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Health Benefits of Extra Virgin Olive Oil

Anka Trajkovska Petkoska and Anita Trajkovska-Broach

Abstract

Extra virgin olive oil (EVOO), also called the “*Elixir of the youth and health*” by the Ancient Greeks, is a cornerstone in the Mediterranean diet, which has been recognized as one of the healthiest and most sustainable dietary pattern and lifestyle. In this chapter, a brief overview of the major and minor components of EVOO is given followed by a review of their health benefits. In particular, the antioxidant, anti-inflammatory, anti-cancer and cardiovascular protective effects of EVOO are emphasized. At the end of this chapter, the reader would benefit by realizing that EVOO, as a functional food, proves the Hippocrates’s quote “*Let food be thy medicine and medicine be thy food*”.

Keywords: Extra virgin olive oil, Mediterranean Diet, health benefits, antioxidative effects, anti-inflammatory effects

1. Introduction

The cultivation of olive trees and production of olive oil have been related to the history and the culture of the people, who lived around Mediterranean Sea. A lot of archeological evidence has witnessed that inhabitants in this region consumed olives since the copper age. Over the millennia, olive oil has been used not only as a dietary ingredient, but also as lamp fuel, for cosmetics and pharmacological uses, for special rituals such as anointing royalty, warriors, etc. Greek philosophers have showed interest to examine its nutritional and medicinal benefits, while Aristotle and Hippocrates have recommended the olive oil for treatment of many diseases, such as dermatitis, stomach and intestine problems, as well as sun protection and burnt skin [1–4].

Nations with different ethnic, historical, and cultural backgrounds and religious beliefs have lived in the Mediterranean region, where olives have been cultivated [5]. Over the past several decades, experts are recognizing that the diet of the people in the Mediterranean is among the healthiest diets in the world, because of the lower incidences of many chronic diseases, like cardio-vascular and age-related diseases among these people [6–8]. In particular, in 1960’s, the phrase *Mediterranean Diet (MD)* was coined by Ancel Keys based on his research of the traditional culinary practices in the rural areas of Southern Italy, Crete, and other countries in the Mediterranean basin. His research, which started as a part of the Seven Countries Study with a special focus directed to the nutritional practices for the prevention of coronary heart diseases by replacing saturated fats (saturated fatty acids, SFA) with unsaturated fats, including polyunsaturated fatty acids (PUFA) and mono-unsaturated fatty acids (MUFA), mainly sourced from the olive oil, showed that people living in the Mediterranean basin indeed have less cardiovascular events

Figure 1.
Mediterranean diet pyramid (© 2009 Oldways preservation and exchange trust).

and reduced risk of other diseases [1, 7, 9–11]. Half century later, in 2010, MD even became a part of the UNESCO’s intangible cultural heritage, where it is defined as “a set of skills, knowledge, rituals, symbols and traditions concerning crops, harvesting, fishing, animal husbandry, conservation, processing, cooking, and particularly the sharing and consumption of food” [1, 5, 12].

The traditional Mediterranean cuisine emphasizes an abundant intake of variety of vegetables, fruits, legumes, whole grains, and nuts, moderate intake of seafood and fish, and a low consumption of red meat, sweets and other processed food, while red wine is usually consumed with the meals. Olive oil (OO), known as the *liquid gold*, and mainly used as a virgin olive oil (VOO) or as extra virgin olive oil (EVOO), is the hallmark of the MD [12, 13]. It is, in fact, the main source of healthy fats in the diet, which along with the other OO bioactive components, such as polyphenols, are often associated to the longevity, well-being and a lower incidence of chronic diseases, particularly cardiovascular diseases (CVDs) in the populations living in the Mediterranean region [9, 14, 15].

Figure 1 below is a schematic presentation of MD with the foods consumed in abundance at the bottom of the pyramid and those consumed rarely at the top of the pyramid. Important part of MD is the social aspect of the Mediterranean lifestyle, conviviality and daily physical activity, also presented at the bottom of MD pyramid.

