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Review Article

Cardioprotective effects of moderate red wine consumption: Polyphenols vs. ethanol

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ABSTRACT

Since decades, it has been suggested that regular, moderate consumption of red wine, a major component of Mediterranean diet, at main meals, may contribute to explain the healthy properties attributed to this traditional dietary style. Despite preclinical *in vitro/in vivo* data have shown a significant cardioprotective activity of grape phytochemicals, mostly polyphenols, evidence in humans is still debated. This lack of consensus may be due to the equilibrium between the two main components of wine relevant for health: ethanol and bioactive compounds or phytochemicals, which include not only polyphenols, but also newly detected molecules, such as melatonin and phytosterols. The state of art related to this delicate equilibrium represents the starting point for designing future clinical trials, in perspective of clinical recommendations. A better comprehension of the wine chemistry complexity with its major components embodies a pivotal issue in biomedicine, involving the fields of diet-related environmental medicine as well as chronomedicine. In this paper, we briefly reviewed putative beneficial effects of moderate red wine intake in humans, focusing on the reduction of cardiovascular risk.

Introduction

Mediterranean diet includes a number of different nutritional habits, although some common key elements can be recognized in dietary patterns of Mediterranean populations: high consumption of fruit, both fresh and dried (e.g. figs, raisin); raw and cooked seasonal vegetables; whole-cereal products; fish and seafood; dairy products, goat and ewe milk in fermented forms of cheese and yoghurt; nuts; lean meat such as rabbit and chicken; aromatic herbs and spices; extra-virgin olive oil as main dressing; moderate alcohol drinking, particularly based on red wine. However, in the southern Mediterranean region, due to cultural and religious reasons, wine is usually replaced with black tea as a main source of phytochemicals, mainly polyphenols. The particular structure and composition of traditional Mediterranean diets, besides their variety and assortment, have been proposed to explain the low prevalence of cardiovascular diseases and the improved life expectancy in some countries which face Mediterranean sea basin (Iriti and Vitalini, 2012).

Even if wine is an alcoholic beverage, a plethora of beneficial biological and pharmacological activities has been

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ascribed, in the past decades, to some grape and wine metabolites, under the name of ''bioactive compounds''. In particular, polyphenols, a large group of phenylalanine derivatives, have been extensively investigated. These phytochemicals, divided into flavonoids (including anthocyanins), stilbenes (e.g. resveratrol) and proanthocyanidins (or condensed tannins) (Figs. 1 and 2), possess different molecular and biochemical targets both in healthy and diseased cells (Iriti and Faoro, 2009). Their main mechanisms of (cardio) protection include high antioxidant and antiinflammatory activities; resveratrol, in particular, has been reported to stimulate endothelial production of nitric oxide, reducing oxidative stress, decreasing vascular inflammation and preventing platelet aggregation (Li and Förstermann, 2012). Furthermore, the diversity of grape and wine chemistry has been recently improved by the discovery of new bioactive molecules in these products, i.e. melatonin and phytosterols (Figs. 2 and 3). Melatonin is an indoleamine traditionally considered a vertebrate neurohormone, secreted from the pineal gland with a circadian rhythm, and significantly present in grapevine products (Vitalini et al., 2013). It plays a pivotal role in human chronobiology, since it regulates the biological clock and circadian physiological functions, such as sleep and appetite (Rodella et al., 2013). On what concern cardiovascular protection, melatonin has been shown to improve blood pressure parameters as suggested by the results of a meta-analysis (Grossman et al., 2011), not only acting on heart with a central effect, but also by reducing vessel oxidation, nitric oxide metabolism and improving endothelial functions (Cicero and Borghi, 2013).

In addition to melatonin, three phytosterols, i.e. β-sitosterol, stigmasterol and campesterol, effective hypocholesterolizing agents, have been detected in grapes and wine (Ruggiero et al., 2013). Phytosterols have been reported to play a key role against dyslipidemias, with hypocholesterolemic effects: daily intake of plant sterols or stanols of 1.6–2.0 g/day is able to decrease intestinal cholesterol absorption from the gut by about 30%, as well as plasma total and LDL cholesterol levels, thus reducing the cardiovascular risk (Marangoni and Poli, 2010). Therefore, it can be hypothesized that these and, possibly, other phytochemicals may maximize the healthy properties of polyphenols by additive and/or synergistic effects.

Despite polyphenols are considered the archetype of health benefits attributed to a moderate red wine consumption, as demonstrated by a huge amount of *in vitro*/*in vivo* experimental models (Iriti and Faoro, 2009), the in human evidence is still inconclusive, possibly because of the presence of ethanol in wine, which can counteract or nullify, to some extent, the protective effects of polyphenols in conditions of heavy or binge (episodic heavy) wine intake (Barbero-Becerra et al., 2011). As an example, despite a vast preclinical literature on resveratrol, clinical evidence on its cardioprotective potential is still largely open to doubt (Cicero and Borghi, 2013).

