Chapter

Beneficial Effects of Extra Virgin Olive Oil Rich in Phenolic Compounds on Cardiovascular Health

Imen Ghorbel, Mariem Chaâbane, Naziha Grati Kammoun and Najiba Zeghal

Abstract

The Mediterranean diet (Med-diet) includes a high consumption of cereals, fruits, legumes and vegetables, a moderate fish intake and a low consumption of red meat. Olive oil is a basic component of the Med-diet due to its numerous health benefits. In the last decade, many epidemiological studies have confirmed the protective role of extra virgin olive oil (EVOO) against several chronic illnesses including cardiovascular diseases. EVOO is mainly composed of triacylglycerols, with oleic acid as the dominating esterified fatty acid, and other minor compounds. Among them, phenolic compounds, such as hydroxytyrosol and its derivatives (oleuropein and tyrosol), are the principal components responsible for the cardioprotective effects. They are endowed with wide biological activities, including strong antioxidant properties, allowing the prevention of cardiovascular risk factors, such as atherosclerosis, plasma lipid disorders, endothelial dysfunction, hypertension, obesity and type 2 diabetes. The aim of the present chapter was to elucidate the beneficial effect of EVOO, as part of the Mediterranean-style diets, on cardiovascular risk factors and to discuss the underlying mechanisms by which polyphenols exert their effects.

Keywords: olive oil, phenolic compounds, cardiovascular diseases, endothelial dysfunction, atherosclerosis, type 2 diabetes mellitus

1. Introduction

The Mediterranean diet (Med-diet) is beneficial for the human health as it provides for the consumer foods rich in biological active substances. It is composed of fish, unsaturated fats, whole grains, fruits and vegetables, nuts and legumes. Olive oil has been traditionally used as the main fat in the Mediterranean regions, and recently, it has become more popular worldwide. Extra virgin olive oil (EVOO) is obtained from the fruit of the olive tree by mechanical or other physical means as follows: washing, decantation or centrifugation, and filtration. A Med-diet rich in olive oil supplies an average of 10–20 mg of phenols per day [1]. The lipophilic fraction

represents 90.0–99.0% of EVOO and it is mainly composed of phospholipids and triacylglycerols, while the hydrophilic fraction (0.5–1.5%) contains hydrocarbons, aliphatic alcohols, sterols, pigments, and several volatile and phenolic compounds [2]. Phenols are the organic molecules characterized by the existence of a hydroxyl group attached directly to the benzene ring. The major classes of phenolic compounds present in olive oil are phenolic acids, phenolic alcohols, secoiridoids, and flavonoids [3]. They have the capacity to donate the hydrogen atom of the phenolic hydroxyl group to free radicals. Hydroxytyrosol (HT), one of the main phenolic compounds of EVOO, reduces oxidative stress by improving lipid profile and inhibiting inflammatory cells [4]. The wide biological activities of HT are associated with its strong antioxidant and radical-scavenging activities [5]. HT and oleuropein, another major phenolic component of EVOO, are potent scavengers of hydroxyl radicals ($OH^{\cdot}$), peroxynitrite (ONOOH), and superoxide radicals ($O_2^{\cdot-}$) [5]. Phenols are able to modulate redox status through direct action on enzymes, proteins and different signaling pathways. The oxidative stress process plays a crucial role in the development of cardiovascular diseases (CVDs). It contributes to the pathogenesis of atherosclerosis, endothelial dysfunction, plasma lipid disorders and hypertension. It has been reported that EVOO has beneficial effects on cardiovascular risk factors, such as coagulation, platelet aggregation, fibrinolysis, endothelial dysfunction and lipid metabolism alteration [6]. Moreover, EVOO shows potential actions on markers of inflammation related to CVD, such as interleukin 6 and C-reactive protein [7].

The aim of the present chapter was to present some evidence from previous studies demonstrating the beneficial effect of EVOO, as part of the Mediterranean-style diets, on cardiovascular risk factors, namely atherosclerosis, plasma lipid disorders, endothelial dysfunction, hypertension, obesity and type 2 diabetes mellitus (T2D), and to discuss the underlying mechanisms by which polyphenols exert their effects.

