Diet and prevention of coronary heart disease: the potential role of phytochemicals

Francesco Visioli*, Luisa Borsani, Claudio Galli

University of Milan, Institute of Pharmacological Sciences, Via Balzaretti 9, 20133 Milan, Italy

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Abstract

Epidemiological studies, and some clinical trials, demonstrate that a proper diet reduces the rate of occurrence of cardiovascular disorders. Several in vitro studies suggest that some components of plant foods, most of which sharing a phenolic structure, are endowed with interesting 'pharmacological activities'. This article reviews the evidence that links a high dietary intake of phytochemicals from various sources with a reduced incidence of coronary heart disease. © 2000 Elsevier Science B.V. All rights reserved.

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1. Introduction

Several epidemiological studies have shown that a proper diet, in which plant foods provide the major portion of caloric intake, may reduce the development of certain diseases like cancer and atherosclerosis [1]. Although fats and proteins in plants, as opposed to those of animal origin, are responsible to some extent for these protective effects, the contribution of other plant food components may also be relevant. The human body cannot synthesize lipid- and water-soluble vitamins that, therefore, must be derived from food; moreover, plants’ secondary metabolism (the shikimate and acetate pathways, in particular, Fig. 1) generates products that currently are grouped under the rubric of ‘phytochemicals’ or, incorrectly, ‘polyphenols’.

Whole foods or fortified, enriched, or enhanced foods are often referred to as ‘functional foods’, ‘nutraceuticals’ or ‘designer foods’. Claims are made that phytochemicals in these foods, when consumed at effective levels as part of a varied diet, may provide some health benefits [2]. This review will examine the role of such micronutrients and their potential contribution to the prevention of atherosclerotic cardiovascular disease.

2. Overview

Phenolics are derivatives of benzene (cyclic derivatives in the case of polyphenols) with one or more hydroxyl groups associated with their ring. They can be conveniently classified into at least 10 different classes depending on their chemical structure [3].

Two main synthetic pathways (Fig. 1) originate phenolic compounds in plants: the acetate and the shikimate pathways [3]. The term polyphenols includes several classes of compounds that share a common structure; among polyphenols, flavonoids constitute the most important single group, including more than 5000 compounds that have been thus far identified [4].

Phenolics are important to plant physiology, contributing to resistance to micro-organisms and insects, pigmentation and organoleptic characteristics (odor and flavor). It is noteworthy that fruits and vegetables require a variety of
Evidence indicating such healthful effects in vitro and in vivo is accumulating. Most researchers have focused on the activities of phytochemicals of widely consumed foods and beverages, such as fruits, vegetables, legumes, chocolate, tea, wine and olive oil.

2.1. Soy isoflavones

The substitution of animal protein with soy has been associated with favorable effects on blood lipid profile [12]. Soybeans contain variable (around 5 mg/kg protein) amounts of isoflavones that likely play a relevant role in the healthful effects of soy on the cardiovascular system [12], in addition to exerting other interesting health-promoting activities. In particular, genistein and daidzein are endowed with weak proestrogenic or antiestrogenic activities and thus have the potential to interact with estrogen receptors and decrease serum cholesterol concentrations [13]. Moreover, in vitro studies have shown that genistein — a specific inhibitor for tyrosine kinases [14] — might prevent the development of atheroma by inhibiting cell adhesion and proliferation, by inhibiting LDL oxidation, and by altering growth factor activity; finally, a soy isoflavone-rich diet improved coronary vascular reactivity in monkeys, similar to that observed with estrogens [13].

It is difficult to separate the individual effects of soy components [13]; thus, the mechanisms responsible for the observed reduction of cholesterol concentrations by soy are still unclear: apart from the potential cholesterol-lowering effects of other soy constituents such as soluble fibers, saponins, and oligosaccharides, an upregulation of the LDL receptor by soy proteins has been demonstrated in vitro and ex vivo but, as the inhibition of tyrosine kinase by soy isoflavones should result in a hypercholesterolemic effect, this may not be the exclusive mechanism of action of soy components [15].

