OCL 2014, 21(5) D512

DOI: 10.1051/ocl/2014029

OCL Oilseeds & fats Crops and Lipids

Available online at:
www.ocl-journal.org

RESEARCH ARTICLE – DOSSIER OPEN ACCESS

OLIVE OIL
HUILE D'OLIVE

DOSSIER

Olive oil and health effects: from epidemiological studies to the molecular mechanisms of phenolic fraction

Marie Josèphe Amiot[1,2,3,⋆]

[1] INRA, UMR 1260 "Nutrition, Obesity and Risk of Thrombosis", 13385 Marseille, France
[2] INSERM, UMR U1062, 13385 Marseille, France
[3] Aix-Marseille Université, Faculté de Médecine, 13385 Marseille, France

Received 27 May 2014 – Accepted 10 June 2014

Abstract – Olive oil is a key component of the Mediterranean diet which is recognized to contribute to its health benefits. Recent prospective studies point towards a protective effect from an olive oil-rich diet in relation to the incidence of cardiovascular diseases and an improvement of cardiometabolic markers such as blood pressure, glycaemia and dyslipidemia, notably by reducing LDL cholesterol and LDL oxidation. The role of minor phenolic fraction was evidenced in intervention trials where lipid profiles showed greater improvement in participants receiving olive oil with higher phenolic content. The phenolic fraction of olive oil is composed of simple phenols (hydroxytyrosol), phenolic secoiridoids (oleuropein aglycone), lignans (pinoresinol), flavonoids and hydroxyisochromans. All these compounds have diverse biological activities that are described in the present review, supporting the protective effects of olive oil against degenerative diseases found in large cohorts monitored in Southern European countries.

Keywords: Olive oil / phenolic fraction / cardiovascular diseases / cancer / lipid metabolism / antioxidant / anti-inflammatory / platelet aggregation / endothelial function / chemoprevention / nutrigenomic effects

Résumé – L'huile d'olive et ses effets sur la santé : des études épidémiologiques jusqu'aux mécanismes moléculaires de la fraction phénolique. L'huile d'olive est une composante clé de l'alimentation méditerranéenne, reconnue pour contribuer à ses bienfaits sur la santé. Les analyses d'études prospectives récentes convergent vers un effet protecteur d'une alimentation riche en huile d'olive vis-à-vis de l'incidence des maladies cardio-vasculaires ainsi qu'à une amélioration de marqueurs cardio-métaboliques tels que la pression artérielle, la glycémie et la dyslipidémie, notamment par la réduction du LDL cholestérol et de l'oxydation des LDL. Le rôle de la fraction phénolique de l'huile d'olive a été mis en évidence dans des essais d'intervention, dans lesquels les profils lipidiques ont été davantage améliorés chez les consommateurs d'huiles d'olive les plus riches en composés phénoliques. La fraction phénolique de l'huile d'olive est composée de phénols simples (l'hydroxytyrosol), de sécoïridoïdes phénoliques (l'oleuropéine aglycone), des lignanes (le pinorésinol), de flavonoïdes et d'hydroxyisochromans. Tous ces composés ont des activités biologiques diverses qui sont décrites dans cette revue et soutiennent les effets protecteurs de l'huile d'olive contre les maladies dégénératives mis en évidence dans de grandes cohortes suivies en Europe du Sud.

Mots clés : Huile d'olive / fraction phénolique / maladies cardiovasculaires / cancer / métabolisme lipidique / antioxydant / anti-inflammatoire / anti-aggrégant plaquettaire / fonction endothéliale / chimiopréventif / effets nutrigénomiques

1 Introduction

Olive oil is a key component of the Mediterranean diet and recognized to contribute to its health benefits, especially in preventing cardiovascular diseases (CVD) (Lopez-Miranda *et al.*, 2010). Recent trials on olive oil supplementation point towards a protective effect against cardiometabolic risk factors. The dietary benefits of olive oil were initially linked to its high oleic acid content, a monounsaturated fatty acid (18:1 n-9), which ranges from 55% to 83% of total fatty acids. This has been the basis of the authorized health claim for olive oil labelling by the food and drug administration in 2004. However, experimental-based evidence has accumulated on the health benefits of minor bioactive components of olive oil such as polyphenols which have specific structures and are found in high quantities in virgin and extra-virgin olive oil. Among

⋆ Correspondence:
marie-josephe.amiot-carlin@univ-amu.fr

these structures, hydroxytyrosol was recently reported to protect the blood lipids against oxidative damage as reported by the European food safety authority (EFSA) panel on dietetic products, nutrition and allergies. The Panel considered that in order for olive oil to bear the "heart-health" claim, 5 mg of hydroxytyrosol and its derivatives (*e.g.* oleuropein complex and tyrosol) in olive oil should be consumed daily (EFSA, 2011; Martin-Pelaez *et al.*, 2013).

The present review compiles the latest results from epidemiological studies and dietary intervention in large cohorts. The mechanisms by which the minor phenolic fraction of olive oil could protect against degenerative chronic diseases are described using the modulation of disease biomarkers and gene expression assessed in human trials.

2 Prospective studies, meta-analysis and dietary intervention studies with olive oil

The analysis of epidemiological studies on different outcomes, cardiovascular disease, cancer, cognitive decline and weight gain are reported in Table 1.

