Review

The influence of olive oil on human health: not a question of fat alone

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Olive oil is the most representative food in the traditional Mediterranean diet and its most important source of MUFA. The healthy benefits of MUFA-rich diets on plasma cholesterol levels, were the first to generate interest in this dietary model. In addition to the benefits conferred by its lipids, olive oil has other biological effects, some of them also related to MUFA. However, most recent studies have shown that there are a number of properties that depend on, or are potentiated by, the consumption of olive oil, such as virgin olive oil, that is rich in microcomponents. This foodstuff, thanks to its double set of benefits, thus tends to produce a better lipid profile and a less prothrombotic environment, promoting antioxidant and anti-inflammatory effects, with a greater endothelial protective capacity. In view of these effects, it would appear that when olive oil is the basic source of dietary alimentary fat it has a major antiatherogenic capacity, which is not shared to the same extent by other oils that are rich in oleic acid but lack its characteristic micronutrients.

Keywords: Atherosclerosis / Cholesterol / Endothelium / Thrombosis / Olive oil

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1 Introduction

The past decade has seen a rise in interest in the Mediterranean diet (MD), even among nutritionists from geographical regions to which this diet has traditionally been restricted. This is largely due to the fact that consumption of the MD has been linked to longevity, improved quality of life and a lower incidence of cardiovascular disease, cancer and cognitive deterioration, in spite of being an alimentary model with a high content of fat, in contrast to the diets recommended for many decades by nutritionists from other parts of the world [1]. However, the MD also shares many features with other healthy diets, such as the vegetarian diet, that of Latin countries and those with oriental populations [2], although it does have one peculiarity of its own. This is its high fat content, which makes it of particular gastronomic interest, in that the fat makes the diet more palatable and gives it a particularly high degree of popular acceptance. However, unlike other fat-rich diets such as the Western diet, most of the fat content of the MD comes from a single food component, olive oil, given that estimates suggest that this provides some 85% of the fat content of this diet. This explains why the MD is low in saturated fats and cholesterol, lacking *trans* fatty acids, while it has a high content of MUFA, particularly oleic acid. Furthermore, given the fact that olive oil possesses certain special gastronomic characteristics, thanks to its richness in several microcomponents that give it odour, colour and taste, the addition of olive oil to certain dishes makes it easier to consume certain products such as fruit and vegetables, legumes, and cereals, all of which contain high proportions of low glycemic index carbohydrates with high health-promoting potential [3]. The same is also true of fish, which is frequently eaten as part of the MD, in the form of dishes fried in olive oil. The benefits of the MD are thus not due exclusively to olive oil itself, but to the combination with its other health-promoting components, whose presence is favoured by the use of olive oil as a gastronomic ingredient.

For centuries, olive oil production was restricted to the Mediterranean area, which meant that diets with the above

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Abbreviations: **HMG CoA,** 3-hydroxy-3-methylglutaryl coenzyme A; **MD**, mediterranean diet; **NF-κB**, nuclear factor kappa B; **PAI-1**, plasminogen activator inhibitor type 1; **VCAM-1**, vascular cell adhesion molecule 1

