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Olive Oil: Antioxidant Compounds and Their Potential Effects over Health

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Abstract

Olive oil is considered as a key component of the healthy property of the Mediterranean diet due to its fatty acid, vitamin and polyphenol composition. High monounsaturated fatty acids, and in particular oleic acid, are responsible for the benefits obtained from consuming olive oil. Also, the known benefits are considered to be due to a combination of several phytochemicals. There are more than 200 minor components in olive oil with biological activities. The most abundant antioxidants in olive oil are tocopherols, β -carotene, lutein, squalene, lipophilic and hydrophilic phenols. Phenolic acids and derivatives (vanillic acid, gallic acid), phenolic alcohols (tyrosol, hydroxytyrosol), secoiridoids (oleuropein, oleocanthal), lignans (pinosresinol), and flavones (luteolin) are phenolic compounds of olive oil. Olive oil polyphenols have antioxidant, anti-inflammatory, antimicrobial, antiviral, anti-atherogenic, anti-thrombotic, anti-mutagenic and hypoglycemic characteristics. Hydroxytyrosol, tyrosol, oleuropein and oleocanthal are the phenolic compounds that are mainly responsible for antioxidant activity, protection from blood lipid oxidation, anti-inflammatory activity, the anticarcinogenic potential, the oxidative stress resistance, and other positive impacts over human health. Additionally, olive oil contains oleocanthal, which may have an effect on several inflammatory diseases. Olive oil rich diet protects human health from cardiovascular diseases (cardiometabolic markers such as blood pressure, glycaemia and dyslipidemia, notably by reducing LDL cholesterol and LDL oxidation), type-2 diabetes, obesity, cancer, inflammation, and oxidative stress.

Keywords: olive oil, oleic acid, minor components, phenolic compounds, health benefits

1. Introduction

Olive oil is one of the basic components of Mediterranean diet with health protective characteristics [1]. It has been used for centuries due to its preventive and therapeutic characteristics [2, 3]. Olive oil have positive effects on preventing or improving atherosclerosis, cardiovascular diseases, serum lipoprotein levels, oxidative stress, obesity, type 2 diabetes, inflammation and cancer [4–8].

Health protective effect of olive oil is based on its chemical composition [4, 5, 9, 10]. Olive oil's chemical composition may be divided into major and minor components. Major components of olive oil are related with its fatty acid content.

Primary monounsaturated fatty acid (MUFA) of olive oil is oleic acid [3]. Minor components of olive oil constitute nearly 2% of the weight of olive oil and include more than 230 minor chemical compounds [3, 10]. These chemical compounds include aliphatic alcohols, triterpene alcohols, sterols, hydrocarbons, pigments, volatile compounds, and phenolic compounds [2, 3]. Olive oil has at least 30 phenolic compounds. These are phenolic acids and derivatives, phenolic alcohols, secoiridoids, lignans and flavones [10–12].

Oleic acid, which is the basic fatty acid of olive oil [8, 13], and the minor compounds of olive oil, including tocopherols, β -carotene, lutein, squalene, lipophilic and hydrophilic phenols, are considered to be responsible for its positive impacts on human health [3, 14]. Olive oil protects human health by changes in epigenetic, metabolic and physiologic mechanisms [2]. This chapter reviews the fatty acid composition and minor components of olive oil and their effects on human health.

2. Fatty acid content of olive oil

Triglycerides constitute 98–99% of total weight of olive oil. Basic fatty acid of olive oil is oleic acid (55–83%), which is one of the MUFA. Besides, olive oil contains fatty acids such as palmitic acid, stearic acid, linoleic acid and α -linolenic acid (**Table 1**) [3, 10].

Positive impact of olive oil over human health is related with its oleic acid content [9]. MUFA in olive oil is considered to reduce hypercholesterolemia, hypertension, atherosclerosis and cardiovascular mortality [8, 13]. Besides, olive oil consumption increases MUFA intake rather than saturated fatty acids (SFA), which, in turn, protects from cardiovascular diseases [15–17].