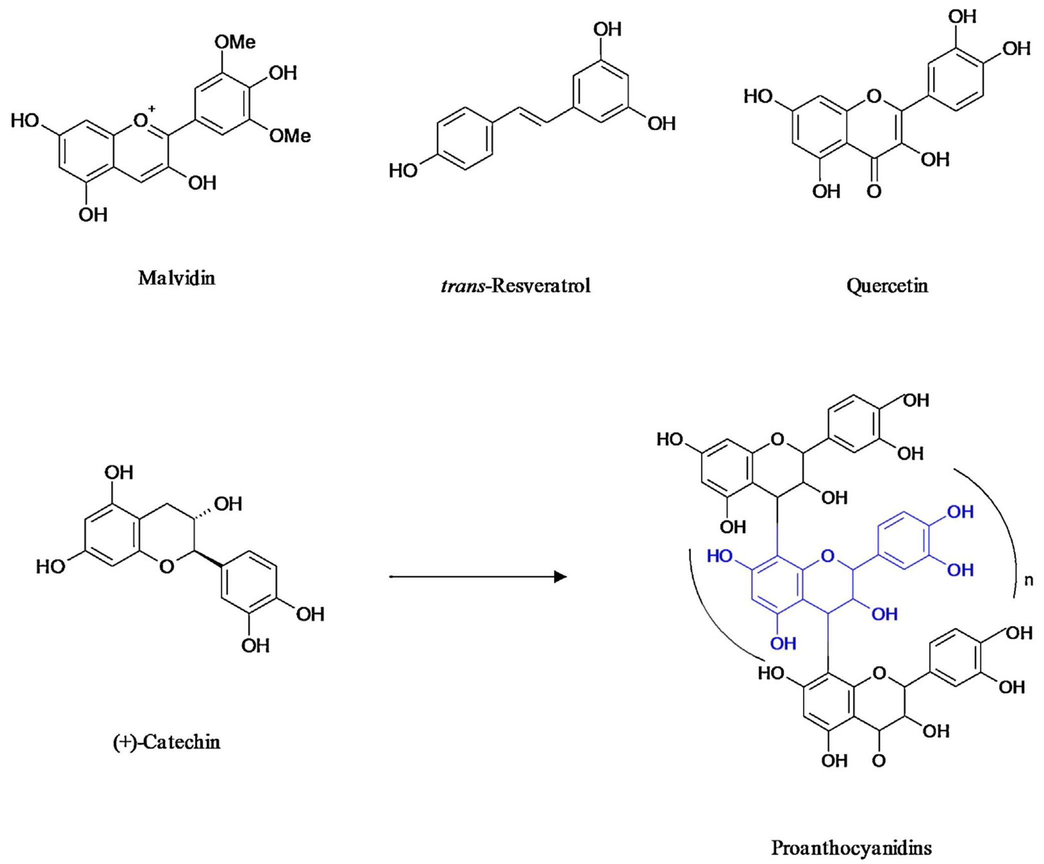

Fig. 1 – Typical bioactive polyphenols present in red wine include anthocyanidins (malvidin), stilbenes (resveratrol), flavonols (quercetin), flavan-3-ols [(+)-catechin] and proanthocyanidins or condensed tannins, oligo- and polymeric derivatives of flavan-3-ol units.

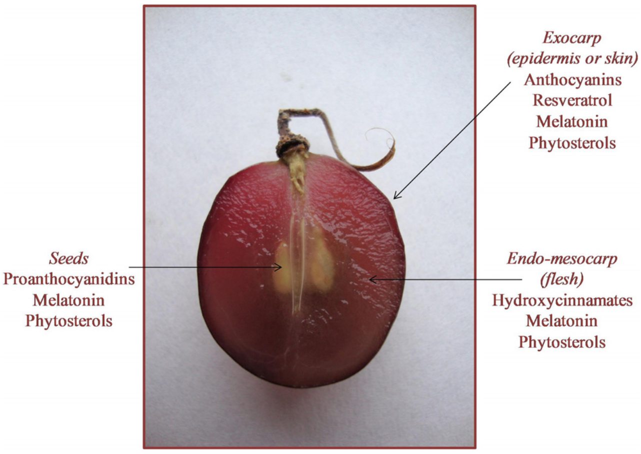

Fig. 2 – Presence of main polyphenols (anthocyanins, resveratrol and proanthocyanidins), phenolic acids (hydroxycinnamates) and new phytochemicals (phytosterols and melatonin) in grape berry and seed tissues.

In this perspective, to date, the equilibrium between ethanol and bioactive phytochemicals contained in wine is under discussion, involving those biomedicine-related studies exploring effects of diet on disease development and prevention (Berger, 2011).

In this review, we briefly examined the health-promoting effects of moderate red wine intake in humans, focusing on the suggested association with cardiovascular protection. We focused on studies which compared wine and spirit consumption, with strongly different ethanol/phytochemicals ratios. Meta-analyses on wine and cardiovascular disease were also considered. Our work aims to provide an updated knowledge on this issue in order to stimulate and encourage future biomedical research, mainly in the field of diet-related environmental medicine and of chronobiology as well.

