Chapter

Anti-Cancer and Cardiovascular Properties of Phenolic Compounds Present in Virgin Olive Oil

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Abstract

Cancer and cardiovascular diseases (CVD) are the leading cause of death worldwide. Furthermore, current cardiovascular and cancer therapy is accompanied by various side effects, which considerably reduce the quality of life. Epidemiological studies suggest that the Mediterranean diet has been related to a lower risk of non-communicable diseases such as CVD and cancer. This lower incidence has been partially attributed to the regular intake of virgin olive oil (VOO) which is the main fatty component of the traditional Mediterranean die. In addition to monounsaturated fatty acid, VOO contains various phenolic compounds, which have shown a broad spectrum of pharmacological properties due to their antioxidant activity. This chapter summarizes current knowledge on the effects of the main phenolic compounds isolated from VOO on different cancers and CVD as well as the plausible action mechanisms involved.

Keywords: olive oil, phenolic compounds, cancer, cardiovascular disease, health benefits

1. Introduction

Cardiovascular diseases (CVD) and cancer, which are the main causes of morbidity and death worldwide, occurring as a result of complex factors such as stress, hypertension, hypercholesterolemia, obesity, smoking, inadequate diet and physical inactivity [1]. In addition, current anti-cancer and cardiovascular therapy is based on conventional drugs that have limited effectiveness and adverse side effects such as toxicity of chemotherapeutic drugs on normal cells and reduction of the quality of life. Thus, the need for newer and more effective drugs for the management of cancer and CVD is of great interest. Several epidemiological studies have shown a lower incidence of CVD and certain kinds of cancer in the Mediterranean region due to the Mediterranean diet (MD) which is rich in vegetables, cereals, fruit, fish, and olive oil [2]. In addition, several epidemiological studies suggested that olive oil intake is involved in preventing various cancers as well as CVD mortality and incidence [3–7]. In this sense, a clinical study by Estruch et al. reported that the consumption of 50 mL/day of extra-virgin olive oil (EVOO) reduced the incidence of major cardiovascular events [8]. Besides the traditional benefits on the high level of monounsaturated fatty acid provided by olive oil intake, a broad spectrum of benefits on cardiovascular risk factors and cancer is

now emerging associated with olive oil consumption [9]. Thus, the anticancer and cardioprotective properties of olive oil seem to correlate with the antioxidant and anti-inflammatory activity of multiple minor components such as hydroxytyrosol, tyrosol, and their secoiridoid derivatives. Further research have shown that olive oil phenolic compounds exert a possible chemoprotective and anticancer effects in different types of cancers such as breast cancer [10, 11], colon [12], prostate [13] and melanoma [14]. These phenolic compounds exist mainly in extra virgin and VOO and give the oil its health properties. The huge number and variety of phenolic compounds in olive oil might explain the unique health benefits of this culinary oil [15].

2. Virgin olive oil in the Mediterranean diet

The traditional MD contains a considerable proportion of fruits, vegetables, cereals, fish, milk and olive oil. VOO represents the main dietary source of fat in the MD [16]. Olive oil is a flavorsome, tasty and nutritious edible fat obtained directly from pressing ripe olives. Intake of olive oil in the Mediterranean countries is estimated to be 30–50 g/day in Greece, Italy, and Spain. Evidence supports the hypothesis that the health benefits properties of the MD and its ability to reduce the incidence of some degenerative diseases, such as CVD and cancer, may be attributed, at least in part, to VOO [5]. Historically, the high nutritional quality and the health benefits effects of EVOO intake were first attributed to the high concentration of monounsaturated fatty acids [17, 18]. However, greater attention has recently focused on a fraction of minor components (about 2% of oil weight), such as phenolic compounds which have a strong antioxidant activity [19]. These compounds are responsible for EVOO oxidative stability and sensorial properties (such as bitterness and pungency) [20].

3. Phenolic compounds present in virgin olive oil

Olive oil is composed of two fractions, the saponificable and the nonsaponificable fraction. The main constituents of the saponificable fraction are triglycerides (98–99%). The nonsaponificable fraction (1–2%) contains the minor constituents of olive oil such as tocopherols, sterols, chlorophylls, carotenoids, alcohols, waxes, aldehydes, esters, ketones and phenolic compounds [21].