In 1985, it was noticed that the replacement of SFA with MUFA intake in diets reduce low-density lipoprotein (LDL) cholesterol level [18]. It was found that the replacement of carbohydrates in diet with MUFA reduced triglycerides (TG), very low-density lipoprotein (VLDL) cholesterol, blood pressure, C-reactive protein (CRP)

Fatty acids	Common name
Saturated	Myristic acid
	Palmitic acid
	Margaric acid
	Stearic acid
	Arachidic acid
	Behenic acid
	Lignosceric acid
Monounsaturated	Palmitoleic acid
	Heptadecenoic acid
	Oleic acid
	Eicosenoic acid
Polyunsaturated	Linoleic acid
	α -linolenic acid

Table 1.
Fatty acids composition of olive oil.

and increased high-density lipoprotein (HDL) cholesterol and apolipoprotein A1 (Apo-A1) levels [19–21]. In an another study with the replacement of SFA with olive oil, which has the same amount of energy in diet, LDL cholesterol levels decreased whereas HDL cholesterol levels did not change [22]. Replacement of partially hydrogenated vegetable oil with MUFA had positive impact on cardiovascular risk parameters, such as LDL cholesterol, TG, Apo-A1 and Apo-B levels [23]. It was indicated that following a MUFA rich diet increased HDL cholesterol levels and decreased TG levels [24]. In a meta-analysis it was found that replacement of SFA with MUFA or polyunsaturated fatty acids (PUFA) significantly reduced total and LDL cholesterol levels [25]. In an another meta-analysis it was determined that consuming diets high in MUFA can improve metabolic risk factors among patients with type 2 diabetes [26]. In a meta-analysis of 12 randomized controlled studies high MUFA diets (>12%) were compared to those with low MUFA diets (\leq 12%). Significant differences between high- and low-MUFA diets were determined with respect to fat mass, systolic blood pressure and diastolic blood pressure. Therefore, high MUFA diets are important dietary regimens for obesity and cardiovascular disease [27].

Such positive impacts of olive oil on human health are related with high oleic acid, proper amount of linoleic and α -linolenic acid, and limited amount of SFA that it contains. High amount of oleic acid and proper amount of linoleic acid helps cells to protect their integrity and slows down the process of aging. Besides, low levels of α -linolenic acid demonstrate anti-inflammatory and vasodilatory effects [2].

3. Minor compounds of olive oil

Olive oil is rich in terms of minor compounds with antioxidant characteristics, such as polyphenols, carotenoids, squalene and tocopherols. Tyrosol, hydroxytyrosol, flavonoids (apigenin, luteolin), oleuropein and oleocanthal are among the phenolic compounds of olive oil with antioxidant characteristics (Table 2) [2, 6].

The amount of squalene, which is the basic hydrocarbon in olive oil ranges between 0.8 and 13 g/kg. Squalene has antioxidant activity and helps to lower serum cholesterol levels. Regular squalene intake by using olive oil in diets protects human health from cancer and cardiovascular diseases [28]. The most important carotenoids in olive oil are luteolin and β -carotene. These compounds have antioxidant characteristics that maintain the neutralization of reactive oxygen species (ROS) [2].

Triterpenes have also antioxidant and anti-inflammatory effects [11]. Regular consumption of olive oil maintains antioxidant intake. These compounds reduce

Minor components
<ul style="list-style-type: none">• Non-glyceride esters and waxes• Aliphatic alcohols• Triterpene alcohols: erythrodiol and uvaol• Sterols: β-sitosterol, campesterol, stigmasterol• Hydrocarbons: squalene, volatile hydrocarbons, carotenoids• Pigments: chlorophylls and pheophytins• Volatile compounds• Phenolic compounds<ul style="list-style-type: none">• Lipophilic: tocopherols and tocotrienols• Hydrophilic

Table 2.
Minor components of olive oil.

free radicals and prevent damages to the cellular membrane, mitochondria, and DNA, with beneficial effects on aging and cancer risk. Especially, phenolic compounds in olive oil have strong antioxidant effect [2, 6].