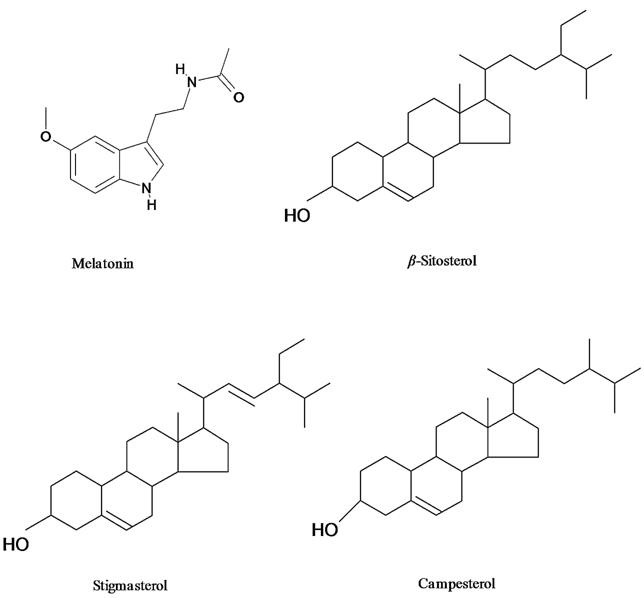

Fig. 3 – Recently discovered bioactive phytochemicals in wine are indoleamines (melatonin) and phytosterols (β-sitosterol, stigmasterol and campesterol).

Interventional studies

Several in humans studies have been recently carried out to elucidate the relation among types of alcoholic beverage (wine, spirit, beer), under different drinking patterns, and cardiovascular risk. Interventional studies investigated effects on surrogate outcomes, mainly serum biomarkers and functional changes.

Variation of serum biomarkers

The different effects of red wine and gin consumption on inflammatory biomarkers of atherosclerosis were investigated in a randomized, crossover, single-blinded clinical trial. Forty healthy men (mean age 37.6 years) consumed 30 g of ethanol per day, for 28 days, as either red wine (two 160 mL glasses) or gin (100 mL), the latter a beverage with a very low polyphenol content. Blood sample analyses indicated that both wine and gin drinking had anti-inflammatory effects by reducing plasma fibrinogen (by 9 and 5%, respectively) and cytokine interleukin-1α (IL-1α) (by 21 and 23%, respectively) levels. However, only wine had two additional effects: (i) a 21% decrease in C-reactive protein (CRP); (ii) a reduction of monocyte and endothelial adhesion molecules including very late activation antigen 4 (VLA-4) (−32%), monocyte chemoattractant protein (MCP-1) (−46%), soluble vascular cell adhesion molecule-1 (VCAM-1) (−17%) and intercellular adhesion molecule-1 (ICAM-1) (-9%) (Estruch et al., 2004). Similarly, 4-week supplementation of red wine decreased plasma fibrinogen levels in 15 healthy male volunteers, who were instructed to drink 250 mL/day of this beverage (12% alcohol, 1.2 g/L total polyphenols, 0.64 g/L total anthocyanins and 1.0 g/L total proanthocyanidins). However, the authors also found an increase of mean platelet volume and serum levels of inflammatory and endothelial cell activation markers, as ICAM-1, E-selectin and IL-6 (Tozzi Ciancarelli et al., 2011). On the other hand, 150 mL/day of red wine (15 g/day of alcohol) for 3 weeks failed to reduce serum CRP levels and only slightly decreased fibrinogen concentrations in 87 Norwegian healthy volunteers 35–70 years old (mean age 50.0 years) (Retterstol et al., 2005).

In another randomized, crossover clinical trial, 20 g/day of ethanol as red or white wine (1 glass of 100 mL at lunch and dinner) were administered to 35 healthy women aged 20–50 years (mean age 38.0 years) for 4 weeks. Both wines reduced serum biomarkers of inflammation and endothelial activation in subjects, even if anti-inflammatory effects associated with moderate red wine consumption were higher than those produced by white wine, probably because of a different polyphenol content (Sacanella et al., 2007).

The moderate intake of red wine or an alcoholic beverage with a very low polyphenol content was investigated in terms of influence on serum antioxidant vitamins, antioxidant status, lipid profile and oxidability of low-density lipoprotein

(LDL) particles. Forty healthy men aged 30–50 years (mean age 38.0 years) received 30 g of ethanol per day as red wine (two 160 mL glasses at dinner) or gin (100 mL at dinner), for 28 days. In particular, compared to gin intervention, wine intake reduced plasma superoxide dismutase (SOD) activity, malondialdehyde (MDA) and oxidized LDL levels (Estruch et al., 2011).

By a similar study design (a randomized, crossover clinical trial), the same authors also demonstrated that red wine exerted higher protective effects on glucose metabolism and lipid profile than other alcoholic beverages. Sixty-seven men aged 55–75 years were instructed to consume gin (100 mL/day, containing 30 g of ethanol), red wine (272 mL/day, containing 30 g of ethanol and 798 mg of total polyphenols), or de-alcoholized red wine (272 mL/day, containing 1.14 g of ethanol and 733 mg of total polyphenols) for 4 weeks. Participants were at high cardiovascular risk, reporting family history of premature cardiovascular disease and/or presence of diabetes, hypertension, dyslipidemia and overweight/obesity. Plasma insulin and insulin resistance decreased after interventions with both wines; high-density lipoprotein (HDL)-cholesterol, apolipoprotein (Apo)A-1 and ApoA-2 increased after red wine and gin administration. On the other hand, only red wine reduced lipoprotein plasma concentrations (Chiva-Blanch et al., 2013a). In another study, the same authors showed that both ethanol and non-alcoholic components of red wine may regulate soluble inflammatory mediators in high-cardiovascular risk patients, whereas only phenolic compounds may modulate leukocyte adhesion molecules (Chiva-Blanch et al., 2012a). De-alcoholized red wine also decreased systolic and diastolic blood pressures in patients at high cardiovascular risk, and these variations correlated with increased concentration of plasma nitric oxide (NO) (a potent vasodilator) (Chiva-Blanch et al., 2012b).