- *Cardiovascular diseases*: all prospective studies pointed towards a beneficial effect on health from an olive oil-rich diet on the incidence of cardiovascular diseases. The biggest studies were carried out in Southern European countries. In a Spanish population, the association between olive oil intake and all-cause as well as cause-specific mortality was studied. The greatest reduction in risk was observed for CVD mortality. This amounted to 44% for the highest olive oil quartile of consumers in comparison with nonconsumers. A gradual increased intake of olive oil was associated with a decreased risk of CVD mortality (each 10 g per 2000 kcal increase was linked to a 13% decrease in risk) (Buckland *et al.*, 2012). In two recent prospective studies, the level of olive oil consumption was compared with the incidence of coronary heart disease (CHD). In a large cohort of Italian women (EPICOR STUDY), a significant reduction in CHD risk (–44%) was associated with the highest quartile of olive oil consumption compared with the lowest one (> 31, 2 g/d *versus* ≤15 g/d) (Bendinelli *et al.*, 2011). In a Spanish cohort taken from the European Prospective Investigation into Cancer study, a more modest reduction of CHD (–22%) was observed in the upper quartile consumers > 28.9 g/d (Buckland *et al.*, 2012). There was a 7% reduction in CHD risk for each 10g/d per 2000 kcal. In the Three-City Study conducted in France, participants who used olive oil intensively had a 41% lower risk of stroke than those who never used it (Samieri *et al.*, 2011). All these prospective studies confirmed the cardiovascular protective effect of olive oil previously reported in case-control studies (Bertuzzi *et al.*, 2002; Fernandez-Jarne *et al.*, 2002; Kontogianni *et al.*, 2007).
- *Diabetes*: there is no epidemiological study specifically regarding olive oil consumption and diabetes. However, olive oil-rich diets do appear effective in the prevention of diabetes. A lower incidence of diabetes was associated to a higher adherence to a Mediterranean diet in healthy subjects (Martinez-Gonzalez *et al.*, 2008) as well as in patients with recent myocardial infarction (Mozaffarian *et al.*, 2007).
- *Obesity*: no incidence on weight gain was found in the SUN prospective cohort study (Bes-Rastrollo *et al.*, 2006).
- *Cancer*: a recent systematic review and meta-analysis of observational studies revealed that, overall, olive oil consumption was associated with lower odds of developing cancer (Psaltopoulou *et al.*, 2011). The greatest reduction in risk was found in breast cancer and digestive system cancers.
- *Cognitive decline*: Berr *et al.* (2009) examined the link between olive oil use and cognitive deficit and decline in a large elderly population. It showed there was no difference for global cognitive functioning between participants with moderate or intensive use of olive oil compared to those who never used olive oil, but there was a significant difference between intensive users in relation to visual memory and to a lesser extent, verbal fluency.
- *Disease risk biomarkers*: dietary interventions were performed on large cohorts and showed the improvement of disease risk markers. In the PREDIMED dietary intervention trial, it has been demonstrated that a Mediterranean diet enriched with extra virgin olive oil is beneficial for numerous cardiometabolic factors such as blood pressure, glycaemia, dyslipidemia (by decreasing triacylglyceride increasing HDL-cholesterol and lowering total and LDL-cholesterol) and additional risk factors such as oxidative stress (by reducing susceptibility of LDL to oxidation) and inflammation (by decreasing pro-inflammatory markers such as C-reactive protein and IL-6) (Carluccio *et al.*, 2007; Salas-Salvado *et al.*, 2008). All these findings in large cohort studies are consistent with the protective role of olive oil consumption on health. The role of minor phenolic fraction was evidenced in the EUROLIVE controlled study (Covas *et al.*, 2006) where the improvement of the lipid profile is linked to increasing phenolic content As concerns blood pressure, the Greek European Prospective Investigation into Cancer and Nutrition (EPIC) study showed that olive oil intake was inversely associated with both systolic and diastolic blood pressure (Psaltopoulou *et al.*, 2004). A moderate consumption of olive oil was suggested as an effective recommendation to reduce systolic blood pressure in healthy men who do not typically consume a Mediterranean diet (Bondia-Pons, *et al.*, 2007).

3 Minor compounds of olive oil and phenolic fraction: characterisation and bioavailability

Minor compounds of olive oil are classified into two categories; unsaponifiable (non-polar) and the soluble (polar) fractions, including phenolic compounds (Cicerale *et al.*, 2009). The phenolic fraction of olive oil (olive oil phenols, or OOP's) varies both in quantity and quality. Owen *et al.* (2000) reported an average concentration of phenolic compounds of 230 mg/kg in extra virgin olive oil. The phenolic quantity varied from 50

Table 1. Epidemiological studies on olive oil and health outcomes.

