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Review Article
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Health-Promoting Effects of Traditional Mediterranean Diets – A Review

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Epidemiological studies have suggested that the adherence to Mediterranean diet (in Greek Μεσογειακή Διατροφή, Mesogiaki diatrofi) is correlated to a low risk of cardiovascular diseases. Mediterranean diet offers a nutritional model enriched by diverse cultures which, over centuries, has essentially maintained the same structure. In general, this diet is rich in plant foods (fruit, vegetables, whole grain cereals, legumes, nuts), with moderate amounts of seafood, extra virgin olive oil as main dressing and regular, moderate red wine consumption at meals. Furthermore, it has been assumed that some bioactive constituents of Mediterranean foods are, at least in part, responsible for the observed health-promoting effects ascribed to this dietary style. Among these, polyphenols have been extensively studied for their biological activities, though hundreds of different secondary metabolites are present in plant foods. Therefore, it is plausible that additive and/or synergistic effects of phytochemicals may maximize the health potential of the traditional Mediterranean diet.

INTRODUCTION

The study of traditional dietary habits is important both for healthy and cultural aspects: it provides scientific evidence on the effects of traditional foods on health and contributes to preserve elements of our nutritional and cultural inheritance. In general, traditional foods are considered healthy, though their effects should be better substantiated by an appropriate scientific approach. The Mediterranean basin has been for millennia a crossroads of people and civilizations where boats, carriages, merchandises, but also creative ideas and religions have converged. Mediterranean diet originated from the ancient inhabitants of this region, the Greek and Roman ancestors.

In countries surrounding Mediterranean Sea, food is heavily influenced by the climate of the basin. Traditionally, Mediterranean diet originated in areas where olive (*Olea europea* L.) and grape (*Vitis vinifera* L.) were cultivated, olive oil and wine produced and regularly consumed. The archaeological record suggests that cultivation of the domesticated grape, *Vitis vinifera* subsp. *vinifera*, began 6000–8000 years ago in the Near East from its wild progenitor, *Vitis vinifera* subsp. *sylvestris*. The hundreds of grape cultivars in use today have been generated since then by vegetative propagation and by crosses [McGovern, 2003]. Olive tree was domesticated approximately 6000 years ago in the east Mediterranean area. Since Roman times, the cultivation and the techniques of producing olive oil had spread to all parts of the Mediterranean basin, but they did not expand, except in some regions of Spain and North Africa, much beyond the limits of the wild olive tree, at least partly because of the very specific climatic requirements for its successful growth [Grigg, 2001].

Mediterranean diets vary amongst countries because of different culture, ethnic background, religion, agricultural production and economy. However, some common traits can be identified: (*i*) high consumption of fresh fruit, seasonal vegetables, whole cereals and legumes (daily); (*ii*) small portions of nuts (daily); (*iii*) low to moderate amounts of dairy products, seafood and lean meat (poultry, lamb) (weekly); (*iv*) low intake of eggs (weekly) and red meat (monthly); (*v*) healthy fats such as extra virgin olive oil; and (*vi*) regular and moderate red wine consumption at meals.

The first scientific approach to study the health benefits of Mediterranean diet was the well-known Seven Countries Study by Ancel Keys and colleagues, which introduced this nutritional style to the scientific community. In this study, deaths from coronary heart disease were correlated with serum cholesterol in 15 populations of 7 countries: Italy, Greece, former Yugoslavia, the Netherlands, Finland, USA and Japan. Increased consumption of fruit, vegetables, whole grains, pulses, fish and nuts, olive oil as main dressing and moderate amounts of red wine were associated with a long and healthy lifespan, mainly in Greece and Italy, where the lowest rates of coronary heart disease and the longest life expectancy were observed [Keys, 1980].

Furthermore, some (non-dietary) lifestyles may contribute to improve the health-promoting effects of Mediterranean diets, including a moderate physical activity (walking every day) and resting in the middle of the day after an enjoyable family meal (*siesta*) [Naska *et al.*, 2007].

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THE SCIENTIFIC EVIDENCE ON NUTRITION AND CARDIOVASCULAR DISEASES

Cardiovascular diseases are the first cause of death globally: more people die annually from these disorders than from any other cause. The most important behavioural risk factors of heart disease and stroke are unhealthy diet, physical inactivity and cigarette smoking. Therefore, these factors are responsible for about 80% of coronary heart disease and cerebrovascular accidents. Individuals can reduce their risk of cardiovascular disorders by engaging in regular physical activity, avoiding tobacco use and second-hand tobacco smoke, choosing a diet rich in fruit and vegetable and limiting foods that are rich in saturated fat, refined sugar and salt, and maintaining a healthy body weight (body mass index, BMI) [http://www.who.int/mediacentre/factsheets/fs317/en/index.html].