3.1 Phenolic compounds of olive oil

Polyphenols are compounds with diverse characteristics, which protects human health from chronic diseases [6]. They are described as phenolic compounds, which consists of one or more hydroxyl groups and aromatic rings [10]. Phenolic

Phenolic compounds	Common compound name
Flavonoids	
<ul style="list-style-type: none"> • Flavones 	<ul style="list-style-type: none"> • Apigenin • Luteolin
<ul style="list-style-type: none"> • Flavonol 	<ul style="list-style-type: none"> • (+)-Taxifolin
Lignans	
	<ul style="list-style-type: none"> • (+)-Pinoresinol • (+)-1-Acetoxy-pinoresinol • (+)-1-Hydroxy-pinoresinol
Phenolic acids and derivatives	
<ul style="list-style-type: none"> • Phenolic acids-benzoic acid derivatives 	<ul style="list-style-type: none"> • Benzoic acid • p-Hydroxybenzoic acid or 4-Hydroxybenzoic acid • Vanillic acid • Gallic acid • Syringic acid • Protocatechuic acid • Gentistic acid
<ul style="list-style-type: none"> • Phenolic acids-cinnamic acid derivatives 	<ul style="list-style-type: none"> • Cinnamic acid • o-Coumaric acid • p-Coumaric acid • Caffeic acid • Ferulic acid • Sinapinic acid
<ul style="list-style-type: none"> • Other phenolic acids and derivatives 	<ul style="list-style-type: none"> • p-Hydroxyphenylacetic acid • 3,4-Dihydroxyphenylacetic acid or Dopacetic acid • 4-Hydroxy-3-methoxyphenylacetic acid • 3-(3,4-Dihydroxyphenyl) propanoic acid
Phenolic alcohols	
	<ul style="list-style-type: none"> • Tyrosol or p-hydroxyphenyl-ethyl alcohol or p-HPEA • Hydroxytyrosol or 3,4-dihydroxyphenyl-ethyl alcohol or 3,4-DHPEA • Tyrosol acetate • Hydroxytyrosol acetate
Secoiridoids	
	<ul style="list-style-type: none"> • Oleuropein • Oleuropein aglycon or 3,4-DHPEA-EA • Ligstroside aglycon or p-HPEA-EA • Dialdehydic form of oleuropein aglycon • Dialdehydic form ligstroside aglycon • Dialdehydic form of decarboxymethyl elenolic acid linked to 3,4-DHPEA or 3,4-DHPEA-EDA or oleacein • Oleocanthal or Dialdehydic form of decarboxymethyl elenolic acid linked to p-HPEA or p-HPEA-EDA

Table 3.
Phenolic compounds in olive oil.

compounds in olive oil are classified as phenolic acids, flavonoids, secoiridoids, lignans, and phenolic alcohols (**Table 3**).

Phenolic compounds in olive oil may have lipophilic and hydrophilic characteristics. Tocopherols are among the lipophilic phenols. Alpha-tocopherols are the most common type of tocopherols in olive oil. Tocopherols especially prevent lipid oxidation in cellular membrane. Due to this reason, they are considered as the most important antioxidant agents in structures that contain lipid [14]. Tocopherols may be found in other oil types. However, hydrophilic phenols (phenolic acids and alcohols, secoiridoids, flavonoids and lignans) do not exist in oil types other than olive oil [3, 10]. Oleuropein, hydroxytyrosol and tyrosol are among the important phenolic compounds of olive oil [2, 6].

On average, olive oil consists of 500 mg/kg phenol [29] and the amount of phenol in different types of olive oil may range between 40 and 1000 mg/kg [10]. A study conducted in Spain found that daily polyphenol intake from olive and olive oil was 90.4 mg, which constitutes 11% of total daily polyphenol intake [30].

Phenolic compounds display a board spectrum of health promoting characteristics, including lipid-improving, anti-oxidant, anti-inflammatory, anti-atherogenic, anti-thrombotic, anti-mutagenic, anti-microbial effects [6–8]. Beneficial effects of olive oil's phenolic compounds on human health include improvements in oxidative stress, lipid metabolism, platelet and endothelial functions, and inflammation [6, 8, 14]. Oleuropein and hydroxytyrosol are principal minor phenolic components of olive oil and these antioxidant components prevents diabetes, cardiovascular diseases, neurodegenerative diseases, cancer, inflammation and oxidative stress through its nutrigenomic and immunomodulatory effects [4, 5]. Also oleacein has antioxidant, anti-inflammatory, anti-proliferative and antimicrobial properties and it may play a special role in decreasing the progression of atherosclerosis [31].

