disease patients as an additional intervention to the pharmacological treatment.

M Fitó, M Cladellas, R de la Torre, J Martí, D Muñoz, H Schröder, M Alcántara, M Pujadas-Bastardes, J Marrugat, M C López-Sabater, J Bruguera, M I Covas, Anti-inflammatory effect of

virgin olive oil in stable coronary disease patients: a randomized, crossover, controlled trial. ***Eur J Clin Nutr. 2008*** *Apr;62(4):570-4. doi: 10.1038/sj.ejcn.1602724. Epub 2007 Mar 21.*

9. Protection of LDL from oxidation by olive oil polyphenols is associated with a downregulation of CD40-ligand expression and its downstream products in vivo in humans

Abstract

Background: Recently, the European Food Safety Authority approved a claim concerning the benefits of olive oil polyphenols for the protection of LDL from oxidation. Polyphenols could exert health benefits not only by scavenging free radicals but also by modulating gene expression.

Objective: We assessed whether olive oil polyphenols could modulate the human in vivo expressions of atherosclerosis-related genes in which LDL oxidation is involved.

Design: In a randomized, crossover, controlled trial, 18 healthy European volunteers daily received 25 mL olive oil with a low polyphenol content (LPC: 2.7 mg/kg) or a high polyphenol content (HPC: 366 mg/kg) in intervention periods of 3 wk separated by 2-wk washout periods.

Results: Systemic LDL oxidation and monocyte chemoattractant protein 1 and the expression of proatherogenic genes in peripheral blood mononuclear cells [ie, CD40 ligand (CD40L), IL-23α subunit p19 (IL23A), adrenergic β-2 receptor (ADRB2), oxidized LDL (lectin-like) receptor 1 (OLR1), and IL-8 receptor-α (IL8RA)] decreased after the HPC intervention compared with after the LPC intervention. Random-effects linear regression analyses showed 1) a significant decrease in CD40, ADRB2, and IL8RA gene expression with the decrease of LDL oxidation and 2) a significant decrease in intercellular adhesion molecule 1 and OLR1 gene expression with increasing concentrations of tyrosol and hydroxytyrosol in urine.

Conclusions: In addition to reducing LDL oxidation, the intake of polyphenol-rich olive oil reduces CD40L gene expression, its downstream products, and related genes involved in atherogenic and inflammatory processes in vivo in humans. These findings provide evidence that polyphenol-rich olive oil can act through molecular mechanisms to provide cardiovascular health benefits. This trial was registered at www.controlled-trials.com as ISRCTN09220811.

Olga Castañer 1, María-Isabel Covas, Olha Khymenets, Kristiina Nyyssonen, Valentini Konstantinidou, Hans-Franz Zunft, Rafael de la Torre, Daniel Muñoz-Aguayo, Joan Vila, Montserrat Fitó. Protection of LDL from oxidation by olive oil polyphenols is associated with a downregulation of CD40-ligand expression and its downstream products in vivo in humans. ***Am J Clin Nutr. 2012*** *May;95(5):1238-44. doi: 10.3945/ajcn.111.029207. Epub 2012 Mar 21.*

10. Antioxidant effect of virgin olive oil in patients with stable coronary heart disease: a randomized, crossover, controlled, clinical trial

Abstract

The Mediterranean diet, in which olive oil is the main source of fat, has been associated with a reduced incidence of coronary heart disease (CHD) and low blood pressure levels. Virgin olive oil (VOO), besides containing monounsaturated fat, is rich in phenolic compounds (PC) with antioxidant properties. The aim of this study was to examine the antioxidant and anti-hypertensive effect of two similar olive oils, but with differences in their PC (refined: 14.7 mg/kg versus virgin: 161.0 mg/kg), in 40 males with stable CHD. The study was a placebo controlled, crossover, randomized trial. A raw daily dose of 50 mL of VOO and refined olive oil (ROO) were sequentially administered over two periods of 3 weeks, preceded by 2-week washout periods in which ROO was used. Lower plasma oxidized LDL ($p < 0.001$) and lipid peroxide levels ($p = 0.003$), together with higher activities of glutathione peroxidase ($p = 0.033$), were observed after VOO intervention. Systolic blood pressure decreased after intake of VOO ($p = 0.001$) in hypertensive patients. No changes were observed in diastolic blood pressure, glucose, lipids, and antibodies against oxidized LDL. Consumption of VOO, rich in PC, could provide beneficial effects in CHD patients as an additional and complementary intervention to the pharmacological treatment.