Outcome	Cohort name (country)	First author Year of publication	Type of study	Participants Age mean or range	Duration	Consumption measurement of olive oil	Main findings high *versus* low	Reduction risk
Coronary heart disease	EPICOR (Italy)	Bendinelli 2011	Prospective	29 689 (only women) 35–74 y	7.85 y	Quartiles in (g/d): 16.8; 21.6; 25.6; 35.0	*HR (95% CI) 0.56 (0.31, 0.99) $p = 0.04$	–44% high *vs.* low
Coronary heart disease	EPIC (Spain)	Buckland 2012	Prospective	40 142 (38% men) 29–69 y	10.4 y	Quartiles in (g/d): < 10.0; ≥ 10.0–20.1; ≥ 20.1–28.9; > 28. 9	*HR (95% CI) 0.78 (0.59, 1.03) $p = 0.079$	–22% high *vs.* low –7% for each 10 g/d per 2000 kcal
Stroke	Three-City Study (France)	Samieri 2011	Prospective	7625 65 y	5.25 y	Intense, moderate and non-users	*HR (95% CI) 0.59 (0.37–0.94) $p = 0.03$	–31% intense user *vs.* non user
Weight gain	SUN (Spain)	Bes-Rastrollo 2006	Prospective	7 368	28.5 mon	Quintiles: Upper: 46 g/d Lowest: 6 g/d	95% CI): –0.16 (–0.42 to +0.11) ns	No association
Cancer	Different cohorts	Psaltopoulou 2011	Systematic review and meta-analysis (19 case control studies)	37 140	–	High *versus* low	Combined effect log OR 95% CI for log OR, p for heterogeneity All cancers: –0.41 (–0.53, –0.29) $p < 0.001$ Breast cancer: –0.45 (–0.78, –0.12) $p < 0.001$ Digestive and Others: ns	Reduction of risk of cancer, especially breast cancer
Cognition decline	Three-City Study (France)	Berr 2009	Prospective	6947 65 y	4 y	Intense, moderate and non-users	*OR Visual memory: 0.83 (0.69–0.99) $p = 0.04$ Verbal fluency: ns	–17% of visual memory decline
Cardiovascular diseases	PREDIMED	Estruch 2013	Intervention	7447 (57% women) 55–80 y	4.8 y	Mediterranean diet + olive oil (50 g, approximately 4 tbsp)	*HR (95% CI) 0.70 (0.54–0.92) $p = 0.01$	–30%

* After full adjustment.

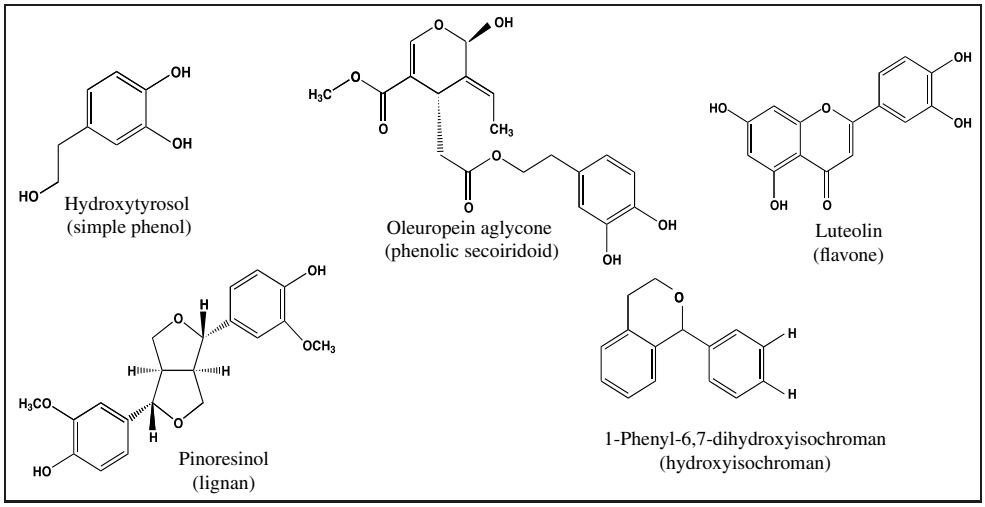

Fig. 1. Phenolic structures of olive oil and their sub-categories (in brackets).

to 800 mg/ (Perona *et al.*, 2006) while the phenolic composition depends on various factors, including the variety of olive, the environment (soil and climate), farming practices, the maturity of olive fruits, the manufacturing process and storage conditions (Amarowicz *et al.*, 2009). OOP's can be classified into five main structures. These are simple phenols, phenolic secoiridoids, lignans, and flavonoids and hydroxyisochromans (Fig. 1). Oleuropein aglycone, found in ripening olives and olive oil, is a phenolic secoiridoid liberated from the glucoside form, oleuropein, upon the action of a ß-glucosidase. In olive oil, oleuropein is degraded into elenolic acid, the secoiridoid moiety, and hydroxytyrosol, the phenolic moiety. Oleuropein aglycone and hydroxytyrosol are characterized by the ortho-diphenolic structures, but in olive oil, there are also corresponding mono-phenolic structures of ligstroside aglycone and tyrosol. Tyrosol, hydroxytyrosol, and their corresponding secoiridoid derivatives constitute around 90% of the total phenolic content of virgin olive oil (de la Torre-Carbot *et al.*, 2006). Hydroxyisochromans are formed by reaction between hydroxytyrosol and aromatic aldehydes (vanillin and benzaldehyde) under very mild conditions (Bendini *et al.*, 2007).

OOP's were reported to be highly bioavailable compared to other plant polyphenols. OOP absorption efficiency was evaluated about 55–66 mol% in humans (Vissers *et al.*, 2004). Tyrosol and hydroxytyrosol are absorbed by humans in a dose-dependent manner in relation to the phenolic content of the olive oil administered (Visioli *et al.*, 2000). Tyrosol and hydroxytyrosol are extensively metabolized and found in urine as conjugates, glucuronide and monosulphate as well as methylated derived simple phenols, homovanillic alcohol and homovanillic acid (Corona *et al.*, 2009). These metabolites have been identified in LDL (de la Torre-Carbot *et al.*, 2007).

4 Molecular mechanisms of specific olive oil compounds

The main mechanisms by which OOP's could act are reported in Figure 2.

