Effects of virgin olive oil phenolic compounds on health: solid evidence or just another fiasco?

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SUMMARY: Current research suggests that virgin olive oil (VOO) phenolics are potent preventive and therapeutic agents against metabolic diseases associated with inflammation and oxidative stress. Evidence-based medicine requires these effects be proved in randomized controlled trials (RCT), which are then assessed in meta-analyses, to ensure that the alleged health benefits really proceed in humans. The available evidence is limited to the ability of VOO phenolic compounds to protect lipoproteins from oxidation and to reduce systolic pressure in hypertensive individuals. No RCT assessing the effects of VOO phenolics on diabetes and neurodegenerative diseases have been performed, and those focused on osteoarthritis and cancer provided very scarce information. Therefore, RCT in extensive and diverse population groups, with different disorders and phenolic doses adjusted to usual VOO consumptions are necessary to achieve high quality scientific evidence before nutritional recommendations can be given to the general public.

KEYWORDS: Evidence; Health; Hydroxytyrosol; Oleocanthal; Phenolic Compounds; Virgin Olive Oil

RESUMEN: Efectos de los compuestos fenólicos del aceite de oliva virgen en la salud: ¿evidencia sólida o simplemente otro fiasco? Las investigaciones actuales indican que los compuestos fenólicos del aceite de oliva virgen (AOV) son potentes agentes preventivos y terapéuticos contra las enfermedades metabólicas asociadas con la inflamación y el estrés oxidativo. La medicina basada en la evidencia requiere que estos efectos se prueben en ensayos aleatorizados controlados (RCT), que son después evaluados en meta-análisis, para garantizar que los supuestos beneficios para la salud realmente se registran en humanos. La evidencia disponible se limita a la capacidad de los compuestos fenólicos del AOV para proteger las lipoproteínas de la oxidación y reducir la presión sistólica en individuos hipertensos. No se han realizado RCT que evalúen el efecto de estos compuestos sobre la diabetes y las enfermedades neurodegenerativas, y los que se centraron en la osteoartritis y el cáncer han proporcionado información muy escasa. Por lo tanto, nuevos RCT, en grupos de población extensos y diversos, con diferentes patologías y con dosis de fenoles ajustadas a los consumos habituales de VOO, deben desarrollarse, para lograr evidencia científica de alta calidad antes de que se puedan dar recomendaciones nutricionales al público en general.

PALABRAS CLAVE: Aceite de Oliva Virgen; Compuestos Fenólicos; Evidencia; Hidroxitirosol; Oleocantal; Salud

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1. INTRODUCTION

In 2014, Francesco Visioli published an editorial response to a review by Tang et al., (2014) on the effects on cardiovascular health of resveratrol, a natural phenolic compound found in red wine (Visioli, 2014). Resveratrol was alleged to interact with multiple targets in a variety of cardiovascular disease models to exert protective effects or induce a reduction in cardiovascular risks. However, Visioli’s article was entitled “The resveratrol fiasco” and concluded that after more than 20 years of well-funded research, resveratrol had no proven human activity. He claimed that there was a lack of clinical trials and the majority of available evidence came from cell culture and animal models. He also suggested that the resveratrol fiasco is not the only one of that kind in pharma-nutrition research. Considering that the association of virgin olive oil (VOO) phenolic compounds and health was initiated in the late 90s (some of the early studies were carried out by Visioli himself (Visioli et al., 1998)) and that the bulk of experimental data were obtained from in vitro and animal models, are VOO phenolics another example of scientific fiasco? In order to answer this question, the present review summarizes the current knowledge on the effects of VOO phenolic compounds on human health, focusing on the data obtained from randomized clinical trials (RCT) and their meta-analyses and systematic reviews, which provide the highest level of scientific evidence.