characteristics were only feasible in the countries in this region. During the past few years, and thanks to modern technology, other types of oil with a similar fat composition have become available for human consumption, such as those extracted from certain seeds, some of whose varieties are rich in oleic acid. These include sunflower, soya and rapeseed oils with high contents of oleic acid. This has generated a new concept of the MD, which now includes the Lyon Diet Heart Study diet and the Indo-Mediterranean Diet, in which alimentary oleic acid is not derived primarily from olive oil but rather from different types of seeds [4, 5]. However, these oils possess a fundamental difference from that derived from the olive, which is that the latter is a real juice, a natural product that contains hundreds of non-fat components with great biological potential, including vitamin E, the carotenes, squalene, chlorophyll and, in particular, a number of phenolic compounds. The majority of the latter belong to three groups; the simple phenols (tyrosol and hydroxytyrosol), the secoiridoids (oleuropein and its conjugated forms) and the lignans [6]. Unlike olive oil, oils derived from seeds need to be refined for human consumption, which means that they lose the vast majority of their original microcomponents, leaving them almost exclusively mere sources of fat; colourless, odour-free and insipid, for which reason they are of no gastronomic interest. On the market we also find a number of commercial varieties of oil derived from olives. Two products are a real juice: "Virgin olive oil" and "Extra virgin olive oil", named from now under the general term "virgin olive oil" because both have similar chemical composition and the differences between them are of a gastronomic nature. Another product is sold simply as "Olive oil", and contains a small percentage of virgin olive oil (5–10%), which is added to previously refined olive oil, with the result that the content of microcomponents is lower than that of virgin olive oils, although it is higher than those derived from seeds. Finally, there exists oil known as "Olive-pomace oil", a blend of refined pomace olive oil and virgin olive oil, which cannot be commercially named olive oil. This is a good source of MUFA but contains also very limited amounts of the microcomponents that characterise virgin olive oil. These considerations are important, because this special issue discusses the benefits of diets rich in virgin and extra virgin olive oil, the original MD, whose effects are derived not solely from its content of MUFA but also from the other health-promoting substances found in virgin olive oil. As a result of the Seven Countries Study and the well-known works of Keys, a great deal of interest in elucidating the effects of MUFA on cholesterol metabolism has been aroused [7, 8]. However, and particularly in the course of the past decade, a new paradigm has emerged, with the demonstration that the effects of this diet go much further than cholesterol and even traditional risk factors, as we have described in previous studies [9–13]. This is summarised in Table 1 and will be discussed in this review.

Table 1. Benefits of a virgin olive oil-rich diet on cardiovascular risk factors and other mechanisms related to atherogenesis

Level of evidence	Type of effect
Demonstrated	1. Reduces triglycerides and increases HDL cholesterol levels when it replaces carbohydrate-rich diets 2. Lowers LDL cholesterol levels when it replaces saturated fat-rich diets 3. Increases resistance of LDL to oxidation 4. Improves glucose metabolism in diabetes
Possible	1. Improves the endothelium dependent vasodilatation 2. Ameliorates the inflammation induced by intake of high saturated-fat diets 3. Reduces the activation of mononuclear cells 4. Reduces arterial blood pressure and the need for antihypertensives 5. Induces a less prothrombotic plasma environment

2 Olive oil and cardiovascular risk factors

The benefits of MUFA-rich diets on plasma cholesterol levels were the first to generate interest in the MD. As a consequence of research in this area, in 2004 the US Food and Drug Administration (FDA) authorised the use of health claims for olive oil. The FDA report makes it clear that a dose of two teaspoonfuls (23 g) per day as a replacement for the same amount of saturated fats is capable of reducing the risk of coronary disease (http://www.fda.gov/bbs/topics/news/2004/NEW01129.html). It is worth noting that the report is based on data from 73 clinical trials carried out in the course of the past few decades [14–17], which established that consumption of this dietary component maintains levels of HDL cholesterol and reduces those of LDL cholesterol, when it is substituted for a source of saturated fat. Moreover, the isocaloric substitution of MUFA for carbohydrates reduces plasma triglyceride levels in the context of low-fat diets [8]. Given that this effect on triglycerides and LDL and HDL cholesterol has been demonstrated in every fat with a high content of MUFA, irrespective of origin, the lipid effect cannot be regarded as one of olive oil alone but should also be extended to refined oils that are rich in oleic acid [18]. 3-Hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase is the rate-limiting enzyme in cholesterol synthesis and is highly regulated by a variety of factors. Pallottini *et al.* have found a high correlation between the production of reactive oxygen species and increased HMG CoA reductase activity in rat livers [19]. However, more recent studies have indicated that polyphenols from virgin and extra virgin olive oil may have an additional influence on lipid metabolism, in that they reduce the activity of HMG CoA reductase [20]. Furthermore, Covas

et al. have very recently shown that consuming virgin olive oil, rich in phenolic compounds, for three weeks, significantly raises plasma HDL levels [21]. Although the mean increase in HDL level was small (mean 0.99 mg/dL), this is of great interest because it is the first time that a human study has led us to suspect that virgin olive oil induces its effects on lipid metabolism via different mechanisms than those induced by its fatty acids. The mechanisms by which dietary phenolic compounds raise HDL cholesterol levels are currently unclear. It is believed that one mechanism involved in that beneficial effect may be improved insulin sensitivity [22].