Both epidemiological (population) studies and (dietary) intervention trials have correlated Mediterranean-type diets with a low incidence of cardiovascular diseases. The association between fruit and vegetables consumption and risk of major chronic diseases was examined in two large cohorts of men (37,725 participants in the Health Professionals' Follow-up Study) and women (71,790 enrolled in the Nurses' Health Study) followed up for more than a decade. Both men and women who consumed five or more servings of fruit and vegetables per day reduced their risk of heart attack and stroke by 12% compared to individuals who did not consume these foods [Hung *et al.*, 2004].

In the INTERHEART Study, involving more than 30,000 subjects from 52 countries representing all continents, eight risk factors, all modifiable through diet and lifestyle, were identified: they accounted for 90% of all heart diseases in men and 94% in women, regardless of race or country where they live. The eight factors affecting risk are: eating fruit and vegetables daily; regular physical activity; abnormal blood lipids (high level of low density lipoprotein, LDL); smoking; high blood pressure; diabetes; abdominal obesity; psychosocial factors ('stress') [Yusuf *et al.*, 2004].

Data collected on 22,071 men, followed up for 13 years in the Physician's Health Study, have indicated that eating carotenoid-rich fruit and vegetables significantly reduces the risk of ischemic stroke [Hak *et al.*, 2004].

In the Coronary Risk Factors for Atherosclerosis in Women (CORA) Study, who consumed high amounts of meat, margarine, poultry and sauces and low intakes of vegetarian dishes, wine and whole-grain cereals experienced a higher risk for coronary artery disease compared to women following the opposite dietary pattern [Hoffmann *et al.*, 2004].

In addition to fruit and vegetables, eating fish (rich in omega-3) may significantly lower the risk of stroke. The revision of 8 independent studies, involving more than 200,000 subjects ranging in age from 34 to 103 years, showed that consumption of fish 1–3 times per month lowered the risk for any type of stroke by 9%, once a week by 13%, 2–4 times a week by 18%, 5 or more times a week by 31%. When types of stroke were compared, risk for ischemic stroke was more affected than that of the hemorrhagic one [He *et al.*, 2004].

In the Mediterranean Diet, Cardiovascular Risks and Gene Polymorphisms (Medi-RIVAGE) Study, the effects of a Mediterranean-type diet (Med group) and a low-fat diet (low-fat group) were evaluated in 212 volunteers (men and women) with moderate risk factors for cardiovascular disease. Med group participants based their meals on whole grains, fruit, vegetables, nuts, olive oil and they were instructed to eat fish 4 times a week, but red meat only once a week. According to the plasma cholesterol levels, it was predicted a 9% reduction in cardiovascular disease risk with the low-fat diet and a 15% reduction with the Mediterranean diet [Vincent-Baudry *et al.*, 2005].

The traditional Mediterranean diet is rich of hearth-protective fats including oleic acid, a monounsaturated fatty acid found in olive oil, and α-linoleic acid, an omega-3 fatty acid abundant in plant foods (vegetables, nuts). In addition, it is low in saturated fats of animal origin, which increase the levels of LDL or 'bad' cholesterol, and pro-inflammatory omega-6 (found in non olive vegetable oils) [de Lorgeril & Salen, 2006].

Besides the role of Mediterranean diet in the prevention of cardiovascular disease, it may be also effective in reducing the risk of myocardial infarction in heart patients. In the Greek Study of Acute Coronary Syndrome (GREECS), a high adherence to Mediterranean diet was associated to lower levels of heart disease biomarkers and reduced risk of another heart attack [Panagiotakos *et al.*, 2006].

In the PREDIMED Study, a long-term multicenter trial, subjects at high cardiovascular risk were assigned to a low-fat diet and two different traditional Mediterranean diets, with olive oil or nuts. Consumption of the olive oil Mediterranean diet reduced levels of oxidized LDL more than the nut-rich Mediterranean diet. Conversely, the latter was more effective in increasing HDL (high density lipoproteins), or 'good' cholesterol, and in decreasing triglyceride levels. No changes were observed in the low-fat diet group, and both Mediterranean diets decreased systolic and diastolic blood pressure [Fitó *et al.*, 2007].

