Review Article

Virgin olive oil in preventive medicine: From legend to epigenetics

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Among vegetable oils, extra virgin olive oil (EVOO) has nutritional and sensory characteristics that make it unique and a basic component of the Mediterranean diet. EVOO has always been used over the centuries for its preventive and therapeutic properties, as well as precious and valuable dietary lipidic condiment. Benefic effects of a diet rich in EVOO on the human health, especially in prevention and/or reduction of hypercholesterolaemia, serum lipoprotein levels and atherosclerosis, hypertension, cardiovascular diseases and thrombotic risk, oxidation and oxidative stress, obesity and type 2 diabetes, inflammatory processes and cancer are discussed in these review. Recent studies suggest also its role in regulating the sense of satiety. The chemical compounds of EVOO that may contribute to its overall therapeutic characteristics, the epigenetic and physiological mechanisms involved are focused, taking into account the most important studies in the literature of the last years.

Practical applications: Many studies on various aspects of nutrition indicated that many human diseases are influenced by lifestyle, in which the diet has an important aspect. The use of extra virgin olive oil is especially important from early childhood and throughout adult life to contribute to hinder the aging process. The importance of preventive and sometimes curative action, carried out by its various components in several pathological conditions has emerged from clinical, experimental, and epidemiological studies which, in many cases, are accompanied by indisputable scientific evidences. Taking into account the most important studies in the literature of the last years, the chemical compounds of extra virgin olive oil and the physiological mechanisms involved in their curative/health effects are the focus of this article.

Keywords: Extra virgin olive oil / Human health / Physiological mechanisms / Therapeutic

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Abbreviations: COX, cyclooxygenase; **eNOS,** nitric oxide synthetase; **EPO,** erythropoietin; **EVOO,** extra virgin olive oil; **FASN,** fatty acid synthase; **HER2,** human epidermal growth factor receptor 2; **HIF-1,** hypoxia inducible factor-1; **H_2O_2**, hydrogen peroxide; **IBD,** inflammatory bowel disease; **ICAM-1,** intercellular adhesion molecule-1; **IL-6,** interleukin-6; **iNOS,** inducible form of nitric oxide synthase; **LTB4,** leukotriene B4; **MCP-1,** monocyte chemotactic protein-1; **MD,** Mediterranean diet; **NF-kB,** nuclear factor k-B; **NO,** nitric oxide; **NST,** nucleus of the solitary tract; **OEA,** oleoiletanolamide; **OH,** hydroxyl radical; **O_2^-**, anion superoxide; **PAI-1,** plasminogen activator inhibitor type 1; **PPAR-alpha,** peroxisome proliferator-activated receptor alpha; **PPAR-gamma,** peroxisome proliferator-activated receptor gamma; **PPAR-receptors,** peroxisome proliferator-activated receptors; **PVH,** paraventricular nucleus of the hypothalamus; **SFA,** saturated fatty acids; **TNF-alpha,** tumor necrosis factor-alpha; **TXB2,** inflammatory markers B2; **VCAM-1,** vascular cells adhesion molecule-1; **VEGF,** vascular endothelial growth factor

1 Early history

Since ancient times, extra virgin olive oil (EVOO) has been considered to have characteristics between a food product and a medicine (Table 1), and most likely in the past it was used for therapeutic purposes [1]. The history of olive oil seems to begin during the copper age (6th millennium BC), when humans began hunting, fishing and agricultural activities: from a spiny bush with small fruits, big kernel and a little pulp, a thick-oily-beneficial-tasty liquid could be obtained. The plant and its fruit were then improved over the centuries. In addition to dietary purposes, olives and in particular olive oil have been used by wizards, con-artists, priests, shamans and physicians to clean injuries, favoring healing and relief from pain, and for recovery of muscular and articular function in fighters through massages. Called by Homer (9th–8th century BC) the ''liquid gold,'' it has been employed to care burned skin, dermatitis, stomach, liver and intestinal pains, and as sun protection. In the first Olympic games in 776 BC,

Table 1. Use of olive oil over the centuries

Period	Event/function
Copper age (6th millennium BC)	First extraction of thick-oily liquid from olive fruit for dietary purposes
7th millennium BC	Use of olive oil for cosmetic and basic medical purposes
9th–8th century BC	Use for care of burned skin, dermatitis, stomach, liver and intestinal pains, and as sun protection
776 BC	In the first Olympic games the winners of various competitions were rewarded with an olive twig
6th century BC	Solone decreed the first law for the preservation of the olive trees
5th century BC	Tucide sustained ''The Mediterranean people ceased to be barbarians when they began to cultivate the olive tree and grape vines''
460–377 BC	Even for Hippocrates, father of western medicine, olive oil was highly regarded
106–43 BC	Cicero wrote of the healthy aspects of ''pinguis liquor olivae''
70–19 BC	Virgil mentioned the olive oil produced by ''dolci olivi (the sweet olive trees)'' from ''mite lago di Garda (the mild Garda lake)''
24–79 AD	Pliny the Elder in his ''Historia Naturalis'' listed 48 medicines made with olive oil
146–211 AD	Under the Roman emperor Settimo Severo: free distribution of olive oil was given to the urban masses
4th century AD	Under Constantine: at least 250 bakeries and 2300 olive oil distributors
Middle ages	The medical monks of the abbeys used preparations containing olive oil to treat burned skin and swellings, as well as different infections
Renaissance	The jars containing olive oil were present in all pharmacies
19th century AD and today	Olive oil is still used as a home remedy for several ailments

the winners of various competitions were rewarded with an olive twig, both in honor to the goddess Athena and as a sign of fraternity and peace, and with amphora ''Panatenaiche'' filled with the highest quality olive oil (the first ''certified'' olive oil) to be used for health and nutrition. The importance of olive oil in antiquity also arises from the fact that Solone, one of the seven wise men, decreed the first law for the preservation of the olive tree in the 6th century BC: whoever cut an olive tree would be subject to capital punishment. Tucide, in the 5th century BC, sustained that ''The Mediterranean people ceased to be barbarians when they began to cultivate the olive tree and grape vines.'' Even for Hippocrates (460–377 BC), father of western medicine, olive oil was highly regarded. Subsequently, Cicero (106–43 BC) wrote of the healthy aspects of ''pinguis liquor olivae,'' and Virgil (70–19 BC) mentioned the olive oil produced by ''dolci olivi (the sweet olive trees)'' from ''mite lago di Garda (the mild Garda lake).'' Pliny the Elder (24–79 AD), in his ''Historia Naturalis,'' listed 48 medicines made with olive oil [2, 3]. Under the Roman emperor Settimo Severo (146–211 AD), free distribution of olive oil was given to the urban masses. Such habits were so common up to the 4th–5th century that under Constantine (4th century AD) there were at least 250 bakeries and 2300 olive oil distributors.