During the past few years, postprandial lipemia has attracted the interest of investigators, since it represents a metabolic situation characterised by an increase in total triglycerides and particles rich in triglycerides of intestinal origin and in less amount of hepatic origin. This situation lasts for much of the day, due to the current habit of people who enjoy a high standard of living, of eating several meals a day. A number of studies have suggested that these particles contribute to the development of arteriosclerosis, and observational studies have demonstrated that when the postprandial lipemic curve is more elevated, the risk of cardiovascular disease also rises [23]. A mechanism that may be capable of explaining this situation acts via the inflammatory phenomena that accompany the ingestion of fats, inducing a pro-oxidative state that activates the genes that are implicated in the inflammatory response during the postprandial period [24]. The data obtained from an *in vitro* model of early atherogenesis based on cultured endothelial cells provide evidence supporting the idea that the incorporation of oleic acid [25] or some olive oil phenols (oleuropein and hydroxytyrosol) [26] into the cultures, reduces messenger RNA levels for vascular cell adhesion molecule 1 (VCAM-1), interfering with the activation of the most important transcription factor controlling endothelial activation, nuclear factor kappa B (NF-κB). Postprandial lipemia is also influenced by the type of fat in the diet [27]. The chylomicrons that form after consuming olive oil enter the circulation more rapidly and are cleared more rapidly than those that form after the ingestion of saturated fats [28]. This peculiarity gives olive oil a less atherogenic character, even when the degree of postprandial lipemia is similar to that caused by other types of oil. Furthermore, various types of MUFA-rich oils may give rise to similar levels of plasma lipids in the basal state, although the postprandial response may be different. Abia *et al.* have thus demonstrated that consuming virgin olive oil rather than high-oleic acid sunflower oil reduces the postprandial response of triglyceride-rich lipoproteins [29]. This suggests that other factors in the composition of olive oil, such as linoleic acid levels or the positional distribution of fatty acids into the triacylglycerol molecules, may be responsible for these metabolic effects. A new concept that is currently being studied concerns the influence of the habitual diet on the postprandial response to ingestion of lipids. Silva *et al.* compared a diet rich in saturated fats (control) with two other diets containing moderate or high proportions of MUFA [30]. Following the intervention, the diets richest in MUFA reduced the production of apolipoprotein B-48, which suggests that the chylomicrons increase in size with this fat, with the result that larger and potentially less atherogenic chylomicrons are formed. This issue also discusses in detail this subject, which could prove to be a key to the explanation of the protective effect of olive oil against the risk of cardiovascular disease.