The relative importance of the individual components of the Mediterranean diet in generating the inverse association between increased adherence to this diet and overall mortality was investigated in the participants of the Greek segment of the European Prospective Investigation into Cancer and Nutrition (EPIC), including 23,349 men and women. The high consumption of the main components of Mediterranean diet, vegetables, fruit, nuts, olive oil and legumes, and moderate red wine intake scored as a predictor of lower mortality [Trichopoulou *et al.*, 2009].

Mediterranean lifestyles have been also investigated in healthy individuals. Midday napping (*siesta*) was inversely associated with coronary mortality, particularly among working men, after controlling for potential confounders including comorbidity, diet and physical (in)activity [Naska *et al.*, 2007].

Other lifestyles characteristic of Mediterranean populations may improve the general health status. In the Ikaria Study, 89 males and 98 females over the age of 80 years were studied. In Ikaria Island, Greece, the percentage of people over the age of 90 years was much higher than the European population average. The majority of the oldest participants reported daily physical activity, healthy eating habits, avoidance of smoking, midday naps, frequent socializing and low rate of depression, thus showing that the interaction of environmental, behavioural together with clinical traits may influence longevity [Panagiotakos *et al.*, 2011].

NON-NUTRIENT CONSTITUENTS OF MEDITERRANEAN FOODS RELEVANT TO HEALTH: FOCUS ON POLYPHENOLS

The health-promoting effects ascribed to traditional Mediterranean foods are attributed, at least in part, to some of their bioactive phytochemicals (or nutraceuticals), besides their content of healthy fats, as previously stated. In general, the former are secondary metabolites involved in the plant--ecosystem interaction, exerting a plethora of ecological roles such as defense against pathogens and phytophagy, attraction of pollinators, repelling of noxious arthropods, allelopathic effects against competing plants, shading from high light irradiance and UV radiation, detoxification from pollutant exposure and so on [Iriti & Faoro, 2009]. In food plants, some phytochemicals are considered as non-nutrient constituents relevant to human health. In particular, polyphenols have been extensively studied in the last decades in a myriad of preclinical (*i.e. in vitro* and in animal) studies. These metabolites, exclusively produced in the Plant Kingdom, arise from the essential aromatic amino acid phenylalanine and are included in the large class of phenylpropanoids. In turn, polyphenols consist of three main groups: flavonoids (including anthocyanins), stilbenes (with resveratrol) and proanthocyanidins (or condensed tannins) (Figure 1) [Iriti & Faoro, 2004].

One of the most investigated biological activity of polyphenols is the antioxidant activity, *i.e.* the capacity of scavenging free radicals and reactive oxygen species by donating electrons and stopping radical chains, thus preventing damages to macromolecules (lipids, proteins, DNA) and cell structures. Pathological conditions mechanistically linked to oxidative stress include inflammation, atherosclerosis and carcinogenesis. Therefore, it is not surprising that foods rich in antioxidants, as well as single food components, may play an essential role in the prevention of cardiovascular diseases, cancer, degenerative neurological disorders such as Parkinson's and Alzheimer's diseases, and premature aging, as extensively reported both on cell and animal models [Scalbert *et al.*, 2005; Afaq & Katyar, 2011; Lin, 2011; Mendoza & Burd, 2011; Visioli & Davalos, 2011].

With regard to cardioprotection, polyphenols exert many pharmacological activities both in *in vitro* and in animal models. These compounds improve endothelial function stimulating vasorelaxation due to the release of nitric oxide by the endothelial nitric oxide synthase, and reducing the synthesis of endothelin, a potent vasoconstrictor, by the vascular endothelium [Corder *et al.*, 2001; Wallerath *et al.*, 2002; Perez-Vizcaino *et al.*, 2006]. As antioxidant and anti-inflammatory molecules (the powerful cyclooxygenase-inhibitory compound salicylic acid is a phenolic compound), polyphenols block the inflammatory cascade leading to the synthesis of pro-inflammatory mediators (eicosanoids and cytokines), and modify the activity of redox-sensitive transcription factors (as nuclear factor κB) [Martinez & Moreno, 2000; Zern *et al.*, 2005; Csiszar *et al.*, 2006]. Furthermore, they prevent the oxidation of LDL and the uptake of oxidized LDL by macrophages, thus blocking the progression of these immune cells to foam cells and the deposition of fatty steaks in the subendothelial space (the site of atheromatous lesions) [Stein *et al.*, 1999]. The inhibition of platelet (re)activity (adhesion and aggregation) and the improvement of fibrinolysis are responsible for the antithrombotic activity of polyphenols [Abou-Agag *et al.*, 2001; Shanmuganayagam *et al.*, 2002]. The inhibition of abnormal vascular smooth muscle cell proliferation and migration, in the arterial intima, plays another important role in the prevention of atherosclerosis [Araim *et al.*, 2002].