The numerous amphorae (ancient olive oil containers), in large part manufactured in Spain, were placed in a specific dump yard when broken, the earthenware dump-yard (from the Latin: ''testa testae''), and formed a huge heap that during the centuries became increasingly larger and today is an area of the city of Rome, so called Monte Testaccio. In the middle ages, the medical ''monacus infirmorum (monk)'' of the abbeys used preparations containing olive oil to treat burned skin and swellings, as well as different infections (i.e., gynaecological): a large part of these therapeutic indications were included during the 10th–12th centuries in the texts of the ''Scuola Medica Salernitana (Salernitana Medical School),'' the first western medical school. In the Renaissance, this practice continued. In fact, the ''Oleum'' jar was present in all pharmacies since olive oil had recognized healing properties in heart conditions, fever, anti-diabetic, soothing, diuretic and hypertension [4, 5]. Moreover, during the 19th century olive oil was also used to treat otitis, dermatitis, and eczemas. It was considered a mild laxative and, until few years ago, used by farmers as source of vitamin D to treat the rickets and pyorrhea, for neuritis, distortions, stomach pain, to extract thorns, foot calluses, and hair loss. Today it is still used as a home remedy for several ailments, in which EVOO is a fundamental constituent.

2 Towards evidence-based medicine

The enormous scientific and technical progresses and the progressive evolution of medicine to evidence based medicine has led a large number of scientists to investigate whether or not the therapeutic effects of olive oil handed down over the centuries are valid.

The purpose of the present review is overview the possibility that EVOO is effective in prevention and/or reduction of hypercholesterolaemia, serum lipoprotein levels and atherosclerosis, hypertension, cardiovascular diseases and thrombotic risk, oxidation and oxidative stress, obesity and type 2 diabetes, inflammatory processes, and cancer (Table 2 and Fig. 1).

Table 2. Benefic effects of a diet rich in EVOO on the human health

Benefic effect	Component of EVOO involved	Ref.
Hypercholesterolaemia, serum lipoprotein levels and atherosclerosis		
Reduction of risk factors, such as hypercholesterolaemia, atherosclerosis and hypertension, and mortality for cardiovascular diseases		[21–23]
Reduction of mortality due to cardiovascular disease by 9%, cancer by 6%, total mortality by 9% and the incidence of Parkinson's and Alzheimer's disease by 13%		[20]
Reduction of LDL cholesterol		[25, 26]
Reduction of triglyceridemia and increase in HDL		[25, 26]
Reduction of LDL oxidation process	Phenolic compounds	[61, 62]
Arterial hypertension		
Decrease in diastolic and systolic pressure observed in both hypertensive subjects and normotensive subjects		[29–33]
Prevention of damages to vascular endothelium	Phenolic compounds, hydroxyl-oleic acid derived from oleic acid	[37, 38]
Thrombotic profile		
Inhibition in the formation of blood clots by decreasing monocyte adhesion and increasing fibrinolysis	Oleic acid	[20]
Inhibition of platelet aggregation and alteration of the platelet/vascular wall, reduction of fibrinogen, factor VII and the principal suppressant of hemostasis, thereby increasing fibrinolysis	Phenolic compounds	[44–49]
Reduction of TXB2 and LTB4 in both hyperlipaemic subjects and patients with type 2 diabetes		[44, 50]
Chemo-protective action and improvement of the endothelium function	Phenolic compounds (hydroxytyrosol and tyrosol)	[44, 50]
Preventive action against thrombotic and microthrombotic events in patients with type 2 diabetes and hyperlipaemic subjects	Hydroxytyrosol	[44, 50]
Reduction of risks for patients with cardiac pathologies		[25]
Oxidation and oxidative stress		
Maintenance of cellular integrity and reduction of ageing	High level of oleic acid and lack of excess of linoleic acid	[56]
Anti-inflammatory and vasodilatative action	α-linolenic acid (ALA)	[60]
Delay of atherosclerosis	Phenolic compounds	[16, 44, 59, 60]
Prevention of oxidation of cells-membrane lipids and plasma lipoproteins, reducing the risk of atherosclerosis	Tocopherols	[43, 60]
Reduced production of free radicals and prevention of damages to the cellular membrane, mitochondria, and DNA, with beneficial effects on aging and cancer risk		[66, 67]
Inflammation		
Anti-inflammatory action by non-selectively inhibition of the COX-1 and COX-2 enzymes	Oleocanthal	[38, 69]
Protection against various pathological conditions (10 types of tumors including colon, stomach, breast, prostate, lung, and Alzheimer's disease)	Oleocanthal	[72, 73, 78]
Obesity and diabetes		
Reduction of risk by inhibition of the activation of NF-kB at the cellular level	Phenols, carotenoids, and tocopherols	[60, 92]
Protective action on mitochondria, reduced production of free radicals and protection against DNA oxidation		[60, 92]
Reduction of insulin requirements, with an improvement of both the lipid profile and the glycemic index	Oleic acid	[60, 92]
Improvement of sensitivity to insulin, without increasing its secretion		[25]
Benefits for obese individuals by inhibition of the inflammatory response	ALA	[25]
Neoplasm		
Reduction of the incidence of cancer		[16, 93]
Antineoplastic activity	Oleuropein	[96]
Inhibition of the oncogenic HER2 gene in the presence of high levels of the enzyme FASN (fatty acid sithase)	Oleic acid	[98–100]
Increase the inhibitory effect of herceptin on breast cancer cells	Oleic acid	[98–100]
Other benefic effect		
Increase in the sense of satiety	OEA	[104–113]