The relationship between body mass index (BMI) and plasma triglycerides was investigated in 42 Brazilian individuals (64% men, mean age 46.0 years, mean BMI 25.13 kg/m^2) consuming 250 mL/day of red wine at meals for 2 weeks. In general, red wine increased plasma levels of triglycerides and the triglycerides/HDL-cholesterol ratio. When subjects were divided into three categories, according to their BMI, the authors reported that individuals with higher BMI, although non obese, were at higher risk for elevation in plasma triglycerides and the triglycerides/HDL-cholesterol ratio after short-time red wine consumption (Cesena et al., 2011).

Possible prebiotic effects associated with red wine intake were recently suggested. Ten healthy male volunteers received red wine (272 mL/day), de-alcoholized red wine (272 mL/day) or gin (100 mL/day) for 20 days. Total fecal DNA analysis by real-time qPCR revealed that, compared with baseline, daily consumption of red wine polyphenols significantly increased the number of *Enterococcus*, *Prevotella*, *Bacteroides*, *Bifidobacterium*, *Bacteroides uniformis*, *Eggerthella lenta*, and *Blautia coccoides–Eubacterium rectale* groups. In parallel, systolic and diastolic blood pressures, triglyceride, total cholesterol, HDL-cholesterol and CRP concentrations decreased significantly. Besides promoting the growth of probiotic bacteria, red wine polyphenols also inhibited pathogenic bacteria in the human microbiota, such as *Clostridium* spp (Queipo-Ortuño et al., 2012).

As previously mentioned, health benefits of moderate wine consumption have, at least in part, been attributed to grape polyphenols. Protection against oxidative damage of a Mediterranean diet compared with a western (US) diet, with or without the concomitant intake of red wine, was assessed in 42 young adults (20–27 years old). Volunteers were randomly assigned to either the Mediterranean diet group or the western diet group for 3 months and, only during the second month, they received 240 mL/day of red wine. Mediterranean diet increased plasma vitamin C and β-carotene levels and total antioxidant activity, while western diet raised only vitamin E content. Wine supplementation, analyzed combining both diet groups, increased: (i) plasma vitamin C, β-carotene and uric acid concentrations and total antioxidant activity; (ii) plasma and urinary total polyphenols and (iii) red blood cell glutathione levels, while decreasing plasma vitamin E and glutathione contents. Western diet group also showed higher concentrations of 8-hydroxy-2′-deoxyguanosine (8-OHdG, a marker of oxidative DNA damage), in DNA of peripheral blood leukocytes, and plasma nitrotyrosine (a marker of oxidative protein damage) when compared with Mediterranean diet group. Wine intake significantly reduced 8-OHdG and plasma nitrotyrosine in both diets, particularly in the western group. The authors concluded that moderate red wine consumption counteracted the oxidative damage caused by western diet (Urquiaga et al., 2010).

Furthermore, ever if on few participants, it was shown that 300 mL/day of alcohol-free red wine for 1 week increased the activities of antioxidant enzymes (superoxide dismutase, catalase and glutathione reductase) in 8 volunteers aged 25–40 (mean age 28.0) following a low phenolic diet (Noguer et al., 2012). However, despite a general consensus attributing antioxidant benefits to sustained wine consumption in healthy volunteers, Covas and colleagues concluded, in a review paper, that there is no evidence, at present, that supports as wine consumption is associated with antioxidant benefits other than to counteract a possible prooxidant effect of the ethanol. On the contrary, data on the antioxidant protective effects of red wine in conditions of oxidative stress are promising (Covas et al., 2010). These conclusions are consistent with our recent results showing that red wine drinking was not associated to a reduced salivary antiradical capacity, which, conversely, was greatly improved by the intake of a capsule of red wine extract (Varoni et al., 2013).

Finally, perspectives of a moderate red wine intake in secondary prevention of cardiovascular diseases were evaluated. Thirty-nine post myocardial infarct patients (32 men and 7 women, mean age 65.0) were divided into 2 groups: 'red wine drinkers', administered with 250 mL/day of red wine (3.81 g/L total polyphenols) at main meals for 2 weeks, and 'water drinkers'. During this period, all subjects received a 'western prudent' diet, inspired by the Mediterranean diet principles. Moderate red wine intake reduced total cholesterol and LDL-cholesterol, and improved erythrocyte membrane fluidity (Rifler et al., 2012).