Lipid metabolism: high levels of total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) are recognized risk markers for atherosclerosis. This is considered to be the primary cause of cardiovascular diseases (CVD) while high density lipoprotein cholesterol (HDL-C) is assumed to be protective. As previously mentioned, lipid profiles were improved in participants of the crossover human study EUROLIVE, which enrolled 200 European participants receiving olive oil for three weeks (Covas *et al.*, 2006). Participants were randomly assigned to three groups of olive oil differing in their phenolic content (low, medium and high). HDL-C linearly increased with the phenolic content, whereas TC/HDL-C ratio linearly decreased. LDL-C/HDL-C ratio and triglycerides decreased in those consuming medium and high phenolic olive oils. Smaller human trials confirmed that phenol rich olive oil improves lipid profiles in terms of circulating HDL-C, decreasing LDL-C (Damasceno *et al.*, 2011) and larger but fewer triacylglycerol-rich lipoproteins (TRL) (Cabello-Moruno *et al.*, 2007).

Oxidative stress: there is a recognised link between oxidative stress produced by reactive oxygen species (ROS) and degenerative diseases such as atherosclerosis, certain cancers and neurodegenerative diseases. OOP's were reported to have antioxidant effects on lipid and DNA oxidation that were greater than those of vitamin E (Fito *et al.*, 2000; Masella *et al.*, 2004; Owen *et al.*, 2000). LDL oxidation (oxLDL) is considered to be a major risk factor for the development of atherosclerosis and CVD. In the EUROLIVE study, oxidized LDL levels decreased linearly with increasing phenolic content (Covas *et al.*, 2006). The increased resistance of LDL to oxidation following a phenolic rich olive oil supplementation was confirmed in different short term studies, although three studies compiled by Covas (2007) and Cicerale *et al.* (2010) showed no effect. The binding capacity of phenolic compounds to LDL could explain the increased resistance of LDL to oxidation (Fito *et al.*, 2007). Besides LDL oxidation, other oxidative markers also showed improvements. Thus, phenol-rich virgin olive oil administered to human subjects reduced F2-isoprostanes (Visioli *et al.*, 2000), improved the balance between reduced and oxidized gluthatione GSH and GSSG (Covas *et al.*, 2006) or increased

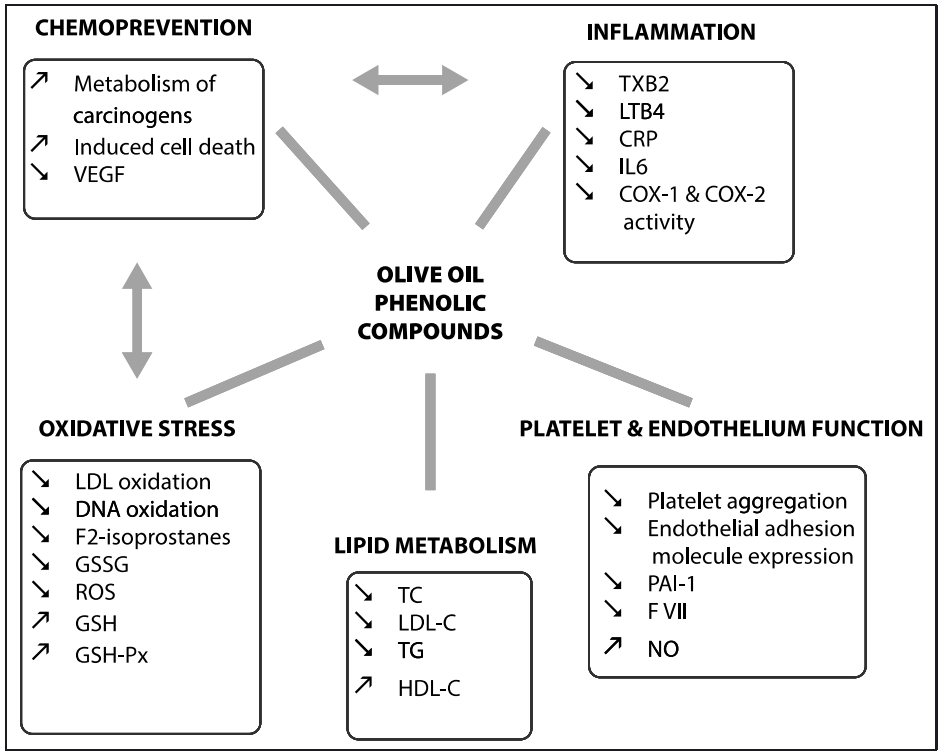

Fig. 2. Different actions of olive oil phenolic compounds.

glutathione peroxidase activity GSH-Px (Weinbrenner *et al.*, 2004).

Inflammation: elevated concentrations of inflammation markers in serum are associated with increased cardiovascular risk. Plasma thromboxane B2 (TXB2) and leukotriene B4 (LTB4) are considered as proinflammatory agents. In the inflammatory pathway, the inhibition of cyclooxygenases (COX) results in the reduction of arachidonate into eicosanoids, prostaglandins and thromboxane. OOP's were shown to have anti-inflammatory properties (Bogani *et al.*, 2007). Oleocanthal and an ester of tyrosol, was found to inhibit COX-1 and COX-2, mimicking the effect of ibuprofen (Beauchamp *et al.*, 2005; Smith *et al.*, 2005). Moreover, inflammatory markers like C-reactive protein (CRP) and Interleukin-6 (IL-6) have also been shown to be predictors for CVD. The PREDIMED study showed that CRP and IL-6, as well ICAM-1, and VCAM-1 were reduced in participants following the Mediterranean diet supplemented with olive oil compared with the low-fat diet group (Estruch *et al.*, 2006). In a placebo-controlled crossover randomized trial on 28 stable coronary heart disease patients, IL-6 and CRP levels significantly decreased after virgin olive oil intervention (Fito *et al.*, 2008).