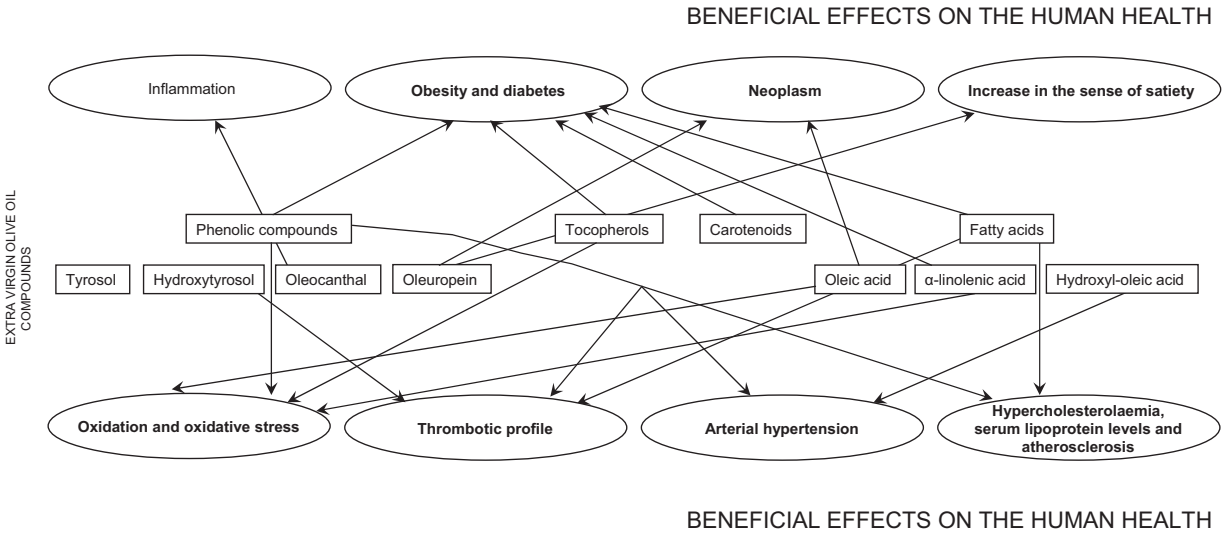

Figure 1. Healthy effects of extra virgin olive oil compounds.

2.1 Hypercholesterolaemia, serum lipoprotein levels and atherosclerosis

In 1908, Ignatowski noted for the first time the onset of atherosclerotic lesions in rabbit due to diet, and some years later was verified that the cause was related to a diet rich in cholesterol and saturated fatty acids (SFA). During the 1950s, it was observed that dietary SFA and cholesterol increase the level of cholesterolaemia and, consequently, atherosclerosis and the risk of cardiovascular disease [6]. This led to the assumption that diet, and in particular SFA, had a role in hypercholesterolaemia and cardiovascular diseases [7, 8]. Epidemiological research in the 1950s and 1960s, much carried out by A. Keys, the father of the Mediterranean diet (MD), studies the beneficial properties of EVOO, which were then confirmed by several experimental studies in vivo and in vitro, in animals and humans, even on large cohorts [9–20]. In fact, it was found that the MD, in which the lipidic component is somewhat high (>25–30% of total calories, and is represented almost entirely by EVOO, rich in MUFA oleic acid, reduced some risk factors, such as hypercholesterolaemia, atherosclerosis and hypertension, and mortality for cardiovascular diseases. Moreover, a decrease of 56% in total mortality and 61% in cancer risk was seen [14–16, 21]. In the Seven Countries study (Italy, Greece, Ex-Yugoslavia, Holland, Finland, USA, and Japan, a study on human subjects between 40 and 59 years old), atherosclerotic cardiovascular disease fluctuated between 2 and 10% in southern Europe, where the MD is widespread and the use of EVOO is high (Turkey: 1 kg/year; Italy and Spain: 10–12 kg/year), while it was 10–18% in Northern Europe and USA (USA: 0.45 kg/year). Mortality in the first 15 years in the subjects under investigation was lower in consumers of EVOO, which contains low amounts of SFA and an high ratio of MUFA/SFA, in Italy, Greece and Ex-Yugoslavia. Subsequently, the Lion Diet Heart study revealed a smaller incidence in the number of re-infarction and death in 50–70% of subjects who, after a first infarction, followed the MD enriched in α-linolenic acid, in addition to standard diet. Such a result was seen after 27 months, but was also confirmed after 46 months [21–23]. Confirmations have subsequently been obtained from many investigations about the MD, highlighting a low frequency in several pathologies (hypercholesterolaemia, hypertension, atherosclerosis, diabetes, and obesity). Today, it is well known that saturated fat intake, especially when high, can cause post-prandial hyperlipaemia and hypercolesterolemia, increasing the level of total triglycerides, in particular those having an intestinal origin rather than hepatic. When such a lipidaemic state is long-lasting it can contribute to the development of atherosclerosis through activation of inflammatory genes [18, 24]. Recently, a review pointed out that adequate compliance with the MD can reduce mortality due to cardiovascular disease by 9%, cancer by 6%, total mortality by 9% and the incidence of Parkinson's and Alzheimer's disease by 13% [19]. Concerning with the lipoprotein profile, it is well known that the LDL cholesterol is decreased when EVOO substitutes the same caloric value of the saturated fat, leaving the HDL level unaltered, while if the caloric value is too high in carbohydrates, it leads to a reduction in triglyceridemia and an increase in HDL [25, 26]. In reality, some of the results reported can be partially obtained with any type of oil that contains high quantities of oleic acid, following genetic modifications in plants, although it has been demonstrated that in humans the better results are due to the combined action of oleic acid and EVOO minor compounds, such as some phenols. Therefore, the existence of several metabolic pathways involved in these benefits, and adding these to the other

beneficial properties of EVOO may together improve the therapeutic effects [25, 27, 28].

2.2 Arterial hypertension

The endothelium has a defining role in thrombotic activity and coagulation since it synthesizes several molecules in response to different stimuli. Its dysfunction gives rise to an inflammatory process, reducing NO and releasing cytokine and pro-inflammatory chemokines: it therefore precedes the development of atherosclerosis [29]. NO, a major endothelial compound produced by the action of NO synthetase (eNOS), inhibits platelet aggregation, modifies the expression of the inter-cellular adhesion molecules (ICAM-1 and VCAM-1), has a relaxing effect and, together with heparan sulfate and prostacyclin, has a vasodilatory effect. In contrast, the thromboxane A2, prostaglandin H2 and endothelin 1 all have a vasoconstrictive action [29, 30].