The beneficial effects of the MD are mainly attributed to the antioxidant property of olive oil phenolic compounds. EVOO contains much higher amounts of polyphenols than common olive oil. The phenolic concentration in EVOO ranges from 50 to 800 mg/kg [22]. Phenolic compounds identified in EVOO includes three categories: simple phenols (such as vanillic, gallic, coumaric and caffeic acids, tyrosol and hydroxytyrosol), secoiridoids (such as oleuropein, oleocanthal, and oleacein), and lignans (1-acetoxypinoresinol and pinoresinol) [23]. Secoiridoid derivatives are the most abundant phenols in olive oil. Hydroxytyrosol and tyrosol, which originate from the hydrolysis of oleuropein, are part of the phenolic alcohol group. There is approximately 2 grams of hydroxytyrosol per 100 grams of olive [24]. The concentration of hydroxytyrosol and tyrosol increases as the fruits ripen, in parallel with the hydrolysis of compounds of higher molecular weight, while the total amount of phenolic compounds and α-tocopherol decreases as the fruits ripen [18, 25–27]. Hydroxytyrosol and tyrosol have been the subject of numerous investigations. To date, more than 36 phenolic compounds have been isolated from

EVOO and identified, although they are present at very different concentrations (0.02–600 mg/kg) [28]. Oleuropein is the main polyphenol found in olive oil, both in this form and as the aglycone. It has been shown that the oleuropein content is higher in the first stages of fruit maturation and in green cultivars than in black olives [18]. The phenolic compounds are mainly responsible for the organoleptic characteristics (aroma and flavor) [29, 30] and oxidative stability of the olive oil [31, 32]. The concentration of phenolic compounds in VOO is influenced by a number of factors such as the area of growth, the climate, the variety, the ripeness of the olive, the olive storage and maturation conditions, the production process and the olive tree age [33, 34].

4. Cardiovascular properties of olive oil phenolic compounds

Cardiovascular diseases are a leading cause of death and disability worldwide. They include a group of disorders such as coronary heart disease (CHD), cerebrovascular disease, peripheral arterial disease, pulmonary embolism, rheumatic heart disease, and congenital heart disease and deep vein thrombosis. Several cardiovascular risk factors, such as hypertension, dyslipidemia, diabetes mellitus, obesity and smoking, cause endothelial dysfunction, which lead to the onset of the inflammatory process in atherosclerosis [35]. Remarkably, these pathologies can be largely preventable since unhealthy diet contributes to nearly 80% of risk factors [36, 37]. In this sense, the low rate of cardiovascular mortality found in southern European-Mediterranean countries, in comparison with other westernized countries, despite a high prevalence of coronary heart disease risk factors could be attributed to the olive oil consumption. In addition, numerous randomized clinical trials have shown that consumption of olive oil is associated with beneficial effects on different cardiovascular biomarkers, such as blood lipids, blood pressure, inflammation and thrombosis [38]. Many authors have reported that VOO exerts a preventive effect against CVD [4, 9, 39] by improving many CVD risk factors including blood pressure, glucose metabolism and antithrombotic profile [40]. As evidenced by various scientific studies, the major beneficial properties of VOO have been attributed to the antioxidant of its phenolic compounds. In fact, it has been shown that increased oxidative stress is associated to the pathogenesis of various risk factors of CVD including hypertension, diabetes, platelet hyperactivity and atherosclerosis [41]. Guasch-Ferré et al. [40] found that greater consumption of total olive oil, especially EVOO (rich in phenolic compounds repetition), was associated with reduced CVD: each 10 g/d increase in total olive oil consumption is associated with a 16% reduction in cardiovascular mortality. Low-density lipoprotein (LDL) oxidation plays a critical role in the development of atherosclerosis and coronary heart disease. Various *in vitro* and *in vivo* studies have shown that the polyphenolic compounds of EVOO play an important role in the prevention of atherosclerotic damage through their inhibition of LDL oxidation [42–45].