2. Composition of olive oil

The *major* components of OO are saponifiable lipids (~98%), which are mostly *triglycerols*, MUFA (oleic acid, 55%–83%), PUFA (linoleic acid, 2.5%–21%) and SFA (palmitic acid, 7.5%–20%). The *minor* (unsaponifiable) fraction (~2%) has more than 200 chemical compounds among which more than 30 are *phenolic compounds*,

such as hydroxytyrosol, oleuropein, oleocanthal and tyrosol, phenolic acids (vanillic acid, syringic acid, gallic acid, etc), flavonoids (eriodictyol, apigenin, luteolin, etc.), secoiridoids (oleacein, oleocanthal, etc.) and lignans [8, 11, 16–23].

The lipid fraction (MUFA, PUFA) in OO gives its lipophilic character responsible for protective properties on coronary, autoimmune and inflammatory disorders, granting anti-thrombotic and regulation effects of blood pressure [24]. The minor components like α -tocopherol, tocotrienols, and carotenoids, such as β -carotene and lutein, squalene and other triterpenes, sterols, and pigments are also important for human health and they are responsible for the oil taste and aroma of olive oil. The chlorophyll (a non-oily component) in OO, determines the color of the OO that can be lost in the refining process. Its role is a facilitator of cell growth, and its part in the stimulation of the formation of blood cells (hematopoiesis) has been reported [3]. The bioactivity of the phenolic compounds is related to different properties, antioxidant and anti-inflammatory, although the molecular mechanism of these compounds in relation to many diseases could have different cellular targets [16]. Their content in OO varies depending on climate, cultivar, ripeness of the olives at harvesting, as well as the production process of the olive oil [14, 21, 25–30].

Different olive oil types are classified according to their acidity, expressed as amount of oleic acid (*International Olive Council (IOC) standard*). For instance, extra virgin olive oil (EVOO) has a free acidity of <0.8 grams / 100 grams, virgin olive oil (VOO) has a free acidity of <2 grams / 100 grams, and ordinary OO has a free acidity of <3.3 grams/100 grams. During the refining process some of the important components, like phenolic compounds and squalene, are lost; thus, *EVOO is the olive oil with the highest phenolic compound content* with the mean total polyphenol content of >55 mg/100 g [14].

Among the many constituents of olive oil, particular attention has been focused to the *phenolic compounds* due to their antioxidant effects, but also to their anti-inflammatory activities since that inflammation is an important etiologic factor for several non-communicable diseases [16, 24, 25, 31]. There are various OO phenolic compounds, which can be classified as simple phenols (hydroxytyrosol, tyrosol), secoiridoids (oleuropein) and lignans. Among them, *oleuropein, hydroxytyrosol and oleocanthal* are the most studied compounds with proven benefits, such as being strong antioxidant compounds counteracting reactive oxygen species' formation [18, 20, 32–35].

3. Oxidative stress and inflammation

Oxidative stress is defined as an imbalance between the oxidant and antioxidant systems of the body, in favor of the oxidants. It occurs when excessive generation of free radicals, reactive oxygen species (ROS) and reactive nitrogen species (RNS), produced during the normal cell metabolic processes or by external factors (pollution, smoke, radiation and chemicals) is unbalanced by the body's antioxidant defense system. The oxidative stress has been implicated in the etiology of many diseases; in particular, the oxidative stress is one of major cellular features in the onset of pathological conditions, such as neurodegenerative disorders (Alzheimer's and Parkinson diseases), renal disease, diabetes, ischemia, atherosclerosis, pulmonary dysfunction, cancers, and aging [3, 8, 25, 36–40].

The oxidative stress can activate a variety of transcription factors, which lead to the differential expression of some genes involved in different inflammatory pathways [38–41]. Inflammation and oxidative stress are interrelated and closely linked to many pathophysiological processes; one of them may occur before or after the other. In most of the cases, both of them take part in the pathogenesis of the chronic

diseases [37]. The oxidative stress and inflammation, when unbalanced by the antioxidant defense system, can lead to changes of the crucial biomolecules in the body. Namely, ROS and RNS as highly reactive molecules can damage cell structures, such as the carbohydrates, nucleic acids, lipids, proteins and alter their functions through lipids' peroxidation, DNA damage and proteins' oxidation that lead to cell mutation, abnormal cellular growth, apoptosis, and necrosis (**Figure 2**) [30, 38].

