

Red Wine Consumption and Cardiovascular Health

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Wine is a popular alcoholic beverage that has been consumed for hundreds of years. Benefits from moderate alcohol consumption have been widely supported by the scientific literature and, in this line, red wine intake has been related to a lesser risk for coronary heart disease (CHD). Experimental studies and meta-analyses have mainly attributed this outcome to the presence in red wine of a great variety of polyphenolic compounds such as resveratrol, catechin, epicatechin, quercetin, and anthocyanin. Resveratrol is considered the most effective wine compound with respect to the prevention of CHD because of its antioxidant properties. The mechanisms responsible for its putative cardioprotective effects would include changes in lipid profiles, reduction of insulin resistance, and decrease in oxidative stress of low-density lipoprotein cholesterol (LDL-C).

Keywords: red wine ; resveratrol ; polyphenols ; alcohol ; cardioprotective ; antioxidants

1. Introduction

Coronary heart disease (CHD) and stroke are the leading causes of mortality, disability, and death in developed countries ^[1]. Most CHDs are due to atherosclerosis, a degenerative process of the arteries which is triggered by oxidative stress and chronic inflammatory status ^{[2][3]}. Smoking, arterial hypertension, hypercholesterolemia, diabetes mellitus, overweight/obesity, lack of physical activity, and genetic factors are known to play a role in determining cardiovascular risk ^[4].

Although excessive alcohol intake is associated with the development of chronic diseases and other serious problems, a wealth of data from scientific evidence support an inverse relationship between moderate alcohol consumption and the risk of CHD ^[5]. Moderate alcohol consumption is defined in the Dietary Guidelines for Americans 2015–2020 as up to one unit of alcohol per day for women and up to two units of alcohol per day for men ^[6].

Several studies provide evidence that light–moderate alcohol consumption is associated with a higher level of high-density lipoprotein cholesterol (HDL-C), a lower incidence of type-2 diabetes (T2D), and a reduction of lipid oxidative stress ^{[7][8][9][10]}. Such epidemiological studies have supported that red wine consumption is more CHD-preventative in comparison to the intake of other alcoholic beverages ^[11]. It is uncertain whether the apparent beneficial properties for health attributed to the consumption of red wine are due solely to the presence of alcohol or also to the concerted action of alcohol and antioxidant compounds other than alcohol present in red wine ^[12]. In addition to alcohol, red wine contains a wide range of active compounds—polyphenols—with antioxidant and anti-inflammatory properties that could contribute to protection from atherosclerotic pathologies ^[13].

Light–moderate drinking of red wine has been proposed as a possible explanation for the epidemiological phenomenon known as the “French Paradox” ^[14], which indicates that the French population shows relatively lower CHD incidence/mortality rate compared with other Western populations, despite their diets contain higher amounts of total fat and saturated fatty acids.

2. Bioactive Components in Red Wine

Red wine contains high concentrations of polyphenolic compounds such as flavonoids (catechin, epicatechin, quercetin, anthocyanins, and procyanidins), resveratrol (3,5,4'-trihydroxystilbene), and polymeric tannins ^[15]. In general, red wine is rich in polyphenols and may be considered as an important polyphenols source in the diet ^[16]. The presence of phenolic compounds in red wine seems to be crucial, since scientific studies have reported that these important secondary metabolites are responsible for desirable biological actions, including cardiovascular protection effects ^{[17][18][19]}.

2.1. Non-Flavonoid

Non-flavonoid phenolic components of grapes and wine include three main groups: stilbenes, benzoic acids, and cinnamic acids [20]. The last two groups can be present as hydroxybenzoic and hydroxycinnamic acids. Benzoic acids are present in the grape as well as in oak wood and, during storage, can migrate into wine [21]. In general, this group of compounds is present in red wine at concentrations ranging from 60 to 566 mg/L.