2. Phenolic compounds present in EVOO

In olive oil, both simple and complex phenolic compounds contribute to its stability and affect its sensory properties. Polyphenols are a large and heterogeneous group of phytochemicals containing phenol rings. According to Bajoub et al. [3], the most abundant phenolic compounds can be classified according to their chemical structure as follows: secoiridoids (oleuropein, oleuropein aglycone, oleocanthol), simple phenols (tyrosol, HT), lignans (pinoresinol, syringaresinol), flavonoids (luteolin, apigenin) and phenolic acids (**Figure 1**). It has been demonstrated that the variability of those phenols can be related to a combination of agronomic and technological processes [8]. Indeed, once ingested, olive oil polyphenols give rise to different metabolites which are able to reach tissues and exert their beneficial effects [9]. Natural phenols have been demonstrated to modulate cell redox status through direct actions on enzymes, proteins, receptors and different signaling pathways [10, 11].

3. EVOO polyphenols and CVD

In recent years, several studies have demonstrated the cardiovascular health benefits associated with the regular consumption of olive oil with a high polyphenol content. Hence, understanding the mechanisms contributing to the favorable effect

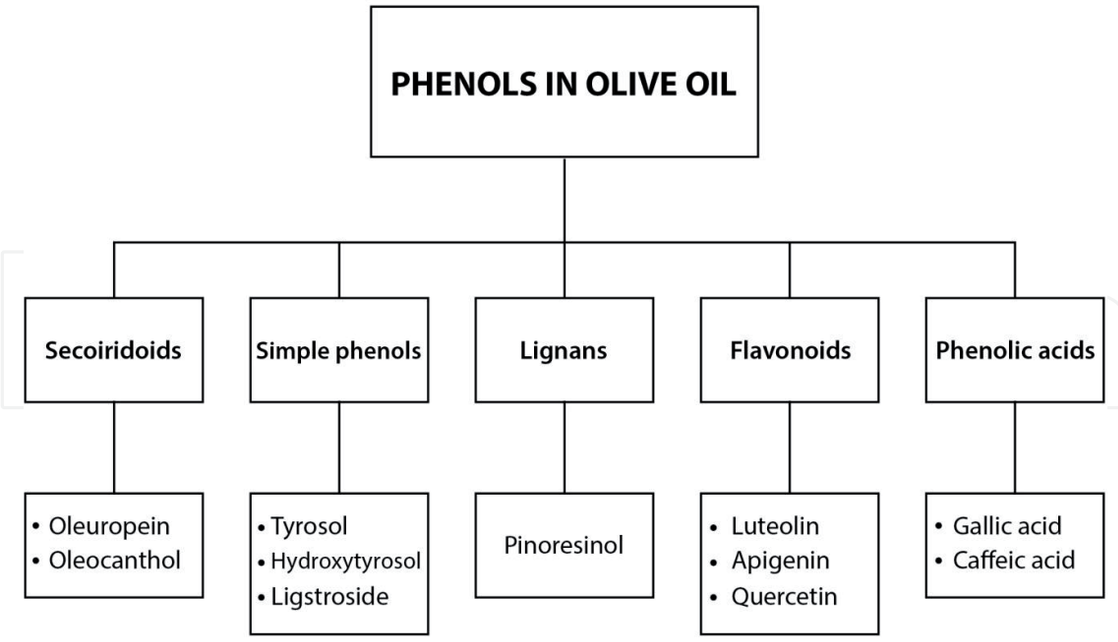

Figure 1.
The phenolic compounds present in olive oil.

