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Health Benefits of Traditional Culinary and Medicinal Mediterranean Plants

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Abstract
The Mediterranean diet is rich in fruits and vegetables, monounsaturated fatty acids from olive oil, and is complemented with the traditional use of culinary and medicinal herbs and spices. An important feature of this diet is the negative association with the incidence of metabolic syndrome, which is characterized by increased risk of cardiovascular disease. Conformity to the Mediterranean diet has also been linked to a decreased risk of cardiovascular disease and cancer in US populations. Plants that originated in the Mediterranean basin have been used for centuries in botanical therapies. Many of these plants are believed to prevent and/or cure a wide spectrum of ailments based on their content in bioactive components that exert anti-oxidant, anti-inflammatory, anti-carcinogenic, anti-diabetic, and anti-thrombotic functions. This chapter underlines the health benefits that may derive from utilization through dietary assumption or medicinal applications of a selected group of plant products including extracts and specific bioactive components found in rosemary, licorice, chamomile, and olive oil. Each section provides a scientific analysis of the most recent literature and attempts to highlight the mechanisms of action and molecular targets of bioactive components derived from these plants.

Keywords: Mediterranean plants, health, disease, culinary, medicinal

INTRODUCTION
In recent history, the Mediterranean diet has been the subject of much interest because of its association in Mediterranean populations with reduced incidence of some chronic diseases including cancer, coronary heart disease (CHD), and cardiovascular disease (CVD), which represent in industrialized
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countries, ~75% of deaths for individuals of age 65 and older [1]. The beneficial effects of the Mediterranean diet have been ascribed at least in part to high intake of antioxidants from fruits and vegetables, nuts, the prevalent consumption of monounsaturated fatty acids from olive oil, a moderately high intake of fish, and a regular but moderate intake of wine primarily during meals [2,3]. The health benefits of the Mediterranean diet have also been attributed to ingestion of a variety of botanical preparations from herbs and spices, which provide rich sources of flavor-giving and bioactive components including phenolic compounds that possess antioxidant properties [4]. The literature concerning the cultivation and culinary use of vegetables, herbs, and spices in the Mediterranean area date back to the ancient Egyptian, Greek, and Roman civilizations [5]. In modern history, there has been an increasing research focus to define the health benefits of dietary constituents found in traditional Mediterranean foods [6] with the objective of identifying bioactive components and develop strategies for their functional use in preventive medicine and maintenance of health [7, 8]. Traditionally, herbs are referred to as leafy parts of plants, whereas the term spices is generally adopted for preparations from roots, seeds, root bark, berries, flower parts, fruits, or other plant parts. The main objective of this chapter is to discuss the health benefits of a selected group of traditional culinary and medicinal Mediterranean plants for which we deemed sufficient scientific literature information is available to support their potential use in food preparations or for preventative and therapeutic applications (Table 26.1). Purposely, we have not covered vegetables and herbs that have been covered extensively in previous scientific reviews and limited our focus to selected traditional Mediterranean plants. Specific emphasis is given to the profile of bioactive components; the chemistry and mechanisms of action of bioactive compounds; the health benefits associated with intake; potential toxicity; and recommendations for consumption.

ROSEMARY

Rosemary (Rosmarinus officinalis Linn. Family Labiatae) is a perennial plant native of the Mediterranean area. Rosemary extracts are used routinely for cooking, preservation of foods, cosmetics, or in herbal medicine for anti-inflammatory and antimicrobial applications [9, 10], and for the prevention and treatment of diabetic and cardiovascular diseases [11]. At least 30 components have been identified in essential oils, which have been shown to possess olfactory properties that influence cognitive performance including memory [12]. Rosemary extracts contain many bioactive components including phenolic mono-terpenes (α-pinene, camphene, limonene) [13], diterpenes (carnosic acid, carnosol), flavones (genkwanin, isoscutellarein 7-O-glucoside), and caffeoyl derivatives (rosmarinic acid). The highest accumulation of these groups of compounds occurs in leaves and it is related to young stages of plant development.
### TABLE 26.1 Mediterranean Plants and Health Benefits