2. VOO PHENOLIC COMPOUNDS

There is ample evidence indicating that VOO consumption provides benefits in key processes associated with the development of a number of diseases and pathophysiological conditions. These include atherosclerosis, diabetes mellitus, obesity, metabolic syndrome, cancer, arthritis and neurodegenerative diseases (Covas et al., 2015). Despite its high oleic acid content, VOO is more than just a monounsaturated fatty acid-rich fat. VOO contains minor compounds with potent pharmacological activity, which are classified into two large groups: those that form part of the unsaponifiable fraction and those with a phenolic nature. The former are lipophilic and may be extracted with organic solvents after saponification of the oil, while the latter are water soluble.

More than 30 phenolic compounds that can play a role in the health promoting qualities of VOO have been identified, among which there is considerable variation regarding their concentration (0.02 to 600 mg/kg) (Servili et al., 2009). This variability depends on the type of phenolic compound, but also on many other factors such as the olive tree variety, geographical origin, cultivation techniques, ripening stage at the time of harvest, processing and storage. Among VOO phenolics, secoiridoids are present in the greatest amount, but the most interesting ones from the point of view of health are probably oleuropein aglycone and its metabolite hydroxytyrosol. However, the presence of oleocanthal should not be ignored, as this compound has received a great deal of attention since it was suggested that it might have anti-inflammatory activity (Beauchamp et al., 2005).

Several experimental studies in in vitro systems and animal models have shown that the possible benefits of VOO phenolics are associated with their anti-inflammatory, antioxidant and vasodilatory activity, which in theory makes them key preventive or therapeutic agents for metabolic diseases related to oxidative stress and inflammation (Covas et al., 2006). However, most of these investigations used supraphysiological doses of phenolics (> 10 μM) (Catalán et al., 2015) and, therefore, it is difficult to translate their results into physiological relevance for humans. VOO phenolics are bioavailable in humans, i.e. they are susceptible to being absorbed and to exert a bioactive effect on the organism (de la Torre, 2008). It has been proposed that in humans hydroxytyrosol is dose-dependently absorbed and excreted in urine after the intake from VOO (Rubió et al., 2012; Oliveras-López et al., 2014). However, a more recent study in Sprague-Dawley rats suggested that different dosages of hydroxytyrosol do not provide a linear, dose-dependent plasma concentration or excretion in urine (Dominguez-Perles et al., 2017). Nevertheless, it has been estimated that the amount of phenolics ingested from VOO consumption does not exceed 9 mg/day in Mediterranean countries (Parkinson and Cicerale., 2016).

Since 2011, the European Food Safety Authority (EFSA) accepts a claim about the benefits of daily intake of VOO rich in phenolic compounds over the oxidation of low density lipoproteins (LDL), maintenance of normal (fasting) blood levels of triglycerides, HDL-cholesterol and blood glucose...
(EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2011). The acceptance of these claims by EFSA authorizes their inclusion on the labels of olive oil bottles. However, this health claim is focused on the protection provided by hydroxytyrosol and there are currently no accepted claims for the other benefits that have been attributed to VOO or its phenolic compounds.

Although a large number of in vitro and experimental animal studies are available, according to Evidence-Based Medicine (Woolf et al., 1990), the healthy properties of a food and/or its components must be proved in RCT, in order to ensure that the alleged health benefits really stand out. The highest degree of scientific evidence is obtained through meta-analyses and systematic reviews of these RCT. However, at the moment the number and variety of RCT carried out using VOO phenolic compounds is very limited and there is only one meta-analysis and less than five systematic reviews assessing the healthy effects of VOO phenolic compounds. With regard to RCT, there are currently about 50 published articles that can be classified as such in which the effect of VOO phenolic compounds on health has been evaluated. A high number of these studies were published by the group of Covas and their collaborators and the rest by three or four research teams, the absolute majority of which were Spanish or Italian.

3. VOO PHENOLIC COMPOUNDS AND CARDIOVASCULAR DISEASE

The role of VOO phenolics as cardiovascular protectors has been a matter of research for a long time. However, as very recently displayed by Visioli et al., (2020), most investigations used isolated compounds in pharmacological in vitro approaches, rather than more nutritional human trials. Still, enough data from human studies assessing surrogate markers of cardiovascular disease have been generated (Bogani et al., 2007; Visioli et al., 2005; Covas et al., 2006) to allow for the completion of a meta-analysis of RCT (Hohmann et al., 2015) and two systematic reviews (Bahramsoltani et al., 2019; Schwingshackl et al., 2019).