Platelet function: blood platelets were shown to play a role in the development of atherosclerosis. The development of CHD has been linked to high plasma levels of coagulation and fibrinolytic factors such as plasminogen activator inhibitor-1 (PAI-1) and factor VII (FVII). Virgin olive oil with a high phenolic compound content (400 mg/kg) has been demonstrated to inhibit PAI-1 and FVII (Delgado-Lista *et al.*, 2008). Hydroxyisochromans were shown to inhibit platelet aggregation (Togna *et al.*, 2003) and cAMP-phosphodiesterase inhibition was shown as one mechanism by which platelet aggregation was inhibited in presence of OOP's (Dell'Agli *et al.*, 2008).

Endothelium dysfunction: in different human trials, the consumption of meals with phenolic rich olive oil was shown to improve endothelium function in the postprandial period (Vogel *et al.*, 2000; Karatzi *et al.*, 2008; Fuentes *et al.*, 2008; Ruano *et al.*, 2007). Experimental studies carried out in different animal models of atherosclerosis, hypertension, hypercholesterolemia supported the link between endothelial dysfunction and oxidative stress. The different actions of polyphenols on endothelial and smooth muscle cells through nitric oxide (NO) stimulation have been reviewed (Andriantsitohaina *et al.*, 2012). OOP's were reported to contribute to increased NO levels and prevent the powerful oxidant peroxynitrite forming (Perona *et al.*, 2006). Moreover, OOP's were found to decrease homocysteine, which has been linked to increased adhesiveness of the endothelium (Manna *et al.*, 2009).

Chemoprevention: while the antioxidant properties of OOP's against DNA damage and their anti-inflammatory actions are well characterized, OOP's may also exert anticarcinogenic effects through their ability to act on the metabolism of carcinogens (Hashim *et al.*, 2005). The various anticarcinogenic mechanisms of phenolic compounds have been reviewed by Yang *et al.* (2001). Furthermore, olive oil is rich in lignans (Owen *et al.*, 2000; Bendini, 2007) and it is assumed that foods containing high amounts of lignans appeared to protect against breast cancer *via* their anti-estrogenic effects (Saarinen *et al.*, 2007). In addition, in cell experiments, oleuropein and hydroxytyrosol have been shown to induce cell death of MCF-7 human breast cancer cells (Han *et al.*, 2009). Recent findings

have provided clearer evidence that hydroxytyrosol is a potent inhibitor of the vascular endothelial growth factor (VEGF-2) signalling pathway that regulates tumour angiogenesis (Lamy *et al.*, 2014).

Other actions: as reducing agents, OOP's are supposed to spare vitamin E. As vitamin E (tocopherols) has been shown to exert antioxidant activities, OOP's could act indirectly in preventing CVD.

Nutrigenomic effects: the beneficial effects for atherosclerotic processes could be explained by the variation in gene expression following a diet rich in olive oil, resulting in improving risk biomarkers as reported in Figure 2. Two human trials demonstrated that the minor phenolic fraction of olive oil plays a role in the downregulation of pro-atherogenic genes in microarray analyses (Konstantinidou *et al.*, 2010; Camargo, 2010). In a randomised trial, in vivo gene expression changes were assessed in the mononuclear cells of healthy volunteers after an intake of high or low-phenolic olive oil as part of the Mediterranean diet (Konstantinidou *et al.*, 2010). Significant changes in inflammation and oxidative stress-related gene expression were found between the Mediterranean diet pattern and the control group. Moreover, a significant linear decreasing trend was observed in connection with the phenolic content of olive oil in inflammation-related gene expression (interferon gamma, Rho-GTPase-activating protein 15) and oxidative stress (adrenergic beta 2 receptor). In another study involving patients with metabolic syndrome, the intake of a breakfast enriched in high phenolic content virgin olive oil decreased the inflammation-related gene expression of NF-κB and COX-2 (Camargo *et al.*, 2010). Moreover, another diet intervention with 737 participants showed that a Mediterranean diet rich in virgin olive oil may reverse the effects of the IL6 (–174G/C) gene variant on 3-year body weight change (Razquin *et al.*, 2010). In a study context of oxidative stress and chemoprevention, changes in gene expression were evaluated using genome-wide mRNA-Sequencing in various cell lines exposed to hydroxytyrosol (Rafehi *et al.*, 2012). The results indicated that hydroxytyrosol promotes the cell's own protection against oxidative stress by a significant upregulation of enzymes involved in antioxidant defence systems. The greatest upregulation was found for heme oxygenase-1. The growth of breast tumours could be stimulated by estradiol leading to the regulation of gene expression and signal transduction pathways inducing cell proliferation. It was shown that hydroxytyrosol could act as a chemopreventive agent in breast cancer cell proliferation via the inhibition of estrogen-dependent rapid signals involved in uncontrolled tumour cell growth (Sirianni *et al.*, 2010).

5 Conclusions

The added value of virgin olive oil in protecting against cardiovascular disease found in large prospective studies has been supported by numerous dietary intervention trials. These provided evidence that phenolic compounds display a broad spectrum of bioactive properties, including lipid-improving, antioxidant, anti-inflammatory and vasodilatory effects. Numerous studies have been focused on hydroxytyrosol as compiled in Hu's review (Hu *et al.*, 2014). Olive oil is also rich in lignans which are considered to be promising molecules in decreasing the risk of cardiovascular disease, despite the fact that their mechanisms have not yet been clarified (Peterson *et al.*, 2010). Moreover, the role of olive oil polyphenols in human microbiotia remains to be explained, taking into account recent findings in this field (Cardona *et al.*, 2013). Since it was recently shown that a long-term intervention of a virgin olive oil-rich diet resulted in a better cognitive function compared to a control diet (Martinez-Lapiscina *et al.*, 2013), further studies are needed to specify the role of the minor phenolic fraction of olive oil in cognition and neurodegenerative diseases.