The beneficial effects of EVOO on blood pressure are well known, and it has been highlighted that the beneficial effects of the MD in hypertensive subjects are more than that achieved with a diet that is rich in polyunsaturated fatty acids (PUFA). These effects on diastolic and systolic pressure have been observed in both hypertensive subjects (in which it was possible to reduce medical care) and normotensive subjects. However, there were no effects in subjects for whom sunflower oil was used (beneficial effects observed in 48% of subjects consuming EVOO, and in 4% of subjects consuming sunflower oil), which may be related to the fact that all refined fats and oils are completely lacking polyphenols [31–35], demonstrating the importance of antioxidant and PUFA synergy. In fact, a recent randomized, double-blind, cross-over study carried out in healthy, young subjects in which EVOO and red wine were administered in moderate quantities (50 g EVOO; 250 mL red wine), showed that the association of the antioxidant properties of these two products led to a reduction on both diastolic and systolic pressure, as well as hemodynamic and vascular function [36]. Moreover, from an analysis of the pulse wave, and considering as a reference parameter the index of increase, it was apparent that EVOO and red wine intake, after meals, led to improvement in elasticity (stiffness) of arterial walls. The mechanism of this phenomenon may be related to the action of EVOO minor compounds and phenols (refined olive oil and oleic acid enriched sunflower oil do not show the same effect), in addition to a compound present in red wine, namely resveratrol, due to its antioxidant action and increased production of nitric oxide (NO) caused by it [32–34]. Moreover, correlation between the increase of NO metabolites and an enhanced endothelial function was observed in a recent investigation [37], in which volunteers received a meal containing high-phenolic virgin olive oil, improving ischemic reactive hyperemia. As reported by Fitó et al. [38], the intake of EVOO rich in phenols could provide beneficial effects in hypertensive patients, due to a decrease in the systolic blood pressure. Thus, the consumption of EVOO can be considered as an additional and complementary intervention to the pharmacological treatment.

According to other investigators, the antioxidant action of EVOO (decreased production of the leukotriene B4, or LTB4, at the level of the 5-lipoxygenase, and a reduction in the production of free oxygen radicals) should prevent damages to vascular endothelium, which may be a precursor of hypertension [39]. In favor of this hypothesis, a reduction of the inflammatory markers B2 (TXB2) and LTB4 has been observed with an increase in serum antioxidant action only in subjects given EVOO; this effect was not observed in subjects when refined olive oil or corn oil was given [40]. Another evidence is that even the hydroxyl-oleic acid derived from oleic acid might have a regulatory action on blood pressure through by an inotropic effect on myocytes [41]. Recently, the importance of the MD in prevention of cardiovascular disease has been confirmed, although considering variable other than diet (The Hellenic SCORE), it is possible to predict the subjects with higher risk for hypercholesterolaemia, hypertension, cardiovascular disease, obesity and type 2 diabetes, and intervene with specific dietary changes [42, 43].

2.3 Thrombotic profile

In recent years, a possible role of EVOO is increasingly evident as oleic acid inhibits the formation of blood clots by decreasing monocyte adhesion and increasing fibrinolysis. The phenols, on the other hand, in addition to protecting both humans and experimental animal models from the harmful action of free radicals and reducing TXB2, also inhibit platelet aggregation and alteration of the platelet/vascular wall, reduce fibrinogen, factor VII and the principal suppressant of hemostasis (plasminogen activator inhibitor type 1, or PAI-1), thereby increasing fibrinolysis [44–49]. The anti-thrombotic role of EVOO phenols in addition to their antioxidant and anti-inflammatory properties are well characterized, was and they has been demonstrated to reduce TXB2 and LTB4 after a meal containing high quantities of EVOO [47]. The EVOO phenols hydroxytyrosol and tyrosol also have a chemo-protective action and they improve endothelium function, thus reducing the expression of adhesion cells and increasing NO levels. The administration of hydroxytyrosol to adult volunteers has been shown to reduce the production of TXB2, an effect that is observable in both hyperlipaemic subjects and patients with type 2 diabetes. In the latter group, a reduction of 46% in serum TXB2 was observed, with a preventive action against thrombotic and microthrombotic events [44, 50]. It has also been known for many years that patients with cardiac pathologies, who may have chronic activation of thrombogenic mechanisms (prothrombotic situation) may get benefits from EVOO [28].

2.4 Oxidation and oxidative stress

According to the free radical theory, ageing is due both to normal metabolism of the organism and to oxidative stress that results from pathologies, trauma, toxic substances, etc., leading to the production of waste products inside cells, called free radicals. These are ROS, such as anion superoxide (O_2^-), the hydroxyl radical (OH), and hydrogen peroxide (H_2O_2), which are oxidizing agents that are highly aggressive against the principal biological components of the organism: lipids, sugars, proteins, mitochondria, and DNA. When the lipids in the cell membrane are subjected to this action, oxidation takes place thereby altering membrane fluidity, followed by ageing of cells. When enzymes, mitochondria, and proteins are subjected to this phenomenon, they can give rise to metabolic disorders, inflammation in several parts of the organism (blood vessels, heart, kidneys, joints); when DNA undergoes oxidation, it can cause alterations in the genetic code and increase the risk of cancer. Early ageing of cells and the development of some serious diseases such as atherosclerosis, diabetes, multiple sclerosis, rheumatoid arthritis, pulmonary emphysema, cataract, Alzheimer and Parkinson's disease, senile dementia, breast—prostate—colon—skin cancer, have all been related to continuous oxidative damage to cells [16, 29, 30, 51, 52]. Oxidative damage can be partially prevented by adequate defense systems of the organism and the contribution of antioxidant substances from breast milk (in infants) and by diet sources (in particular fruit, vegetables and EVOO), which inactivate free radicals by donating protons [16, 29, 30, 51–53]. Since the first studies on the MD, the beneficial effects of EVOO have been attributed to the high content in oleic acid, the adequate contribution of linoleic acid (18:2, $n-6$) and α-linolenic acid (18:3, n − 3) (which are present in a optimal ratio), and to the limited presence of SFA [15, 54]. The high level of oleic acid of EVOO (considered by some nutritionists as an essential fatty acid because of its slow endogenous production), and the lack of excess of linoleic acid, have been revealed crucial for maintaining cellular integrity and reducing ageing [55]. In fact, oleic acid belongs to the group of MUFA, and due to the low level of unsaturation it shows a modest potential for oxidation, while the low amount of α-linolenic acid has beneficial effects due to its anti-inflammatory and vasodilatative action [56]. In addition, the intake of lipoproteins rich in MUFA consumed with EVOO are less susceptible to oxidation than those rich in PUFA [29]. Moreover, EVOO contains important minor compounds that have antioxidant action: carotenoids, polyphenols, squalene, tocopherols, etc. (Table 3). The most important carotenoids are β-carotene (endogenously converted into vitamin A in the intestinal mucosa) and lutein: these substances have antioxidant action, neutralizing the oxygen singlet. Among phenols, which are the major natural antioxidants in EVOO together with squalene, tyrosol, hydroxytyrosol, the by-products oleuropein and oleocantal, the flavonoids apigenin, luteolin, and quercitin are worthy of mention. As recently mentioned by the EFSA [57], polyphenols contribute to the protection of blood lipids from oxidative damage. They also conclude that the polyphenols healthy effect can be expressed as 5 mg of hydroxytyrosol present in EVOO that can be easily consumed in the context of a balanced diet.