Functional changes

Hypertension and blood pressure variations can be considered useful indirect indicators to analyze a potential protective effect of wine against cardiovascular diseases. In terms of alcohol intake, an increase of the risk of hypertension has been reported with a regular drinking pattern, in a dose-dependent manner (Taylor et al., 2009), or with consumption outside meals, independently from the ethanol amount (Stranges et al., 2004), while a moderate intake of alcohol appeared not to affect blood pressure in a normotensive population (Okubo et al., 2001). As Chiva-Blanch et al. pointed out, diverse effects of different alcoholic beverages on blood pressure can be mainly related to their different polyphenol content (Chiva-Blanch et al., 2013b), as shown on high cardiovascular risk subjects, where moderate alcohol consumption, in the form of gin or red wine, did not affect blood pressure, differently from de-alcoholized red wine which reduced this parameter (Chiva-Blanch et al., 2012b).

Atrial fibrillation is a less common, but relevant risk factor exposing patient to cardiovascular events. In a meta-analysis focusing on high risk populations already affected by cardiovascular events, a slight/moderate alcohol intake (5–25 g/day) was significantly associated with a lower incidence of secondary cardiovascular and all-cause mortalities, while long-term moderate alcohol consumption was related to the development of these conditions: the authors recommended to avoid alcohol consumption in these patients (Costanzo et al., 2010).

Genetic variations

1B gene (ADH1B) encodes for alcohol dehydrogenase (ADH), the enzyme representing the first step of ethanol metabolism (Edenberg, 2007); a single nucleotide polymorphism (rs1229984) has been recently associated with low levels of alcohol consumption and blood ethanol and with reduced risk of alcohol dependence among drinkers (Yokoyama et al., 2014). Based on a very large sample (260,000 participants), a recent study reported that carriers of the A-allele had slight lower risk of ischemic stroke with an odds ratio of 0.83 (Kato et al., 2011; Drogan et al., 2012; Lawlor et al., 2013; Holmes et al., 2014). In particular, Holmes and coworkers identified relation between carriers of this allele and cardiovascular traits (non-HDL cholesterol, interleukin 6 and C reactive protein) including coronary heart disease (Holmes et al., 2014). These data are consistent with Asian studies on the rs671 genetic variant of the aldehyde dehydrogenase 2 gene (ALDH2), enzyme with a reduced ability to detoxify ethanol and related negative effects on blood pressure, body mass index and non-HDL cholesterol levels (Kato et al., 2011; Lawlor et al., 2013).

Observational studies

The beneficial properties of red wine are known since more than three decades. In 1979, St. Leger and colleagues first described a significant inverse relationship between wine consumption and risk of death from coronary heart disease (St. Leger et al., 1979). More recently, evidence of a health-promoting effect of red wine on cardiovascular health emerged from many epidemiological studies. In a prospective study, Djoussé and collaborators investigated the association between alcohol consumption and both risk and mortality for cardiovascular diseases in 26,399 ('non-Mediterranean') participants from the Women's Health Study, with a mean follow-up of 12.2 years. As compared with abstainers, alcohol intake of 5–15 g/day was associated with 26%, 35% and 51% lower risk of cardiovascular disease, total mortality and cardiovascular disease-related mortality, respectively. In moderate drinkers, 86% of reduced cardiovascular disease risk was explained by effects on lipids, glucose metabolism, inflammatory/haemostatic factors and blood pressure. Furthermore, no differential association for beverage type, i.e. beer, wine or spirits, and studied outcomes was observed by the authors (Djoussé et al., 2009). Similarly, in a cohort ($N = 31{,}367$) of US adult men from the prospective Aerobic Center Longitudinal Study, ≤6 drinks/week reduced the risk of cardiovascular disease mortality of about 29%. When alcohol consumption was stratified by type (wine, beer and liquor), no difference was observed (Howie et al., 2011).

In a large French population, the urban Paris-Ile-De-France Cohort, composed of 149,773 subjects (97,406 men and 52,367 women with a mean age of 47.6 ± 15 and 47.0 ± 12 years, respectively), relationship between alcohol intake and cardiovascular risk was investigated. The subjects were divided into four groups according to alcohol consumption: never, low (<10 g/day), moderate (10–30 g/day) and high (>30 g/day). With the exception of the subgroup of young subjects (<30 years of age), alcoholic beverages mainly consisted of wine. In addition, wine consumption increased with age, whereas those of beer and appetizers decreased. Moderate alcohol drinkers showed more favorable clinical and biological profiles associated with lower cardiovascular risk factors, including low BMI, waist circumference, heart rate, blood pressure, fasting triglycerides, fasting glucose, plasma LDL-cholesterol and high levels of plasma HDL-cholesterol (Hansel et al., 2010).

The Italian Longitudinal Study on Aging is a cross-sectional multi-center study on 1896 men aged 65–84 years, mainly moderate wine consumers (98%) as a lifelong habit. Participants were divided into six alcohol consumption groups: lifelong abstainers, ≤12 g/day, 13–24 g/day, 25–47 g/day, 48–96 g/day and >96 g/day. Among drinkers, mean daily intakes of alcohol from wine, beer and spirits were 26.7 g/day, 0.6 g/day and 3.8 g/day, respectively. Long-lasting moderate drinkers showed lower levels of systemic inflammatory markers, better hematological parameters and safer metabolic and glycemic profiles. In particular, moderate alcohol consumption in older age was associated to lower values of fibrinogen and insulin resistance, and higher levels of HDL-cholesterol and ApoA-1 lipoprotein, even if this pattern of drinking was also associated with higher LDL-cholesterol and systolic blood pressure (Perissinotto et al., 2010).