A study conducted on 200 healthy male participants, administered 25 ml/day of three olive oils that had low (2.7 mg/kg), medium (164 mg/kg) and high (366 mg/kg) phenolic content. The study found that higher phenolic content was associated with decrease in oxidative stress markers and improvements in lipid profile [32].

Phenolic compounds in olive oil have strong antioxidant characteristics and radical scavenging activities [29]. Regular olive oil consumption maintains phenolic compound intake and protects human health [14]. Taking these into consideration, we may suggest that biological characteristics of olive oil decrease the prevalence of chronic diseases [6, 8, 14].

4. Olive oil and potential effects over health

Olive oil rich diet protects human health from cardiovascular diseases, hypertension, inflammation, oxidative stress, obesity, type-2 diabetes, and cancer [4–8].

4.1 Olive oil consumption and cardiovascular diseases

Cardiovascular diseases arise from malfunctioning of heart and blood vessels and include problems, such as coronary heart disease, atherosclerosis, cerebrovascular diseases, peripheral artery disease, congenital heart disease, deep venous thrombosis, pulmonary embolism, myocardial infarction and stroke. Eating habits, and especially total fat and fatty acid intake are among the reasons of cardiovascular diseases [33]. 'Prevención con Dieta Mediterránea' (PREDIMED) study that conducted in Spain and randomly assigned participants, who were at high cardiovascular risk, to one of three diets: a Mediterranean diet supplemented with extra-

virgin olive oil (EVOO), a Mediterranean diet supplemented with mixed nuts, and a control diet that was advised to reduce dietary fat. Compared to the control group, the Mediterranean diet supplemented with EVOO or mixed nuts was associated with 30% lower risk of major cardiovascular events for a period of 5 years [34]. In another study, it was found that olive oil consumption, specifically EVOO, is associated with reduced risks of cardiovascular disease and mortality in individuals at high cardiovascular risk. For each 10 g/day increase in extra-virgin olive oil consumption, cardiovascular disease and mortality risk decreased by 10 and 7%, respectively [35].

A study that followed stroke incidence in three French cities for an average of 5.25 years found that the participants with high olive oil consumption had a 41% lower risk of stroke compared to those who never used olive oil. The same study found that higher plasma oleic acid was associated with lower stroke incidence and that the participants with higher plasma oleic acid levels had a 73% reduction of stroke risk compared to the participants with lower plasma oleic acid levels [36]. Another study, which followed Italian women for an average of 7.85 years, found that cardiovascular disease risk was lower for women in the highest quartile of olive oil intake (35.0 ± 0.1 g/day) compared to those in the lowest quartile of olive oil intake (16.8 ± 0.1 g/day) [37].

Another study conducted in five Spanish regions compared non-consumers of olive oil with participants that consumed ≥ 29.4 g/2000 kcal/day and found that the highest quartile of olive oil consumption was associated with a 26% reduction in risk of overall mortality and a 44% reduction in cardiovascular disease mortality. The study also found that for each increase in olive oil intake of 10 g/2000 kcal/day, there was a 7% decreased risk of overall mortality and a 13% decreased risk of cardiovascular disease mortality [38].

EVOO that is frequently consumed in Mediterranean countries, tends to produce a less prothrombotic environment, promoting antioxidant and anti-inflammatory effects with a greater endothelial protective capacity, which in turn, prevents cardiovascular diseases [22]. Besides, another study in which, healthy participants were administered virgin olive oil (VOO) for 3 weeks found that VOO supplementation altered the expression of 10 genes related to atherosclerosis development and progression [39].

Phenolic compounds of olive oil protect blood lipids from oxidative damage [8]. LDL oxidation is among the main risk factors that contribute to the development of atherosclerosis and cardiovascular diseases. Oxidation of LDL results in the formation of plaque within the arterial wall. Oxidized LDL levels should be taken into consideration as an indicator of oxidative damage and subclinical atherosclerosis. Oxidation of lipids and LDL apolipoproteins is taken by scavenger receptors on monocytes, smooth muscle cells and macrophages in an uncontrolled process, which, in turn, leads to formation of foam cells as an early feature of atherosclerosis [40]. Phenolic compounds delay atherosclerosis by reducing the expression of oxidized LDL and cellular adhesion molecules [2, 14]. Consumption of VOO, which is rich in terms of phenolic compounds significantly decreased LDL cholesterol levels in 1 week [41].