The phenolic compounds, delay atherosclerosis due to their capacity to reduce the expression of both oxidized LDL and cellular adhesion molecules at the endothelial level [16, 44, 58, 59]. Today, the level of oxidized LDL is considered both a marker for oxidative damage and subclinical atherosclerosis as a predictive index of acute cardiovascular disease. This is because oxidation of lipids and LDL apoprotein leads to conformational changes, promoting the atherosclerotic process (monocytes-macrophages can pass through the arterial wall easily) [60, 61]. A higher level of oxidized LDL has also been associated with an increased frequency of metabolic syndrome [62].

The α-tocoferol, also known as vitamin E, is undoubtedly the most present tocopherol in EVOO. Tocopherols are

Table 3. Compounds with antioxidant activity present in olive oil

Chemical Class	Subclass	Compound
Carotenoids	Carotenes (Hydrocarbons); Xanthophylls	Beta Carotene; Lutein; Neoxanthin; Violaxanthin; Luteoxanthin; Antheraxanthin; Mutatoxanthin; Beta-cryptoxanthin
Chlorophylls	Chlorophylls and derivatives	Pheophytin alpha; Pheophytin beta; Chlorophyll alpha; Chlorophyll beta; Pyropheophytin alpha
Hydrocarbons	Triterpenes; Squalene	Squalene
Phenolic compounds	Phenolic acids; Tyrosol; Hydroxytyrosol and derivatives	4-Hydroxybenzoic acid; Protocatechuic acid; Gallic acid; Vanillic acid; Syringic acid; 4-hydroxyphenylacetic acid; Homovanillic acid; Coumaric acid; *p*-coumaric acid; Caffeic acid; Ferulic acid; Sinapic acid; Tyrosol; Hydroxytyrosol; Oleuropein; Oleuropein aglycon; Dialdehyde form of oleuropein aglycon; Decarboxymethyl form of oleuropein aglycon; Ligstroside aglycon; (+)-Pinoresinol; (+)-1-acetoxypinoresinol; Apigenin; Luteolin; Quercetin; Elenolic acid; Cinnamic acid
	Lignans; Flavonoids; Closely related non phenolic compounds	
Tocopherols		Alpha-, beta-, gamma- and delta-Tocopherols

considered the most important natural antioxidant agents in the lipidic fraction because they prevent oxidation of lipids (in particular in the cell membrane) and plasma lipoproteins, reducing the risk of atherosclerosis [30, 59]. On the other hand, it is important to highlight that the quantities of vitamin E in olive oil that can be daily consumed are far below from those tested to be effective in clinical trials. [63, 64]. Due to their antioxidant and anti-inflammatory action, the triterpenes eritrodiol and oleanolic acid should be mentioned [30].

Thus in summary, EVOO provides nutrients and antioxidants to the human diet, contributing to a reduction in free radicals, and prevent damages to the cellular membrane, mitochondria, and DNA, with beneficial effects on aging and cancer risk [65, 66].

2.5 Inflammation

Our Latin forefathers used the terms ''rubor, tumor, calor, dolor et lesa functio'' to indicate an inflammatory process subsequent to an infective, traumatic, chemical, or immune stimulus, characterized by the accumulation of leucocytes, mastocytes, and platelets that release different types of mediators. These latter substances have a different origin: from lipids (eicosapenanoids), proteins (cytokines and chemokines), and gases (NO, carbon monoxide and reactive oxygen species), which attempt to delimit the interested area, initiate an immune response, eliminate the triggering stimulus, and re-establish cellular integrity. Thus, an inflammatory reaction is a beneficial process, at least in the initial phase, and is important defense mechanism of the organism. This defense mechanism is subject to complex regulation that is able to programme its termination based on genetic and other factors [67]. The anti-infective therapy is generally able to control the majority of acute infective-inflammatory pathologies. Nevertheless, despite notable scientific progress, the problem of chronic degenerative inflammatory pathologies, such as cardiovascular diseases, rheumatoid arthritis, asthma, pulmonary fibrosis, Alzheimer's disease, inflammatory bowel disease (IBD), multiple sclerosis, major depressive disorder, and obesity is still largely unresolved. Indeed, the problem of inflammation has gained such public importance that in February 2004, Time magazine dedicated its front cover to inflammation or ''the secret killer'' [67]. Increasing interest was also raised in September 2005 when a group of 8 investigators published their research about the anti-inflammatory action of EVOO [68]. In that publication, it was ascertained that EVOO intake (especially when fresh) stimulated a tingling sensation in the back of the mouth, similar to the effect of the ibuprofen, a known anti-inflammatory, anti-pyretic, and analgesic agent. After further study, it was understood that the tingling sensation was caused by oleocanthal [dialdehydic form of (−) deacetoxy-ligstroside aglycone, where the name ''oleocanthal'' is derived from oleo (olives), canth (sting), and al (aldehyde)], and that the intensity of this sensation is dependent on the amount present. Assuming

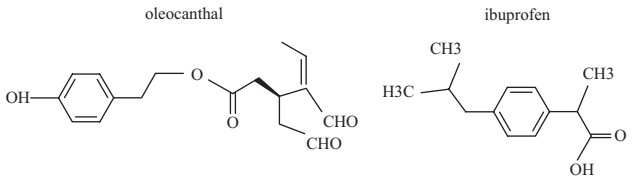

Figure 2. Structure of oleocanthal and ibuprofen.