On the other hand, the human *antioxidant defense system* includes endogenous and exogenous antioxidants. Enzymes, such as superoxide dismutase, catalase, glutathione reductase, glutathione and glutathione peroxidase, metal binding proteins form the body exogenous antioxidant system, then some elements or compounds (selenium, zinc, vitamins A, C and E, phenols), mainly derived from the diet, belong to the group of exogenous antioxidants. Therefore, the level and the diversity of antioxidants in the body are very important for *counteracting and neutralizing the oxidative stress*, which is critical for cell viability, activation, proliferation, and organ function. Enzymatic and nonenzymatic antioxidants are usually effective in blocking the harmful effects of ROS. However, in the human cells, *de novo* antioxidant production is very limited. Also, in pathological conditions, the antioxidant systems can be overwhelmed. Hence, the intake of external antioxidants can assist in fighting the oxidative stress. In this context, the role of *dietary antioxidants*, such as polyphenols, carotenoids, tocopherols, tocotrienols and others is very important. EVOO, as a rich source of antioxidants, has been recognized and recommended by many experts, medical doctors, dieticians, nutritionists to help in protection against the oxidative stress, inflammation and related diseases [25]. In this context, the European Food Safety Authority (EFSA) in 2011 has approved a health claim stating that the dietary intake of VOO's polyphenols is able to protect blood lipids from oxidative damage. However, in order this claim to be valid, 5 mg/day of hydroxytyrosol and its derivatives should be consumed (Commission Regulation, EU, 432/2012) [16, 42–44].

Figure 2.
Oxidative stress and inflammation and their effects on different organs.

4. Health benefits of EVOO

4.1 Antioxidative and anti-inflammatory effects of EVOO bioactive constituents

The benefits of OO, especially those of EVOO, in the human organism are well established, and they are mainly due to its composition. The predominant MUFA present in EVOO is the oleic acid. Also, the microconstituents, such as phytosterols, squalene, tocopherols, phenolic compounds, terpenic acid derivatives, etc. have particular beneficial effects on the human health and well-being. Among them, the phenolic compounds are the most studied and proven for their remarkable antioxidant activities. It is worth noting that secoiridoids and alcoholic phenols (hydroxytyrosol) are present in much higher amounts in EVOO compared to refined OO. These phenolic compounds are characterized by a broad spectrum of biological activities, such as reducing the morbidity, prevention and slowing the progression of diseases associated with oxidative stress, due to their antioxidant activity [2, 6, 8, 37, 39, 45–49].

The benefits of EVOO phenolic compounds, are closely related to their chemical structure, specifically due to the presence of hydroxyl groups. The action mechanism could be attributed to the electron donating ability of the hydroxyl groups and subsequent formation of intramolecular hydrogen bonds with the free radicals. In addition to the antioxidant effect, *i.e.* the direct scavenging of reactive species, the EVOO polyphenols' modulation of gene expression plays a key role in their anti-inflammatory properties. A strong scientific evidence supports the association of phenolic compounds with the prevention or reduced risk of diseases caused and characterized by oxidative stress or inflammation, such as cancers, digestive disorders, metabolic syndrome, obesity, atherosclerosis and CVDs [19, 24, 27, 31, 49–51]. Beside antioxidant and anti-inflammation effects, polyphenols are also responsible for antihepatotoxic, antidiarrheal, anti-ulcerous in the digestive system, anti-allergic, anthelmintic, anti-osteoporosis effects, but also have anti-bacterial and antiviral effects [3, 4].

It is worth mentioning that the EVOO phenolic compounds' antioxidant and anti-inflammatory effects are synergic in nature giving rise to the profound bioactivity of EVOO against chronic diseases and different pathologies, where the oxidative stress has been implicated as underlying mechanism (neurodegenerative, digestive disorders, cancer, and metabolic syndrome). In particular, a large body of scientific evidence supports EVOO's phenolic compounds having the following beneficial effects (**Figure 3**):

- Anti-cancer and chemo-preventive effects
- Cardiovascular protective effects
- Antibacterial, antiviral and antifungal activity
- Respiratory effects
- Endocrine effects
- Gut- and immuno-modulatory effects
- Neuro-protective activity, etc.

In the next section, the health benefits of EVOO through the biological activities of some of its constituents, in particular the major phenolic compounds, are reviewed.

