Polyphenols are medicine: Is it time to prescribe red wine for our patients?

Alfredo C Cordova MD[1], Bauer E Sumpio MD PhD FICA[2]

AC Cordova, BE Sumpio. Polyphenols are medicine: Is it time to prescribe red wine for our patients? Int J Angiol 2009;18(3):111-117.

Alcohol, specifically red wine, has been suggested to play a key role in the prevention of cardiovascular disease and other chronic pathologies, including cancer. Its regular and moderate consumption has been found in numerous epidemiological studies to correlate inversely with vascular disease and mortality, despite the presence of risk factors such as high consumption of saturated fats, elevated smoking and low physical activity. This phenomenon, known as the 'French Paradox', would be explained mainly by the high levels of polyphenols present in red wine, making it more advantageous than beer, spirits and even white wine. The habit of having one or two drinks of red wine every day with meals may translate to a longer, healthier and better quality of life.

Key Words: *Cardiovascular disease; French Paradox; Polyphenols; Red wine*

Cardiovascular disease (CVD) is a multifactorial pathology and a grave problem of public health. As the most important cause of morbidity and mortality in western industrialized nations, CVD accounts for more than 500,000 deaths from coronary artery disease (CAD) and 170,000 deaths from stroke every year in the United States (US), as reported by the American Heart Association and the American Stroke Association (1). This represents approximately 40% of the total annual mortality in the US. Additionally, in 2008, the estimated direct and indirect cost of CAD and stroke were US$156.4 billion and US$65.5 billion, respectively, for a grand total of US$448.5 billion for all CVDs. In comparison, the estimated cost reported for all cancers in 2007 was US$219 billion (1). The estimated cost for new cases of HIV/AIDS in 2002 was US$36.4 billion (2). Worldwide, cardiovascular pathology accounts for over 16 million deaths every year, which is approximately 30% of the total global mortality (3).

Hypercholesterolemia, arterial hypertension, nicotine abuse, diabetes mellitus and genetic predisposition are all major risk factors for CVD. On the other hand, epidemiological data, multiple clinical trials, animal models, and in vivo and in vitro studies suggest an association between moderate and regular alcoholic beverage consumption, particularly red wine, and a lower risk for CVD (4-7).

In 1786, Heberden was the first to suggest alcohol's beneficial effects on the cardiovascular system (8,9); he noticed the relief of angina pectoris by 'spirituous cordialis'. In 1819, international comparisons suggested the beverage choice as a protective factor (9). One century later, in 1904, Cabot (10) was the first to report an inverse association between alcohol consumption and arteriosclerosis based on observational data. Also in the early 20th century, pathologists observed an inverse association between alcohol and atherosclerosis (9). However, it was not until 30 years ago, when epidemiological studies arose referring to the inverse relationship between alcohol and a lower incidence of CVD, that more interest was given to the topic (11). Furthermore, in 1979, St Leger et al (4) narrowed this association to the consumption of red wine. They based their study on data collected from 18 different developed European and American countries in which mortality from ischemic heart disease was assessed when considering different factors such as health service, gross national product per capita, saturated and monounsaturated fat intake, and alcohol consumption. Renaud et al (7) reported the same correlation in 1992 and introduced the concept of the 'French Paradox'. Their study was based on the MONItoring system for CArdiovascular disease (MONICA) project (12), which included seven million men and women between 35 and 64 years of age from 37 European, American and Asian populations, including the US, Canada, United Kingdom, France and China, among others. This was a tremendous effort by the World Health Organization in which collaborating investigators from 21 countries followed the subjects over a period of 10 years, from the mid-1980s to the mid-1990s. France presented a markedly lower annual mortality from CAD compared with other industrialized nations, despite the fact that cardiovascular risk factors such as cigarette smoking, blood pressure, body mass index and serum cholesterol concentration were similar among these countries; furthermore, it had a three-fold higher intake of saturated fats than that of the US and the United Kingdom, which are not well known for their healthy eating (4). The French consume 2.8 times more lard and 3.8 times more butter than Americans; however, they have a 2.5-fold lower death rate due to CVD (13). There is solid evidence supporting red wine's cardiovascular protective effects. The present review is an effort to get to know and better understand red wine, and present relevant data showing its advantages over other alcoholic drinks, present its mechanisms of action in the vascular system and introduce its role in other pathological processes.