References

Amarowicz R, Carle R, Dongowski G, *et al.* 2009. Influence of postharvest processing and storage on the content of phenolic acids and flavonoids in foods. *Mol. Nutr. Food Res.* 53: S151–S183.

Andriantsitohaina R, Auger C, Chataigneau T, *et al.* 2012. Molecular mechanisms of the cardiovascular protective effects of polyphenols. *Br. J. Nutr.* 108: 1532–1549.

Beauchamp GK, Keast RS, Morel D, *et al.* 2005. Phytochemistry: ibuprofen-like activity in extra-virgin olive oil. *Nature* 437: 45–46.

Bendinelli B, Masala G, Saieva C, *et al.* 2011. Fruit, vegetables, and olive oil and risk of coronary heart disease in Italian women: the EPICOR Study. *Am. J. Clin. Nutr.* 93: 275–283.

Bendini A, Cerretani L, Carrasco-Pancorbo A, *et al.* 2007. 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* 12: 1679–1719.

Berr C, Portet F, Carriere I, *et al.* 2009. Olive oil and cognition: results from the three-city study. *Dement Geriatr. Cogn. Disord.* 28: 357–364.

Bertuzzi M, Tavani A, Negri E, La Vecchia C. 2002. Olive oil consumption and risk of non-fatal myocardial infarction in Italy. *Int. J. Epidemiol.* 31: 1274–1277; author reply 6–7.

Bes-Rastrollo M, Sanchez-Villegas A, de la Fuente C, de Irala J, Martinez JA, Martinez-Gonzalez MA. 2006. Olive oil consumption and weight change: the SUN prospective cohort study. *Lipids* 41: 249–256.

Bogani P, Galli C, Villa M, Visioli F. 2007. Postprandial anti-inflammatory and antioxidant effects of extra virgin olive oil. *Atherosclerosis* 190: 181–186.

Bondia-Pons I, Schroder H, Covas MI, *et al.* 2007. Moderate consumption of olive oil by healthy European men reduces systolic blood pressure in non-Mediterranean participants. *J. Nutr.* 137: 84–87.

Buckland G, Mayen AL, Agudo A, *et al.* 2012. Olive oil intake and mortality within the Spanish population (EPIC-Spain). *Am. J. Clin. Nutr.* 96: 142–149.

Buckland G, Travier N, Agudo A, *et al.* 2012. Olive oil intake and breast cancer risk in the Mediterranean countries of the European Prospective Investigation into Cancer and Nutrition study. *Int. J. Cancer* 131: 2465–2469.

Buckland G, Travier N, Barricarte A, *et al.* 2012. Olive oil intake and CHD in the European Prospective Investigation into Cancer and Nutrition Spanish cohort. *Br. J. Nutr.* 108: 2075–2082.

Cabello-Moruno R, Perona JS, Osada J, Garcia M, Ruiz-Gutierrez V. 2007. Modifications in postprandial triglyceride-rich lipoprotein composition and size after the intake of pomace olive oil. *J. Am. Coll. Nutr.* 26: 24–31.

Camargo A, Ruano J, Fernandez JM, *et al.* 2010. Gene expression changes in mononuclear cells in patients with metabolic syndrome after acute intake of phenol-rich virgin olive oil. *BMC Genomics* 11: 253.

Cardona F, Andres-Lacueva C, Tulipani S, Tinahones FJ, Queipo-Ortuno MI. 2013. Benefits of polyphenols on gut microbiota and implications in human health. *J. Nutr. Biochem.* 24: 1415–1422.

Cicerale S, Conlan XA, Sinclair AJ, Keast RS. 2009. Chemistry and health of olive oil phenolics. *Crit. Rev. Food Sci. Nutr.* 49: 218–236.

Cicerale S, Lucas L, Keast R. 2010. Biological activities of phenolic compounds present in virgin olive oil. *Int. J. Mol. Sci.* 11: 458–479.

Corona G, Spencer JP, Dessi MA. 2009. Extra virgin olive oil phenolics: absorption, metabolism, and biological activities in the GI tract. *Toxicol. Ind. Health* 25: 285–293.

Covas MI. 2007. Olive oil and the cardiovascular system. *Pharmacol. Res.* 55: 175–186. doi: 10.1016/j.phrs.2007.01.010.

Covas MI, de la Torre K, Farre-Albaladejo M, *et al.* 2006. Postprandial LDL phenolic content and LDL oxidation are modulated by olive oil phenolic compounds in humans. *Free Radic. Biol. Med.* 40: 608–616.

Covas MI, Nyyssonen K, Poulsen HE, *et al.* 2006. The effect of polyphenols in olive oil on heart disease risk factors: a randomized trial. *Ann. Intern. Med.* 145: 333–341.

Damasceno NR, Perez-Heras A, Serra M, *et al.* 2011. Crossover study of diets enriched with virgin olive oil, walnuts or almonds. Effects on lipids and other cardiovascular risk markers. *Nutr. Metab. Cardiovasc. Dis.* 21: S14–20.

de la Torre-Carbot K, Chavez-Servin JL, Jauregui O, *et al.* 2007. Presence of virgin olive oil phenolic metabolites in human low density lipoprotein fraction: determination by high-performance liquid chromatography-electrospray ionization tandem mass spectrometry. *Anal. Chim. Acta.* 583: 402–410.

Delgado-Lista J, Lopez-Miranda J, Cortes B, *et al.* 2008. Chronic dietary fat intake modifies the postprandial response of hemostatic markers to a single fatty test meal. *Am. J. Clin. Nutr.* 87: 317-322.