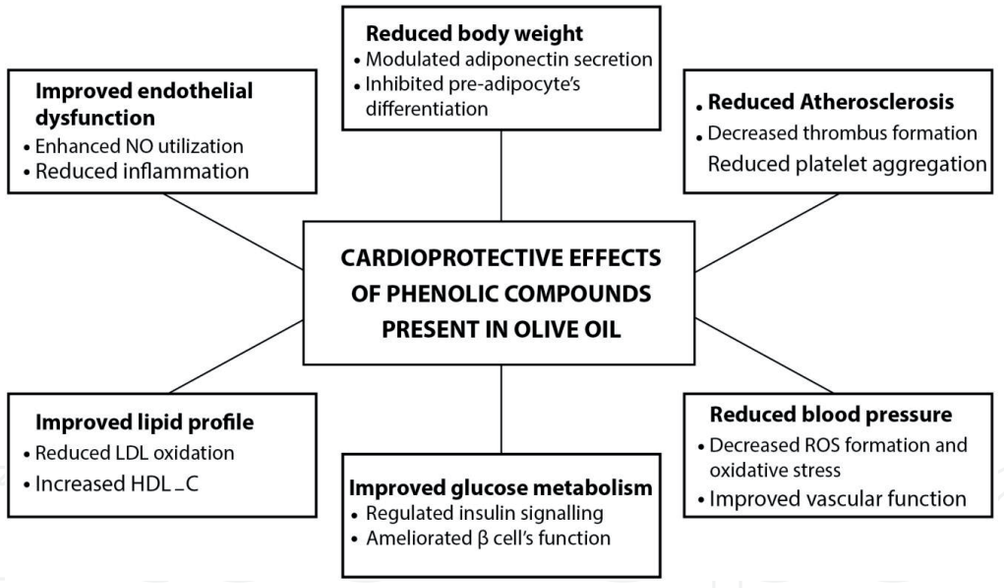

Figure 2.
Cardioprotective effects of phenolic compounds present in olive oil.

of these bioactive compounds is of crucial importance. In this setting, the main mechanisms responsible for the cardioprotective effects of olive oil polyphenols against atherosclerosis, plasma lipid disorders, endothelial dysfunction, hypertension, obesity and T2D will be reviewed (**Figure 2**).

3.1 Polyphenols and atherosclerosis

It has been known that several CVD are directly related to thrombus formation [12]. The oxidative stress process, an imbalance between reactive oxygen species

(ROS) production and endogenous antioxidant defense system, plays a crucial role in the development of heart diseases. An excessive production of ROS causes oxidative damage to the vascular endothelium [13] by promoting vascular cells proliferation, apoptosis, and necrosis which may result in the formation of atherosclerotic plaques leading to thrombosis [13, 14]. The uncontrolled ROS formation alters the vascular tone, which is mediated by a decrease of nitric oxide (NO) bioavailability, the most potent endogenous vasodilator [15]. A low NO level is associated with the promotion of platelet aggregation, adhesion of inflammatory cells and fibrinolysis which are responsible for the developmental process of atherosclerotic plaques [16]. Olive oil intake contributes to the homeostasis of the thrombogenic profile by improving the production of coagulation factors and biomarkers related to platelet aggregation [17]. Oleuropein and HT have been shown to exert several protective effects *in vivo* on a model of atherosclerosis inhibiting endothelial activation and monocyte-endothelial cell adhesion [18]. Besides, these simple phenolic compounds have been described as the potent inhibitors of platelet aggregation in several *in vitro* experiments [19].

3.2 Polyphenols and plasma lipid disorders

Plasma total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels are included in CVD risk assessment tools. The elevated levels of TC and LDL-C have been considered as risk factors for atherosclerosis, which is the primary cause of CVD. LDL-C is the main carrier of circulating cholesterol to the target vascular cells. Consequently, circulating LDL-C is a valuable indicator of the amount of lipid accumulation in the arterial wall. Their oxidation is considered to be the triggering factor for the biochemical processes leading to atherosclerotic plaque formation in the sub-endothelial space [20]. Apolipoprotein B (Apo B) is the primary protein component of LDL-C, while apolipoprotein A (Apo A) is the primary protein component of HDL-C. Polyphenols affect apolipoproteins (Apo) A and B, modify LDL-C particles, and reduce plasma triglyceride (TG) levels by increasing the lipoprotein lipase activity, which decreases LDL-C concentrations in the blood circulation [21, 22]. The mechanism by which polyphenols reduce hepatic Apo B production relies on their binding with the plasma membrane transport P-glycoprotein, which inhibits cholesterol esterification [23]. The administration of EVOO phenols to rats co-exposed to aluminum and acrylamide leads to the improvement of their blood lipid profile by reducing TC and increasing HDL-C levels [11]. It has been reported that oxidized LDL-C concentration decreases after a high-phenolic olive oil intake [24]. Moreover, the 3-month consumption of a Med-diet supplemented with virgin olive oil reduces TC and LDL-C and increases HDL-C in high-cardiovascular-risk participants [25].