Another important risk factor for the onset of atherosclerosis is a high blood concentration of cholesterol and particularly LDL cholesterol. The 3-hydroxy 3-methylglutaryl (HMG)-CoA reductase is an enzyme involved in the synthesis of cholesterol. Some studies have focused attention on the effect of the polyphenolic compounds from VOO on the activity of HMG-CoA reductase. It has been demonstrated that the activity of HMG-CoA reductase decreased significantly in the liver microsomes of rats fed with polyphenols extracted from VOO [46]. The inhibition of HMG-CoA reductase by VOO phenolic compounds may thus play an important

role in the prevention of CVD. Other research has shown that hydroxytyrosol can prevent CVD by reducing the expression of adhesion molecules on endothelial cells and preventing the oxidation of LDL [47].

Summarizing, the data indicate that olive oil phenolic compounds are associated with a beneficial impact on CVDs. Clinical studies confirm these beneficial effects as shown by the reduction by olive oil polyphenols intake of the inflammatory processes involved in degenerative and chronic diseases such as CVD and cancer.

5. Anti-cancer effects and molecular mechanisms induced by olive oil phenolic compounds

Cancer is a growing health concern worldwide, especially associated with unhealthy lifestyle and physical inactivity. Natural compounds can provide a real benefit as a chemopreventive and/or treatment of this complex disease. EVOO seems to have a protective effect against cancer. Actually, different authors have stated the cancer lowered incidences to olive oil intake, at least in part. The anticancer properties of olive oil polyphenols have been confirmed in several studies. In fact, several epidemiologic studies demonstrated an inverse association between the consumption of olive oil and a reduced risk of different types of cancers such as breast [48–50], prostate [51], lung [52], laryngeal [53], colorectal [54] and ovarian [55] cancer. Numerous studies have investigated the anticancer effect of olive oil phenolic compounds using different experimental models. For instance, the olive oil phenolic (−)-oleocanthal (OLCT), a natural compound present in EVOO, has recently been reported to exert anti-cancer activity in a variety of human cancer types. Recently, our research group investigated the role of OLCT in the development of different cancer hallmarks including proliferation and migration in triple negative MDA-MB-231 cells, as well as in the regulation of intracellular Ca^{2+} homeostasis. Our results indicate that OLCT induced selective anti-proliferative and anti-migrative effect on the triple negative MDA-MB-231 and the luminal MCF7 cell lines, without having any effect on the non-tumoral MCF10A cells. Furthermore, we demonstrated for the first time selective activation of TRPC6-dependent Ca^{2+} influx and TRPC6 downregulation by olive oil-derived OLCT in breast cancer cell lines, which might be responsible for the inhibitory effects of OLCT on cell proliferation and migration [56]. Additionally, several lines of evidence suggest that OLC is active against different types of cancers including hepatocellular carcinoma, multiple myeloma and breast, prostate and pancreatic cancer [10, 57, 58]. The anticancer molecular mechanisms of OLC (comprehensively reviewed in [59]) may involve various cellular signaling pathways such as modulation of the apoptotic pathway and inhibition of the HGF/c-Met and the STAT3 signaling pathways. Mechanisms of anticancer activity of olive oil phenolic compounds are summarized in **Figure 1**.

A recent trial evaluated the *in vitro* anticancer and chemopreventive potential of two EVOO extracts (tyrosol and hydroxytyrosol) and secoiridoid derivatives (oleocanthal and oleacein) on cutaneous non-melanoma skin cancer models. Results demonstrated that phenolic EVOO extracts can block molecular steps that occur after the initial UV radiation exposure and before or during tumor development. In particular, these results indicated that secoiridoid derivatives contribute more than simple phenols to the mechanism of action of EVOO extracts [60]. In a recent review, Farooqi et al. reported that oleuropein acts as an anticancer agent by several cellular mechanisms, such as targeting HER2, epigenetic modifications,