Limitations to the hypothesis that soy isoflavones are responsible for the lower cholesterol levels observed in soy consumers, e.g., Asians, include the gut flora-dependent, limited bioavailability of genistein and daidzein, the still controversial hormonal effects, and the lack of selective human studies [15].

Finally — although not strictly related to the phytochemicals topic of this review — it should be observed that the proteic components of soy exhibit remarkable cholesterol-lowering properties [15], more evident in hypercholesterolemic subjects, that render a soy-based hypocholesterolemic diet very cost-effective [16].

2.2. Phenolics in tea

Tea — the most widely consumed beverage in the world — is a rich source of micronutrients. In fact, tea may very well be the major source of antioxidants worldwide (Katan MB, personal communication), due to the very high concentration of these compounds, e.g., quercetin, kaem-
pferol, myrecitin, and epigallocatechin gallate, in tea combined with the frequent consumption of this beverage; polyphenols constitute more than 35% of the dry weight of tea leaves [17]. Several in vitro studies have shown the potent antioxidant activities of tea extracts [18,19], which also possess interesting tumor-inhibiting properties [20,21]. Also, epidemiological studies carried out in The Netherlands [22], correlated a higher flavonoid intake with a lower incidence of coronary heart disease (CHD) [23–25]. However, as far as protection from the development of atherosclerosis is concerned, mixed results have been obtained in vivo [26–34]; it is noteworthy that the Caerphilly Study reported increased mortality from CHD among Welsh male tea drinkers, possibly a consequence of the habitual addition of milk to tea in that area, thus preventing absorption of flavonoids [35], or due to other unidentified confounders.

2.3. Phenolics in wine

The observed inverse correlation between moderate alcohol intake and mortality from cardiovascular disease has stirred considerable interest toward the components of alcoholic beverages, including alcohol itself. The most popular example involves the so-called ‘French paradox’, i.e., low mortality rate from cardiovascular disorders recorded in France despite a high saturated fat intake and the presence of other established risk factors for cardiovascular disease, such as cigarette smoke and high cholesterol levels [36]. This apparent paradox was first revealed to the lay society on the American television program Sixty Minutes (CBS Television, 17 November 1991), prompting an increase in sales of red wine in the United States by 39% during the following year. The rationale is based on the fact that red wine, as opposed to other alcoholic beverages, contains substantial amounts of pytochemicals, most of which are phenolic in nature, and that are synthesized by red grapes as a form of self-protection from the relatively high temperatures known to exist within a dark grape. In fact, wines contain a wide array of compounds, including 0.8–1.2 g of aromatic molecules per liter [6]. Such compounds, which are also present in white wines but are more concentrated in red wines, are determinant contributors to the wine’s flavor and fragrance. Many of such wine components exhibit strong in vitro antioxidant activities [37]. Yet, in vivo studies, as in the case of tea, have reported mixed results. Increased plasma antioxidant capacity, increased resistance of LDL to chemically induced oxidation has been recorded following wine or wine-phenolic intake [38–41]. Conversely, negative results have also been reported [42,43]. Other cardioprotective properties suggested for red wine and grape juice include improved endothelial function [44], inhibition of platelet activity and subsequent thrombosis in stenosed canine coronary arteries [45], suggesting that the antiplatelet activities of wine phenolics thus far exhibited in vitro are retained in the bloodstream (yet, in this study the active compounds were administered intravenously, so that potential adsorption following oral ingestion was not investigated).

Out of all the wine components, over the past few years research has been focused on the biological properties of trans-resveratrol, which has been shown in vitro to be a strong antioxidant [46–48], a phytoestrogen [49], and inhibitor of tumorigenesis [50], a vasorelaxant [51], an inhibitor of platelet aggregation [52,53], an inhibitor of cyclooxygenase-2 [54], and an inhibitor of human polymorphonuclear leukocytes [55]. It is noteworthy that the only in vivo study reported thus far actually noted that trans-resveratrol accelerated the development of atherosclerosis in rabbits [56]. Finally, the strong antioxidant hydroxytyrosol (3,4-dihydroxyphenylethanol), typical of extra virgin olive oil (see below), is also present in wine [57] and can thus contribute to the strong antioxidant potency of wine extracts.