Indeed, this meta-analysis was aimed at assessing the effects of high phenolic olive oil on risk factors for cardiovascular disease. It was published in 2015 and included the results of 8 human RCT (Hohmann et al., 2015). The sample size of these trials was quite variable, ranging from 24 participants in the study published by Moreno-Luna et al., (2012), to 200 individuals in the one carried out by Covas et al., (2006). In addition, there was variability in the health status of the participants. In five of these studies, the subjects were healthy and in the remaining three ones, the recruited individuals already had a cardiovascular event. The doses used in these tests ranged from 0 to 19.5 mg of total phenolics. Furthermore, in all these trials what was compared was the intake of a high phenolic VOO with a refined olive oil. Therefore, only the total phenolic content was considered and the concentrations in different phenolic compounds were not distinguished.

The intake of high phenolic VOO only seemed to produce a modest but significant reduction in oxidized LDL-cholesterol (Z=1.98, \( p=0.05 \)) and blood pressure (Z=4.04, \( p<0.001 \)). For the rest of parameters related to cardiovascular disease (malondialdehyde, LDL-cholesterol, HDL-cholesterol, total cholesterol and triglycerides), no significant effects were found. Therefore, the conclusion of this meta-analysis was that a high phenolic VOO provides small beneficial effects on systolic pressure and plasma oxidative status. No association between the intake of phenolic compounds from VOO and cardiovascular risk could be obtained.

In addition to this meta-analysis, two systematic reviews were published, both of them in 2019. Bahramsoltani et al., (2019) published a comprehensive review about dietary phenolic compounds and atherosclerosis and, even more recently, Schwingshackl et al., (2019) carried out a systematic review and network meta-analysis to assess the impact of different types of olive oil on cardiovascular risk factors.

The review by Bahramsoltani et al., (2019) included only six RCT, while the aforementioned meta-analysis by Hohmann and collaborators included eight. Of these 6 trials, only one reached a score of 3 on the Jadad Scale (Jadad et al., 1996) which measures the methodological quality of a clinical trial from 0 (very poor) to 5 (rigorous) points. The others stayed at 2 or below. What was observed in the best designed study (Covas et al., 2006) was an effect on the postprandial isoprostane F2 levels in plasma, which is a biomarker of oxidative stress. In this double-blind trial, 40 mL of three olive oils
with different phenolic contents were administered in a single dose: low (2.7 mg/kg), medium (164 mg/kg) and high (366 mg/kg). The authors observed that the concentration in total phenolic compounds in LDL increased in the postprandial period in a direct relationship with the phenolic content of the oils ingested. Moreover, plasma concentrations of tyrosol, hydroxytyrosol, and 3-O-methylhydroxytyrosol correlated with changes in the total phenolic compound contents in LDL. The other RCT included in the review also confirmed these results, as well as reduced lipid peroxidation (measured as 8-iso-PGF2α) and inflammation (assessed as intercellular adhesion molecule-1, ICAM-1).

The systematic review by Schwingshackl et al., (2019) included thirteen RCTs with 611 participants (mainly healthy) and compared refined olive oil, commercial olive oil (blend of refined and virgin olive oils), low-phenolic extra VOO and high-phenolic VOO. No differences for total cholesterol, HDL-cholesterol, triglycerides, and diastolic blood pressure were observed. However, the phenolic content positively correlated with a slight reduction in LDL-cholesterol (mean difference -0.14 mmol/L, 95%-CI: -0.28, -0.01) and oxidized LDL-cholesterol (standardized mean difference: -0.68, 95%-CI: -1.31, -0.04). Both, high- and low-phenolic VOO reduced systolic blood pressure compared to refined olive oil (range of mean difference: -2.99 to -2.87 mmHg).

