

## Review

# Bioactive effects of olive oil phenolic compounds in humans: reduction of heart disease factors and oxidative damage

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**Abstract.** Oxidative stress is defined as an imbalance between the oxidant and antioxidant systems of the body, in favour of the oxidants. Oxidative stress produced by free radicals has been linked to the development of several diseases such as cardiovascular, cancer, and neurodegenerative diseases. Olive oil is the main source of fat of the Mediterranean diet which has been shown to be effective against oxidative stress associated diseases and also with the ageing. Besides its richness in monounsaturated fatty acid, the oleic acid, olive oil contains minor components with antioxidant properties. Here, we update the state of the art, and degree of evidence, of the body of knowledge concerning the protective role on lipids and lipid oxidative damage in humans of the olive oil phenolic compounds.

**Key words:** Olive oil – Polyphenols – LDL oxidation – DNA oxidation – Antioxidants

## Introduction

The Mediterranean diet, in which olive oil is the main source of fat has been associated with a decrease in overall, cardiovascular, and cancer mortality (Trichopoulou et al., 2003; Knuops et al., 2004). The beneficial effects of olive oil on coronary heart disease (CHD) risk factors are now recognized but often only attributed to the high monounsaturated fatty acid (MUFA) content of the olive oil. Olive oil, however, is a functional food which besides having a high MUFA level, the oleic acid, contains multiple minor components with biological properties (Covas et al., 2006). The content of the

minor components of an olive oil varies, depending on the cultivar, climate, ripeness of the olives at harvesting, and the processing system employed to produce the types of olive oil currently present on the market: virgin, ordinary, or pomace (Gimeno et al., 2002). Virgin olive oil is produced by direct pressing or centrifugation of the olives. Virgin olive oils with an acidity greater than or equal to 3.3 degrees (International Olive Oil Council Regulation/T.15/NC.n3.Rev2. Nov 24, 2006), or 2 degrees in Europe (European Regulation N. 1513/0) are submitted to a refining process in which some components, mainly phenolic compounds, and to a lesser degree squalene, are lost (Owen et al., 2000). By mixing virgin and refined olive oil an ordinary olive oil (olive oil, UE 1991) is produced and marketed. After virgin olive oil production the rest of the olive drupe and seed is again processed, submitted to a refining process, and the resulting pomace olive oil, to which a certain quantity of virgin olive oil is added, is put on the market.

Oxidative stress produced by reactive oxygen species (ROS) has been linked to the development of several diseases such as atherosclerosis, cancer, and neurodegenerative diseases (Southom and Powis, 1998; Witzum, 1994). Targets for ROS are lipids, deoxyribonucleic acid (DNA), and proteins (Gutteridge, 1995). Oxidation of the lipid part (Steinberg et al., 1989), or directly to the apolipoprotein B (Hazen and Heinecke, 1997), of the low density lipoproteins (LDL) leads to a change in the lipoprotein conformation by which the LDL is better able to enter into the monocyte/macrophage system of the arterial wall, and develop the atherosclerotic process, thus promoting cardiovascular disease (Witzum, 1994). In addition, 3-chloro- and 3-nitro-tyrosine generation, via myeloperoxidase activity, in high density lipoprotein (HDL), converts the lipoprotein in a pro-inflammatory HDL, and reduces its capacity to remove cholesterol from cells and to counteract the LDL oxidation (Fogelman, 2004). Nucleic acids are also targets of free radicals. Oxida-

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tive stress leads to mutagenic deoxyribonucleic acid (DNA) lesions in purines, pyrimidines, deoxyribose, and DNA single- and double-strand breaks (Poulsen et al., 1998; White-man et al., 2002). Accumulation of mutations from oxidative DNA damage is considered to be a crucial step in human carcinogenesis (Cooke et al., 2003; Evans et al., 2004).

On November 2004, the Federal Drug Administration (FDA) of the U.S.A permitted a claim on olive oil labels concerning: "the benefits on the risk of coronary heart disease of eating about 2 tablespoons (23 g) of olive oil daily, due to the monounsaturated fat (MUFA) in olive oil" (Food and Drug Administration. Press release P04-100, 2004). However, if the effect of olive oil can be attributed solely to its MUFA content, any type of olive oil, rapeseed oil, or a MUFA-rich food would provide the same health benefits. Thus, Public Health implications exist as to whether a specific type of MUFA fat or olive oil should be recommended as individualized eating strategies for oxidative stress associated diseases prevention