2.2. Flavonoids

Flavonoids are plant-derived phytochemicals with antioxidant properties that account for over 85% of the phenolic components in red wine [22]. Flavonoids share a common basic structure consisting of a three-ring system with a central oxygen-containing ring (C ring) [23]. The substitution of the central pyran ring and the different oxidation degree are responsible for their chemical diversity [24]. On the basis of these differences, the flavonoids comprise a wide range of compounds such as flavones, flavonols, flavanols, anthocyanidins, and anthocyanins [25]. Natural flavonoids can exist in their free form (aglycone) or as glycosides condensed with the hydroxyl group of a sugar such as glucose, galactose, rhamnose, glucuronide, xylose, and arabinose [26]. They are widely distributed primarily in vegetables, seeds, nuts, spices, herbs, cocoa, and grape skin. The total level of flavonoids can vary from 150 mg/L to 650 mg/L.

Over the last decade, a large amount of experimental and epidemiological investigations has supported the protective effect of flavonoids on cardiovascular and chronic degenerative diseases [27][28]. The cardioprotective effects ascribed to flavonoids against atherosclerosis development might be due to the ability of flavonoids to improve the lipid profiles and reduce insulin resistance and oxidative stress, especially of LDL-C, as suggested by several studies [29][30][31][32].

3. Factors Influencing Bioactive Compounds and Composition of Wine

The genetic factors (variety) of grapes and the vinification conditions are considered the main factors that influence the wine polyphenolic composition [33]. Moreover, some studies have shown that other different variables can also act on grapes phenolic accumulation [34][35]. The agroecological factors that mostly influence the qualitative–quantitative polyphenol content of the grapes can be summarized in the geographic origin of grapes, the climatic and soil conditions, the exposure to diseases, and the degree of ripeness [36]. In red wine production, the methods of winemaking (maceration, fermentation, clarification, aging, etc.) and the processing operations (ionic exchange, filtration, centrifugation) can modify significantly the composition and the concentration of phenolic compounds [37][38]. Moreover, during wine maturation and aging, the concentration of monomeric phenols present in wine declines constantly, while complex and stable molecules derived from the condensation of catechins, anthocyanins, and proanthocyanidin are formed [38][39]. Consequently, the polyphenolic composition of grapes differs from that of their corresponding wines. Some of the reactions occurring during the winemaking process are enzymatic oxidation, electrophilic substitution, complexation, and hydrolysis [40][41]. Moreover, new polyphenolic compounds may also be present in wine for environmental reasons like aging in oak barrels, which promotes the extraction of low-molecular-weight phenolic compounds such as flavonoids and of hydrolyzable tannins, modifying the organoleptic characteristics as well as the health impact of a wine [42].

4. Putative Mechanisms of Action

A large number of epidemiological studies and meta-analysis have consistently shown that light–moderate drinking of red wine has a protective effect against CHD [43][44]. Several plausible underlying biological mechanisms have been postulated to explain the beneficial effects of light–moderate red wine consumption as well as of the phenolic compounds contained in red wine on the development of CHD and atherosclerosis [45][46]. Understanding the mechanisms by which light–moderate drinking of red wine improves the cardiovascular function is crucial for the treatment and prevention of CHD.

4.1. Lipid Profile

Epidemiological studies have consistently shown associations between hyperlipidemia and risk of developing CHD, obesity, and T2D. Light–moderate drinking of alcohol, especially red wine, is associated with beneficial changes in lipid homeostasis, as shown by the results of several clinical trials and meta-analyses.

Da Luz et al. [47] evaluated the association between moderate red wine consumption and changes in HDL-C levels and in the coronary vasculature. The study included 205 subjects (101 and 104 drinkers and abstainers, respectively) aged around 60 years. Red wine drinkers displayed an HDL-C level significantly higher than the abstainers and a protective effect on coronary lesions.