3.3 Polyphenols and endothelial dysfunction

Endothelial cells are able to synthesize molecules, such as NO and endothelin 1 (ET-1), substances with vasodilator and vasoconstrictor activities, respectively [26, 27]. An imbalance between vasodilating and vasoconstricting molecules induces endothelial dysfunction. At the cellular level, ROS can neutralize the vasodilator NO, inactivate protein tyrosine phosphatases, increase intracellular free calcium concentrations, and act as second messengers within redox-dependent signaling pathways [28]. Endothelial dysfunction, a critical event in the development of hypertension, is controlled by several vasoactive peptides such as angiotensin II and endothelin-1 [29].

The high content of phenolic compounds present in EVOO may slow the atherogenic process by inhibiting oxidative damage and restoring endothelial function. In fact, EVOO phenols decrease endothelial NO synthase phosphorylation, and consequently intracellular NO levels, and increase endothelin-1 synthesis in ECV304 cells incubated with high glucose and fatty acid concentrations [30].

3.4 Polyphenols and hypertension

Hypertension is a serious medical condition characterized by a persistent elevation of the blood pressure in the arteries and reflects a hypersensitivity of the vascular smooth muscle to vasoconstrictor stimuli [31]. It corresponds to a systolic blood pressure (SBP) of 140 mmHg or more and/or to a diastolic blood pressure (DBP) of 90 mmHg or more [32]. It is recognized as one of the strong causes leading to cardiovascular stroke and myocardial infarction [33]. Oxidative stress has been shown to be the fundamental mechanism responsible for hypertension [34]. Other factors, such as inflammation, endothelial dysfunction and vascular remodeling, have been also documented as key contributors to this condition [33]. Reactive oxygen species are involved in the homeostasis of the vascular wall, and particularly in the modulation of the vasomotor system. Superoxide anion can even play the role of a vasoconstrictor agent and it can rapidly react with NO, decreasing the bioavailability of this vasodilator molecule [35]. Enhanced ROS generation and reduced NO levels, in addition to reduced antioxidant status, have been reported in hypertensive humans and animals [36, 37].

On the other hand, several studies have demonstrated that olive oil polyphenols have vasoprotective effects on blood pressure. Moreno-Luna et al. [38] have shown that the daily intake of a polyphenol-rich olive oil diet during 8 weeks is effective in reducing peripheral SBP and DBP in young women with mild hypertension. Recently, Sarapis et al. [39] have reported a decrease in both central and peripheral SBP in healthy adults after the daily consumption of EVOO with high polyphenols content during 3 weeks. The anti-hypertensive effects of olive oil have been mainly attributed to its phenolic compounds. In fact, administration of isolated polyphenols from olive oil, like oleuropein, has shown a positive correlation with the improvement of the hypertensive state [40]. Several mechanisms have been proposed for the blood-pressure lowering effects of olive oil polyphenols. They include, for example, suppression of the oxidative stress and inflammatory processes, enhancement of the endothelial synthesis of NO [38], and modulation of the expression of genes connected to the renin–angiotensin system [41].

3.5 Polyphenols and obesity

During the past few decades, obesity has been considered as a chronic disease resulting from multiple interactions between genetic and lifestyle factors. It is characterized by an increase in the number and size of adipocytes in adipose tissue leading to the development of T2D, CVD and hyperlipidemia [42]. Adiponectin, a major adipocyte -secreted adipokine, is abundantly present in the circulation of healthy humans exerting anti-diabetic and anti-inflammatory activities [43]. In obese individuals, its levels are decreased through mechanisms involving chronic inflammation, oxidative stress and atherosclerosis, which are factors responsible for the development of CVD [43]. Therefore, dietary strategies are effective in modulating adiponectin secretion by the improvement of inflammation-associated