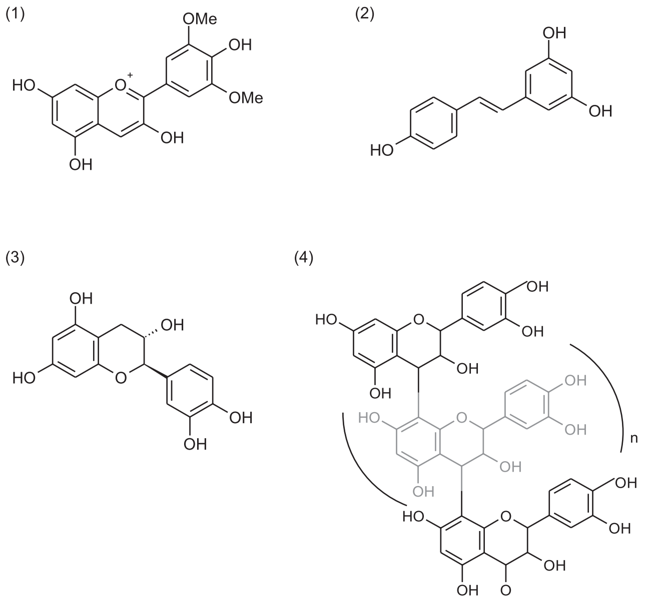


FIGURE 1. Dietary polyphenols include three main groups: flavonoids such as catechin (1) and malvidin (an anthocyanidin) (3); stilbenes with resveratrol (2) as lead compound; and proanthocyanidins (4), oligo- and polymeric derivatives of flavonoid/catechin units (1).

Recent experimental data have demonstrated that polyphenols can exert their cardioprotective effects *via* the activation of several powerful prosurvival cellular pathways. These involve metabolic intermediates, microRNAs, sirtuins and mediators involved in the recently described reperfusion injury salvage kinases (RISK) and survivor activating factor enhancement (SAFE) pathways [Lecour & Lamont, 2011].

Because polyphenols are recognised as xenobiotics by human organism, to produce beneficial effects they must be absorbed, after oral ingestion, before reaching target tissues and organs by the blood stream [Yang *et al*., 2008; Requena *et al*., 2010]. As briefly introduced, biological activity has been demonstrated for some polyphenols in many experimental systems, though the effective concentrations *in vitro* (sub- to low-micromolar levels) are at least one order of magnitude higher than those normally measured in human plasma (tens to hundreds of nanomolar) [Manach *et al*., 2005]. To reach effective concentrations at their sites of action, ingested polyphenols must overcome a number of barriers represented by the gastrointestinal tract [Scheepens *et al*., 2010]. In general, the bioavailability of dietary polyphenols is limited not only by their physicochemical properties, but also because of active efflux or biotransformation by phase I and phase II enzymes, including the first-pass hepatic metabolism, and gut microbiota [Yang *et al*., 2008; Requena *et al*., 2010]. In particular, colon is an active site for polyphenol metabolism, and it has been estimated that 90–95% of dietary polyphenols are not absorbed in the small intestine, but accumulated and metabolized in this tract [Clifford, 2004]. Therefore, in view of the poor bioavailability of these phytochemicals, the mechanisms behind their healthy properties suggested by epidemiological studies are still not clear.

A NEW HYPOTHESIS: MELATONIN AS A BIOACTIVE CONSTITUENT OF MEDITERRANEAN DIET

Though polyphenols represent the archetype of the health-promoting effects of Mediterranean diet, many other bioactive phytochemicals contribute to improve these benefits. The (food) chemistry of Mediterranean diet is quite complex. Besides these metabolites, Mediterranean foods are rich in carotenoids, phytosterols, aromatic volatile isoprenoids, glucosinolates mainly in Brassicaceae (cauliflower, broccoli, cabbage) and sulfides in edible Liliaceae (onion, garlic, leek) (Figure 2) [Schreiner, 2005]. Recently, it has been suggested that (dietary) melatonin may add a new element in this scenario (Table 1) [Iriti *et al.*, 2010].