Thus far, human-volunteer studies yielded mixed results, leaving an open question as to whether the decreased mortality from CHD observed in moderate drinkers is attributable to wine phytochemicals, to ethanol itself, or even the diet of wine consumers [58]. In addition, several studies have failed to note any difference among different alcoholic beverages, i.e., wine, beer or spirits, with respect to their protective effects on the cardiovascular system [59–61]. The contribution of important confounders such as higher socioeconomic status of moderate drinkers (notably in the United States), the fact that wine consumption is usually associated with meals (possibly favoring the absorption of other nutrients or limiting the formation and absorption of products of oxidation from the gut), or discrepancies in the coroners’ systems of various countries [62] — just to name a few — is yet to be fully elucidated.

Finally, it should always be kept in mind that heavy drinking is certainly devoid of beneficial effects on human health and actually causes serious diseases such as liver cirrhosis, gastritis, pancreatitis, hypertension, cardiomyopathy, degenerative disorders of the nervous system, and cancers of the upper GI tract, and liver, not to mention other aspects of alcohol-related mortality and morbidity such as drunk driving and violent crime [63]; thus, a U-shaped relation between the amount of alcohol consumed and total mortality has been observed. All anecdotal as well as experimental data regarding the potentially positive effects of drinking any form of alcohol — including red wine — should be accompanied by such a warning/disclaimer [64].

2.4. Phenolics in olive oil

According to current regulations, olive oil is classified into different grades depending on its chemical properties [65]. Due to the presence of its minor components (Table 1), extra-virgin olive oil is characterized by a distinguish-
able flavor that sets it apart from ‘plain’ olive oil. In fact, during the refining process — necessary when the free acidity of an oil exceeds the legal limit — almost all the minor components — phenols in particular — are destroyed, thus dramatically reducing sharpness of the flavor. In many olive oil-producing countries, though, extra-virgin olive oil accounts for just 10% of all the oil produced.

Olive oil contains a lower amount of vitamin E than other vegetable oils, which are extracted from seeds [66], due to the fact that almost all the oil derives from the olive mesocarp; thus, most of the vitamin E, which is found in the endocarp, remains in the solid waste (cake). Accordingly, olive oil’s higher stability, with respect to seed oils, has been attributed to its phenolic content [67–71] rather than to tocopherol content.

The importance of phenols is also reflected in the organoleptic quality of olive oil (this also applies to other foods and beverages such as wine). A high phenolic content confers a very bitter and pungent zest to the oil. The effect of bitterness and pungency results from complex interactions between ‘minor constituents’ and the taste buds. In particular, phenolic acids such as phenol and cinnamic acid are responsible for the bitter sensation that can be detected on the lateral and posterior areas of the tongue, while secoiridoids confer the oil’s peculiar pungency. As a result, organoleptic sensations reminiscent of pepper or chili peppers can be found in the phenol-rich olive oils most favored by gourmets. Conversely, ‘sweet’ oils are almost devoid of phenols. It should, however, be noted that a very high load of phenols may result in excessive and unpleasant bitterness; therefore, phenol content alone is not synonymous with quality. In turn, high phenol levels in virgin olive oils are very likely to confer a high stability and a strong, fruity flavor, indicating a high organoleptic quality of the oil.

Recently, the availability of pure compounds, either from commercial sources or extracted and purified from olive oil, prompted investigations on antioxidant and other biological properties of olive-oil phenols. In fact, the observed low incidence of CHD in the Mediterranean area, where olive oil constitutes the principal source of fat, could find a partial explanation in the high dietary intake of antioxidants, including those found in extra-virgin olive oil.

The antioxidant activities of olive oil phenolics, particularly those of the complex phenol oleuropein — the bitter principle of olives — and its derivative hydroxytyrosol, have been elucidated through a variety of experimental models, including transition metal ion- and chemically induced oxidation of LDL and the generation of reactive-oxygen species such as superoxide, trichloromethylperoxy radicals and hypochlorous acid (the latter should be more appropriately termed ‘reactive chlorine species’) [72–79]. The antioxidant properties of oleuropein and hydroxytyrosol have also been demonstrated in cellular and animal models [80,81].