| Plant extracts and bioactive food components | Health benefits | References |
|---------------------------------------------|-----------------|------------|
| **Rosemary** (*R. officinalis*) | Anti-oxidant | 15, 18, 19 |
| **Extracts** | Reduced hepato-toxicity | 20 |
| | Anti-viral (*H. simplex*) | 25 |
| | Anti-microbial (*H. pylori*) | 26 |
| | Anti-thrombotic | 28 |
| | Food packaging | 55–57 |
| **Rosmarinic acid** | Epidermal anti-inflammatory | 34 |
| | Anti-allergic | 35, 36 |
| | Inhibits angiogenesis | 37 |
| **Carnosol, Carnosic acid** | Anti-oxidant, anti-inflammatory | 41, 42 |
| | Anti-diabetic | 50 |
| **Licorice** (*G. glabra*) | Anti-inflammatory, anti-allergenic | 67 |
| **Extracts** | Anti-viral | 59 |
| **Glycyrrhizic acid** | Inhibits cortisol metabolism | 63 |
| **Isoliquiritigenin** | Anti-oxidant | 68 |
| **Chamomile** (*M. recutita* and *A. nobilis*) | Treatment of gastro-intestinal spasm, anti-inflammatory, bacterial skin disease, wound healing | 65, 72, 79 |
| **Extracts** | | |
| **Apigenin** | Anti-cancer | 74 |
| **Olive oil** (*O. europaea*) | Cardio-protective | 99 |
| **Extracts** | Anti-oxidant, anti-inflammatory | 97, 100 |
| **Oleic acid, phenolic compounds** | Reduce hypertension, anti-thrombotic | 108–110 |
| | Anticancer (prostate, breast, colon, oral cavity) | 114–117 |
| | Anti-diabetic | 126 |

In general, rosmarinic acid is present at the highest concentration in all rosemary plant organs. Carnosic acid and carnosol are found in stems during young stages, but their concentrations decrease in the vascular system following aging. However, high levels of phenolic diterpenes and rosmarinic acid are found in flowers as a result of *in situ* biosynthesis and transport from other plant organs. Rosemary extracts in both aqueous and lipid medium have been shown to possess antioxidant activity, which is due to the presence of a catechol group in the aromatic ring of the phenolic terpenes, and catechols conjugated with a carboxylic acid group in rosmarinic acid. Interestingly, rosmarinic acid is more effective as antioxidant in bulk oil whereas carnosol and carnosic acid perform better in oil-in-water emulsions. These differences in antioxidant efficacy have been attributed to interfacial partitioning of these compounds [15].
Many studies have investigated the health benefits of extracts from rosemary plants and documented that extracts exhibited protective effects against oxidative damage to DNA by scavenging hydroxyl and singlet oxygen radicals [16], and prevented the activation of carcinogens by members of P450 family of metabolizing enzymes while increasing detoxification [17, 18]. Aqueous extracts of the young sprouts of rosemary were found to exert anti-lipoperoxidant activity, and protected against radiation-induced hepatotoxicity in Swiss albino mice [19]. Similarly, the oral administration (250 mg/kg body weight) of rosemary extracts to male Sprague-Dawley rats reduced tetrachloride-induced acute hepatotoxicity [20]. Moreover, dietary rosemary extracts at doses ranging from 0.5% to 1.0% were reported to suppress the binding of dimethylbenz[a]anthracene (DMBA) metabolites to DNA in female Sprague-Dawley rats [21, 22], DNA damage by the carcinogen benzo[a]pyrene [23], and at doses of 500 mg/kg body weight DMBA-induced skin tumors in mice [24]. Exports of rosemary have also been shown to possess antiviral effects against Herplex simplex [25] and inhibited the growth of the gram-negative bacterium Helicobacter pylori, which is recognized as the primary etiological factor in the development of gastritis and peptic ulcer disease [26]. In association with vitamin D3, rosemary preparations and carnosic acid enhanced differentiation of HL60 cells in vitro and exerted antileukemic activity in Balb/c mice [27]. A recent study that screened herb extracts for antithrombotic effects in vitro and in a mouse model reported that rosemary along with thyme extracts showed significant antithrombotic activity possibly through an inhibitory effect on platelet reactivity [28]. Interestingly, the same study reported that the anti-platelet activity of rosemary was heat-stable suggesting that the active components may remain preserved after cooking.