The relative importance of the main components of Mediterranean diet in producing the inverse association between increased adherence to this dietary style and all-cause mortality was investigated in the Greek segment of the European Prospective Investigation into Cancer and nutrition (EPIC). The population of this prospective cohort study consisted of 23,349 men and women, without a previous diagnosis of cancer, coronary heart disease and diabetes. After a follow-up of 8.5 years, the contributions of individual components of Mediterranean diet to this association were moderate ethanol consumption (23.5%, men >10 g/day and

<50 g/day, women >5 g/day and <25 g/day, mostly in the form of wine at main meals), low intake of meat and meat products (16.6%), high consumption of vegetables (16.2%), fruit and nuts (11.2%), monounsaturated to saturated lipid ratio (10.6%) and legumes (9.7%) (Trichopoulou et al., 2009).

The association between alcohol consumption and coronary heart disease was investigated in the Spanish EPIC cohort. Participants included 15,630 men and 25,808 women and the median follow-up period was 10 years. Subjects who reported an alcohol intake higher than 5 g/day at either 20, 30, 40 or 50 years of age, but not during the 12 months prior to recruitment were categorized as former drinkers. Never-drinkers were defined as subjects who did not report any consumption higher than 5 g/day at any age and 0 g/day in the 12 months prior to recruitment. Alcohol intake was classified in six categories for men (former drinkers, never-drinkers, low ethanol intake of 0–5 g/day, moderate ethanol intake of 5–30 g/day, high ethanol intake of 30–90 g/day and very high ethanol intake of more than 90 g/day) and five categories for women (former drinkers, never-drinkers, low ethanol intake of 0–5 g/day, moderate ethanol intake of 5–30 g/day and high ethanol intake of 30–90 g/day). In men aged 29–69 years, moderate, high and very high ethanol consumptions were associated with a reduced cardiovascular risk, with a more than 30% lower incidence of coronary heart disease. This association was only statistically significant in men, probably due to the low number of coronary heart disease cases in women ($N = 128$). The type of alcohol consumed (wine, beer, fortified wines) did not affect hazard ratios (Arriola et al., 2010).

The Turkish Adult Risk Factor Study prospectively assessed the long-term impact of alcohol consumption on different outcomes, in 3443 men and women (mean age 47.6 years) included at baseline and followed-up for a mean of 7.4 years. End-points included overall mortality, coronary heart disease, diabetes and metabolic syndrome. Daily alcohol intake was categorized as follows: light drinking, less than 1 drink (1 unit of alcohol, i.e. 30 mL spirits or 300 mL beer or 120 mL wine); moderate drinking, 1 to 3 units of alcohol; heavy drinking, >3 units. Heavy alcohol consumption increased the risk for diabetes, coronary heart disease and, in men, all-cause mortality and metabolic syndrome, even if without a strong statistical significance. Conversely, moderate intake of alcohol was not associated with any adverse outcome, but it was associated to a borderline decrease of cardiovascular risk, overall mortality and, in women, to a significantly lower risk for metabolic syndrome. Interestingly, 62% of ethanol consumed in Turkey is as beer, more than 30% as spirits and only 5% as wine, a very different drinking pattern compared with populations of South Europe (Italy, French and Spain), where wine predominates (Onat et al., 2009).

Association of alcohol consumption and cardiovascular disease outcomes has been investigated in systematic reviews and meta-analysis. Data from 84 eligible studies reported a relative risk (RR), for moderate alcohol drinkers compared with non-drinkers, of 0.75, 0.71 and 0.75 referring to cardiovascular disease mortality, incident coronary heart disease and coronary heart disease mortality, respectively (Ronksley et al., 2011). In another meta-analysis, a previously reported J-shaped dose–response relationship between wine and alcohol consumption and the risk of cardiovascular events and all-cause mortality was confirmed (Costanzo et al., 2011). In J-shaped curve, regular and moderate wine drinking, at the nadir of J, is beneficial, whereas abstinence and heavy intake, on the short and long arm, respectively, are both detrimental, though to a different extent (Di Castelnuovo et al., 2002). A meta-analysis of 34 prospective cohort studies, with more than 1 million subjects and almost 100,000 death by any cause, showed a J-shaped association between self-reported alcohol consumption and mortality (Di Castelnuovo et al., 2006). Another study reported that the maximum intake of wine at which protection was still apparent decreased from 72 to 66 or to 41 g/day when either combined fatal and non-fatal vascular events, or cardiovascular mortality or total mortality were considered as endpoints, respectively. The minimal doses of wine at which its maximal protection could be obtained were 21, 24 and 10 g/day for the three respective endpoints (Costanzo et al., 2011). The same authors described a J-shaped dose-response curve in patients with cardiovascular risk, with light to moderate alcohol consumption (5–25 g/day) significantly associated with a lower incidence of cardiovascular and all-cause mortalities (Costanzo et al., 2010).