Another risk factor that is also closely related to diet is blood pressure. The ability of olive oil to modify arterial pressure is less well known than its effects on lipid metabolism, although they emerged some years ago in observational studies and recently in the Spanish cohort of the SUN project [31]. Some recent clinical studies of healthy subjects have also looked in depth at the benefits of the MD, and have demonstrated a reduction in blood pressure compared with low-fat and high saturated-fat diets [32, 33]. A similar effect has been observed in type 2 diabetic patients [34] and, in a very interesting study, Ferrara *et al.* [35] referred to the beneficial effect of olive oil on hypertensive patients, finding that those who followed a diet rich in polyunsaturated fat needed more treatment for hypertension than those who consumed olive oil. In that study twenty-three hypertensive patients were assigned randomly to MUFA or PUFA diet for six months and then crossed over to the other diet. A slight reduction in saturated fat intake, along with the use of virgin olive oil, lowered the daily antihypertensive dosage requirement, possibly through enhanced nitric oxide concentration stimulated by olive oil phenols. It has also been shown that with the ingestion of isocaloric amounts of olive oil or sunflower oil, the first of these reduced systolic pressure in hypertensive elderly people [36], a finding that was not confirmed in a comparison of virgin olive oil and soya oil in hypertensive patients [37]. However, the most recent, and particularly interesting, data are those of Esposito *et al.,* who showed, in a population of 180 metabolic syndrome patients, that the MD was associated with a significant long-term (two-year) reduction in systolic and diastolic blood pressure, and also reduced many other anti-inflammatory and metabolic effects, as we will discuss later in this review [38]. Although the global model of the MD contains other nutrients that are capable of reducing blood pressure, the important contribution of calories made by olive oil gives it a particularly prominent role. Most recently, Psaltopoulou *et al.,* in a Greek cohort of the EPIC study, which comprised more than 20 000 persons, observed that adherence to the MD was associated with lower blood pressures, with olive oil being an individual predictor of this effect [39]. A possible cause of olive oil's hypotensive effect could be the increase in nitric oxide bioavailability behind the observed improvement in ischemic reactive hyperemia after the intake of extra virgin olive

oil [40]. On the other hand, there also exist studies that suggest that this action need not be an effect of oleic acid alone, but also of the microcomponents of virgin olive oil. A clinical study of hypertensive women found that the beneficial effects on blood pressure were particularly clear with this type of oil, but less so when they consumed oleic-rich sunflower oil [41]. Although these findings have not always been confirmed in healthy subjects [42], the possibility remains that the non-fat components may have their own hypotensive effect. This possibility is suggested by the study of Fito *et al*., who observed that olive oil, with its high content of phenols, reduces systolic pressure in hypertensive patients with coronary disease, compared with a refined oil of the same origin [43]. Perhaps effects of this kind vary among different population groups, which may limit the generalisability of the results as long as we lack prospective clinical studies in sufficiently large populations [44]. Nevertheless, this topic may be much more complex, as we may deduce from the study of Soriguer *et al*. [45], who found an inverse relationship between MUFA consumption and arterial blood pressure in a well-controlled population, linking the risk of hypertension to the presence of polar compounds in the oil used to fry their food.

Another major cardiovascular risk factor is type 2 diabetes mellitus. A study now regarded as a classic demonstrated that a MUFA-rich diet (33% of the daily caloric content) reduced the insulin requirements of diabetic patients, compared with another carbohydrate-rich diet [46]. Several studies appear to have corroborated these data, and a meta-analysis has shown that compared with carbohydrates, MUFA improve both the lipid profile and the glycemic index, with similar levels of basal insulin and glycated haemoglobin [47]. Since then, a number of clinical trials have produced various results, in that they have not always confirmed differences in either glycemic control or the lipid profile, either in patients or in persons at high risk of developing type 2 diabetes [48–50]. A study performed by our group on a sample of healthy young adults found no differences in peripheral sensitivity to insulin following the ingestion of MUFA-rich and carbohydrate-rich diets [51]. We thus lack conclusive data that would confirm that the latter increase peripheral insulin resistance in normal persons. Another question concerns what happens in persons with reduced insulin sensitivity, in whom the ingestion of carbohydrates would increase the supply of glucose to the tissues, augmenting the need for the hormone, a situation that would translate into a deterioration of carbohydrate metabolism. In such cases, the isocaloric ingestion of MUFA would improve glucose metabolism, reducing the need for insulin [52–55]. Yet another situation occurs with saturated fats, as Vessby *et al.* have recently demonstrated in the KANWU study, in which modifying the proportions of fatty acids by reducing the intake of saturated fats and increasing MUFA improved insulin sensitivity in healthy subjects, although the rate of insulin secretion remained unchanged [56]. Furthermore, the mechanisms linking the type of dietary fat with insulin resistance are not completely understood. Cell membrane lipid composition is influenced by the fatty acid composition of dietary fat. The specific fatty acid profile of cell membranes might affect insulin action in a number of ways, such as insulin receptor binding and the ability to influence ion permeability and cell signalling. The effect of dietary fat on glucose metabolism may thus be an important link with the effects of olive oil on cardiovascular risk, as is discussed in more detail elsewhere in this issue.