Rosmarinic acid, which was first isolated from Rosmarinus officinalis by two Italian scientists [29], is an esterification product of caffeic acid which originates from the amino acid phenylalanine, and 3,4-dihydroxyphenyllactic acid which is produced from tyrosine [30]. However, other medicinal herbs have been shown to contain rosmarinic acid including lemon balm (Melissa officinalis), sage (Salvia officinalis, Salvia aegyptiaca L.), olives (Olea europaea L), tobacco (Nicotiana tabacum), and peppermint (Mentha piperita L.) [31]. In plants, rosmarinic acid may exert a protective role against pathogens and herbivores. In humans, rosmarinic acid is absorbed, conjugated, and methylated in the intestine and liver and it is present in plasma and urine in a conjugated form (glucuronide and/or sulfated). Metabolites of rosmarinic acid have been shown to be excreted within few hours [32, 33].

Studies have investigated in animal models the biological activity of rosmarinic acid and reported that it inhibited epidermal inflammatory responses by reducing neutrophil infiltration, myeloperoxidase activity, cyclooxygenase-2 mRNA expression, and reactive oxygen radical production [34]. In humans, rosmarinic acid reduced the incidence of allergic rhinoconjunctivitis by inhibiting the inflammatory response and scavenging of reactive oxygen species
Recent studies have documented that rosmarinic acid inhibited a number of processes involved in angiogenesis and ROS-associated VEGF expression and IL-8 release [37].

Several studies have investigated the mechanisms of action of rosmarinic acid. In B16 melanoma cells, it induced melanin synthesis (melanogenesis) through activation of CREB via PKA signaling in a cAMP-independent manner [38]. Other effects of rosmarinic acid included protection against adriamycin-induced apoptosis in H9c2 cardiac muscle cells [39] and inhibition of Ca^{2+}-dependent pathways of T-cell antigen receptor-mediated signaling [40].

Carnosol and carnosic acid are diterpenes, which contribute to the antioxidant and anti-inflammatory activity of rosemary extracts [41, 42]. In rosemary plants, carnosic acid protects chloroplasts from oxidative stress by scavenging free radicals [43]. Studies documented that carnosol exerted a variety of preventive effects by reducing DMBA-induced rat mammary tumorigenesis and in vivo DMBA–DNA adduct formation [44], skin tumorigenesis [45], the invasion of melanoma cells [46], progression through the cell cycle [47], aflatoxin B1-induced oxidative stress [48], and platelet aggregation [49]. Both carnosol and carnosic acid have been shown to be activators of the human peroxisome proliferators-activated receptor gamma [50] thus raising the possibility these compounds may exert hypoglycemic and anti-diabetic effects.

Toxicity related to rosemary has been reported for skin applications of rosemary alcohol which induced contact dermatitis in one patient [51]. The dietary administration to Sprague-Dawley rats of rosemary at levels of 500 mg/kg of body weight for 63 days was associated with reduced fertility in females and a decline in spermatogenesis [52]. However, the clinical implications of these results to traditional dietary consumption of rosemary in human populations of the Mediterranean basin remain unknown.

These cumulative data suggest that rosemary extracts contain several bioactive components including phenolic diterpenes, phenolic acids, and flavonoids that may enhance the health benefits of the Mediterranean diet by acting as antioxidants and improving the detoxification systems [20, 53]. Also, rosemary extracts or selected constituents exert anti-inflammatory, anti-thrombotic, and anti-tumor actions [54] which could be exploited for the routine preparation of foods as well as for the development of prophylactic dietary protocols.

Rosemary extracts have been used in a variety of applications. The addition of rosemary to ground chicken had an overall positive effect on raw meat appearance during storage and cooked meat flavor, and improved redness [55]. Similarly, antioxidant films have been developed to incorporate a natural extract of rosemary and are intended for contact with foods [56]. A study that examined the clinical safety and efficacy of NG440, a phytochemical-based anti-inflammatory formula consisting of a combination of rho iso-alpha acids from hops, rosemary, and oleanolic acid, concluded that NG440 reduced pain scores in patients with joint discomfort suggesting that phytochemical preparations containing rosemary may be used as an alternative to specific
COX2 inhibitors [57]. Aromatherapy acupressure in stroke patients with lavender, rosemary, and peppermint exerted a positive effect on hemiplegic shoulder pain compared to acupressure alone [58].