that this sensation might be determined by the presence of other minor compounds in EVOO, after having synthesized oleocanthal it was found that the irritating throat effect was caused only by the action of this compound, with an effect that was similar and dose-dependent to that one determined by oleocanthal from EVOO. It was also demonstrated that the oleocanthal had the same anti-inflammatory action of ibuprofen since it non-selectively inhibited the cyclooxygenase (COX) COX-1 and COX-2 enzymes, which catalyze certain steps in the arachidonic acid inflammatory cascade. Therefore, it was demonstrated that ibuprofen and oleocanthal, while having a different chemical formula, have the same inhibitory action on COX, but did not act on 15-lipoxygenase (Fig. 2) [67]. It was also noted that daily intake of 50 mL of EVOO (equivalent to two spoons of EVOO for meal, in a main dish and in vegetables, respectively) contains 200 mg/mL of oleocanthal (of which 60–90% is absorbed), for a daily intake of about 9 mg [69, 70]. This dose is only around one-tenth of what is recommend for an adult for a painful illness, but it is known that small doses of aspirin, another COX inhibitor, have beneficial effects on several serious cardiovascular conditions [71–73]. Moreover, it is known that prolonged administration of ibuprofen or aspirin is associated with a reduced risk of about 7–10 types of tumors including colon, stomach, breast, prostate, lung, and for the reduction of beta-amyloid-42 levels in animal models, which are responsible for Alzheimer's disease [74–76].

It was concluded that such a component of EVOO, with inhibitory activity on COX (anti-inflammatory activity), may help to protect against various pathological conditions (mentioned above) when consumed regularly and continuously, due to an action similar to non-steroidal anti-inflammatory drugs [71, 72, 77]. The anti-inflammatory action of EVOO has been confirmed by the study of Bogani et al. [40] in normolipemic subjects by assaying the inflammatory markers TXB2 and LTB4 before and after 2 and 6 h following consumption of a high-fat meal containing EVOO, olive oil or corn oil. The above markers were significantly reduced only in subjects who consumed EVOO, confirming its anti-inflammatory action. Furthermore, in cell cultures from normal subjects, the EVOO incorporated into lipids of cell membranes reduces the expression of genes involved in the inflammatory response such as intercellular adhesion molecule-1 (ICAM-1), the VCAM-1, the monocyte chemotactic protein-1 (MCP-1), and interferes with the activation of a major transcription factor that controls inflammatory endothelial

activation, namely nuclear factor k-B (NF-kB) [25]. Moreover, the addition of oleic acid and selected phenols (oleuropein, hydroxythyrosol, etc.) to cells in vitro, similar to EVOO, can reduce the mRNA of vascular cells adhesion molecule-1 (VCAM-1), preventing the action of the NF-kB [58]. Sunflower oil enriched in oleic acid does not show the same properties [78]. It is possible that other factors present in EVOO, such as minor compounds (phenols, squalene, phytosterols), an adequate level of linoleic/linolenic acid, the fatty acid position in the triglyceride molecule, or the reduced production in apolipoprotein B-48, is involved in these metabolic effects [25, 27, 79].

2.6 Obesity and diabetes

Obesity, a first step towards hypercholesterolaemia, hypertension, atherosclerosis, and diabetes, has become a public health problem worldwide. In the USA, obesity affects 40% of adults and 32% of adolescents. Unfortunately, many other countries show obesity rates that are only slightly less than that in the USA. Until a few years ago, obesity was considered only a condition in which there is an excess accumulation of fat in adipocytes. Recently, however, some studies have shown that the white fat accounting for more than half of mature adipocytes and the remaining of pre-adipocytes, fibroblasts, endothelial cells and macrophages, is a true endocrine organ that plays an important role in both inflammatory and metabolic mechanisms [80, 81]. In fact, adipocytes produce at least 50 adipokines, several substances that release chemotactic proteins, complement proteins (adipsin), proteins involved in blood pressure control, angiogenesis, and molecules involved in the metabolism of glucose and lipids including adiponectin, resistin, visfatin, apelin, vaspin, hepcidin, chemeria, and omentin [81, 82]. Adipocytes in obese subjects, unlike subjects with normal weight, release a larger amount of proteins from white fat with pro coagulant activity, such as plasminogen activator inhibitor type 1 (PAI-1), factor VII and the inducible form of nitric oxide synthase (iNOS), which at least partly explains the increased risk of cardiovascular disease in obese subjects. They also release cytokines with typical pro-inflammatory activities including leptin, the MCP-1, the tumor necrosis factor-alpha (TNF-alpha), and the interleukin-6 (IL-6), thereby promoting a state of chronic inflammation, as shown by the abundant number of macrophages secreted in circulation by white adipose tissue. They also release free fatty acids and glycerol, promoting resistance to insulin, and leading to type 2 diabetes and metabolic syndrome, although the mechanisms behind this remain uncharacterized [80, 81, 82–86]. They are consistently elevated in obese subjects and in type 2 diabetes in subjects with a high risk of coronary heart disease and rheumatoid arthritis, leading to an increase in lipolysis and lipid oxidation [80, 82–84, 87–89]. It should also be noted that the stimulation to produce pro-inflammatory adipokines during the growth phase of white fat tissue is determined by a condition of local hypoxia that leads to increased expression of genes induced by hypoxia such as vascular endothelial growth factor (VEGF), erythropoietin (EPO) and hypoxia inducible factor-1 (HIF-1). It is, however, believed that not only pro-inflammatory cytokines but also reactive oxygen species and free fatty acids contribute to the development of these diseases through intracellular mechanisms involving NF-kB proteins and enzymes [90].

Recent studies have shown that minor compounds of EVOO such as phenols, carotenoids, and tocopherols inhibit the activation of NF-kB at the cellular level. They also have a protective action on mitochondria, decrease the production of free radicals, and protect against DNA oxidation. Compared with a diet rich in carbohydrates, a diet rich in oleic acid (33% of total daily calories) reduces insulin requirements, thereby improving both the lipid profile and glycemic index, without altering the levels of glycosylated hemoglobin, through the activation of the peroxisome proliferator-activated receptor gamma (or PPAR-gamma)-2 gene. This latter gene enhances the action of insulin and improves lipid metabolism and thus has a preventive effect on these diseases [59, 91]. Moreover, by reducing the intake of SFA and increasing that of oleic acid (modifying the proportion of fatty acids on cell membranes), there is an improved sensitivity to insulin, without increasing its secretion, although the mechanisms involved in this phenomenon remain to be clarified [25]. Obese individuals would therefore benefit from the important compounds found in EVOO, such as ALA, since these substances can contribute to lowering the inflammatory response [25].