3 Effects of olive oil on other mechanisms of arteriosclerosis

On the basis of the highly interesting results of the Lyon Diet Heart Study, a prospective, randomised single-blinded secondary prevention trial in which the cardiovascular benefits of a Mediterranean α-linolenic acid-rich diet could not be explained by the modification of risk factors, researchers began to think that foods induce much more complex effects than those due to its action on traditional risk factors [5]. This was the point of departure for a growing research confirming the multiple pleiotrophic effects of MUFA [57]. However, there also exist data which indicate that virgin olive oil has further beneficial effects, which also depend on its minor components, in particular on its phenols, as we discuss below.

3.1 Beneficial effects on haemostasis

This area is of particular interest in view of the fact that persons at high risk of cardiovascular disease may suffer chronic activation of thrombogenic mechanisms, placing them in what might be called a "prothrombotic environment" [58]. Some years ago, Sirtori *et al.* [59] observed that in healthy persons, an olive oil-rich diet reduced sensitivity to the aggregation of platelets exposed to collagen, while corn oil raised the threshold of aggregation to arachidonic acid. Since then, a number of groups have studied the potential haemostatic effects of olive oil in more depth, as discussed in another paper in this issue. It should be emphasised that the most recent studies appear to support the existence of a beneficial effect of ingesting MUFA on coagulation and fibrinolysis, although the presence in olive oil of antioxidants, particularly of phenolic compounds, suggests an additional value that explains the discrepancies that are occasionally found when we study oils of different origin and with different contents of antioxidants. Visioli *et al.* observed that 40 mL per day of virgin olive oil rich in phenolic compounds was accompanied after seven weeks by a lowering of plasma levels of thromboxane B2, unlike an oil with a lower content of these compounds [60]. More recently, the same author has confirmed these findings, this

time on the basis of experiments carried out during the post-prandial phase of consumption of two types of oil similar to those utilised in the earlier study [61]. Another finding of interest was that the habitual diet of the individual is capable of modifying the effects of an acute ingestion of fats. This has been demonstrated by the observation that the postprandial activation of factor VII, following a fat-enriched breakfast, can be avoided by the habitual consumption of olive oil [62]. Similar results have been found with the prolonged consumption of a MUFA-rich diet (18% of the contribution of energy), in comparison with other diets that are poorer in this type of fat (15%) derived from refined oils. This finding, which has been confirmed by other authors, can be justified by the fact that the MUFA-rich diet favours a decrease in the number of postprandial chylomicrons, which attenuates the activation of factor VII [63]. The effects of MUFA on fibrinogen are less well known, perhaps because, as an inflammatory marker, its levels may depend primarily on the underlying inflammation, and the MD would reduce them, in parallel with other inflammatory parameters [64, 65]. Finally, fibrinolysis has also merited interest, as a key mechanism in the reabsorption of recently formed thromboses, and particularly in the study of the principal inhibitor of this haemostasis route; plasminogen activator inhibitor type 1 (PAI-1). In this aspect, it is of interest that discrepancies have been observed on studying MUFA-rich fats of various origins, perhaps because the non-fat components of olive oil may be responsible for the decrease in this factor [66–69]. Interestingly, activator protein-1 binding to a regulatory sequence region in the promoter region of the PAI-1 gene, induces a three-fold rise in PAI-1 transcription rate in the presence of oxidative stress, as occurs in the postprandial state; this could be a regulatory target for those olive oil micronutrients [70].