Figure 3. Chemical structures of olive oil main phenolic compounds and the antioxidant and anti-inflammatory benefits of olive oil.

4.1.1 Hydroxytyrosol

As presented in **Figure 2**, hydroxytyrosol, oleocanthal and oleuropein are the most studied and most important polyphenols found in EVOO.

Hydroxytyrosol [14, 52–55] is considered to have the highest antioxidant and anti-inflammatory potency compared to the other EVOO's polyphenols. Its beneficial properties for human health are strongly related to the ability of the molecule to scavenge free radicals, ROS and RNS, as well as to activate endogenous antioxidant systems in the body. For instance, it is known, ROS are involved in the endothelial dysfunction contributing to atherosclerosis development. *In vitro* studies have shown that EVOO polyphenols are able to lower the oxidative stress and inflammatory-related sequelae associated with chronic degenerative diseases. It was found that hydroxytyrosol regulates the intracellular ROS levels in vascular endothelial cells and provides a molecular basis for the prevention of CVDs [56–58]. Another scientific evidence is relating hydroxytyrosol to a potential risk reduction for developing type 2 diabetes mellitus [22]. Its antioxidant activity has been shown to be efficient against oxidative damage *in vitro* in retinal pigment epithelial cells, which occurs in age-related macular degeneration lesions. Moreover, an *in vivo* assay revealed that oral supplementation of EVOO and specifically hydroxytyrosol reduces brain lipid peroxidation, acting as a powerful brain antioxidant [59]. The anti-inflammatory capacity of hydroxytyrosol has been also shown against acute ulcerative colitis. Namely, patients with inflammatory bowel disease are at increased risk for developing colorectal cancer. *In vivo* studies have showed that the diet enriched in polyphenols resulted in less incidence and multiplicity of tumors [60, 61].

Hydroxytyrosol in EVOO has also shown anti-HIV activity *in vitro*. It inhibited the viral integrase enzyme and the fusion of the viral envelope with host cells [58]. It has been considered as a potential microbicide, as well. In particular, more recent studies have shown that hydroxytyrosol has a potent antimicrobial activity against *Clostridium perfringens*, *Escherichia coli*, *Staphylococcus aureus*, *Salmonella enterica*, *Yersinia* sp., and *Shigella sonnei* [53, 62].

4.1.2 Oleocanthal

Oleocanthal [63–66] is ~10% of the total phenolic content in EVOO; it has pronounced antioxidant and anti-inflammatory activity and is responsible for the pungency of the fresh olive oil. *Oleocanthal*' anti-inflammatory activity is presented by inhibition of COX-1 and COX-2, cyclooxygenase enzymes, which catalyze important steps in inflammation pathways. It has been found that it has effects similar to Ibuprofen [8, 32, 65, 67, 68]. Although *oleocanthal* and ibuprofen are not chemically similar, they have similar anti-inflammatory properties that help reduce the risk of cancer and CVDs; *oleocanthal* was found to be even more potent than ibuprofen and is more effective in preventing inflammation. Other studies have been focused on its pharmacological effects, such as in cancer and neurodegenerative diseases, including the multiple myeloma cells, as well as activation of cytoprotective pathways promoting healthy aging [22, 40, 59, 69–75].

4.1.3 Oleuropein

Oleuropein is responsible for the characteristic bitter taste of unprocessed olives [1, 33, 76–78]; it has been found to perform a wide spectra of properties: antioxidant, anti-aging, anti-inflammatory, anti-atherogenic, anti-cancer, antimicrobial, antiviral, skin- and cardio-protective. Its hypolipidemic, hypoglycemic and neuroprotective activities have been studied, too [22, 76, 77].

Oleuropein was found to be effective against various strains of bacteria, viruses, fungi, as well as molds and parasites. Moreover, it also inhibits platelet aggregation. Oral treatment with *oleuropein* resulted in a reduced number of blood vessels providing strong anti-angiogenic properties to inhibit macrophage-mediated low-density lipoprotein (LDL). There are numerous studies confirming the anticancer activity of *oleuropein*, as observed in human cancer cell lines, such as breast adenocarcinoma, melanoma, urinary bladder carcinoma, colorectal adenocarcinoma, prostate cancer, lung carcinoma, glioblastoma, renal cell adenocarcinoma, etc [22]. Several experimental studies provide strong evidence that *oleuropein* exhibits beneficial hepatoprotective effects on the liver as the liver has been identified as one of the target organs of oxidative stress [76, 79, 80].