Marques-Vidal et al. [48] had similar results in a large cohort. The study included 5409 subjects categorized as abstainers (0 drinks/week, $n = 1463$), moderate alcohol drinkers (1–13 drinks/week, $n = 2972$), high alcohol drinkers (14–34 drinks/week, $n = 867$), and very high alcohol drinkers (≥ 35 drinks/week, $n = 107$). The results showed that alcohol consumption increased HDL-C levels rather than polyphenols in light moderate drinkers and partly explained the cardioprotective effect displayed by alcohol consumption.

These results were corroborated by Park et al., [49] who investigated the benefits of moderate consumption of alcohol in a hypertensive population with a focus on the lipid profile. The study included 2014 participants aged 20–69 years. The results showed that alcohol consumption was negatively associated with prevalence of low HDL-C, whereas the amount of triglycerides increased with a higher alcohol intake.

Magnus et al. [50] investigated the hypothesis that moderate alcohol intake exerts its cardioprotective function by increasing HDL-C levels with a cohort study of 149,729 participants. The results showed that increasing HDL-C levels is not a relevant mechanism by which ethanol exerts its cardioprotective effect.

A recent meta-analysis [51] examined the effect of moderate alcohol consumption on lipid profile, concluding that alcohol consumption significantly increased the levels of HDL-C, apolipoprotein A1, and adiponectin. Moreover, the results showed that alcohol did not significantly change triglycerides levels.

The findings above-reported support an increase in the plasma HDL-C concentration level as a result of chronic, moderate alcohol consumption. Higher HDL levels have been consistently observed in cohort studies regarding alcohol consumption and attributed to alcohol itself. In fact, alcohol, rather than polyphenols, appears to be responsible for the increase of plasma HDL in wine light–moderate drinkers.

4.2. Glucose Metabolism

The cardioprotective effect of red wine consumption may partly be explained by the association between moderate red wine consumption and a lower incidence of T2D.

Chiva-Blanch et al. [52] showed that moderate consumption of red wine (30 g of alcohol per day) and dealcoholized red wine decreased the homeostasis model assessment of insulin resistance values (HOMA-IR) and plasma insulin after 4 weeks in 67 men at high cardiovascular risk. These results suggest that the beneficial effects could be mediated by antioxidant compounds present in red wine, while alcohol did not seem fundamental to obtain such effects.

Brasnyó et al. [53] investigated the effects of low doses of resveratrol (2×5 mg/day) on glucose metabolism in 19 T2D patients. After 4 weeks, resveratrol improved insulin resistance and increased the phosphorylation of protein kinase B (AKT), which plays a key role in insulin signaling by interfering directly with glycogen synthesis. Therefore, it was concluded that resveratrol might be used for medicinal application.

Da Luz et al. [54] evaluated the association of moderate red wine consumption with changes in glucose levels and diabetes. The study included 205 subjects (101 and 104 drinkers and abstainers, respectively) aged around 60 years. Red wine drinkers displayed a significantly lower incidence of diabetes and lower glucose levels compared to abstainers.

A recent meta-analysis [55] of 20 cohort studies comprising 477,200 subjects confirmed the U-shaped relationship between moderate amounts of alcohol consumption and risk of incident T2D for both sexes compared with lifetime abstainers. The amount of alcohol that showed higher protective effects was 22 g/day for men and 24 g/day for women, while over 60 and 50 g/day of alcohol were deleterious for men and women, respectively. Therefore, in this study, the amount of polyphenols was not considered, and the protective effect was attributed to alcohol.

The cardioprotective effects of moderate alcohol consumption were corroborated by Mekary et al. [56] through a large prospective study including 81,827 participants on the impact of alcohol consumption and the positive association between glycemic load (GL) and the incidence of T2D. They found that a high alcohol intake (≥ 15 g/day) attenuated the effect of GL on T2D incidence.

Ramadori et al. [57] conducted a study on diet-induced obese and diabetic mice to evaluate the impact of approximately 79.2 ng/day intracerebroventricular infusion of resveratrol on glucose metabolism. The results showed a normalized hyperglycemia and improved hyperinsulinemia by the activation of SIRT 1 expressed in the brain.