**licorice (or liquorice)**

The first documented use of licorice (*Glycyrrhiza glabra*) in Europe is provided by the Greek botanist and pharmacologist Theophrastus in the third century BC, who was a disciple of Plato and Aristotle [59]. The genus name of the licorice plant, *Glycyrrhiza*, is derived from the ancient Greek words for “sweet root” (*glykos* = sweet and *rhiza* = root) [60]. The sweetness of licorice is from the glycyrrhizin contained in the root and is 50 times sweeter than sucrose [61]. Native to southeastern Europe, the licorice root was used as something sweet to chew on and the black juice extract was taken as a refreshing drink by both the Greeks and Romans. Today licorice is found in candies, soft drinks, tobacco products, cough syrups, Guinness beer, and sambuca [60]. Medicinal uses of licorice throughout antiquity included treatment for asthma, cough, skin lesions, ulcers (bladder, stomach, and kidney pain), and diseases of the liver and arteries. Licorice also shows anti-inflammatory and mineralocorticoid properties due to the activity of glycyrrhizinic acid and its metabolite glycyrrhetinic acid, which inhibit cortisol metabolism. Recent studies have shown licorice to possess antiatherogenic effects, and that the presence of saponins and flavonoids in the root provide antioxidant activity [59]. Modern research has verified these uses finding licorice to be an effective expectorant and antiviral agent, as well as an aid for healing stomach and duodenal ulcers [61].

The principle chemical component of the licorice root is glycyrrhizin. Glycyrrhizin is a triterpenoid saponin glycoside which occurs as a mixture of calcium and potassium salts of glycyrrhizic acid. Following hydrolysis, glycyrrhizin is converted to two molecules of glucuronic acid and the aglycone glycyrrhetinic acid [59]. Glycyrrhizic acid and glycyrrhetinic acid competitively inhibit the enzyme 11β-hydroxysteroid dehydrogenase [62]. 11β-Hydroxysteroid dehydrogenase normally catalyzes the oxidation of the active cortisol in the kidney, to the inactive cortisone. The inhibition of cortisol metabolism by glycyrrhizic/glycyrrhetinic acid increases cortisol activity in the kidney. Cortisol has the same affinity to the aldosterone receptors as aldosterone and the effects mimic aldosterone excess [63]. The resulting hypermineralocorticoidism is characterized by sodium retention, hypokalemia, and hypertension [64].

Licorice may be used as a demulcent for sore throats and as an expectorant in facilitating the discharge of mucus from the upper respiratory tract [65]. Licorice is useful in treating gastric and duodenal ulcers as it reduces stomach secretions and produces protective mucus for the lining of the digestive tract [66]. The anti-inflammatory and anti-allergenic activity of licorice arises
mainly from the presence of the flavones liquiritin and liquiritigenin which can treat rheumatism and arthritis. These properties are further extended to the treatment of atopic dermatitis; reducing erythema, edema, and itching [67]. Licorice possesses anti-viral properties and has long been used in the treatment of chronic viral hepatitis [61]. *In vitro* studies have reported anti-viral effects for the influenza virus, the severe acute respiratory syndrome (SARS) corona virus, the Hepatitis B virus, and the Epstein Barr virus [59]. The antioxidant activity of licorice stems from the presence of saponins and flavonoids which are known for their antioxidant activity. Of the flavonoids present in the root, isoliquiritigenin is among the most potent [68]. Licorice is also useful as a gentle laxative [66].

The most widely reported side effects from licorice are caused by the inhibition of cortisol metabolism by glycyrrhetinic acid causing hypertension and edema. Prolonged use and excessive consumption (more than 20 g/day) not only produce hypertension and edema, but can also induce hypokalemia and reduce plasma aldosterone levels [65]. These symptoms are reversible with withdrawal from the herb. The acceptable daily intake of the active component glycyrrhizin is 0.015–0.229 mg/kg body weight [61].