In the section below, the protective effects of EVOO in relation to particular diseases are briefly reviewed.

4.2 Protective effects of EVOO in different diseases

4.2.1 Cardiovascular diseases

Cardiovascular diseases (CVDs) often called “silent killers,” are mostly common in urban community populations [13, 17]. Initially, the mechanism of EVOO as cardio-protector was based on the incidence on the so-called traditional risk factors (lipids and blood pressure), but the modern cardiovascular risk factors are extended to inflammation, oxidative stress, coagulation, platelet aggregation, fibrinolysis, endothelial function or lipids, or even modulation of the conditions, which are predispositions for CVDs, such as obesity, metabolic syndrome or type 2 diabetes melitus [81]. However, among the major CVD risk factors are still considered the hypercholesterolemia, hypertension, and atherosclerosis. CVD is a group of disorders such as chronic heart disease, stroke, rheumatic heart disease, peripheral arterial disease, congenital heart disease, pulmonary embolism, deep vein thrombosis and most of them proliferate in general by the accumulation of fatty deposits on the inner walls of the blood

vessels causing a blockage of blood circulation to the arms, legs, brain, or heart [7, 17]. There is an evidence that EVOO's fatty acids play an essential role in the management of CVDs and do not cause deposits and blockage in the blood vessels [3, 4, 17, 82]. Current recommendations for primary prevention of CVD highlight the importance of dietary patterns including dietary sources of healthy fats, such as those high in unsaturated fat and low in saturated fat. EVOO is a perfect example as a dietary CVD preventor due to the presence of MUFA and PUFA [3, 13, 19, 35].

It is not only the unsaturated fatty acids in EVOO, but its phenolic compounds that have shown favorable results in modulation of oxidative balance markers of CVDs. These beneficial effects of EVOO were more pronounced in healthy patients compared to unhealthy subjects. EVOO benefits were also observed in insulin sensitivity, glycaemia, modulation of transcription of genes involved in lipid and glucose metabolism, inflammation, significant reduction of oxidized LDL, increased high density lipoprotein (HDL) cholesterol levels, etc. In fact, it has been shown that EVOO lowers the total blood cholesterol, LDL-cholesterol and triglycerides, while increasing the HDL-cholesterol level, which helps fend off the formation of fatty patches, thus stimulating the elimination of LDLs. Controlled clinical trials have shown that 1% reduction in total and LDL-cholesterol concentrations results in an $\approx 1.5\%$ reduction in the incidence of CVD [3, 4, 83–87]. In addition, EVOO is capable of blunting oxidative stress by regulating the platelet oxidative stress and endothelial dysfunction. In humans, the role of EVOO as an anti-atherosclerotic nutrient is also supported by its ability to modulate expression of atherosclerosis-related genes in which LDL oxidation is involved. Another relevant mechanism of EVOO in modulation of CVDs is its anti-inflammatory effect in the vascular walls [88]. There are many long- and short-term studies that have shown that EVOO intake is also associated with a significant decrease in inflammatory markers, namely Thromboxane-B2 (TXB2) and Leukotriene-B4, which indicate EVOO's anti-thrombotic and anti-inflammatory activity in a postprandial state. Studies on subjects at high cardiovascular risk showed reduction in both blood pressure values, the systolic and the diastolic pressure [89, 90].

An inverse relationship between OO intake and coronary heart diseases' mortality and incidence has been reported within the EPIC (European Prospective Investigation into Cancer and Nutrition) cohorts [8], as well as during the PREDIMED (PREvención con Dieta MEDiterránea) study which included 7,216 men and women at high cardiovascular risk, aged 55 to 80 years [26]. The study linked EVOO and reduced risks of CVDs and mortality in individuals at high cardiovascular risk. More specifically, EVOO intake in the context of MD was associated with a reduction in the risk of CVD by 30% compared to controls subjected to low-fat-diet and reduced mortality in older high cardiovascular-risk individuals [91]. Estruch et al. have showed that EVOO consumption, but not MUFAs alone, was associated with a reduced risk of all-cause mortality, CVD events, and stroke which indicates that the minor constituents in EVOO could be also responsible for its health benefits. Furthermore, a study conducted by Guasch-Ferré et al. have suggested that 10 g/day of EVOO intake were associated with a 10% reduction in the risk of cardiovascular problems [92]. Another study suggests that EVOO is associated with lower CVD rates in people adhering to MD; in general, those consuming >0.5 tablespoon/day of olive oil had a 14% lower risk of CVD and an 18% lower risk of coronary heart disease [93].