RED WINE, WHITE WINE, BEER OR SPIRITS?

Presently, there are numerous epidemiological studies reporting alcohol's favourable effects on CVD and other pathologies. It has been widely suggested that regular and moderate intake of

[1]*Division of Surgery, Lahey Clinic Medical Center, Burlington, Massachusetts;* [2]*Department of Vascular Surgery, Yale University School of Medicine, New Haven, Connecticut, USA*

Correspondence: Dr Bauer E Sumpio, Department of Vascular Surgery, Yale University School of Medicine, 333 Cedar Street, FMB 137, New Haven, Connecticut 06510, USA. Telephone 203-785-2561, fax 203-785-7609, e-mail bauer.sumpio@yale.edu

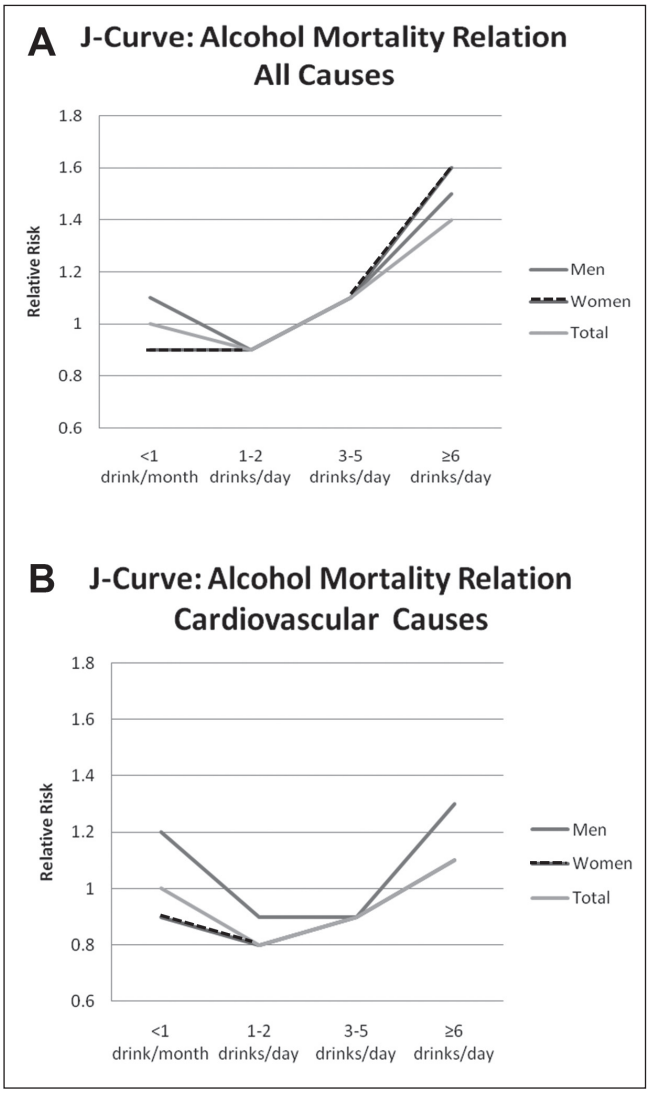


Figure 1) *Alcohol has protective effects against death from all causes* (**A**)*, but excessive amounts of alcohol begin to have detrimental effects on overall health. A notable difference between the effects of alcohol on mortality due to cardiovascular disease* (**B**) *compared with all causes is that consuming three to five drinks per day is protective against death due to cardiovascular disease, but it has an increased RR of death due to other causes. One drink is defined as 15 mL of alcohol, which is equivalent to approximately 120 mL of wine (one half-glass), 355 mL of beer or 30 mL of spirits. Adapted from reference 77*