Due to vessel damage, endothelial adhesion molecule expression, platelet activity and aggregation is stimulated. Circulating macrophages and other molecules are adhered to the endothelium, which scavenge LDL and TG, becoming foam cells [42]. Phenolic compounds in olive oil prevent endothelial adhesion molecule expression and platelet aggregation. Hydroxytyrosol, oleuropein, aglycon and luteolin are crucial to prevent platelet aggregation [8]. Oleocanthal-rich extra virgin olive oil may influence platelet aggregation responses in healthy male adults [43]. Oleacein by inhibiting neutral endopeptidase activity, adhesion molecules

expression and elastase release might play a role in the protective effects of olive oil against endothelial injuries [44]. Oleacein enhances anti-inflammatory activity of human macrophages by increasing CD163 expression. It could play a potential role in the prevention of inflammatory disease related to atherosclerosis [45]. Additionally, oleacein possess ability to diminish the destabilization of carotid plaque and it could be useful in the reduction of ischemic stroke risk [46]. For that reasons it is possible to emphasize that olive oil rich diet protects human health from cardiovascular diseases.

4.2 Olive oil consumption and hypertension

Positive effects of EVOO consumption on blood pressure have been noticed. EVOO intake contributes to the decrease in diastolic and systolic blood pressure in hypertensive individuals. When compared with vegetable oil that is rich in terms of PUFA, EVOO consumption has a positive effect on blood pressure [47]. A study conducted in five European countries found that consumption of 25 ml/day olive oil significantly decreased systolic blood pressure [48].

In a meta-analysis conducted in the recent years compared dietary regimes with a high amount of MUFA (>12%) with those $\leq 12\%$ for a period of more than 6 months and found that diets with high amount of MUFA decreased systolic blood pressure, and diastolic blood pressure [27].

Antioxidant effect of EVOO is related with the fact that EVOO consumption reduces the generation of ROS. This effect prevents endothelial dysfunction, which is responsible for hypertension [49]. Related with this, the comparison of EVOO with olive oil or corn oil reveals that inflammatory markers (TXB2 and LTB4) decreased and serum antioxidant capacity increased only in the group of participants, who were administered EVOO [50].

4.3 Olive oil consumption and oxidative stress

Increase in oxidative stress causes an increase in ROS. Superoxide anion (O_2^-), hydroxyl radical (OH), and hydrogen peroxide (H_2O_2), which are also known as ROS, are the oxidizing agents that highly aggressive against the principal biological components of the organism, including lipids, proteins, mitochondria, and DNA. When lipids in the cell membrane are subjected to this action, oxidation that alters membrane permeability takes place. This, in turn, results with early aging of cells. When enzymes, mitochondria and proteins are subjected to this phenomenon, they can lead to metabolic disorders and inflammation in blood vessels, heart, kidney or joints. On the other hand, if DNA undergoes oxidation, the risk of cancer increases. Minor components of olive oil protects mitochondria and DNA from oxidation and decreases the generation of free radicals [2, 11]. Both oleuropein and oleacein are important antioxidant compounds of olive oil and they are stronger scavengers of O_2^- and H_2O_2 [51].

Increase in ROS is associated with atherosclerosis, cancer and neurodegenerative diseases. Oxidative stress increases the levels of lipid peroxide and oxidized glutathione (GSSG), and decreases the levels of glutathione (GSH) and glutathione peroxidase (GSH-Px). Consumption of olive oil that is rich in terms of phenols improves the balance of GSH and GSSG, increases GSH-Px levels and decreases lipid peroxide levels. Consequently, cellular oxidative damage may be decreased by consumption of olive oil with high phenol content [32, 52]. In a controlled before and after supplementation trial with 45 healthy adults found that regular consumption of 50 ml/day EVOO rich in phenolic compounds during 30 days increases plasma antioxidant capacity and antioxidant enzyme activity (catalase and

superoxide dismutase). Also it was observed increase in superoxide dismutase and decrease in catalase gene expression [53].