Finally, a meta-analysis of interventional studies was also carried out. The effects of alcohol consumption on 21 biomarkers associated with the risk of coronary heart disease were investigated in adults without known cardiovascular disease. Alcohol significantly increased the levels of HDL-cholesterol, ApoA-1 and adiponectin, but a dose–response relation was observed only for alcohol and HDL-cholesterol. Alcohol decreased fibrinogen levels, but did not affect triglyceride concentrations. Analyses were stratified by type of beverage (wine, beer and spirits), but results were similar (Brien et al., 2011).

Discussion

Despite the main evidences are related to variations of surrogate factors or risk factors, such as serum inflammatory mediators or functional studies and thus a conclusive statement is not completely possible, the polyphenol content of red wine appears to overcome the (detrimental) effects of ethanol, at least when considering a regular light to moderate red wine intake at main meals and not in a high risk population. Indeed, the balance between these two components seems to be greatly dependent on the specific type of beverage considered, as noticeable not only in view of wine over spirits or beer (Estruch et al., 2004, 2011; Chiva-Blanch et al., 2012a, 2013b), but also by comparing white and red wine, the latter at higher content of polyphenols (Sacanella et al., 2007). Noteworthy, the comparison between red wine and de-alcoholized red wine decreased blood pressure in patients at high cardiovascular risk (Chiva-Blanch et al., 2012b), excluding atrial fibrillation.

These findings can be, at least in part, explained by current evidences related to wine chemicals, thus we suppose that beneficial effects of wine on reducing inflammatory and vascular biomarkers could be ascribed not only to phenolic content, but also to the presence of many other phytochemicals, such as melatonin and phytosterols, as recently reported (Ruggiero et al., 2013; Vitalini et al., 2013). Melatonin protects against atherosclerosis-related cardiovascular diseases, resulting from direct free radical-scavenging activity, indirect antioxidant properties and anti-inflammatory activity (Favero et al., 2013). Similarly, phytosterols have been reported to reduce the risk of cardiovascular diseases by inhibiting the absorption of intestinal cholesterol and re-circulating endogenous biliary cholesterol, promoting its excretion (Dhankhar, 2013).

Another additional topic is related to the significant increase of several pre-biotic bacteria after daily consumption of red wine, associated with a decrease of serum biomarkers of cardiovascular disease (Queipo-Ortuño et al., 2012). Changes of bacterial population appear to be caused by wine polyphenols, increasing gut microbiota energy metabolism which, in turn, enhances host lipid metabolism and triglyceride clearance (Queipo-Ortuño et al., 2012).

A further element which strongly affects ethanol vs. phytochemicals equilibrium can be related to genetic factors of individuals, on what concerns genetic variants encoding alcohol metabolizing enzymes (alcohol and aldehyde dehydrogenases, AHD and ALDH), resulting in altered exposure to acetaldehyde, a toxic metabolite of ethanol. If carriers of the AHD1Brs1229984 A-allele are associated with a more favorable cardiovascular profile (Holmes et al., 2014), other studies suggested the association of ALDH2 polymorphism with higher risk of coronary heart disease than other alleles (Quertemont and Didone, 2006; Drogan et al., 2012).

On the basis of these results, a regular light to moderate intake of red wine can be considering beneficial for cardiovascular health. As the matter of facts, during the last decades, the definition of ''moderate alcohol consumption'' changed over countries, corresponding to a generally decreased amount of ethanol considered (Chiva-Blanch et al., 2013b).

However, several limitations can be observed throughout studies above reported, contributing to render decisive assertions more difficult. Firstly, a great methodological heterogeneity among different studies can be detected, resulting not only from the outcomes considered, but also from the different amounts of ethanol and polyphenols contained in diverse wines, using different grapes and wine-making techniques. Their ''equilibrium'' potentially changes each time a new type of wine is taken into account. Secondly, most of works did not investigate the role of a further key element influencing the effect of wine on cardiovascular system: the drinking patterns (Bagnardi et al., 2013b). As already concluded by Chiva-Blanch and co-workers, heavy and/or binge alcohol intakes are confirmed to be relevant risk factors for cardiovascular diseases, while the effect of a light wine intake remains still controversial (Chiva-Blanch et al., 2013a,b).

To elucidate this debate, a full comprehension of wine chemistry as well the role of specific (class of) compounds will be pivotal. Biomedicine-related fields could address to this topic, investigating ethanol and bioactive components, to comprehend which constituent predominates. Interestingly, environmental medicine which explores, among the other topics, the effects of diet on pathophysiological states, will be greatly enriched by studies on wine drinking and wine bioactive phytochemicals, also considering the growing role of this beverage all over the world (Berger, 2011). Moreover, the recent findings concerning the presence of melatonin in wine would open a new field of biomedical research, i.e. chronobiology (Berger, 2011), with the potential use of dietary melatonin in regulating circadian rhythms.