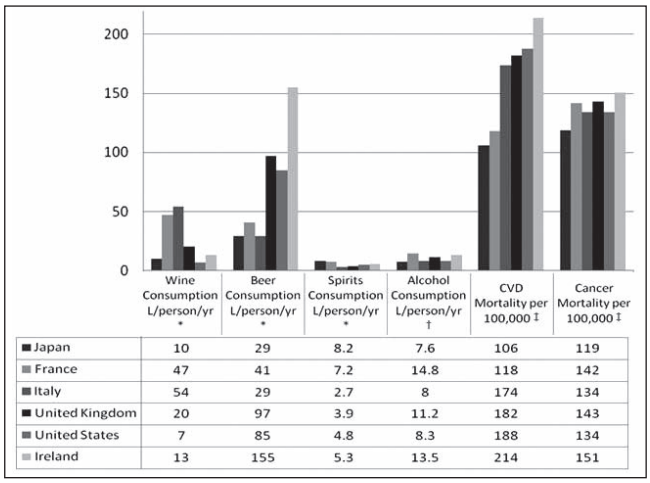
alcoholic beverages, a volume of 32 mL to 52 mL of alcohol per day, is capable of decreasing the risk of CAD by at least 40% (14-17). In a prospective study, 51,529 men without pre-existing cardiovascular or cancer disorders were followed for 12 years with food-frequency questionnaires. The investigators reached the conclusion that ethanol consumption at least three to four times a week is inversely associated with the occurrence of myocardial infarction (Figure 1) (18,19). This relationship was present even with a limited consumption of 15 mL of alcohol per day, which is equivalent to one drink (20). In the majority of reports, one drink is defined as 15 mL of alcohol, which is equivalent to approximately 120 mL of wine (one-half of a wine glass), 355 mL of beer or 30 mL of spirits. It has been suggested that red wine consumption of 20 mL to 32 mL of alcohol per day (150 mL to 265 mL of red wine), which is comparable with the average intake of a French person, has protective properties.

Moderate consumption of alcohol by itself can increase plasma concentrations of high-density lipoprotein (HDL) cholesterol and decrease the adhesiveness of platelets, both of which would prevent or retard the formation of atherosclerosis and thus reduce the risk of CAD (21). Ethanol, present as 8% to 15% of the volume of red wine, has a wide range of biological functions and can act as a fuel source, alter cholesterol composition, impair fluid balance and alter the activity of xenobiotic metabolizing enzymes, such as the cytochrome p450 family, gluthathione S-transferase superfamily and N-acetyl transferases (18,22). Meanwhile, ethanol has been demonstrated to have a pro-oxidant effect (23,24). However, polyphenols, which are present in high amounts in red wine, counteract the potential pro-oxidant effect of ethanol and even confer a net antioxidant activity. In this manner, beverages that have low concentrations of phenolic compounds, such as white wine or beer, may have a pro-oxidant effect (25-27).

Multiple studies have shown that red wine is the most beneficial in reducing the risks of CAD and mortality in general when compared with other alcoholic beverages such as spirits, beer and white wine (Figure 2). The Copenhagen Heart Study (28), which involved 6051 men and 7234 women between 30 and 70 years of age who were followed for 10 to 12 years, reported the association between consumption of different types of alcoholic beverages (wine, beer and spirits) and mortality. This prospective study showed the inverse correlation with overall mortality in people consuming wine, but not in those consuming beer or spirits. Increased consumption of wine decreased the risk of death from cardio- or cerebrovascular disease and from all causes. Compared with abstainers, individuals who consumed three to five glasses of wine a day had an RR of 0.44 (95% CI) for vascular-related deaths and 0.51 for deaths from all causes. Regarding beer, the consumption of three to five glasses a day reduced the RR of cardio- and cerebrovascular deaths to 0.72, compared with an RR of 1.00 for abstainers (19). On the other hand, spirit intake was correlated with an increased risk for both vascular related and other causes of death. In France, alcohol intake is mainly in the form of red wine, thus explaining the low incidence of CVD. However, there are slight variations within France regarding alcoholic preferences and CAD, depending on the area. In Toulouse and the rest of southern France, where the red wine intake is highest, the lowest CAD incidence is observed. In northern cities such as Strasbourg and Lille, more spirits are consumed and there is a relatively higher incidence of this pathological process (18). In another report, Grønbaek et al (29) followed 24,523 men and women between 20 and 98 years of age for a period of 11 years and reached the conclusion that moderate wine drinkers have a 20% lower all-cause mortality risk than nonwine drinkers. These data suggest the relative benefits of wine consumption over other alcoholic drinks.