The authors concluded that high phenolic VOO may improve some cardiovascular risk factors, although the implications for public health were limited due to the overall low or moderate level of evidence provided and also because the duration of these RCTs was too short (≤12 weeks) and no data could be found for relevant outcomes such as cardiovascular events.

From these meta-analysis and systematic reviews, it can be concluded that the protective effect of VOO phenolics is related to blood pressure and LDL oxidation only. Nonetheless, although the oxidative hypothesis of atherosclerosis has been accepted for decades, the true contribution of LDL oxidation to cardiovascular disease is still unclear (Arsenault et al., 2017; Visioli et al., 2020). While the hypothesis is supported by hundreds of in vitro and animal studies, it does not explain why human trials with some antioxidants, such as vitamin E, did not provide sufficient convincing evidence for cardiovascular prevention (Sesso et al., 2008; Guallar et al., 2013). Possibly, the story is not as simple as it was believed. For instance, it has been proposed that LDL can become atherogenic even before oxidation. Modification of these lipoproteins begins with a desialylation and it is followed by a cascade of other physical and chemical alterations that increase LDL atherogenicity, including particle size reduction, increase in its density and negative electrical charge and loss of lipids (Summerhill et al., 2019). Therefore, the effects of VOO phenolics on cardiovascular disease via LDL modification are, as of today, dubious and there is need of more RCT that directly address the claim.

4. VOO PHENOLIC COMPOUNDS AND TYPE 2 DIABETES MELLITUS/METABOLIC SYNDROME

Accumulated data obtained from experimental models indicate that VOO phenolics have the potential to normalize metabolic syndrome and its pathophysiological complications, including diabetes. Diabetes and metabolic syndrome are linked to each other through insulin resistance, and subjects diagnosed with metabolic syndrome have a high risk of developing T2DM (Shin et al., 2013). However, there are currently no RCT aimed at specifically assessing the effect of VOO phenolics on Type 2 diabetes (T2DM) patients, although two systematic reviews on the effects of these compounds on metabolic syndrome have been published (Chiva-Blanch and Badimon, 2017; Saibandith, 2017).

The review by Chiva-Blanch and Badimon (2017) was focused on human intervention trials administering phenolic-rich foods to patients with metabolic syndrome. They included a single RCT, carried out by Venturini et al., (2015), which administered extra VOO (10 mL/day). That trial reported an increase in the total radical-trapping antioxidant parameter (TRAP)/uric acid ratio, with no apparent effects on other markers of oxidative stress. On the other hand, the authors did not find changes in the lipid profile, plasma glucose, insulin resistance or blood pressure.

The systematic review by Saibandith et al., (2017) did assess the effects of VOO phenolics on components of the metabolic syndrome (i.e. glucose levels, blood pressure, central obesity, triglycerides and HDL-cholesterol). They summarized the current knowledge obtained from 18 clinical trials that were...
not specifically aimed at this syndrome. Saibandith and collaborators confirmed the effects of VOO phenolics on systolic blood pressure observed in previous systematic reviews and meta-analyses, but they did not draw significant outcomes on obesity, triglycerides or HDL. Still, some reductions in plasma glucose and in biomarkers associated with glucose homeostasis were reported, but only in three of those trials. Surprisingly, the authors did not include the RCT by Venturini et al., (2015) that had been published a couple of years before, and therefore, they did not analyzed any RCTs involving patients with metabolic syndrome. The systematic review could only conclude that there was good evidence showing that, when consumed at appropriate doses, VOO phenolics may reduce blood pressure in hypertensive subjects and improve plasma glucose in pre-diabetic individuals.

It is noteworthy that the RCT involving patients with metabolic syndrome and published in 2016 by D’Amore et al., was not included in both systematic reviews stated above. In that trial, 12 subjects with metabolic syndrome and 12 healthy controls received a single dose of 50 mL VOO from two olive varieties: coratina, providing 491 ppm of phenolic compounds, and peranzana, which had 270 ppm of phenolics. The most interesting result found in this study was the modification of the transcriptome of peripheral blood mononuclear cells, switching them to a less deleterious inflammatory phenotype. However, no relevant changes in the components of the metabolic syndrome were observed.