3.2 Endothelium

The initial alteration that precedes the development of arteriosclerosis is the endothelial lesion, whereby its cells express adhesion molecules on its endovascular surface that encourages the penetration of circulating mononuclear cells in the sub-intimal region. This initiates the inflammatory process that leads to the loss of its own functions [71]. Of particular relevance among such functions are the vasodilatory response that depends on nitric oxide, and its capacity to reduce the risk of thrombogenesis, to which we have already referred. The cellular mechanism that mediates the expression of the genes involved in the inflammatory response, such intercellular adhesion molecule-1 (ICAM-1), VCAM-1, monocyte chemotactic protein-1, both in the endothelium and the other cells that participate in the inflammation of the vascular wall, depends on transcription factors, of which NF-kB is particularly well known, since it is a nuclear transcription factor that is sensitive to oxidative changes. In this field, an interesting aspect is the demonstration that supplementing an endothelial cell culture with oleic acid reduces the transcriptional activation of this factor in these cells, similar to what is done by α-linolenic acid, an omega-3 fatty acid, and the opposite of the inflammatory effect of linoleic acid [72]. This is in agreement with an earlier study of Carluccio *et al.,* who observed, also in an endothelial cell culture model, that the incorporation of oleic acid into cellular membrane lipids reduced the expression of VCAM-1 [25]. Furthermore, we ourselves have observed that the expression of VCAM-1 and E-selectin in human umbilical vascular endothelial cells, following the addition of minimally oxidised LDL, was less with LDL obtained from persons who had followed a diet rich in olive oil than from persons whose diet was rich in saturated fat [73]. This anti-inflammatory action of MUFA also explains the fact that the enrichment of LDL particles with oleic acid, during the consumption of different types of diet, reduces their capacity to induce monocyte chemotaxis and adhesion [74]. In a further step, we have recently observed that the consumption of olive oil reduces the expression of NF-κB in mononuclear cells obtained from healthy subjects during the postprandial phase, similar to the effect that has also been observed following the ingestion of linolenic acid, and the opposite of the proinflammatory effect of saturated fats. Furthermore, in the same study, olive oil reduced plasma levels of ICAM-1, another adhesion molecule [75]. This anti-inflammatory effect has been observed in metabolic syndrome patients who modified their diet for two years. In the group that followed an MD model, the prevalence of this syndrome was reduced, improved insulin sensitivity and lowered the levels of C-reactive protein (CRP) and interleukin 6, 7 and 18 [76]. More recently, in a sample of more than 700 persons at high risk of cardiovascular disease, it was observed that a diet rich in virgin olive oil lowered CRP levels, as opposed to a fat-poor diet and another that was rich in walnuts. Olive oil consumption also reduced levels of interleukin 6, VCAM-1 and ICAM-1 [77].

Although more data are needed, the anti-inflammatory effect of olive oil needs to be considered in the context of the inflammation that is produced during the ingestion of high-energy diets that may promote overproduction of reactive oxygen species and induce changes in complement fraction 3, with resulting endothelial activation, the adhesion of leukocytes to blood vessel walls and their subsequent emigration to the subendothelial space [78, 79]. Data exist suggesting that nutrients may act as antioxidants or membrane stabilisers and be capable of protecting endothelial cells [80]. In this context, MUFA would have a less pronounced pro-oxidative effect, avoiding the activation of the blood vessel walls. This ability has been recognised for several years, since the demonstration that LDLs increase their oxidation-resistance capacity when the diet contains a large proportion of this type of fat [81–84]. Furthermore, in the