Dell'Agli M, Maschi O, Galli GV, *et al.* 2008. Inhibition of platelet aggregation by olive oil phenols via cAMP-phosphodiesterase. *Br. J. Nutr.* 99: 945–951.

EFSA. 2011. NDA Panel, Scientific Opinion on the substantiation of health claims related to polyphenols in olive and protection of LDL particles from oxidative damage. *EFSA J.* 9: 2033

Estruch R, Martinez-Gonzalez MA, Corella D, *et al.* 2006. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. *Ann. Intern. Med.* 145: 1–11.

Fernandez-Jarne E, Martinez-Losa E, Prado-Santamaria M, Brugarolas-Brufau C, Serrano-Martinez M, Martinez-Gonzalez MA. 2002. Risk of first non-fatal myocardial infarction negatively associated with olive oil consumption: a case-control study in Spain. *Int. J. Epidemiol.* 31: 474–480.

Fito M, Cladellas M, de la Torre R, *et al.* 2008. Anti-inflammatory effect of virgin olive oil in stable coronary disease patients: a randomized, crossover, controlled trial. *Eur. J. Clin. Nutr.* 62: 570–574.

Fito M, Covas MI, Lamuela-Raventos RM, *et al.* 2000. Protective effect of olive oil and its phenolic compounds against low density lipoprotein oxidation. *Lipids* 35: 633–638.

Fito M, de la Torre R, Farre-Albaladejo M, Khymenetz O, Marrugat J, Covas MI. 2007. Bioavailability and antioxidant effects of olive oil phenolic compounds in humans: a review. *Ann. Ist. Super Sanita* 43: 375–381.

Fuentes F, Lopez-Miranda J, Perez-Martinez P, *et al.* 2008. Chronic effects of a high-fat diet enriched with virgin olive oil and a low-fat diet enriched with alpha-linolenic acid on postprandial endothelial function in healthy men. *Br. J. Nutr.* 100: 159–165.

Gimeno E, de la Torre-Carbot K, Lamuela-Raventos RM, *et al.* 2007. Changes in the phenolic content of low density lipoprotein after olive oil consumption in men. A randomized crossover controlled trial. *Br. J. Nutr.* 98: 1243–1250.

Han J, Talorete TP, Yamada P, Isoda H. 2009. Anti-proliferative and apoptotic effects of oleuropein and hydroxytyrosol on human breast cancer MCF-7 cells. *Cytotechnology* 59: 45–53.

Hashim YZ, Eng M, Gill CI, McGlynn H, Rowland IR. 2005. Components of olive oil and chemoprevention of colorectal cancer. *Nutr. Rev.* 63: 374–386.

Hu T, He XW, Jiang JG, Xu XL. 2014. Hydroxytyrosol and its potential therapeutic effects. *J. Agric. Food Chem.* 62: 1449–1455.

Karatzi K, Papamichael C, Karatzis E, *et al.* 2008. Postprandial improvement of endothelial function by red wine and olive oil antioxidants: a synergistic effect of components of the Mediterranean diet. *J. Am. Coll. Nutr.* 27: 448–453.

Konstantinidou V, Covas MI, Munoz-Aguayo D, *et al.* 2010. In vivo nutrigenomic effects of virgin olive oil polyphenols within the frame of the Mediterranean diet: a randomized controlled trial. *Faseb. J.* 24: 2546–2557.

Kontogianni MD, Panagiotakos DB, Chrysohoou C, Pitsavos C, Zampelas A, Stefanadis C. 2007. The impact of olive oil consumption pattern on the risk of acute coronary syndromes: The CARDIO2000 case-control study. *Clin. Cardiol.* 30: 125–129.

Lamy S, Ouanouki A, Beliveau R, Desrosiers RR. 2014. Olive oil compounds inhibit vascular endothelial growth factor receptor-2 phosphorylation. *Exp. Cell Res.* 322: 89–98.

Lopez-Miranda J, Perez-Jimenez F, Ros E, *et al.* 2010. Olive oil and health: summary of the II international conference on olive oil and health consensus report, Jaen and Cordoba (Spain) 2008. *Nutr. Metab. Cardiovasc. Dis.* 20: 284–294.

Manna C, Napoli D, Cacciapuoti G, Porcelli M, Zappia V. 2009. Olive oil phenolic compounds inhibit homocysteine-induced endothelial cell adhesion regardless of their different antioxidant activity. *J. Agric. Food Chem.* 57: 3478–3482.

Martin-Pelaez S, Covas MI, Fito M, Kusar A, Pravst I. 2013. Health effects of olive oil polyphenols: recent advances and possibilities for the use of health claims. *Mol. Nutr. Food Res.* 57: 760–771.

Martinez-Gonzalez MA, de la Fuente-Arrillaga C, Nunez-Cordoba JM, *et al.* 2008. Adherence to Mediterranean diet and risk of developing diabetes: prospective cohort study. *Bmj* 336: 1348–1351.

Martinez-Lapiscina EH, Clavero P, Toledo E, *et al.* 2013. Virgin olive oil supplementation and long-term cognition: the PREDIMED-NAVARRA randomized, trial. *J. Nutr. Health Aging.* 17: 544–552.

Masella R, Vari R, D'Archivio M, *et al.* 2004. Extra virgin olive oil biophenols inhibit cell-mediated oxidation of LDL by increasing the mRNA transcription of glutathione-related enzymes. *J. Nutr.* 134: 785–791.