In order to clarify whether wine represents an independent factor for cardiovascular disease, future studies should stratify investigations by ''unique'' intake of wine, as alcoholic beverage. If throughout interventional studies, long-term wine administration is obviously subjected to many ethical restrictions, both in healthy and diseased subjects, observational studies need to be correctly interpreted, because of many bias and confounding factors, in order not to misinterpret random effect and cause–effect relationship. Indeed, additional risk or protective factors, such as smoking habit or a diet rich in fruit and vegetables, respectively, could influence results, as well as publication bias and the possibility of incorrect reporting of alcohol consumption, mainly in defining different drinking patterns.

Conclusions

The studies examined in this survey suggest as red wine may confer an 'added value' compared to other alcoholic beverages, particularly spirits (Fig. 4). As regards cardioprotection, experiments using wine, de-alcoholized wine and spirits, in conditions of moderate intake, point to health benefits deriving from polyphenols and, possibly, other bioactive phytochemicals that may counteract the detrimental effects of ethanol. On the other hand, because of the positive effects of low amounts of alcohol on HDL-cholesterol and haemostatic factors, ethanol and polyphenols may also exert additive and/or synergistic protective effects on cardiovascular system (Hansel et al., 2012; Li and Förstermann, 2012).

However, even if results from clinical trials represent the highest level of evidence in medicine, studies in humans have some intrinsic and environmental limitations. For interventional studies, wine administration is, obviously, subjected to many ethical limitations, both in healthy and diseased subjects. Similarly, observational studies have to be properly interpreted because of many bias and confounding factors, in order not to misinterpret random effect and cause–effect relationship. For instance, Mediterranean populations seem to be more physically active than the north European counterpart, even only for climatic conditions. Another example is related to wine drinkers, which seem to be more health fanatic than beer or spirit consumers. These aspects may ''confound'' the scenario where the clinical studies are conducted.

To conclude, we would like to further clarify the issue of 'regular, low to moderate red wine consumption at main meals'. This sentence indicates that both pattern and amount and wine intake are relevant. Episodic heavy (or binge) drinking is considered more harmful that consumption of less than or equal to 2 drinks per day, but more than 0, for men, and less than or equal to 1 drink per day, but more than 0, for women (Stockley, 2012; Chiva-Blanch et al., 2013b). Lastly, red wine polyphenols, independently from ethanol, reduced the pro-oxidant effects of a fat-rich meal, thus reducing the postprandial susceptibility of LDL to oxidation (Natella et al., 2001).

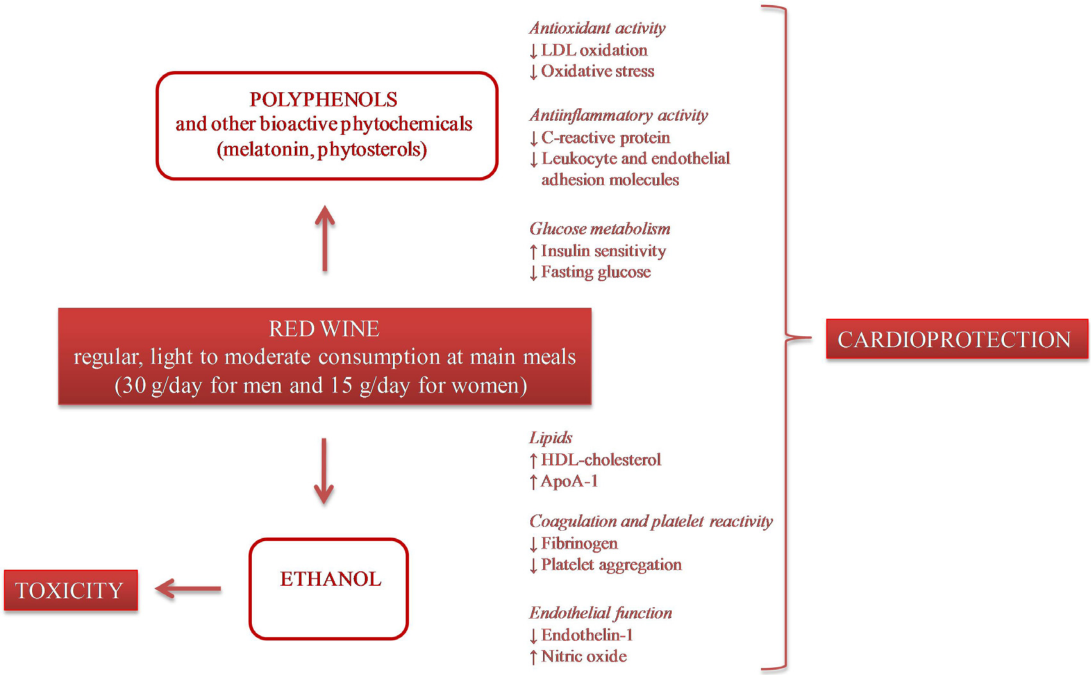

Fig. 4 – Cardioprotective effects attributed to proper red wine consumption are due to both alcoholic and polyphenolic components. Bioactive phytochemicals may also counteract detrimental effects of ethanol. LDL, low-density lipoprotein; HDL, high-density lipoprotein; Apo A-1, apolipoprotein A-1.

Conflict of interests

The authors declare no conflict of interest.

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