4.2.2 Cancers

ROS have been implicated in the etiology of many cancer types; therefore a “control” over them would significantly reduce the risk of developing certain cancers [22]. There is a strong evidence that using EVOO as a main source of fats in someone's diet can suppress certain cancer types, such as breast [4, 7, 82, 90, 94],

colorectal [3, 7, 95], and prostate cancer [3, 94] due to its anti-oxidant and anti-inflammatory effects. The cancer-preventing mechanisms of EVOO, in general, are less known. It has been hypothesized that the anti-cancer actions of EVOO may relate to the ability of its MUFA-oleic acid to specifically regulate cancer-related oncogenes. In fact, oncologists have discovered that MUFA and PUFA suppress the over-expression of an oncogene HER2, which is critical to the etiology, invasion, progression, and metastasis especially of human mammary carcinoma [96, 97]. However, there is a growing interest to identify the role of phenolics from EVOO in carcinogenesis, as well. They can exert an inhibitory action on cancers, acting as blocking and/or suppressive agents at several stages of cancer progression [4, 8].

In vitro studies have reported that some phenolic compounds isolated from EVOO have anticancer activity against different types of cancers. Despite the different molecular mechanisms of the anticancer activities of EVOO phenolic compounds, it can be summarized that most of them inhibit oncogenic factors, including mutations, catalytic activities of predicted metabolic and epigenetic targets and interactions affecting DNA methylation. For instance, the inhibition of prostate cancer by hydroxytyrosol was found to be mediated by inhibition of cell proliferation, adhesion, migration, and invasion. Oleuropein has also demonstrated a chemo-preventive role in the proliferation of breast cancer cells by inhibiting estrogen-dependent signals. Oleocanthal and oleacein have reduced the viability and migration of non-melanoma skin cancer cells, while hydroxytyrosol showed no effect in this cancer type. Moreover, the metabolites produced by the degradation of EVOO phenolic compounds by gut microbiota may have a chemo-preventive effects on colorectal cancer, which is the second most common cancer-related death worldwide [45, 46, 98–102].

Another *in vitro* study of anticancer and chemo-preventive potential of EVOO's tyrosol, hydroxytyrosol and secoiridoid derivatives (oleocanthal and oleacein) on cutaneous non-melanoma skin cancer models have demonstrated that phenolic EVOO's compounds can block molecular steps that occur after the initial UV radiation exposure and before or during tumor development. Another trial investigated whether hydroxytyrosol improves the antitumor response of women with breast cancer undergoing neoadjuvant chemotherapy, influencing plasma levels of molecules involved in cell proliferation, apoptosis, and metastasis (e.g., tissue inhibitor of metalloproteinases, TIMP-1); data showed that in women receiving a dietary supplement with 15 mg/day of hydroxytyrosol combined with a specific chemotherapy treatment, the plasma levels of TIMP-1 decreased [46, 103–105]. Furthermore, EVOO induces molecular changes in tumors, such as in the composition of cell membranes, activity of signaling proteins and gene expression; all these modifications could cause lower proliferation, higher apoptosis and lower DNA damage. For example, there is a beneficial evidence of EVOO on breast cancer risk; consumption of EVOO in moderate quantities and throughout the lifetime appears to be a healthy choice and may favorably influence the breast cancer risk [4]. In another trial, the PREDIMED trial [91], part of the participants were subjected to a traditional MD supplemented with EVOO and compared to the participants subjected to the control low-fat diet. Besides the fact that the main outcome in the trial was the incidence of CVD, the incidence of breast cancer in women was included as a secondary outcome. Among 4152 women included in the analysis, women subjected to the MD supplemented with EVOO group exhibited a 68% lowest risk of incident breast cancer.