5. VOO PHENOLIC COMPOUNDS AND ALZHEIMER’S DISEASE

AD is pathologically characterized by substantial neuronal and synaptic losses, and decreased cognitive abilities, which are associated with cerebral deposits of amyloid-beta-enriched plaques and neurofibrillary aggregates of the Tau protein, as well as with chronic inflammation and oxidative stress (Rosales-Corral et al., 2015) elicited by the pathological activation of glial cells (Scimemi et al., 2013). Brain has revealed nowadays as an insulin-sensitive organ, where the hormone regulates important physiological processes, such as nutrient homeostasis, reproduction, cognition, and memory, and also exerts neurotrophic, neuromodulatory, and neuroprotective effects (Blazquez et al., 2014). Disturbances in insulin signaling in the brain may contribute to the development of several clinical entities, including T2DM and Alzheimer’s disease. The close association between cerebral insulin resistance and Alzheimer’s Disease brought some authors to propose the name “type 3 diabetes” for this illness (de la Monte and Wands, 2008).

For the moment, there are no RCTs available in which olive oil phenolics have been tested on Alzheimer’s disease or other neurodegenerative disorders. Therefore, no systematic reviews or meta-analysis of RCT have been performed so far. All available information refers to observational studies and those carried out in animal models, which, as mentioned above, provide a low level of scientific evidence.

Regarding the potential neuroprotective effects of olive phenolics, it has been reported that dietary supplementation with oleuropein aglycone reduced the amount of amyloid-beta oligomers in the brain of Alzheimer’s model mice (Luccarini et al., 2015), at the same time that they significantly improved their cognitive functions, presenting greater learning and memory capacities (Pantano et al., 2017). Oleuropein also enhanced the endogenous antioxidant response in the CA1 hippocampal area of rats suffering from colchicine-induced cognitive dysfunction, improving the redox status of glutathione, and increasing the activity of antioxidant enzymes, such as superoxide dismutase or catalase (Pourkhodadad et al., 2016). Similarly, hydroxytyrosol has been related to the amelioration of insulin resistance in the brain of mice (Kulas et al., 2020). In APP/PS1 mice, rodent models of AD, hydroxytyrosol improved cognitive function, increased the expression of antioxidant enzymes and phase 2 response genes, and reduced inflammatory factors in the brain of these animals (Peng et al., 2016).

Oleocanthal has also been associated with a reduction in amyloid-beta oligomers, as well as an attenuation of astrocytes activation and a reduction in systemic inflammation in neurons and astrocytes cells lines (Batarseh et al., 2017). Likewise, oleocanthal has demonstrated that it may modulate the astrocyte activation in TgSwDI mice, a model of Alzheimer’s disease (Qosa et al., 2015).

6. VOO PHENOLIC COMPOUNDS AND CANCER

Only one systematic review about the effects of VOO phenolic compounds on cancer has
been published, which implies that there are no meta-analyses available and, in consequence, the highest level of scientific evidence cannot be reached. In their review, Fabiani et al., (2016) included 16 animal studies and 5 RCTs. Most of the animal studies confirmed the ability of secoiridoid compounds to inhibit carcinogenesis at both initiation and promotion/progression phases. However, all human intervention trials included in this review only investigated the effects of VOO phenolics on DNA damage and did not evaluate their effect on the incidence or development of any kind of cancer. These trials only reported determinations related to the oxidation of nucleic acids, in particular the concentrations of 8-oxo-7,8-dihydro-2'-deoxyguanosine, which is a marker of DNA oxidation. Between 10 and 182 subjects participated in these RCT, and the phenolic doses from VOO ranged from 10 to 592 mg/kg. Three of the five human trials showed that VOO phenolics reduced the 8-oxo-7,8-dihydro-2'-deoxyguanosine levels in urine, mitochondrial DNA of mononuclear cells and lymphocyte DNA. The other two trials failed to find a protective effect on DNA oxidation. Four of these studies were conducted by the same research group, and had similar experimental designs (Weinbrenner et al., 2004; Hillestrøm et al., 2006; Machowetz et al., 2007; Romeu et al., 2016). Therefore, there is very little evidence relating the intake of VOO phenolic compounds with cancer. In fact, the authors suggested that further investigations are necessary to clarify the real chemopreventive potential of these compounds and that intervention studies on populations at high cancer risk are needed.