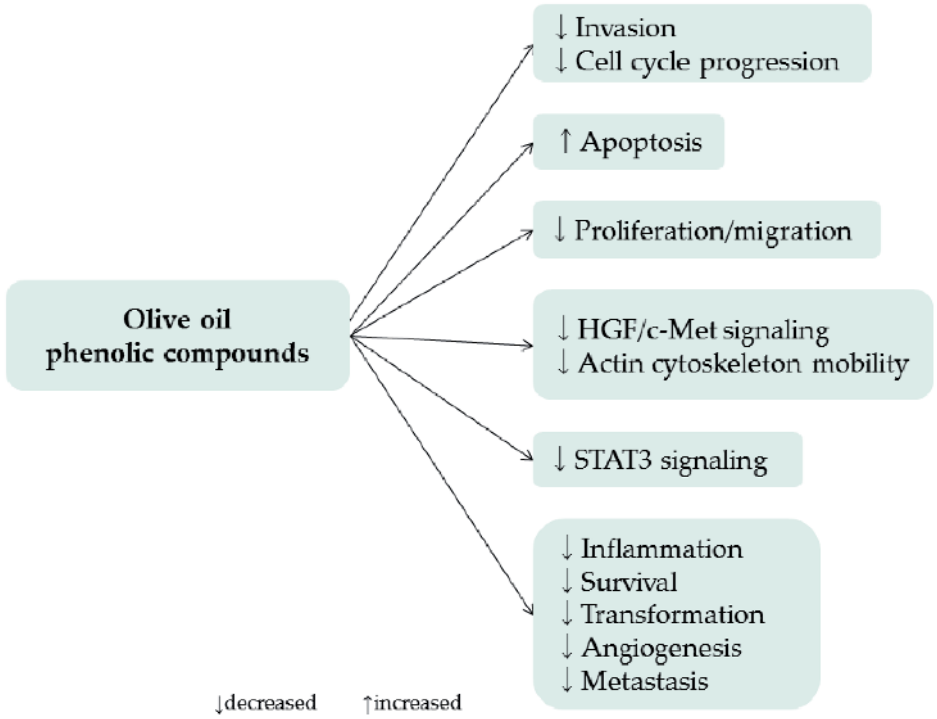

Figure 1.
Anticancer mechanisms of phenolic compounds from olive oil.

interfering with MAPK pathway, modulation of apoptosis and PI3K/AKT signaling axis as well as by reducing ROS production in different cell types [61]. Furthermore, it has been demonstrated that hydroxytyrosol induced apoptosis and cell cycle arrest in cancer cells [47].

6. Conclusion

The protective and preventive benefits of regular consumption of olive oil as part of a healthy diet have been largely documented by various scientific works. As an important component of the MD, olive oil has shown to provide more beneficial health effects to those induced by other vegetable oils.

The literature data showed that normal consumption of EVOO or VOO, which is rich in bioactive compounds, is associated to lower incidence of numerous non-communicable ailments such as CVD and certain types of cancer. The pharmacological properties of olive oil have been attributed not only to its high content of triglycerides but also to the minor fraction of polyphenolic compounds such as tyrosol, hydroxytyrosol, oleuropein and oleocanthal. In fact, these compounds have been shown to exert protective and preventive action against CVD and cancer, particularly through their potent antioxidant and anti-inflammatory activity. Furthermore, olive oil phenolic compounds have been reported to reduce several risk factors of CVD and cancer such as diabetes mellitus, hypertension, dyslipidemia and obesity.

As we have seen, the protective and the preventive effects of olive oil and/or its phenolic compounds against CVD and cancer seem to be pretty encouraging. However, more *in vivo* studies and clinical trials are still necessary to verify the beneficial effect of olive oil on human health.

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Conflict of interest

The author declares no conflict of interest related to this research.

Abbreviations

CVD	Cardiovascular disease
EVOO	Extra-virgin olive oil
HGF	Hepatocyte growth factor
HMG-CoA	Hydroxy-méthyl-glutaryl-coenzyme A
LDL	Low-density lipoprotein
MD	Mediterranean diet
OLCT	(−)-oleocanthal
STAT3	Signal transducer and activator of transcription 3
VOO	Virgin olive oil

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