Cell aging, atherosclerosis, diabetes, rheumatoid arthritis, pulmonary emphysema, cataract, Alzheimer and Parkinson diseases, dementia, and development of breast, prostate, colon and skin cancers are related with continuous oxidative damage of cells. Oxidative damage may be partially prevented when the activation of free radicals is inhibited by nutrients, such as minor compounds of EVOO [2, 11]. In order to protect aging that is caused by the damage of free radicals, EVOO intake should start during the early childhood period [54].

4.4 Olive oil consumption and inflammation

EVOO may prevent inflammation when chronic inflammation is associated with pathological cases, such as obesity. Anti-inflammatory effects of EVOO is depends on its fatty acid content and antioxidant compounds [54]. In a randomized controlled trial in healthy adults found that VOO consumption decreased plasma oxidative and inflammatory status and the gene expression related with both inflammation and oxidative stress [55].

Increase in the concentration of inflammatory markers is associated with a higher risk of cardiovascular disease. Plasma thromboxane B2 (TXB2) and leukotriene B4 (LTB4) are known as the pro-inflammatory agents. TXB2 increases platelet aggregation in blood whereas LTB4 leads to cellular damage [56]. Bogani et al. [50] determined that consumption of EVOO that is rich in phenolic components decreases the concentration of inflammatory markers such as TXB2 and LTB4 and increases the serum antioxidant capacity whereas no such decrease was found for other oil types such as olive oil and corn oil.

Interleukin-6 (IL-6) and CRP, which are among the inflammatory markers increase in case of cardiovascular diseases. Olive oil with high phenolic compounds has anti-inflammatory effect and decreases CRP and IL-6 levels in circulation [57]. Oleocanthal, which is among the phenolic compounds of olive oil, prevents cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) activities, which have roles in the inflammation process. Inhibition of cyclooxygenase (COX) enzymes results in the reduction of arachidonate to the eicosanoids, prostaglandins and thromboxane [58]. It have been proven to possess that oleacein have antioxidant and anti-inflammatory activities. Oleacein enhances anti-inflammatory activity of human macrophages by increasing CD163 expression [45]. For that reasons, anti-inflammatory effects of olive oil enables protection from diseases that are related with inflammation [8].

Additionally, EVOO reduces the expression of genes involved in the inflammatory response, including intercellular adhesion molecule-1 (ICAM-1), vascular cells adhesion molecule-1 (VCAM-1) and monocyte chemotactic protein-1 (MCP-1), and interferes with the activation of major transcription factor that controls the inflammatory endothelial activation, namely nuclear factor kB (NF-kB). It was known that minor compounds of EVOO, such as phenols, carotenoids and tocopherols, prevent the activation of NF-kB at cellular level [2].

The anti-inflammatory effects that arise from the consumption of olive oil phenolic compounds have been shown to provide protection against inflammatory diseases. Thus, due to the reduction of the risk of inflammation, it can be said that the Mediterranean populations have low rate of cardiovascular mortality and certain types of cancer [8].

4.5 Olive oil consumption and obesity

Positive effects of olive oil consumption over weight control are widely known. Olive oil increases postprandial thermogenesis. Besides, it may contribute to an increase in fat oxidation. Furthermore, oleic acid may increase satiety, thus reducing food intake. The effect of fatty acids over weight gain may be related with neurotransmitters, intestinal peptides or thermogenesis [59]. The presence of fatty acids in the small intestine lumen induces a number of changes in the gastrointestinal function and inhibits appetite and energy intake. Gastrointestinal hormones, including cholecystokinin, glucagon-like peptide-1 and peptide YY are crucial to regulate appetite and control nutrition intake [60]. One of the studies found that oleic acid caused a slower gastric emptying, promoted the release of cholecystokinin and peptide YY, and a lower subsequent energy intake for both normal weight and obese participants [61].

Comparison of EVOO with cream, which has the same amount of energy but higher SFA levels indicated that olive oil significantly promoted postprandial fat oxidation and stimulated diet-induced thermogenesis [62]. Due to this reason, SFA may be replaced by MUFA for overweight and obese persons in order to lower body weight and fat weight [63].