7. VOO PHENOLIC COMPOUNDS AND ARTHRITIS

There is currently only one RCT evaluating the effect of VOO phenolic compounds on arthritis (Takeda et al., 2013). This trial was aimed at determining whether hydroxytyrosol intake could reduce knee pain in individuals with gonarthrosis (n=25). An extract of Olea europaea containing approximately 22% of hydroxytyrosol, at a dose of 11 mg/day for 4 weeks, was administrated to the participants. The conclusion of the trial was that the subjects informed a reduction in knee pain, as compared to the administration of a placebo.

8. CONCLUSIONS

The benefits of VOO phenolic compounds on health have been extensively investigated, and recent studies support the belief that these components may play a key role in the amelioration of pathophysiological conditions. In particular, studies on in vitro systems and animal models have shown that oleuropein derivatives, hydroxytyrosol and oleocanthal exert potent pharmacological activities on markers of cancer, atherosclerosis and metabolic diseases. More specifically, on those associated with inflammatory processes and oxidative stress. However, meta-analyses of RCT, from which the highest level of scientific evidence should be obtained, do not support those effects on humans, except for some markers of cardiovascular risk. In fact, the strongest piece of evidence available has been found for the ability of VOO phenolic compounds to protect lipoproteins from oxidation and to reduce systolic blood pressure in hypertensive individuals (Table 1).

Unfortunately, there is not enough high-level evidence at the moment to confirm that the intake of phenolic compounds isolated or as components of the VOO can be healthy (Table 2). No RCT have been carried out to assess the direct effect of VOO phenolics on diabetes or neurodegenerative diseases and very scarce information can be collected from the ones that have focused on osteoarthritis and cancer. Therefore, it is still necessary to develop double-bind RCT in extensive and diverse population groups, with different disorders and with doses of phenols adjusted to usual VOO consumptions, in order to provide a greater degree of scientific evidence before nutritional recommendations may be given to the general population.

ACKNOWLEDGMENTS

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Effects of virgin olive oil phenolic compounds on health: solid evidence or just another fiasco? • 7

Table 1. Availability of studies and degree of evidence for the effect of virgin olive oil phenolics intake on different disorders according to evidence-based medicine.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Meta-Analyses</th>
<th>Systematic reviews</th>
<th>RCT</th>
<th>In vivo (animals)</th>
<th>In vitro (cells)</th>
<th>Degree of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>Yes (1)</td>
<td>Yes (2)</td>
<td>Yes (13)</td>
<td>Yes</td>
<td>Yes</td>
<td>Medium (High por BP and ox LDL)</td>
</tr>
<tr>
<td>Cancer</td>
<td>No</td>
<td>Yes (1)</td>
<td>Yes (5)</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>No</td>
<td>No</td>
<td>Yes (1)</td>
<td>Yes</td>
<td>Yes</td>
<td>Very low</td>
</tr>
<tr>
<td>Arthritis</td>
<td>No</td>
<td>No</td>
<td>Yes (1)</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>No</td>
<td>No</td>
<td>Yes (2)</td>
<td>Yes</td>
<td>Yes</td>
<td>Low (High for BP)</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>No</td>
<td>Yes (2)</td>
<td>Yes (2)</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
</tbody>
</table>

*Numbers in parentheses refer to the published number of studies of that kind. RCT, randomized controlled trial; BP, blood pressure; LDL, low-density lipoprotein.