These findings suggest that a light to moderate alcohol consumption, especially with red wine, may be associated with improved insulin resistance and with a lower incidence of diabetes, providing another potential explanation for the

reduction of cardiovascular events associated with moderate alcohol intake.

4.3. Oxidative Stress

Many important cardioprotective effects of wine polyphenols can be attributed to their capacity to react with reactive nitrogen species (RNS) or to interfere with RNS production. Wine polyphenols are well recognized as potent antioxidant compounds and radical scavengers of peroxynitrite, a reactive substance produced by the reaction between NO and the superoxide anion [58][59]. The inverse association between red wine consumption and mortality from cardiovascular diseases may be explained by the capacity of red wine polyphenols to reduce LDL oxidation [60]. These findings showed that the beneficial effects on LDL oxidation could be exerted by a higher antioxidant activity of red wine compared to beverages with no polyphenolic content.

Estruch et al. [61] studied the benefits of moderate consumption of red wine compared to gin, an alcoholic beverage without polyphenolic content, on the lag phase time of LDL particles. The study was conducted with 40 healthy men aged 38 years, concluding that after 28 days of moderate consumption of red wine (30 g/day). Compared to gin, red wine intake increased up to 11.0 min the lag phase time of LDL oxidation, probably due to its high polyphenolic content.

Similarly, Chiva et al. [62] checked the effects of alcoholic and dealcoholized red wine and gin intake on plasma NO and blood pressure in 67 subjects at high cardiovascular risk. After 4 weeks, the results showed that dealcoholized red wine was able to decrease systolic and diastolic blood pressure and increase plasma NO concentration.

Egert et al. [63] evaluated changes in markers of oxidative stress following quercetin intake in 93 overweight or obese subjects aged 25–65 years. Quercetin is an important flavonoid present in high amounts in red wine and grapes. After 6 weeks, 150 mg/day of quercetin supplementation significantly decreased the plasma concentrations of oxidized LDL. Therefore, it was concluded that quercetin may provide protection against CHD.

Bulut et al. [64] evaluated the effects of alcoholic (red wine and liquor) and non-alcoholic (mineral water and Coke) beverages consumed during a high-fat meal once a week for 4 weeks on circulating microparticles (MPs) in 10 healthy males. Volunteers in the red wine and liquor groups consumed the same amount of alcohol. The results indicated that the number of MPs increased after a single high-fat meal (increase by about 62%), but red wine consumption decreased these negative effects (increase by about 5%).

These findings support that moderate red wine consumption may act as an antioxidant by decreasing oxidized LDL plasma levels and increasing plasma NO concentration. Scientific evidence indicates that oxidized LDL may play a major role in the onset and progression of oxidative stress-associated diseases, such as atherosclerosis [65][66]. Moreover, increased oxidized LDL plasma levels were predictive of future myocardial infarction [67]. Nevertheless, the beneficial effects of moderate red wine consumption on LDL oxidation seem to be independent of its alcohol component.

5. Conclusions

In the last decades, several human and animal studies have indicated that moderate red wine consumption has beneficial effects on health. Phenolic compounds present in red wine have shown antioxidant and anti-inflammatory properties, being able to reduce insulin resistance and to exert a beneficial effect by decreasing oxidative stress. As a consequence, a clear effect on the reduction of risk factors and the prevention of cardiovascular diseases have been observed. Different mechanisms are involved in the cardioprotective effects of moderate red wine consumption: while alcohol appears to be responsible for increasing plasma HDL-C, the polyphenolic component may play a key role in the reduction of T2D incidence and LDL oxidation. In light of these considerations, a moderate intake of red wine may produce cardioprotective effects. However, more in-depth knowledge is required in order to understand the molecular basis of the potential mechanisms involved.

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