**CHAMOMILE**

Chamomile is derived from the Greek words chamos (ground) in reference to its low-growing characteristics and melos (apple), in reference to the apple scent of fresh chamomile blossoms. The two primary types of chamomile are German chamomile (*Matricaria recutita*) and Roman chamomile (*Anthemis nobilis*). References to chamomile are found in medicinal writings of the ancient Egyptian, Greek, and Romans. The writings of Hippocrates, Dioscorides, and Galen contain descriptions of the chamomile plant. The Greeks and Egyptians used crushed chamomile flowers to treat the skin conditions erythema and xerosis caused by dry, harsh weather [69]. Chamomile is one of the most widely used herbs and has been traditionally used for its mild sedative, spasmolytic, anti-inflammatory, and wound healing properties [70]. The German E Commission has approved chamomile for internal use to treat gastrointestinal spasms and inflammatory diseases of the gastrointestinal tract. In addition, the German E Commission has approved external use of chamomile for inflammation of the skin and bacterial skin diseases, and respiratory tract inflammation [65]. In the United States, chamomile is one of the most widely consumed tea ingredients [70].

Over 120 different components have been identified in the chamomile flower [71]. One of the primary bioactive components of chamomile is levomenol (α-bisabolol) and its oxides. Other components of chamomile include apigenin, azulenes, farnesene, spathuleno, and spiroethers [72]. Teas brewed from chamomile contain approximately 10–15% of the essential oils available from the flowers [72]. The coumarins herniarin and umbelliferone make up
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approximately 0.1% of the total constituents of the flower [73]. Apigenin is found in relatively high amounts in chamomile (840 mg/100 g) and it has been reported to possess a number of anti-cancer properties in vitro [74]. Chamomile has also been shown to possess antioxidant properties, although to a lesser degree compared to other medicinal and culinary herbs [75]. Essential oils extracted from chamomile have also been reported to exert antimicrobial properties against certain species of bacteria, fungi, and viruses [72].

Despite its widespread use in traditional medicine, only a few clinical trials have been conducted to evaluate the traditional medicinal claims of chamomile. In young Japanese males, one serving of chamomile tea decreased heart rate and ratings of sadness and depression compared to the placebo group [76]. In heart disease patients hospitalized for cardiac catheterization ($n = 12$), two cups of chamomile significantly decreased the mean brachial arterial pressure [77]. In children with acute, non-complicated diarrhea, a chamomile/apple pectin preparation significantly decreased the duration of the diarrhea compared to the placebo [78].

Several clinical studies have examined the effects of topical preparations of chamomile. A randomized, placebo-controlled trial investigated whether or not chamomile influenced skin reactions induced by radiation treatment. Treatment with chamomile appeared to delay the onset and reduce the frequency of skin reactions, however the results were not statistically significant [79]. Topical preparations of chamomile have been reported to enhance wound healing [80, 81]. In a double-blind study of 14 patients with weeping wounds from dermabrasion following tattoo removal, a compress made of chamomile extract significantly increased would healing and increased the drying of the wound [80]. Another randomized double-blind study investigated whether a chamomile spray relieved post-operative sore throat from intubation. The patients who received the chamomile extract spray (111 mg) did not report any differences from patients receiving a placebo spray [82].

Chamomile is most commonly prepared as a tea using the dried flowers. Tea infusions can be prepared by taking 3 g of the whole flower head into 150 ml of water. For inflammation of the upper respiratory tract, steam vapor from aqueous infusions of chamomile can be inhaled. In other cases, compresses can be made with chamomile.

In rare cases, chamomile may result in an allergic reaction or irritation upon contact [83, 84]. Individuals who are allergic to other members of the aster family (ragweed, asters, chrysanthemums) may also be allergic to chamomile [85]. Chamomile has also been reported to interact with cyclosporine in three renal transplant patients [86]. In addition, coumarin, which is a component of chamomile, may potentiate the effects of warfarin [73, 87].