Table 2. Summary of the studies cited in the text.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Study design</th>
<th>n</th>
<th>Intervention</th>
<th>Dose (day)/time</th>
<th>Time</th>
<th>Main markers</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD</td>
<td>RCT</td>
<td>22</td>
<td>2 olive oils (VOO vs ROO)</td>
<td>40 mL</td>
<td>7 weeks</td>
<td>TXB2, isoprostanes</td>
<td>Visioli et al., 2005</td>
</tr>
<tr>
<td></td>
<td>RCT</td>
<td>200</td>
<td>3 olive oils (different PC)</td>
<td>25 mL</td>
<td>3 weeks</td>
<td>TG, HDL, oxLDL</td>
<td>Covas et al., 2006</td>
</tr>
<tr>
<td></td>
<td>RCT</td>
<td>12</td>
<td>EVOO, OO and CO</td>
<td>50 mL</td>
<td>Postprandial</td>
<td>TXB2, LTB4</td>
<td>Bogani et al., 2007</td>
</tr>
<tr>
<td></td>
<td>RCT</td>
<td>24</td>
<td>2 olive oils (different PC)</td>
<td>30 mg</td>
<td>8 weeks</td>
<td>BP, CRP, ox-LDL</td>
<td>Moreno-Luna et al., 2012</td>
</tr>
<tr>
<td>Systematic review</td>
<td>RCT</td>
<td>6</td>
<td>Olive oils (different PC)</td>
<td>Various</td>
<td>Single-8 weeks</td>
<td>Lipids, oxidation, inflammation</td>
<td>Bahramsoltani et al., 2019</td>
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<tr>
<td>Systematic review</td>
<td>RCT</td>
<td>13</td>
<td>Olive oils (different PC)</td>
<td>Various</td>
<td>3-12 weeks</td>
<td>TC, LDL, HDL, TG, ox-LDL, BP</td>
<td>Schwingshackl et al., 2019</td>
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<tr>
<td>Meta-analysis</td>
<td>RCT</td>
<td>8</td>
<td>Olive oils (different PC)</td>
<td>Various</td>
<td>3-12 weeks</td>
<td>TC, LDL, HDL, TG, ox-LDL, BP</td>
<td>Hohmann et al., 2015</td>
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<tr>
<td>Cancer</td>
<td>RCT</td>
<td>12</td>
<td>3 olive oils (different PC)</td>
<td>25 mL</td>
<td>4 days</td>
<td>8-OHdG</td>
<td>Weinbrenner et al., 2004</td>
</tr>
<tr>
<td></td>
<td>RCT</td>
<td>28</td>
<td>3 olive oils (different PC)</td>
<td>25 mL</td>
<td>3 weeks</td>
<td>Etheno-DNA adducts</td>
<td>Hillestom et al., 2006</td>
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<td></td>
<td>RCT</td>
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<td>2 olive oils (different PC)</td>
<td>25 mL</td>
<td>3 weeks</td>
<td>8-Oxo-guanine</td>
<td>Machowetz et al., 2007</td>
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<td></td>
<td>RCT</td>
<td>33</td>
<td>2-3 olive oils (different PC)</td>
<td>25 mL</td>
<td>3 weeks</td>
<td>8-OHdG</td>
<td>Romeu et al., 2008</td>
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<td>RCT</td>
<td>5</td>
<td>2-3 olive oils (different PC)</td>
<td>25 mL. 50 g</td>
<td>4 days – 8 weeks</td>
<td>8-OHdG</td>
<td>Fabiani et al., 2016</td>
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<td>Alzheimer’s</td>
<td>N/A</td>
<td>Oleocanthal</td>
<td>5 μM</td>
<td>3-7 days</td>
<td>GLT1, GLUT1, IL-6</td>
<td>Batarseh et al., 2017</td>
<td></td>
</tr>
<tr>
<td>Murine model (Tg-CRND8)</td>
<td>6/group</td>
<td>Olearuropeo aglycone</td>
<td>50 mg/kg of diet</td>
<td>8 weeks</td>
<td>Aβ42, pE3-Aβ aggregation</td>
<td>Luccarini et al., 2015</td>
<td></td>
</tr>
<tr>
<td>Murine model (TgSwDI)</td>
<td>6/group</td>
<td>Oleocanthal</td>