adipocyte dysfunction to reduce the risk of obesity-related CVD. Previous studies have suggested that olive polyphenols can inhibit pre-adipocyte differentiation, suppress lipogenesis, induce lipolysis, and regulate adiponectin secretion [44, 45]. HT, at nutritionally relevant concentrations, induces adiponectin down- regulation in human adipocytes through the attenuation of adipogenesis- related genes (JNK-mediated PPARγ) expression [43]. Additionally, Drira et al. [45] have reported that HT and oleuropein at concentrations of 100 and 150 μM and 200 and 300 μM respectively, reduce pre-adipocyte differentiation and lipid accumulation and thus regulate the size of fat cells on 3T3 –L1 cells. It has been proposed that oleuropein may diffuse through the lipid bilayer of the cell membrane and may be absorbed via a glucose transporter [46]. These data indicate that EVOO phenols may play a protective role against excessive fat accumulation by inhibiting the differentiation rate of adipocytes and down-regulation of the adipogenesis-related genes. Therefore, olive oil polyphenols have great effects on the adipogenesis process and can be helpful in the prevention and treatment of obesity-related metabolic and CVDs in humans.

3.6 Polyphenols and diabetes

Diabetes is a chronic metabolic disease which can affect over time the entire body, and particularly the cardiovascular system. Compared to non-diabetic subjects, people suffering from diabetes, notably type 2 diabetes (T2D), have an increased chance of developing CVD [47]. Furthermore, cardiovascular complications represent the main cause of mortality among diabetic patients [48]. These complications can be manifested at the vascular and the cardiac levels. The key pathologic diabetic pathways affecting the vasculature include oxidative stress, alteration of vascular progenitor cells, microvascular dysfunction and impairment in reverse cholesterol transport [49]. Diabetes can also predispose the myocardium to specific structural and functional damages, a condition known as diabetic cardiomyopathy (DCM) in diabetic patients. Several molecular events are known to trigger DCM such as alterations in the metabolism of glucose, ketones, fatty acids and amino acids, impairment of insulin signalling, calcium mishandling, oxidative stress and inflammation [50].

Growing evidence from human and animal researches supports the positive outcome of olive oil consumption, especially EVOO, on diabetes management. Results from the "Prevención con Dieta Mediterránea" (PREDIMED) study have shown a lower incidence of T2D mellitus with an increasing adherence to a Med-diet rich in EVOO in patients at high CVD risk [51]. Also, a Med-diet supplemented with virgin olive oil has been observed to improve glucose metabolism and insulin sensitivity in subjects with T2D [52]. Besides, the daily intake of a polyphenol-rich EVOO during 8 weeks has been demonstrated to significantly reduce the levels of fasting plasma glucose and circulating inflammatory adipokines (cytokines involved in glucose metabolism) in overweight patients with T2D [53]. In an animal study performed on T2D mice, EVOO administration for 24 weeks has been reported to lower fasting glycemia, insulinemia and insulin resistance and to ameliorate β-cells' function [54]. It has been suggested that polyphenols present in EVOO may contribute significantly to its protective role against diabetes [53, 55]. Among them, HT and oleuropein have been demonstrated to display anti-diabetic actions in both *in vivo* and *in vitro* studies [56–58]. Polyphenols might influence glucose metabolism through reducing the digestion and the intestinal absorption of dietary carbohydrates, stimulating insulin secretion, and improving glucose uptake in the tissues by modulating intracellular signaling [59]. Due to their antioxidant properties, these bioactive compounds could

also inhibit the formation of advanced glycation endproducts, which results in the protection of pancreatic β-cells against glucotoxicity [60].

4. Conclusions and future perspectives

In summary, multiple beneficial effects on CVD risk factors have been associated with the consumption of Med-diet patterns rich in EVOO. The cardioprotective effects of polyphenols present in olive oil are mediated through the inhibition of atherosclerosis, hypertension, obesity and diabetes, amelioration of the plasma lipid profile and improvement of the endothelial function. The consumption of a Med-diet supplemented with olive oil is therefore recommended, as it could serve as a functional food beyond basic nutrition. Further efforts are needed to elucidate the pharmacokinetics and pharmacodynamics underlying the potential effect of EVOO phenolic compounds and the dose-dependence of their effects in humans.

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