#### *Human studies on the in vivo antioxidant effect of phenolic compounds from olive oil*

Olive oil rich diets have been shown to be more protective against the *in vitro* LDL oxidation than polyunsaturated fatty acids rich diets (Reaven et al., 1993). Oleate-rich LDL have been shown to be less susceptible to oxidation than linoleate rich LDL (Parthasarathy et al., 1990). Olive oil minor components have been also involved in the antioxidant activity of olive oil. Although squalene or triterpenes have displayed antioxidant activity in experimental conditions (Covas et al., 2006), the antioxidant properties of the phenolic compounds from olive oil have been the most extensively studied. In experimental studies, olive oil phenolic compounds, like other plant-derived polyphenols (Vinson et al., 1995) showed strong antioxidant properties against lipids, DNA, and LDL oxidation (Covas et al., 2006). In animal models, olive oil phenolics retained their antioxidant properties *in vivo* (Visioli et al., 2000) and delayed the progression of atherosclerosis (Aviram, 1996).

However, controversial results were obtained in the human studies on the *in vivo* antioxidant effect of phenolic compounds from olive oil performed up to year 2005 (Covas et al., 2006; Fitó et al., 2007). There were extensive differences among these studies. On their basis, the Consensus Report made by the Expert Panel in the International Conference of Olive Oil and Health held in Jaen, Spain, October 2004 (Covas et al., 2006; Pérez-Jimenez et al., 2005) concluded: 1) data regarding the benefits of olive oil phenolic compounds in humans from real-life daily doses of olive oil were still controversial; 2) the protective effects on lipid oxidation in these trials were better displayed in oxidative stress conditions and in those markers directly associated with LDL oxidation; and 3) carefully controlled studies in appropriate populations (individuals with high oxidative status), or with a large sample size (in the case of healthy individuals), were required to definitively establish in which conditions phenolics from olive oil can exert their most beneficial effect controlling oxidative stress.

The results of the EUROLIVE study have recently provided evidence of the *in vivo* protective role of phenolic compounds from olive oil on lipids and lipid oxidative damage in humans, at real-life olive oil doses (Covas et al., 2006). The EUROLIVE (The effect of olive oil consumption on oxidative damage in European populations) study was a large, crossover, multicentre, clinical trial performed in 200 individuals from 5 European countries. Participants were randomly assigned to receive 25 mL/day of three similar olive oils, but with differences in their phenolic content (from 2.7 mg/kg to 366 mg/kg of olive oil), in intervention periods of 3 weeks preceded by two-week washout periods. All olive oils increased the HDL cholesterol and the ratio between the reduced and oxidized forms of glutathione, and decreased the oxidative damage to DNA (Covas et al., 2006; Machowetz et al., 2007). Consumption of medium- and high-phenolic content olive oil decreased lipid oxidative damage biomarkers such as plasma oxidized LDL, uninduced conjugated dienes, and hydroxy fatty acids, without changes in F<sub>2</sub>-isoprostanes. The increase in HDL cholesterol and the decrease in the lipid oxidative damage was linear with the phenolic content of the olive oil consumed. There were no changes either in the activity of the antioxidant enzymes or in the levels of antioxidant vitamins in plasma.

#### **Discussion and conclusions**

Results of the EUROLIVE study supports the body of research concerning that a rich-MUFA diet can help to reduce triglycerides and raise HDL cholesterol, in accordance with current cardiovascular guidelines (Executive Summary NECP, 2001). The findings also point out an independent effect of olive oil phenolics increasing HDL-cholesterol levels. The enhancement of HDL-cholesterol related with the phenolic content of the olive oil is in line with the results obtained after phenolic-rich food consumption in other human studies (Mursu, 2004). One key conclusion of the EUROLIVE study was that olive oil is more than a MUFA fat. The phenolic content of an olive oil can account for greater benefits on blood lipids and oxidative damage than those provided by the MUFA content of the olive oil. The results of the EUROLIVE study provide evidence to recommend the use of olive oil rich in phenolic compounds as a source of fat in order to achieve additional benefits against cardiovascular risk factors.

From the body of knowledge up to date on the beneficial role of olive oil and its phenolic compounds on risk factors for diseases, several guidelines for olive oil consumption emerge. It must be pointed out, however, that olive oils with high phenolic content are in general more bitter and greener than those with low phenolic content, and for some individuals the taste could be too stronger. Olive oil must not be taken as a medicine, but as a part of a healthy and pleasant dietary pattern. Due to this, recommendations which stem from the EUROLIVE study were: 1) Among the olive oils with a taste that better suits personal preferences, the best choice is that with the highest phenolic content, and 2) For health policy makers, the phenolic content of an olive oil should be present in the olive oil labels.

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