<td>6 mg/kg injection</td>
<td>4 weeks</td>
<td>Aβ, IL-1β</td>
<td>Qosa et al., 2015</td>
<td></td>
</tr>
<tr>
<td>Disorder</td>
<td>Study design</td>
<td>n</td>
<td>Intervention</td>
<td>Dose (day)/time</td>
<td>Time</td>
<td>Main markers</td>
<td>References</td>
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<tr>
<td>Rat model</td>
<td>7/group</td>
<td>Oleuropein</td>
<td>10-20 mg/kg diet</td>
<td>10 days</td>
<td>SOD, Catalase, NO, MDA</td>
<td>Pourkhodadad et al., 2016</td>
<td></td>
</tr>
<tr>
<td>Murine model (APP/PS1)</td>
<td>9/group</td>
<td>Hydroxytyrosol</td>
<td>5 mg/kg gavage</td>
<td>6 months</td>
<td>Cognitive, SOD, inflammation</td>
<td>Peng et al., 2016</td>
<td></td>
</tr>
<tr>
<td>Murine model (Tg-CRND8)</td>
<td>6/group</td>
<td>Oleuropein aglycone</td>
<td>12.5 mg/kg of diet</td>
<td>8 weeks</td>
<td>Aβ42, pE3-Aβ aggregation</td>
<td>Pantano et al., 2017</td>
<td></td>
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<tr>
<td>Arthritis</td>
<td>RCT</td>
<td>25</td>
<td>Hydroxytyrosol</td>
<td>11 mg/day</td>
<td>4 weeks</td>
<td>Knee pain</td>
<td>Takeda et al., 2013</td>
</tr>
<tr>
<td>MetS</td>
<td>RCT</td>
<td>102</td>
<td>Usual diet, EVOO, fish oil</td>
<td>10 mL/day</td>
<td>12 weeks</td>
<td>TRAP, uric acid</td>
<td>Venturini et al., 2015</td>
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<tr>
<td>RCT</td>
<td>24</td>
<td>EVOO two varieties</td>
<td>50 mL</td>
<td>Postprandial</td>
<td>PBMC transcriptome</td>
<td>D’Amore et al., 2016</td>
<td></td>
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<tr>
<td>Systematic review</td>
<td>1 RCT&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Usual diet, EVOO, fish oil</td>
<td>10 mL/day</td>
<td>12 weeks</td>
<td>TRAP, uric acid</td>
<td>Chiva-Blanch and Badimon, 2017</td>
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<tr>
<td>Systematic review</td>
<td>18 RCT&lt;sup&gt;c&lt;/sup&gt;</td>
<td>EVOO, olive leaf extract</td>
<td>Various</td>
<td>1 week -1 year</td>
<td>BP, HbA1C, Glucose insulin, WC</td>
<td>Saibandith, 2017</td>
<td></td>
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</table>

<sup>a</sup>-OHdG, 8-hydroxy-deoxyguanosine; BP, blood pressure; CO, corn oil; CRP, C-reactive protein; EVOO, extra-virgin olive oil; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LTB4, leukotriene B4; OO, olive oil; ox-LDL, oxidized LDL; PC, phenolic content; RCT, randomized controlled trial; ROO, refined olive oil; TG, triglycerides; TXB2, thromboxane B2;<br><sup>AB</sup>, amiloid beta; EVOO, extra-virgin olive oil; GLT1, glutamine transporter 1; GLUT1, glucose transporter 1; HbA1C, glycosylated hemoglobin; IL-1β, interleukin 1 beta; IL-6, interleukin-6; MDA, malodialdehyde; MetS, metabolic syndrome; N/A, not applicable; NO, nitric oxide; PBMC, Peripheral blood mononuclear cell RCT, randomized controlled trial; SOD, superoxide dismutase; TRAP, peroxyl radical-trapping antioxidant potential; WC, waist circumference.<br><sup>b</sup>Review focused on phenolics from different sources. 1 RCT from VOO.<br><sup>c</sup>Review focused on MetS components, no RCT with MetS diagnosed subject.

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