

## Commentary

# International conference on the healthy effect of virgin olive oil

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### Summary

1 Ageing represents a great concern in developed countries because the number of people involved and the pathologies related with it, like atherosclerosis, morbus Parkinson, Alzheimer's disease, vascular dementia, cognitive decline, diabetes and cancer.

2 Epidemiological studies suggest that a Mediterranean diet (which is rich in virgin olive oil) decreases the risk of cardiovascular disease.

3 The Mediterranean diet, rich in virgin olive oil, improves the major risk factors for cardiovascular disease, such as the lipoprotein profile, blood pressure, glucose metabolism and antithrombotic profile. Endothelial function, inflammation and oxidative stress are also positively modulated. Some of these effects are attributed to minor components of virgin olive oil. Therefore, the definition of the Mediterranean diet should include virgin olive oil.

4 Different observational studies conducted in humans have shown that the intake of mono-unsaturated fat may be protective against age-related cognitive decline and Alzheimer's disease.

5 Microconstituents from virgin olive oil are bioavailable in humans and have shown antioxidant properties and capacity to improve endothelial function. Furthermore they are also able to modify the haemostasis, showing antithrombotic properties.

6 In countries where the populations fulfilled a typical Mediterranean diet, such as Spain, Greece and Italy, where virgin olive oil is the principal source of fat, cancer incidence rates are lower than in northern European countries.

7 The protective effect of virgin olive oil can be most important in the first decades of life, which suggests that the dietetic benefit of virgin olive oil intake should be initiated before puberty, and maintained through life.

8 The more recent studies consistently support that the Mediterranean diet, based in virgin olive oil, is compatible with a healthier ageing and increased longevity. However, despite the significant advances of the recent years, the final proof about the specific mechanisms and contributing role of the different components of virgin olive oil to its beneficial effects requires further investigations.

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## Preamble

The major causes of death have a multifactorial origin, usually resulting from the interaction between the genetic background and environmental factors. Among the latter, diet may be the most relevant. During the last few decades, very active research has demonstrated the vast array of biological effects induced by different nutrients and foods. More recently, the focus has been oriented towards more holistic approaches to diet that include both salutary and pleasure components. In this regard, the Mediterranean dietary pattern is being rediscovered as the one that best fulfills the need for nourishment and pleasure.

One of the most well-known and important characteristic of the Mediterranean diet is the presence of virgin olive oil as the principal source of energy from fat. In contrast to other edible oils with a similar fatty composition, namely, sunflower, soybean and rapeseed canola oils, virgin olive oil is a natural juice, while the seed oils must be refined before consumption, thus changing its original composition during this process. Virgin olive oil is a source of healthy unsaturated fatty acids and hundreds of micronutrients, especially antioxidants, as phenol compounds, vitamin E and carotenes [1].

The aim of this report is to summarise the new findings presented in this International Conference regarding the beneficial effects of virgin olive oil, including its fat and non-fat components, and to support that the Mediterranean diet based in virgin oil is a healthy dietary model to achieve healthy aging and to prevent the most important causes of morbidity and mortality around the world.

## Evidence of the beneficial effects of the Mediterranean diet

A relation between diet and heart health had been shown by experimental studies over 100 years ago. However, it was not until the epidemic rise of cardiovascular diseases in many industrialized countries during the middle of the 20th century that the identification of risk factors and the need to put in place preventive measures became crucial. The field of epidemiology provided the first leads to explain such risk factors. This was made possible through the pioneering contributions from the Framingham Heart Study launched in 1948 [2]. However, when it came to the diet–heart hypothesis, one of the most influential seminal works came from the Seven Countries Study led by Keys *et al.* [3]. These investigators demonstrated in their ecological cross-population analyses that dietary saturated fat intake was significantly associated with serum cholesterol and the risk of coronary heart disease, and that serum cholesterol relates to coronary heart disease risk. The outcome of this study brought up the concept of the cardioprotective properties of the dietary habits of Mediterranean populations, which appeared to have as the most common element the consumption of virgin olive oil. For the last few decades, several population studies aimed to solidify the initial observation from the Seven Country Study and demonstrate the