**OLIVE OIL**

Olive oil has been used for centuries in Greece and other Mediterranean countries for its beneficial health properties. Ancient Egyptians and Romans
used olive oil to soothe wounds. Olive oil is extracted from the fruit (*Olea europea*) by crushing the fruit to create a pomace, which is subsequently homogenized before it is pressed to produce the oil [88]. Unlike other oils that are extracted by solvents, virgin olive oil is obtained solely from mechanical or physical means. The leftover pomace is sometimes processed again to extract a lower quality refined virgin olive oil.

The percentage of dietary vegetable fat obtained from olive oil in Mediterranean countries is 71% in Greece, 42% in Italy, and 37% in Spain [89]. Since non-Mediterranean countries have relatively low consumption of olive oil compared to Mediterranean countries, the majority of studies investigating the beneficial health effects of olive oil arise from countries of the Mediterranean basin. In non-Mediterranean countries, monounsaturated fatty acid intake comes primarily from meat and dairy products along with other plant oils. Therefore, it may not be appropriate to equate the health benefits of olive oil intake with those of monounsaturated fatty acids intake in non-Mediterranean populations [90].

The saponifiable fraction of olive oil consists of 98.5–99.5% of olive oil and the remainder accounts for the unsaponifiable fraction [91]. Olive oil consists primarily of oleic acid (55.0–83.0%) [91]. Additional fatty acids present in olive oil include palmitic acid (7.5–20.0%), stearic (0.5–5.0%), linoleic (3.5–21.0%), linolenic (0.0–0.9%), and palmitoleic acid (0.3–3.5%) [91]. Oleic acid (18:1 n9) is a monounsaturated fatty acid containing one double bond, making it less susceptible to oxidation compared to polyunsaturated fatty acids with multiple double bonds. Therefore, olive oil tends to have a longer shelf-life than many other oils containing higher amounts of polyunsaturated fatty acids [92]. In addition, antioxidant phenolic compounds increase the stability of extra-virgin olive oils compared to refined virgin olive oil [93]. Long-term storage and heating can lead to degradation and changes in the composition of olive oil.

Phenolic compounds also contribute to the health benefits of olive oil, of which 30 have been identified. The major phenolic compounds identified in olive oil belong to five different classes: simple phenols (hydroxytyrosol, tyrosol), secoiridoids (oleuropein, ligstroside, and their hydrolysis derivatives), lignans (pinoresinol and acetoxyypinoresinol), flavonoids (luteolin and apigenin), and phenolic acids (*p*-coumaric acid, vanillic acid). The reported total amount of phenolic compounds contained in olive oils ranges widely in the literature (between 200 mg/kg and 1500 mg/kg). The phenolic compounds are found in higher amounts in the less processed extra virgin olive oil [91]. In addition, the concentration of phenolic compounds depends on the cultivar, degree of maturation, climate, and extraction procedures [91, 94]. The phenolic compound that has been implicated for the bitter taste of olive oil is oleuropein [95]. In dried, unripe olives oleuropein accounts for approximately 14% of the dried weight. However, as the olive matures oleuropein undergoes hydrolysis to several simple phenols that contribute to the complex taste of olive oil. The phenols in the olive fruit are present in the more polar and hydrophobic glycoside
form, whereas the phenols present in olive oil are found in the more lipid-soluble aglyconic form. Mediterranean diets rich in olive oil supply approximately 10–20 mg of phenolic compounds per day [96]. In addition to fatty acids and phenolic compounds, olive oil contains thousands of other components including tocopherols (α-, β-, γ-, and δ-) and β-carotene (which along with chlorophylls is responsible for the color of the oil). Olive oil also contains approximately 0.7% squalene [88].

The antioxidant properties of the phenolic compounds in olive oil have been the subject of numerous investigations and may contribute to the healthy properties through a variety of mechanisms. For example, olive oil has been suggested to reduce oxidative stress that leads to lipid peroxidation and formation of DNA adducts [97]. Other mechanisms of action that may contribute to the health benefits of olive oil include modulation of signal transduction pathways, regulation of gene expression, alteration of the immune system, and modification of cell membrane structure and function [98].