The biological activities of olive oil phenolics are not limited to their antioxidant potency but extend to their interaction with relevant enzymatic systems. In particular, olive oil phenolics inhibit platelet aggregation; reduce the formation of pro-inflammatory molecules thromboxane B₂ and leukotriene B₄ by activated human leukocytes; inhibit human neutrophils’ respiratory burst; and increase the production of nitric oxide by mouse macrophages when the latter are challenged with endotoxin, thus potentiating the immune response [82,83–88].

Although data on the absorption and disposition of hydroxytyrosol and other olive oil phenolics subsist [89] but are still limited, evidence exists that lipoproteins isolated from animals fed phenol-rich olive oils are more resistant to oxidation that those of control animals fed equal amounts of oleic acid [90,91]. Studies are in progress to clarify whether olive oil phenolics are indeed absorbed and exert their biological activities in vivo; however, the available in vitro data suggest the adoption of extra-virgin olive oil as the dietary fat of choice.

Finally, it is noteworthy that, during the elaboration of olive oil, a considerable amount of phenols, according to their partition coefficient, are discarded with the waste water. Thus, olive mill waste-waters, produced in extremely large quantities and currently disposed of, contain powerful, as yet unused, antioxidants that could be recovered and employed in preservative chemistry or as nutritional antioxidant supplements [92,93].

### 2.5. Phenolics in chocolate

Cocoa (Theobroma cacao L.) contains appreciable amounts (~20 mg total phenol gallic acid equivalent per g of cocoa powder [94]) of phenolic substances such as (~)-epicatechin. Such phenolics confer chocolate fat a particular resistance to peroxidation [95] and in vitro and
ex vivo studies indicate that they are endowed with biological activities, including antioxidant capacity and immunoregulatory effects [96–99].

In a representative sample of the Dutch population, chocolate contributed 20% of the total catechin intake [100], suggesting that in younger age-groups chocolate provides a significant portion of the daily antioxidant intake and that this contribution should be taken into account in epidemiological studies. Finally, the large use of cocoa in confectionery also represents an often overlooked contributor to the total daily antioxidant intake.

3. Conclusion

As outlined in this chapter, there now exists a great body of evidence to indicate that a diet rich in plant foods lowers the risk of developing CHD [101,102]. Whether this effect is mainly the result of antioxidants present in plant foods or other factors — which may also play an important role — is, at present, unclear. In fact, controversial results have been obtained in prospective studies and following supplementation of humans with phytochemicals such as tea and wine flavonoids and phenolics (see above). Several explanations have been proposed to resolve this contradiction. First of all, the lack of an appropriate methodology to evaluate the phytochemical content of foods and beverages [103] makes it difficult to correctly estimate the amount of administered phytochemicals and thus to correlate it with biochemical or clinical endpoints. Also, in prospective studies of phytochemical intake and CHD, the contribution of confounders that have not been eliminated by multivariate analysis offers a plausible explanation for some of the apparently contradictory results [104]. Finally, the common procedures used to isolate LDL, whose oxidizability is often employed as the biomarker of phytochemical effects, impoverish LDL of non-lipophilic molecules, as in the case of most micronutrients; still, the in vivo process of LDL oxidation likely takes place in the lipid–water interface, where hydrophilic or amphiphilic compounds may exert their protective activity [105]. Likely, the evaluation of plasma (in toto) oxidizability might provide more ‘biologically useful’ information on the effects of phytochemical supplementation.

In turn, the disappointing results of clinical trials on antioxidant vitamins, based on the supplementation of antioxidant vitamins in pure form [106], suggest that the interaction between the above-mentioned dietary components concomitant with a high intake of fibers, a low caloric density, and a paucity of atherogenic foods in the diet are likely — together — to effect protection from these diseases. Also, rather than a single load of antioxidant nutrients, healthful food provides a mixture of bioactive micronutrients that, likely, are responsible for the observed protection from CHD.

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