case of olive oil and through the added effect of its microcomponents, its ability to buffer a pro-oxidative environment would be greater, as has recently been shown [84–86]. The fraction that is probably most heavily implicated in this protection consists of phenolic compounds, including oleuropein, an aglycone whose hydrolysis generates tyrosol and hydroxytyrosol, which in their free form and secoiridoid and conjugated forms make up 80% of the phenolic compounds in virgin olive oil. These products are absorbed by the human intestine in a dose-dependent manner, and experimental studies have shown that they demonstrate antioxidant properties, chemopreventive activity and the ability to improve endothelial function, in that they decrease the expression of cellular adhesion molecules, improve the availability of nitric oxide and neutralise intracellular free radicals. Moreover, they may also modify haemostasis, inhibiting platelet aggregation and displaying antithrombotic properties, both in experimental studies and in interventions in human beings [87]. It has been observed that an intake of virgin olive oil rich in these components increases the total phenolic content of LDL [88], which means that they may be capable of acting in the arterial intima, where the oxidation of LDL takes place. On the other hand, experimental studies have indicated that these compounds decrease LDL oxidation *in vitro* [89], although the antioxidant effect can also be observed *in vivo*, with a volume of ingested virgin olive oil that lies within the normal range of consumption. In fact, an olive oil-rich diet may modulate oxidative cellular stress, modifying lipoproteins and down-regulating inflammatory mediators, and buffering the activation of genes involved in inflammation, probably via the activity of NF-κB or other nuclear transcription factors. Virgin olive oil is very rich in microcomponents, and we still do not know the effects of most of these, but it is even possible that they have a direct effect similar to those of non-steroidal anti-inflammatory agents, inhibiting the cyclo-oxygenase system, without having to mediate their action via the activity of antioxidants [90].

As mentioned above, there is some evidence that an impairment of endothelium-dependent vasodilatation may even be detected in the presence of an isolated risk factor, without the need for a demonstrable anatomical alteration in the arterial wall. This phenomenon is of interest because of its ability to predict the risk of suffering coronary episodes and the possibility to be detected with non-invasive methods, although these have yet to be validated by clinical decision-making [91, 92]. In recent years, it has been demonstrated that certain nutrients and foods, particularly those with the greatest antioxidant capacity, such as folic acid, omega-3 fatty acids, wine and tea, are capable of improving the endothelial vasodilatory response [93, 94]. The vasodilatory effect of MUFA is less well known, since initial studies showed that ingesting any type of fat reduced the vasodilatory response [95]. A study performed by our group showed that an MD model, in patients with moderate hypercholesterolemia, increased endothelial-dependent vasodilatation in comparison with a diet rich in saturated fats, simultaneously lowering plasma P-selectin values [16]. An interesting aspect of this study is that the diet was high in fat, most of which was derived from virgin olive oil, thus opposing the idea that a high level of fat consumption must necessarily have negative effects on health. With the aim of defining the possible role of MUFA and of the microcomponents of virgin olive oil, we have completed a study of hypercholesterolemic patients, in which we observed that endothelium-dependent vasodilatation is induced with the intake of a phenol-rich virgin olive oil. Furthermore, virgin olive oil also raised the bioavailability of nitric oxide, reducing the levels of oxidation markers such as lipoperoxides and F2-isoprostanes [40].

In summary, virgin olive oil is a foodstuff with a wide range of healthy effects, typical of functional foods. Some of these effects are related to its high content of MUFA, although others depend on its richness in microcomponents, especially abundant in virgin olive oil. This food product, thanks to its double set of benefits, favours a better lipid profile and a less prothrombotic environment, and promotes antioxidant and anti-inflammatory effects, with a greater endothelial protective capacity. In the future, the integrated application of approaches that are becoming available in functional genomics, proteomic techniques, metabonomics, and systems biology, will lead to a more highly integrated understanding of its positive effects on health. In any case, when olive oil is the basic source of alimentary fat it has a major antiatherogenic capacity, which is not shared to the same extent by other oils, which lack its characteristic micronutrients.

A number of aspects remain to be studied with regard to the beneficial properties and mechanisms of action of virgin olive oil, primarily its non-saponifiable components. In this order, more needs to be known about the ways in which foodstuffs are processed, some of which may reduce or counteract the benefits associated with the consumption of this unprocessed raw material. Furthermore it would be interesting to dilucidate the threshold level for the ingestion of phenolic compounds necesary to induce their beneficial effects. Also, more work needs to be done on the biotechnology of transgenic plants in order to raise the concentration of the micronutrients found in olive oil. An interesting target for researching is the development of strategies to improve the olive oil production process with the aim of conserving the micronutrients and preventing the formation of undesirable components. Finally, efforts should be put into identifying those micronutrients in olive oil that have the greatest beneficial effects on health.

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