2.7 Neoplasm

From the early studies of Keys a relationship between EVOO consumption and the rates of tumors in patients who followed the MD was found. Subsequent epidemiological studies have confirmed that in countries where it was followed by a MD like Greece, Italy and Spain where the EVOO is the main lipid used in food, the incidence of cancer was much lower [16, 92]. It has also been found that high doses of corn oil can lead to adenocarcinoma in rats, a phenomenon that never occurs with EVOO even at high doses. Oleuropein, one of the most abundant phenols in olives and EVOO, is not toxic even at very high doses; additionally it has antimicrobial, antioxidant, hypotensive, hypoglycemic, and antiangiogenic action [93–95]. For this latter reason, the antitumor activity has been studied in Swiss albino rats that can spontaneously develop fatal single or multiple sarcomas [95]. More specifically, after the appearance of one or more tumors reaching a diameter of >2 cm, 1% oleuropein was administered in drinking water. After examination of histological sections, a strong antineoplastic action, through an anti-angiogenic mechanism, that was due to direct inhibitory action on cells, and at the macroscopic level, led to the disappearance of the tumor mass within 9–12 wk. Treated animals returned to normal life with

no changes in behavior, and died of old age. This study thus confirms, at least in experimental animals, that an important compound in olive oil, namely oleuropein, has significant antineoplastic activity [95]. Support for the antitumoral activity of EVOO in humans was given by the finding that maslinic and oleanolic acid inhibited the proliferation of in vitro cultures of colon adenocarcinoma, without any apparent cytotoxicity and restored apoptosis, the process of primary importance in clearing cells with cancerous changes [96]. Additional confirmation of the antineoplastic action of EVOO has been provided by studies of breast cancer of women. It has been found that oleic acid inhibits the oncogenic human epidermal growth factor receptor (HER2) gene in the presence of high levels of the enzyme fatty acid synthase (FASN, which has been implicated in insulin resistance in type 2 diabetes and cancer), reduces the activity of transcription of this gene, promotes the production of PEA3 Ets protein with a suppressive action in cells with the HER2 gene. It also increases the inhibitory effect of herceptin on breast cancer cells that have become resistant to this drug [97–99].

It was further highlighted that the strong tumoricidal action on HER2 breast cancer cells of EVOO, which is caused by various phenols but mainly determined by oleuropein aglycone (the major bitter compound in EVOO) is related to inhibition of the HER2 gene. The latter gene is present in 20–30% of invasive carcinomas with poor prognosis, through degradation of HER2 proteasome itself, with inhibition of the tyrosine and serine/threonine kinase activity and the mechanisms involved in the formation of metastases and treatment failure [100, 101]. The metabolic and pathophysiological mechanisms through which individual compounds of EVOO play an antitumoral role in human cells has also been demonstrated by preventing their transformation into malignant cells and form metastases, was well as re-sensitizing cancer cells to treatment with the monoclonal antibody trastuzumab (Herceptin) [100–102].

2.8 Sense of satiety

In addition to the numerous beneficial properties of EVOO already described, the capacity of a derivate of oleic acid, namely oleoiletanolamide (OEA), to determine a sense of satiety and increase the time between meals should be added. In fact, studies in experimental animals on the metabolism of oleic acid in the intestine suggest that activation of small-intestinal OEA mobilization, enabled by CD36-mediated uptake of dietary oleic acid, serves as a molecular sensor linking fat ingestion to satiety [103–108]. OEA, a lipid-derived molecule with endogenous hormone-like action is formed, which is structurally similar to the endocannabinoid anandamide (arachidonoiletanolamide). It should be noted, however, that while the action of anandamide has a stimulatory effect on appetite, since it activates cannabinoid receptors (CB1), its analog OEA, through a mechanism independent of cannabinoid receptors, has dose-dependent anorectic, which increases the sense of satiety between meals without interfering other parameters such as fluid intake, physical activity, state of anxiety, or levels of stress hormone. In essence, the production in vivo of OEA in the small intestine serves as a sensor that correlates food intake and satiety [109].

As confirmation of this possibility, the pharmacological administration of OEA in experimental animals regulates satiety and reduces body weight by reducing the frequency of meals by activating the nuclear receptor PPAR-alpha (peroxisome proliferator-activated receptor alpha), which has been involved in a feedback mechanism involving recruitment, utilization, and absorption of dietary fat [108, 110, 111]. According to some authors, the mechanism of action of OEA in regulating appetite in response to the introduction of food, after activating the intestinal receptor PPAR-alpha, consists in the involvement of vagal sensory fibers that carry a stimulus to the first nucleus tractus solitaire (NST) at the base of the brain, and thus the paraventricular nucleus of the hypothalamus (PVH), resulting in the sense of satiety by blockade, a mechanism that can be defined as feedback through food intake (Fig. 3) [108].

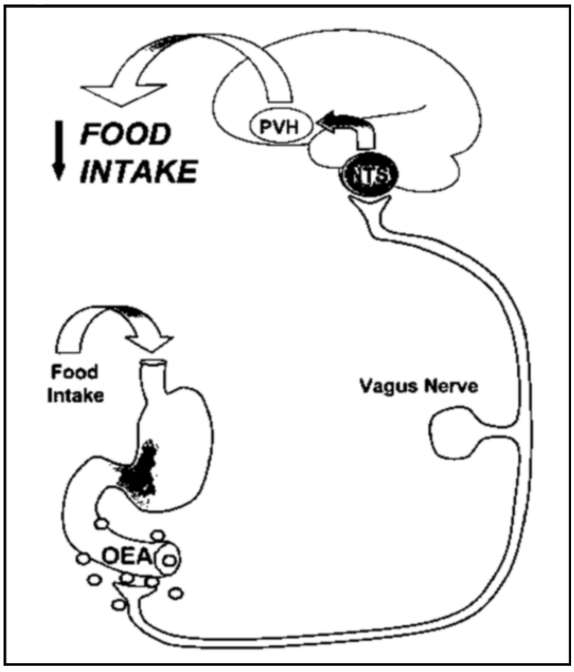

Figure 3. Hypothetical action of OEA in regulation of appetite. OEA that has accumulated in the small intestine in response to the introduction of oleic acid activates intestinal peroxisome proliferator-activated receptors (PPAR-receptors), through involvement of vagal sensitive fibers, thereby stimulating the nucleus of the solitary tract (NST) at the base of the brain and the paraventricular nucleus of the hypothalamus (PVH) determining satiety [106].