Oleoylethanolamide (OEA), which is a by-product of oleic acid, acts as a hormone and may lead to satiety and decrease meal frequency. Nutritional intake of oleic acid stimulates the activation of OEA mobilization in the proximal small intestine, which, in turn, leads to satiety. Oleic acid in diets is precursor of OEA synthesis in erythrocytes. OEA decreases during fasting and increases after meals [64]. OEA production in small intestine serves as a molecular sensor linking fat intake to satiety [65]. In addition, OEA resembles to *endocannabinoid anandamide in structural terms*. Anandamide has an appetizing effect and activates cannabinoid receptors (CB1). Nevertheless, independent of the cannabinoid receptors, OEA has anorectic effect and increases satiety between meals [65].

OEA regulates satiety and appetite, thus contributes to a decrease in body weight. This effect is related with the engagement of peroxisome proliferator-activated receptors- α (PPAR- α). Following food intake, activation of PPAR- α receptor in intestine plays a role in the stimulation of vagus nerves, creating satiety in paraventricular nucleus (PVH) of hypothalamus [64]. OEA decreases meal frequency, increases lipolysis, and modulates the inflammatory response together with PPAR- α by reducing the activity of nuclear factor NF- κ B activity, and increasing the catabolism of LTB₄ in macrophages [2]. For that reasons, it has been suggested that the increase in OEA production may prevent overnutrition [2].

Additionally, proinflammatory cytokines, such as leptin, tumor necrosis factor alpha (TNF- α), MCP-1, and IL-6 are released from adipose tissue and this phenomenon triggers chronic inflammation [66]. EVOO prevents inflammation in cases such as obesity, which are associated with chronic inflammation [54]. EVOO consumption by obese individuals may reduce inflammatory responses [22]. Anti-inflammatory effect of EVOO may be related with its fatty acid content and antioxidant compounds [54].

In addition to all these characteristics, the consumption of olive oil together with legumes, vegetable dishes and salads is believed to have positive effects on digestive system, glycemic responses and weight control [59]. A 3 years follow-up of a Mediterranean diet supplemented by VOO and nuts found that Mediterranean diet, especially rich in VOO is associated with higher levels of plasma antioxidant capacity and the reduction in body weight after 3 years of intervention in a high

cardiovascular risk population [67]. All these reflect the fact that olive oil consumption together with a Mediterranean diet may prevent weight gain [8, 13].

4.6 Olive oil consumption and type 2 diabetes

Olive oil with its MUFA content improves glucose metabolism [8, 13]. When high-MUFA diets were compared with high-PUFA diets, there was a significant reduction in fasting plasma glucose level [26]. In addition, it was determined that decreases of SFA levels and increases of oleic acid levels in cellular membranes do not change insulin secretion but improves insulin sensitivity [2].

Prevention of diabetes might be attributable to the antioxidant property of EVOO, thus, oxidative stress seems to be implicated in β -cells dysfunction and eventually diabetes [68]. After 6 hours of consumption of 50 ml VOO, significant changes occurred in gene expression related with insulin sensitivity [69]. On the other hand, four cohort studies, including 15,784 T2D cases and 29 trials, were included in a recent meta-analysis, which indicated that the highest olive oil intake showed a 16% reduced risk of type 2 diabetes compared with the lowest intake. Additionally, in case of patients with type 2 diabetes, olive oil supplementation resulted in a significant reduction of HbA1c and fasting plasma glucose compared to the control group [70]. Additionally, change from polyunsaturated to monounsaturated diet in type 2 diabetes reduced insulin resistance [71]. For these reasons, olive oil could be beneficial for the prevention and management of type 2 diabetes [70].

Obesity causes an increase in inflammation [54]. Additionally, free fatty acids and glycerol release from adipocytes. Increase in the levels of proinflammatory cytokines, ROS and free fatty acids, result with risk of insulin resistance, which, in turn, may lead to type-2 diabetes [66]. Olive oil consumption contributes to weight loss, which is one of the strongest risk factors for type 2 diabetes [72]. All these reveal that olive oil, which is the fundamental ingredient of Mediterranean diet, may have a preventive role for type 2 diabetes [4–8].

4.7 Olive oil consumption and cancer

Epidemiologic studies found that cancer incidence was lower in countries such as Greece, Italy and Spain, which are characterized by high EVOO consumption [54]. Meta-analysis of 19 case-controlled studies reveals that cancer risk for the highest olive oil consuming group was 60% lower than the lowest olive oil consuming group. Besides, the study demonstrated that the increase in olive oil consumption was associated with protection from breast and gastrointestinal cancer [73].