relevance of virgin olive oil as a key cardioprotective component of the Mediterranean diet [4]. Thanks to these findings, we have learned that the cardiovascular protection from the Mediterranean diet is not brought up only by their effects of plasma lipid risk factors but by effects on several other pathways, including insulin sensitivity, blood pressure, inflammatory markers and arterial wall function [5]. The outcome of these studies consistently support that the classical Mediterranean dietary and lifestyle factors are indeed protective and compatible with healthier ageing and increased longevity. However, current and future studies must take advantage of genetic epidemiology and functional genomics in coordination, and with other experimental approaches within the umbrella of the so-called systems biology, to provide further evidence for the specific protective mechanisms of virgin olive oil in the context of the Mediterranean diet. The combination of technologies and expertise will provide molecular clues about the action of dietary patterns and their individual components. This knowledge will provide huge benefits to the prevention and treatment of chronic diseases.

## Monounsaturated fat (MUFA) and cardiovascular risk

It is well known that the Mediterranean diet, rich in virgin olive oil as a major fat source, vegetables, fruits, legumes and other plant foods, and low in saturated and trans fatty acids and cholesterol, is associated with a low cardiovascular risk. The substitution of a high-MUFA diet for an average American diet lowered total and LDL (low density lipoproteins)-cholesterol levels by 5.5% and 7%, respectively, while HDL (high density lipoproteins)-cholesterol levels are higher and triglycerides are lower on a high-MUFA as compared with low fat-high carbohydrate diet [6]. Furthermore, olive oil improves the postprandial lipoprotein metabolism inducing lower triacylglycerol postprandial concentrations and higher HDL-cholesterol concentrations than did acute saturated fat intake [7]. The Mediterranean dietary pattern may also provide additional benefits by acting on other classical cardiovascular risk factors, including the reduction of blood pressure, both in normal and hypertensive subjects, and the improvement of carbohydrate metabolism both in healthy subjects and in type 2 diabetic patients [8]. Substantial evidence suggests that the Mediterranean diet can modulate biomarkers involved in biological pathways implicated in the development of atherosclerosis [5]. LDL particles from individuals consuming a Mediterranean dietary pattern are protected from oxidative modification as compared with individuals consuming high polyunsaturated fatty acids-enriched diets [9]. The improvement in endothelial-dependent vasodilatation and a decreased response in plasma levels of endothelial soluble inflammatory molecules have also been reported in patients with hypercholesterolemia [10]. The Mediterranean diet elicits a less prothrombotic environment by modifying different haemostatic components, such as platelet

aggregation, fibrinogen, Von Willebrand factor, total plasma factor VII, tissue factor and PAI-1 (plasminogen activator inhibitor type I) plasma levels [9]. The postprandial increase in activated factor VII is reduced by the intake of virgin olive oil in comparison with saturated fats [9]. Future studies must focus on uncovering the mechanisms by which the Mediterranean diet exerts its beneficial effects.

### Oxidative stress and ageing

Ageing represents a great concern in developed countries because of the increasing number of persons reaching advanced age and the number of related pathologies, such as Alzheimer's disease, vascular dementia, Morbus Parkinson, diabetes or cancer. In an older population of Southern Italy, which fulfilled a typical Mediterranean diet, the high monounsaturated fat energy intake appeared to be associated with a reduced risk of age-related cognitive decline [11]. This effect could be related to the role of monounsaturated fatty acids in maintaining the structural integrity of neuronal membranes [11,12]. Moreover, very recent findings have shown that high intake of monounsaturated fat may be protective against Alzheimer's disease, whereas intake of saturated or trans-unsaturated fats may be detrimental [12]. According to the free radical theory, ageing is the result of the oxidative injury, mainly to mitochondria, throughout the lifetime. Some of the oxidative damages can not entirely be counteracted and lead to cellular dysfunction. Mitochondrial membranes are very sensitive to free radical attack because of the presence of double bond carbon-carbon in the lipid tails of its phospholipids. Thus, a low level of fatty acid unsaturation (e.g. that of oleic acid) will decrease cellular oxidative stress [13]. Interestingly, almost every investigation performed to date has shown that fatty acid unsaturation is lower in long-lived (i.e. humans) than in short-lived (i.e. rodents) species [14]. On other hand, the effectiveness of dietary virgin olive oil in a strategy leading to the strengthening of membranes, by increasing their resistance to free radicals-induced modifications following xenobiotic uptake has been reported. It has been also demonstrated that the oxidative modifications produced by the ingestion of fried fats may be successfully buffered when using virgin olive oil [15]. In summary, virgin olive oil consumption leads to the preservation of mitochondrial function and its electron transport chain, with a lower level of free radical production, a blood more capable to fight against free radicals and with a DNA more protected against oxidation.