M Fitó, M Cladellas, R de la Torre, J Martí, M Alcántara, M Pujadas-Bastardes, J Marrugat, J Bruguera, M C López-Sabater, J Vila, M I Covas, Antioxidant effect of virgin olive oil in patients with stable coronary heart disease: a randomized, crossover, controlled, clinical trial. ***Atherosclerosis, 2005*** *Jul;181(1):149-58. doi: 10.1016/j.atherosclerosis.2004.12.036. Epub 2005 Feb 12. DOI: 10.1016/j.atherosclerosis.2004.12.036*

11. The effect of polyphenols in olive oil on heart disease risk factors: a randomized trial

Abstract

Background: Virgin olive oils are richer in phenolic content than refined olive oil. Small, randomized, crossover, controlled trials on the antioxidant effect of phenolic compounds from real-life daily doses of olive oil in humans have yielded conflicting results. Little information is available on the effect of the phenolic compounds of olive oil on plasma lipid levels. No international study with a large sample size has been done.

Objective: To evaluate whether the phenolic content of olive oil further benefits plasma lipid levels and lipid oxidative damage compared with monounsaturated acid content.

Design: Randomized, crossover, controlled trial.

Setting: 6 research centers from 5 European countries.

Participants: 200 healthy male volunteers.

Measurements: Glucose levels, plasma lipid levels, oxidative damage to lipid levels, and endogenous and exogenous antioxidants at baseline and before and after each intervention.

Intervention: In a crossover study, participants were randomly assigned to 3 sequences of daily administration of 25 mL of 3 olive oils. Olive oils had low (2.7 mg/kg of olive oil), medium (164 mg/kg), or high (366 mg/kg) phenolic content but were otherwise similar. Intervention periods were 3 weeks preceded by 2-week washout periods.

Results: A linear increase in high-density lipoprotein (HDL) cholesterol levels was observed for low-, medium-, and high-polyphenol olive oil: mean change, 0.025 mmol/L (95% CI, 0.003 to 0.05 mmol/L), 0.032 mmol/L (CI, 0.005 to 0.05 mmol/L), and 0.045 mmol/L (CI, 0.02 to 0.06 mmol/L), respectively. Total cholesterol-HDL cholesterol ratio decreased linearly with

the phenolic content of the olive oil. Triglyceride levels decreased by an average of 0.05 mmol/L for all olive oils. Oxidative stress markers decreased linearly with increasing phenolic content. Mean changes for oxidized low-density lipoprotein levels were 1.21 U/L (CI, -0.8 to 3.6 U/L), -1.48 U/L (-3.6 to 0.6 U/L), and -3.21 U/L (-5.1 to -0.8 U/L) for the low-, medium-, and high-polyphenol olive oil, respectively.

Limitations: The olive oil may have interacted with other dietary components, participants' dietary intake was self-reported, and the intervention periods were short.

Conclusions: Olive oil is more than a monounsaturated fat. Its phenolic content can also provide benefits for plasma lipid levels and oxidative damage.

María-Isabel Covas 1, Kristiina Nyyssönen, Henrik E Poulsen, Jari Kaikkonen, Hans-Joachim F Zunft, Holger Kiesewetter, Antonio Gaddi, Rafael de la Torre, Jaakko Mursu, Hans Bäumler, Simona Nascetti, Jukka T Salonen, Montserrat Fitó, Jyrki Virtanen, Jaume Marrugat. The effect of polyphenols in olive oil on heart disease risk factors: a randomized trial. ***Ann Intern Med. 2006*** *Sep 5;145(5):333-41. doi: 10.7326/0003-4819-145-5-200609050-00006.*

12. The Effect of Cretan High Phenolic Olive Oil on Fecal Calprotectin Levels in the Course of Multiple Sclerosis

Multiple sclerosis is a chronic immune-related inflammatory disease of the central nervous system that results in demyelination and lesions in the brain. Even though there is a massive research for the whole profile and treatment of the disease, to date, the etiopathology of multiple sclerosis is still unclear and there is no fully successful therapy. The urgent need to find new therapies led us to the search for the potential therapeutic effects of high phenolic early harvest extra virgin olive oil (HP-EH-EVOO) that interacts with the gut-brain axis. Recent research dictates that olive oil polyphenols can confront oxidative damage and inflammation through gut microbiota alterations. Therefore, we conducted a pilot study with relapsing-remitting multiple sclerosis (RRMS) patients. Patients in the experimental group, consumed Eliama Daily Value Gold - HP-EH-EVOO for 4 months, while patients in the control group did not. We used fecal calprotectin measurements at baseline, 2 and 4 months during the oil consumption to observe the inflammation status of the patients and found a decreased inflammation in the experimental group [$F(2,14) = 10.38$, $p = .002$]. Our results gave us an insight on how we can take advantage of our diet to treat multiple sclerosis and other inflammatory diseases. Nonetheless, it is important for future studies with bigger samples to replicate our results and extend the investigation in order for HP-EH-EVOO to be a proper candidate for clinical and therapeutic use.

Greta Wozniak, Marios Kyprou, Magda Tsolaki. “The Effect of Cretan High Phenolic Olive Oil on Fecal Calprotectin Levels in the Course of Multiple Sclerosis”. **EC Neurology 12.11 (2020**): 65-79.