Others have speculated that the OEA may act within the enterocyte, inducing these cells to release an anorectic agent (e.g., apolipoprotein A-IV), led by the mediators of PPAR-alpha, which in turn stimulates vagus triggering inhibition of food intake [112]. At present, however, it cannot be excluded that the pulses initiating in the brain may somehow modulate this mechanism.

Oleic acid in the diet, but not in plasma, in addition to being a precursor in the synthesis of the OEA by enterocytes, influences its own levels through a feedback mechanism, decreasing during fasting and increasing after a meal alternating between a sense of hunger and satiety [108]. OEA, highly expressed in brown adipose tissue, in addition to decreasing the frequency of meals and increasing lipolysis, modulates the inflammatory response together with peroxisome proliferator-activated receptor gamma (PPAR-gamma) by reducing the activity of nuclear factor NF-kB, binding ω-3 fatty acids and increasing the catabolism of LTB4 in macrophages.

The meaning paraphysiological in regulating the sense of hunger, and therefore the weight is further highlighted by the finding of abnormal levels of OEA in the cerebrospinal fluid and plasma of patients with eating disorders in women with anorexia nervosa or anorexia-bulimia. For this reason some have suggested the possibility of an association between therapeutic inhibitor of the cannabinoid receptor CB1 produced by adipocytes (rimonobant) and OEA anorectic action for the treatment of severe obesity and dislipemia [107, 113, 114]. According to others, an enhancement in the production of OAE or its inhibition may represent degradation of the therapy to the treatment of diseases linked to excessive food intake. Discovering that a fatty acid of EVOO (that is a food considered for this award millenary tradition as healthy and now the most important of the so-called MD), may stimulate satiety, it certainly has a dramatic effect and give rise to new and interesting investigations. Chemical stimuli that regulate feelings of hunger and satiety will certainly be clarified in the near future and, very likely, controlled by drug therapy, opening the way to treatment options not only for obesity but also for many disorders including ' anorexia, bulimia and anorexia.

3 Conclusions

After many studies on various aspects of nutrition, it is now clear that many human diseases (including 80% of cancers, especially bowel, breast, prostate) are influenced by lifestyle, in which the diet has an important aspect (in particular lipids, fruits and vegetables, which are the basis of the MD). Knowing this and in light of the theory of aging due to the action of free radicals, the use of dietary EVOO, is especially important from early childhood, when various metabolic systems are committed to healthy development of the organism, and throughout adult life to contribute to hinder the aging process [16, 17]. In various pathological conditions, including obesity, which can be considered a chronic inflammatory disease, the importance of preventive EVOO has emerged from clinical, experimental and epidemiological studies in humans which, in many cases, are accompanied by indisputable scientific evidence [115]. The preventive action carried out by various components of EVOO, such as oleic acid in very high quantities, linoleic acid and ALA in balanced amounts (and similar to breast milk), tocopherol, beta carotene, hydroxytyrosol, oleuropein, oleocanthal, squalene, flavonoids, and caffeic acid is attributed to multiple mechanisms that include the protection against oxidative damage and DNA damage, the rebalancing of lipid metabolism, anti-inflammatory action, and an inhibitory effect on certain oncogenes (e.g., HER2) [16, 102].

Other recent and decisive contributions of the EVOO on the human health came from genetic study. It was reported that significant changes in the expression of genes related to insulin sensitivity occurs in human peripheral blood mononuclear cells (PBMNCs) after few hours an oral fat load of 50 mL of VOO [116]. Moreover, 3-wk consumption of VOO as a principal fat source for healthy human volunteers in a diet low in natural antioxidants, upregulates 10 genes (ADAM17, ALDH1A1, BIRC1, ERCC5, LIAS, OGT, PPARBP, TNFSF10, USP48, and XRCC5) related to prevention atherosclerosis development and progression [117]. Recently, in a randomized controlled trial, it was observed that VOO intake decreases plasma oxidative and inflammatory status and the gene expression related with both inflammation [INF-gamma (INFgamma), Rho GTPase-activating protein15 (ARHGAP15), interleukin-7 receptor (IL7R)] and oxidative stress [adrenergic beta(2)-receptor (ADRB2) and polymerase (DNA-directed)] in PBMNCs [118].

These nutrigenomic studies showed that the intake of EVOO rich in phenol compounds, a broad repertoire of chemical entities, can also act together on multiple targets to differentially activate defense, protective and repair epigenetic mechanisms and provide at least a partial molecular basis for reduced risk of atherosclerosis, cardiovascular disease and many other inflammatory diseases as observed in Mediterranean countries, where virgin olive oil represents a main source of dietary fat [119, 120].

For this reason research into the pharmacological properties of the minor components of olive oil is very active, could lead to the formulation of functional food or nutraceuticals and could provide a valuable phytochemical platform for the design of pharmacologically active phyto-pharmaceutical molecules.

Nevertheless, nutrigenomic cannot provide a complete design about the contribution of all the dietary factors to the phenotype of an individual yet. Other branches are giving important results. Among them, the epigenetic will allow us to understand the role of the changes that affect the phenotype without modifying the genotype, such as the changes that involve the metabolic functions, which are inheritable without modifying the genetic information.

Remembering the Konrad Lorenz's ''imprinting'' concept (Nobel prize in 1973), and in particular the David Barker's ''fetal programming'', we can hypothesize that the daily consumption of EVOO from the childhood, can contribute to plan specific metabolic pathway in the organism and to prevent serious pahologies (obesity, hypertension, diabetes, arteriosclerosis, etc.), conditioning biological and neuropsychological destiny. For this reason, in the near future, the attempt will be to ''plan'' human health, ''controlling'' and ''handling'' the infant feeding. In this field, EVOO is the best ''present'' that we can make for our organism, in order to stay well and have a pleasant and tasty life.

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