4.2.3 Other diseases

Metabolic syndrome (MS) is characterized by a cluster of interrelated markers including obesity, hyperglycaemia, dyslipidaemia and hypertension [4, 21, 42, 106–110]. EVOO's phenolic compounds have been related to the prevention

or inhibition of MS-related diseases. An *in vitro* assay has demonstrated that oleacein acts as an inhibitor of a central epigenetic regulator of metabolic reprogramming in diseases associated with obesity, neurological disorders, and cancer. Inhibitory effects were also found against enzymes related to hyperglycemia associated with hypertension [111]. Positive results were found in a two-year study on subjects with MS, showing a reduction in blood pressure values in women with moderate hypertension supplemented with EVOO versus the control low-fat diet group [112].

Positive modulation of *gut microbiota* as an approach for management of diseases has attracted a lot of scientific attention recently. High intake of phenolic compounds from dietary source, such as EVOO, appears to regulate the CVD and other risk factors, through the modulation of gut microbial populations, their activities and diversity. This is due to the fact that many plants' phenolic compounds are not totally absorbed in the mouth and gastrointestinal track and become available for microbiota utilization as an energy source. This is the case with EVOO's phenolic compounds – reaching the gut and being consumed by its microbiota. This is very important since the gut microbiota, as a key factor in driving metabolic activities, is involved in the regulation of host immunity. Thus, supporting healthy gut microbiota can help boosting the overall immunity [24, 27, 82, 113–115].

Diabetes type II (T2D) could be prevented by using EVOO due to its rich phenolic profile [11, 22, 36, 42]. The specific components of EVOO are considered as novel candidates for improving the glycaemic profile in patients with diabetes mellitus. In an interventional study, it has been shown that oleuropein lowers postprandial glycaemia by reduction of Nox2 activity in healthy subjects. Another evidence is improved glucose metabolism and reduced body weight in the PREDIMED study, thus, preventing T2D in 80 cases of new-onset diabetes cases which were subjected to the MD and EVOO group of participants. More particularly, the positive effects of polyphenols on the metabolic control and the production of specific pro-/anti-inflammatory adipokines in overweight patients with T2D have been confirmed. EVOO consumption significantly reduced fasting plasma glucose and HbA1c levels, as well as body mass index and body weight. Therefore, daily consumption of polyphenol-rich EVOO might improve the metabolic control and circulating inflammatory adipokines profile in overweight T2D patients [110].

Reports on reduction in body weight by using EVOO in the diet have also been published [90, 116, 117]. *Chronic obesity* is a situation of chronic systemic inflammation and can contribute to the development and severity of asthmatic and probably allergic diseases [11, 42]. There is a limited evidence for the EVOO effects on the body weight regarding the reduction of fat mass with consequent increases of muscle mass. However, a trial evaluating the effects of hydroxytyrosol has showed that it can modulate the adipocyte gene expression profile through mechanisms involving a reduction of oxidative stress and NF- κ B inhibition and may blunt macrophage recruitment, preventing the deregulation of pathways involved in the obesity-related diseases [11].

Antimicrobial activities have been found in olive extracts; EVOO components, like tocopherols, carotenoids, have been shown to reduce the growth of foodborne pathogens and stimulation of growth of probiotic microorganisms such as *L. Acidophilus* and *B. Bifidum* [17]. Also, EVOO phenols have been demonstrated to inhibit *in vivo* or delay the growth of bacteria, such as salmonella, cholera, pseudomonas, staphylococcus, fungi, viruses, and parasites. Furthermore, hydroxytyrosol has showed to be highly toxic to *Pseudomonas syringae* pv *savastanoi* and *Corynebacterium Michiganense*, while oleuropein can completely inhibit the growth

of *Escherichia coli*, *Klebsiella pneumoniae*, and *Bacillus cereus*. Also, the phenolics exert *in vitro* strong bactericidal activity against eight strains of *Helicobacter pylori*, which are linked to a majority of peptic ulcers and certain types of gastric cancers [8]. Therefore, there is a strong evidence of the antimicrobial effect of EVOO's phenols that successfully destroy colonies of microorganisms which may cause respiratory tract, intestinal, and genital tract infections [8, 90].