High corn oil diet allows the development of malignant adenocarcinomas in rats whereas high EVOO consumption does not have such an effect. Excessive intake of oleuropein, which is one of the phenols in olive oil, has no toxic effects. Additionally, it has antimicrobial, antioxidant, hypotensive, hypoglycemic and *antiangiogenic* properties. Due to this reason, it is believed that oleuropein has anti-tumor activities. In case of rats with one or more large tumors (>2 cm diameter), addition of 1% oleuropein to drinking water showed strong antineoplastic effects and lead to the disappearance of tumor within 9-to-12 weeks due to antiangiogenic mechanisms that have direct inhibitor effects over cells. The study found that oleuropein in olive oil is an important compound with antineoplastic activity [74].

EVOO has antineoplastic effect on breast cancer in females. EVOO consumption reduces breast cancer risk in postmenopausal women [72]. In the presence of high levels of fatty acid synthase enzyme, oleic acid inhibits the oncogenic effect of epidermal growth factor receptor (HER₂) gene by reducing the transcription activity of this gene. Furthermore, EVOO had a strong tumoricidal action on HER₂ as a

result of phenols, mainly oleuropein aglycon, which is related to inhibition of HER₂ gene [75].

Oxidative damage of DNA starts carcinogenesis. Consumption of olive oil that is rich of phenols may inhibit oxidative DNA damage [76]. Cell proliferation and prevention of cell death are among the other factors that lead to tumor formation and development. Hydroxytyrosol in olive oil may prevent cell proliferation. Besides, oleuropein and hydroxytyrosol induce the death of breast cancer cells [77]. Due to these reasons, phenolic compounds in olive oil maintains the integrity of cells and prevents the development of tumors [8, 77].

Compounds of EVOO may show antitumoral effects as a result of metabolic and pathophysiological mechanisms, and may prevent the transformation of human cells into malignant cells and form metastases [2].

5. Conclusion

Olive oil has protective effects against inflammation and oxidative stress. Besides, it protects human body from various diseases, including, cardiovascular diseases, hypertension, obesity, type 2 diabetes and cancer. The basic fatty acid of olive oil, namely oleic acid, and minor compounds of olive oil, primarily phenolic compounds with their antioxidant activities, are responsible for the positive effects of olive oil over human health. Olive oil polyphenols have antioxidant, anti-inflammatory, antimicrobial, antiviral, anti-atherogenic, anti-thrombotic, anti-mutagenic and hypoglycemic characteristics. Hydroxytyrosol, tyrosol, and oleuropein are the phenolic compounds that are mainly responsible for antioxidant activity of olive oil. Through antioxidant and anti-inflammatory mechanisms, olive oil leads to epigenetic, metabolic and physiologic changes, which protects human health. Due to this reason, regular consumption of olive oil may be effective to decrease the risk of chronic diseases.

Abbreviations

MUFA	monounsaturated fatty acids
SFA	saturated fatty acids
LDL	low-density lipoprotein
TG	triglycerides
VLDL	very low-density lipoprotein
CRP	C-reactive protein
HDL	high-density lipoprotein
Apo-A1	apolipoprotein A1
PUFA	polyunsaturated fatty acids
VOO	virgin olive oil
EVOO	extra-virgin olive oil
PREDIMED	Prevención con Dieta Mediterránea
ROS	reactive oxygen species
O ₂ ⁻	superoxide anion
OH	hydroxyl radical
H ₂ O ₂	hydrogen peroxide
GSSG	oxidized glutathione
GSH	glutathione
GSH-Px	glutathione peroxidase
TXB ₂	thromboxane B ₂

LTB4	leukotriene B4
IL-6	interleukin-6
COX-1	cyclooxygenase-1
COX-2	cyclooxygenase-2
COX	cyclooxygenase
ICAM-1	intercellular adhesion molecule-1
VCAM-1	vascular cells adhesion molecule-1
MCP-1	monocyte chemotactic protein-1
NF- κ B	nuclear factor κ B
OEA	oleoylethanolamide
CB1	cannabinoid receptors
PPAR- α	proliferator-activated receptors- α
TNF- α	tumor necrosis factor alpha
HER ₂	epidermal growth factor receptor


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