Moreno-Luna R, Munoz-Hernandez R, Miranda ML, *et al.* 2012. Olive oil polyphenols decrease blood pressure and improve endothelial function in young women with mild hypertension. *Am. J. Hypertens* 25: 1299–1304.

Mozaffarian D, Marfisi R, Levantesi G, *et al.* 2007. Incidence of new-onset diabetes and impaired fasting glucose in patients with recent myocardial infarction and the effect of clinical and lifestyle risk factors. *Lancet* 370: 667–675.

Owen RW, Giacosa A, Hull WE, Haubner R, Spiegelhalder B, Bartsch H. 2000. The antioxidant/anticancer potential of phenolic compounds isolated from olive oil. *Eur. J. Cancer* 36: 1235–1247.

Owen RW, Mier W, Giacosa A, Hull WE, Spiegelhalder B, Bartsch H. 2000. Identification of lignans as major components in the phenolic fraction of olive oil. *Clin. Chem.* 46: 976–988.

Perona JS, Cabello-Moruno R, Ruiz-Gutierrez V. 2006. The role of virgin olive oil components in the modulation of endothelial function. *J. Nutr. Biochem.* 17: 429–445.

Peterson J, Dwyer J, Adlercreutz H, Scalbert A, Jacques P, McCullough ML. 2010. Dietary lignans: physiology and potential for cardiovascular disease risk reduction. *Nutr. Rev.* 68: 571–603.

Psaltopoulou T, Kosti RI, Haidopoulos D, Dimopoulos M, Panagiotakos DB. 2011. 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.* 10: 127.

Psaltopoulou T, Naska A, Orfanos P, Trichopoulos D, Mountokalakis T, Trichopoulou A. 2004. Olive oil, the Mediterranean diet, and arterial blood pressure: the Greek European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Am. J. Clin. Nutr.* 80: 1012–1018.

Rafehi H, Smith AJ, Balcerczyk A, *et al.* 2012. Investigation into the biological properties of the olive polyphenol, hydroxytyrosol: mechanistic insights by genome-wide mRNA-Seq analysis. *Genes Nutr.* 7: 343–355.

Razquin C, Martinez JA, Martinez-Gonzalez MA, Salas-Salvado J, Estruch R, Marti A. 2010. A 3-year Mediterranean-style dietary intervention may modulate the association between adiponectin gene variants and body weight change. *Eur. J. Nutr.* 49: 311–319.

Ruano J, Lopez-Miranda J, de la Torre R, *et al.* 2007. Intake of phenol-rich virgin olive oil improves the postprandial prothrombotic profile in hypercholesterolemic patients. *Am. J. Clin. Nutr.* 86: 341–346.

Saarinen NM, Warri A, Airio M, Smeds A, Makela S. 2007. Role of dietary lignans in the reduction of breast cancer risk. *Mol. Nutr. Food Res.* 51: 857–866.

Salas-Salvado J, Garcia-Arellano A, Estruch R, *et al.* 2008. Components of the Mediterranean-type food pattern and serum inflammatory markers among patients at high risk for cardiovascular disease. *Eur. J. Clin. Nutr.* 62: 651–659.

Samieri C, Feart C, Proust-Lima C, *et al.* 2011. Olive oil consumption, plasma oleic acid, and stroke incidence: the Three-City Study. *Neurology* 77: 418–425.

Sirianni R, Chimento A, De Luca A, *et al.* 2010. Oleuropein and hydroxytyrosol inhibit MCF-7 breast cancer cell proliferation interfering with ERK1/2 activation. *Mol. Nutr. Food Res.* 54: 833–840.

Smith AB, 3rd, Han Q, Breslin PA, Beauchamp GK. 2005. Synthesis and assignment of absolute configuration of (-)-oleocanthal: a potent, naturally occurring non-steroidal anti-inflammatory and anti-oxidant agent derived from extra virgin olive oils. *Org. Lett.* 7: 5075–5078.

Togna GI, Togna AR, Franconi M, Marra C, Guiso M. 2003. Olive oil isochromans inhibit human platelet reactivity. *J. Nutr.* 133: 2532–2536.

Visioli F, Caruso D, Galli C, Viappiani S, Galli G, Sala A. 2000. Olive oils rich in natural catecholic phenols decrease isoprostane excretion in humans. *Biochem. Biophys. Res. Commun.* 278: 797–799.

Visioli F, Galli C, Bornet F, *et al*. 2000. Olive oil phenolics are dose-dependently absorbed in humans. *FEBS Lett.* 468: 159–160.

Visioli F, Galli C, Plasmati E, *et al.* 2000. Olive phenol hydroxytyrosol prevents passive smoking-induced oxidative stress. *Circulation* 102: 2169–2171.

Vissers MN, Zock PL, Katan MB. 2004. Bioavailability and antioxidant effects of olive oil phenols in humans: a review. *Eur. J. Clin. Nutr.* 58: 955–965.

Vogel RA, Corretti MC, Plotnick GD. 2000. The postprandial effect of components of the Mediterranean diet on endothelial function. *J. Am. Coll. Cardiol.* 36: 1455–1460.

Weinbrenner T, Fito M, de la Torre R, *et al.* 2004. Olive oils high in phenolic compounds modulate oxidative/antioxidative status in men. *J. Nutr.* 134: 2314–2321.

Yang CS, Landau JM, Huang MT, Newmark HL. 2001. Inhibition of carcinogenesis by dietary polyphenolic compounds. *Ann. Rev. Nutr.* 21: 381–406.

Cite this article as: Marie Josèphe Amiot. Olive oil and health effects: from epidemiological studies to the molecular mechanisms of phenolic fraction. OCL 2014, 21(5) D512.