### The benefits of virgin olive oil minor components

Olive oil is a food which, besides high levels of MUFA, contains several minor components with biological properties. Among those of the unsaponifiable fraction its major component squalene has been proposed as a causal factor for the low incidence of cancer in Mediterranean countries.

Although the quantities of  $\alpha$ -tocopherol (vitamin E) and carotenoids present in a daily consumption of virgin olive oil are low, its chronic ingestion contributes to the overall pool of antioxidants in the human body [16]. On the other hand, sterols are bile acid sequestrants and acyl coenzyme A cholesterol acyltransferase activity (ACAT) inhibitors and its consumption leads to lower levels of plasma LDL cholesterol. Triterpenes, such as erythrodiol and oleanolic acid, have shown anti-inflammatory and antioxidant properties in *in vitro* studies and vasodilatory activity in animal models [17]. Further studies are required to test the beneficial effect of these components in humans.

The main phenolic compounds present in virgin olive oil are tyrosol, hydroxytyrosol, its secoroids and conjugate forms, and lignans. They are absorbed by human intestine in a dose-dependent manner and given that free forms of these compounds are not detected in plasma, their *in vivo* biological activity must be referred to its biological metabolites. In experimental studies, these minor components have shown antioxidant properties, chemopreventive activity, and capacity to improve endothelial function by decreasing the expression of cell adhesion molecules, increasing nitric oxide disposability and quenching intracellular free radicals [18]. They are also able to modify the haemostasis, inhibiting platelet-induced aggregation and showing antithrombotic properties both in experimental and human intervention studies [19]. It has been shown that the consumption of virgin olive oil rich in phenolic compounds leads to an increase in the total phenolic content of the LDL, which is likely to exert their action in the arterial intima where the full oxidation of LDL occurs [20]. Phenolic compounds from virgin olive oil may delay the progression of the atherosclerosis by this mechanism. Results of the randomized cross-over clinical trials performed in humans on the antioxidant effects of olive oil phenolic compounds are controversial. The protective effects on lipid oxidation in these trials have been better displayed in oxidative stress conditions, i.e. males, submitted to a very strict antioxidant diet, hyperlipidaemic or peripheral vascular disease patients. Carefully controlled studies in appropriate populations, or with a large sample size, are urgently required to definitively establish the *in vivo* antioxidant properties of the active components of virgin olive oil.

### Prevention and progression of cancer

Approximately 80% of human cancers are associated with lifestyle habits. Diet and fatty acid intake are major players in the lifestyle-associated cancers (in particular gastrointestinal cancers and the hormone-related breast and prostate cancers). Epidemiological studies provide evidence that in the countries in which the populations fulfilled a typical Mediterranean diet, such as Spain, Greece and Italy, where virgin olive oil is the principal source of fat, cancer incidence rates are lower than in Northern European countries [21]. The consumption of virgin olive oil simultaneously ensures an appropriate intake of the essential polyunsaturated fatty

acids. Research in experimental animals has yielded growing evidence about the protective effect of virgin olive oil against cancer [22,23]. The protective effect of virgin olive oil on the initiation of cancer can occur by the prevention of oxidative DNA damage or DNA strand breakage [24]. Some of the compounds present in virgin olive oil can also act as potent antioxidants. The mechanisms by which virgin olive oil exert its potential protective effects on the promotion and the progression of cancer can occur by means of changes in cell membranes, altering tumour eicosanoid biosynthesis and cell signalling pathways, modulating the gene expression, and preventing DNA damage induced by reactive oxygen metabolites [24]. This can be associated with an altered expression pattern of cancer genes (oncogene HER-2/neu, which regulates the expression of c-fos and cox-2), or linked to epigenetic factors [25], that also play a major role in human carcinogenesis. Several of the components of olive oil can have anticancer effects on their own, in addition to the monounsaturated fatty acid oleic acid. These include flavonoids, vitamin E, squalene, caffeic acid, and hydroxytyrosol [1]. The protective effect of the consumption of virgin olive oil can be most important in the first decades of life, which suggests that the dietetic benefit of virgin olive oil intake should be initiated before puberty, and maintained through life.

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