The cardioprotective effects of the Mediterranean diet were brought to light through results from the Seven Countries Study led by Keys [99]. These studies demonstrated that dietary intake of saturated fatty acid was associated with increased serum cholesterol levels and coronary artery diseases. Furthermore, these studies revealed the cardioprotective effect of virgin olive oil. Since then numerous investigations have studied the role of olive oil in cardiovascular diseases. Consumption of olive oil has been associated with several beneficial biological and clinical effects related to lipoprotein metabolism, oxidative damage, endothelial dysfunction, blood pressure, inflammation, thrombosis, and carbohydrate metabolism [100].

In Mediterranean countries, there is a strong correlation between olive oil consumption and reduced hypertension. In the Greek European Prospective Investigation into Cancer and Nutrition (EPIC) study of 20,343 men and women, olive oil consumption and the monounsaturated fatty acid to saturated fatty acid ratio were inversely associated with systolic and diastolic blood pressure [101]. Results from the cross-sectional Italian Nine Communities Study with 4903 men and women, olive oil consumption was also associated with decreased blood pressure [102]. The Suguiimiento Universidad de Navarra (SUN) study in Spain with 6863 men and women noted an inverse association of olive oil consumption and blood pressure in men but not women [103]. However, several cohort or cross-sectional studies conducted in the United States to examine the effects of monounsaturated fat consumption and hypertension have produced conflicting results, possibly due to the fact that meat is the primary source of monounsaturated fatty acids in the Western diet [104].

Several clinical trials have been conducted in controlled environments to examine the effects of olive oil on hypertension. A double-blind, randomized crossover study evaluated the effects of monounsaturated (MUFA) (extra-virgin olive oil) and polyunsaturated fatty acids (PUFA) (sunflower oil) on blood pressure in 23 hypertensive patients. Resting blood pressure was significantly
lowered in patients after 6 months of receiving the MUFA diet (30–40 g/day) compared to PUFA diet along with reduced use of anti-hypertensive medications [105]. In several cross-over trials where olive oil replaced either polyunsaturated fatty acids or carbohydrate, olive oil significantly reduced systolic and diastolic blood pressure [104]. However, not all studies have reported a beneficial effect of olive oil on blood pressure in short-term clinical trials [104].

Olive oil may also influence hemostasis by altering components of platelet function, thrombogenesis, and fibrinolysis [106]. Plasminogen activator inhibitor-1 (PAI-1) is a procoagulant factor that has been linked to coronary heart disease (CHD). Several short-term clinical trials have investigated the effects of olive oil on PAI-1 and overall olive oil or MUFA diets lowered PAI-levels compared to diets rich in saturated fatty acids [106,107]. Furthermore, human clinical trials have reported that interventions with olive oil reduced production of thromboxane A2 (TXA2), which is produced by platelets to increase aggregation [108–110].

Oxidation of the lipids and lipoprotein in LDL is thought to play a major role in development of cardiovascular disease and atherosclerosis. One mechanism through which olive oil may be cardioprotective is by inhibiting of LDL oxidation [96]. Diets high in MUFA reduced the susceptibility of LDL oxidation in comparison to carbohydrate-rich diets [111]. Diets containing extra virgin olive oil increased the resistance of LDL to oxidation [112]. Numerous randomized, controlled, crossover human studies have examined the effects of phenolic compounds from olive oil on markers of DNA and lipid damage [summarized in 100]. Cumulatively, these studies have produced conflicting results in regards to the antioxidant effects of the phenolic olive oil compounds in vivo. However, recent results from the EUROLIVE study provided evidence that phenolic compounds from olive possess in vivo antioxidant properties. The EUROLIVE study was a large, crossover trial conducted with 200 individuals from five different European countries [113]. Participants were given 3 similar olive oils (25 ml/day) with different phenolic contents for intervals of 3 weeks followed by 2-week washout periods. The greatest increases in HDL cholesterol levels and greatest decreases in lipid oxidative damage were observed during ingestion of olive oil containing the highest phenolic content [113].