Autoimmune diseases and immune-mediated inflammatory diseases [7, 90, 118, 119] like inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, sclerosis, psoriasis, etc., can be prevented by the favorable fat profile of EVOO. But, the beneficial effects of EVOO have been attributed, besides to the MUFA content, to the presence of phenolic compounds as well due to their antioxidant, anti-inflammatory and immunomodulatory properties [118]. There are many studies that support the beneficial role of EVOO in certain inflammatory diseases; for example, the positive effects of dietary EVOO on type II collagen-induced arthritis have been reported [4, 118, 119].

Skin treatments with EVOO after burning have resulted in better wound healing; or treatment with oleuropein and olive leaf extract after UV exposure significantly inhibited increase in skin thickness, reduction in skin elasticity, skin carcinogenesis and tumor growth. Furthermore, EVOO polyphenols exerted anti-inflammatory effects on human keratinocytes suppressing the key epidermal cytokines, which have been found as a source of skin inflammation [4, 90, 120].

EVOO has been proposed to promote *healthy aging*, as it is being able to virtually modulate all the features of the aging process, because of its favorable MUFA content and its minor bioactive compounds. Polyphenols are able to modulate abnormal cellular signaling induced by pro-inflammatory stimuli and oxidative stress. In particular, oleocanthal and oleacein are scientifically proved that can activate healthy aging-promoting cytoprotective pathways and suppress the oxidative stress in mammalian cells [4, 21, 47].

5. Summary

Generation of oxidative species in the body, such as free radicals, ROS and RNS, result in oxidative stress that has been implicated in the pathogenesis of many chronic degenerative diseases and aging processes. In particular, the oxidative stress leads to structural and functional damage to the main biomolecules, nucleic acids, lipids, and proteins, which then result in development of many diseases, such as cancer, metabolic disorders, cardiovascular dysfunctions, inflammatory disorders, neurological degeneration, etc. Antioxidants can counteract the effects of the free radicals and other oxidative species, thus reducing the oxidative stress in the body. An imbalance between the production of oxidative species from one side, and the availability of antioxidants from the other side, can be detrimental for the human health. Therefore, the level and the diversity of antioxidants in the body are crucial for counteracting and neutralizing the oxidative stress. *de novo* antioxidant production in the body is limited; therefore, dietary antioxidants, such as polyphenols, carotenoids, tocopherols, tocotrienols, and others, are preferred as they are naturally bioavailable compounds easily absorbed by the human body and ready to counteract the oxidative stress. In this context, EVOO is a great source of variety of powerful and bioavailable components, such as phenolic compounds hydroxytyrosol, oleocanthal and oleuropein. The health properties of EVOO have been directly related to these phenolic compounds. *In vitro* and *in vivo* studies involving humans and animals have demonstrated that EVOO's unsaturated fatty acids and phenolic

compounds have remarkable and beneficial effects due to their pronounced anti-oxidant and anti-inflammatory activity, all acting in a synergistic way. A large body of scientific evidence has shown EVOO's effects on different pathologies, such as different types of cancers, CVDs, neurodegenerative and digestive disorders, MS and gut-related disorders.

In summary, EVOO - the hallmark of the Mediterranean diet - has been proven to have the following health and well-being benefits (**Figure 4**):

- Reduced risk of cancers,
- Improved endothelial function,
- Reduced blood pressure,
- Antithrombotic effects,
- Reduced total cholesterol level,
- Better glycemic control,
- Reduced metabolic-related diseases,
- Antimicrobial activity,
- Reduced inflammation,
- Yields rich gut microbiota,
- Supports healthy aging, etc.

Taking into account the above benefits of EVOO, it is obvious that EVOO should be used in abundance in the daily diet, as it is the case with the people adhering to the remarkable Mediterranean Diet, who are experiencing lower risks of certain diseases that could be avoided via diet. EVOO - the "*Blessed nutrient*" and the "*Elixir of youth and health*" known from the ancient times - is indeed the proof of the Hippocrates's "*Let food be thy medicine and medicine be thy food*".

Figure 4. EVOO's antioxidant and anti-inflammatory compounds efficiently neutralize the oxidative stress and fight the inflammation.

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Conflict of interest

The authors declare no conflict of interest.

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