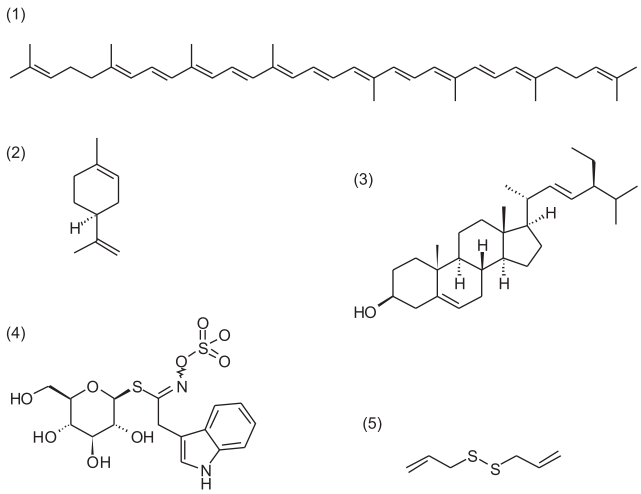
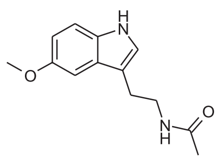


FIGURE 2. Phytochemicals occurring in Mediterranean foods different from polyphenols: lycopene (a tetraterpenic isoprenoid) (1) is the red carotenoid pigment of ripen tomato and a powerful antioxidant and anticancer agent; limonene (2) is a volatile monoterpenic isoprenoid responsible for the aroma of many Mediterranean commodities; stigmasterol (a triterpenic isoprenoid) (3) is a cholesterol-lowering phytosterol; glucobrassicin (4) is an antitumoral glucosinolate present in Brassicaceae (cabbage, cauliflower, broccoli); and diallyl disulfide (5) is an organosulfur compound found in plants of the genus *Allium* (garlic, onion).

TABLE 1. Occurrence of melatonin in some Mediterranean foods.



Grape berry (skin)[1]	9-17 ng/g
Grape berry (flash)[1]	0.2-4 ng/g
Grape berry (seed)[1]	3-10 ng/g
Red wine	4-8 ng/mL
Extra virgin olive oil	71-119 pg/mL

[1] Vitalini *et al.* [2011b].

This indoleamine was long thought to be a neurohormone found exclusively in vertebrates, until its relatively recent detection in bacteria, protozoans, plants including algae, fungi and invertebrates [Hardeland & Poeggeler, 2003]. In humans, in addition to its neurohormonal and physiological functions (such as the regulation of the sleep-wake cycle), this molecule exerts a powerful antioxidant activity with oncostatic properties [Reiter *et al.*, 2009]. Melatonin has been recently reported in important Mediterranean commodities including grape, wine, beer, olive oil and tomato (Table 1) [de la Puerta *et al*., 2008; Iriti *et al.*, 2010; Vitalini *et al*., 2011a]. Interestingly, in animals and humans, an efficient uptake and bioavailability of melatonin from food sources has been demonstrated and, therefore, the intake of foodstuffs containing this indoleamine may contribute to increase its circulating levels [Reiter *et al.*, 2005; Maldonado *et al.*, 2009; Garrido *et al.*, 2010].

CONCLUSIONS

At the end of this short survey, we can argue that Mediterranean diet can really improve the life expectancy and promote a healthy aging by reducing the burden of the main chronic degenerative diseases. These effects arise, at least in part, from some bioactive constituents present in traditional Mediterranean foods, whose effects may be further potentiated by (Mediterranean) non-dietary healthy lifestyles.

The Mediterranean diet is a unique lifestyle ('diet' derives from the Greek word *díaita*, lifestyle) determined by the climate and the history, a system rooted in the respect for territory which ensures the conservation of traditional knowledge. The Mediterranean diet is today a heritage, a complex social practice based on crop cultivation, harvesting, fishery, food preparation, processing, conservation and consumption, which, in the Mediterranean, means eating together around the same table: 'we do not sit at table to eat, but to eat together' (Plutarch) (UNESCO nomination file n. 00394).

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