The clinical efficacy of olive oil on the cancer process is highly controversial. Numerous epidemiological studies have reported an inverse correlation between olive oil consumption and the incidence of cancers of the prostate [114], breast [115], colon [116], and oral cavity [117]. In comparison to other types of fatty acids, fewer experimental animal studies have investigated the role olive oil on tumor development and have produced inconsistent results [118]. Several mechanisms of action have been investigated in vitro for the anti-cancer properties of olive oil and its constituents including modulation of signal transduction pathways, regulation of gene expression, alteration of the immune system, and modification of cell membrane structure and
function [118]. Furthermore, the antioxidant properties of olive oil may reduce the formation of DNA adducts by decreasing oxidative stress from lipid peroxidation [97]. In vitro experiments documented that olive oil down-regulated the expression of cyclooxygenase 2 (COX2) and Bcl-2 [119]. Minor polar compounds from olive oil inhibited NF-kappaB translocation in monocytes and monocyte-derived-macrophages isolated from healthy volunteers [120]. Oleuropein aglycone isolated from extra virgin olive oil was found to inhibit cleavage of the HER2 extracellular domain (ECD) and subsequent HER2 expression in breast cancer cells resistant to trastuzumab (Herceptin) [121]. In addition, the oleanolic acid isolated from olive oil inhibited the invasion of HT115 human colon carcinoma cells in the Matrigel invasion assay [122]. In HL-60 human promyelocytic leukemia cells, hydroxytyrosol inhibited cell cycle progression and altered expression levels of proteins associated with cell cycle regulation including cyclin-dependent kinase (CDK) 6, cyclin D3, p21, and p27 [123]. In colon cancer cells lines, pinoresinol-rich olive oil induced the ATM-p53 cascade [124].

A meta-analysis that compared low-saturated-fat, high-carbohydrate diets vs. high-monounsaturated-fat diets in type 2 diabetic patients reported that the high-monounsaturated fat diets improved lipoprotein profiles and glycemic control [125]. In a prospective cross-over study, obese and type 2 diabetes patients (n = 11) were placed on three different diets including a diet high in saturated fat, a diet rich in monounsaturated fat in the form of extra virgin olive oil, and a diet rich in carbohydrates [126]. The diet rich in olive oil decreased postprandial glucose and insulin concentrations, increased HDL cholesterol, and glucagon-like peptide 1 (GLP-1) concentrations as compared with the carbohydrate rich diet. In another study, the effects of virgin olive oil consumption on changes in membrane fatty acids and signaling proteins were examined in elderly patients with type 2 diabetes (n = 16) compared to a control group (n = 28). After 4 weeks of olive oil consumption, significant modifications were noted in the fatty acid composition of plasma membrane and there was a reduction in G-protein subunits (Gαs and Gβ) and protein kinase C alpha (PKCα). These results suggest that diets rich in olive oil may influence glycemic homeostasis through alteration of membrane lipids and signaling proteins [127].

In addition to protective cardiovascular and anti-cancer effects, olive oil has also been investigated for its antimicrobial properties [128]. In particular, the phenolic compounds hydroxytyrosol and oleuropein have been noted for their inhibitory properties against selected standard bacterial strains [129]. In addition, virgin olive oil extract was reported to exhibit antibacterial effects against eight strains of Helicobacter pylori, which has been linked to peptic ulcers and some types of gastric cancers [130]. These reports also demonstrated that several of the phenolic compounds from the olive oil are stable for hours in an acidic environment similar to that of gastric juices.
Besides dietary consumption, olive oil exerts beneficial effects in topical applications [69]. Skin application of olive oil after UVB exposure reduced 8-hydroxy-2′-deoxyguanosine (8-OHdG), a measure of DNA damage, and decreased the subsequent formation of UVB-induced skin tumors in mice [131]. A topical application of olive oil in combination with honey and beeswax has been shown to be effective in a number of skin and fungal infections including pityriasis versicolor, tinea cruris, tinea corporis, and tinea faciei [132].

In 2004, the United States Food and Drug Administration released a report stating that two teaspoonfuls of olive oil (23 g) per day that replace other saturated fats had the potential to reduce coronary disease [133]. There are no adverse effects associated with consumption of olive oil. However, one concern is the high energy density of olive oil could promote weight gain. Therefore, it is recommended to replace other fatty acids and simple carbohydrates with olive oil, rather than add olive oil in addition to the normal diet [90].

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