RED WINE: MYTH OR REALITY?

Wine has been part of human culture, and has served dietary and socioreligious functions since as early as 5400 years BC; however, North Americans are relative latecomers to



	Wine Consumption L/person/yr *	Beer Consumption L/person/yr *	Spirits Consumption L/person/yr *	Alcohol Consumption L/person/yr †	CVD Mortality per 100,000 ‡	Cancer Mortality per 100,000 ‡
Japan	10	29	8.2	7.6	106	119
France	47	41	7.2	14.8	118	142
Italy	54	29	2.7	8	174	134
United Kingdom	20	97	3.9	11.2	182	143
United States	7	85	4.8	8.3	188	134
Ireland	13	155	5.3	13.5	214	151

Figure 2) *Cardiovascular and cancer mortality, and alcohol consumption. This figure depicts cardiovascular disease (CVD) and cancer mortality in relation to alcohol consumption by type. Note that France, while having the second highest consumption of wine in L/person/year (yr), has the second lowest CVD mortality. Adapted from references *78, †79 and ‡80*

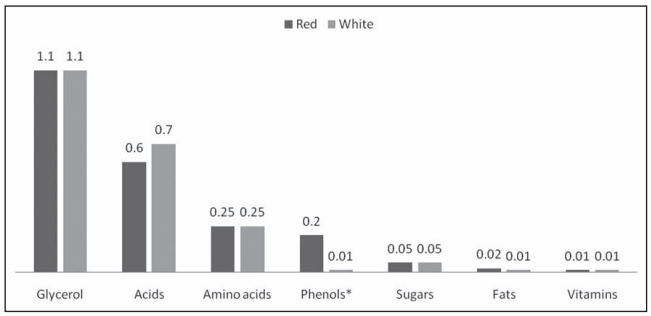


Figure 3) *Components of table wine. Estimates of typical gross composition (percentage weight). *Phenols constitute the major compositional difference between red and white table wines. Water and ethanol content is similar for both types of wine (87% and 10%, respectively). Adapted from reference 30*

viticulture. The first large-scale vineyards were planted by Franciscan missionaries in California only 200 years ago, and were re-established shortly after the repeal of prohibition. Wine grape (*Vitis vinifera*) growing and wine making have been postulated to originate in the South Caucasus, from where they travelled southward to Palestine, Egypt, Syria and Mesopotamia, and later spread to the rest of the Mediterranean and the world predominantly with the spread of Christianity via monastic vineyards. Wine is now produced in many countries throughout the world (30,31).

Red wine is created by a process in which grape juice is fermented for up to two weeks in the presence of the grape skin and seeds. Meanwhile, white wine is produced by pressing the juice away from the grape solids and then allowing it to ferment (32). Influenced by enological techniques, the origin of the grape cultivar and environmental factors, red wine's chemical composition has changed throughout time. Red wine is composed of more than 500 compounds, of which only a few, including water, ethanol, glycerol, sugar and organic acids, are present at levels greater than 100 mg/L. These components are primarily responsible for the taste and mouth sensation of wine. Aromatic compounds, most of which are fusel oil, fatty acid esters and volatile acids, are present at concentrations of 0.8 g/L to 1.2 g/L – fusel oil represents 50% of this total (27). Holding specific sensory characteristics related to its fragrance, red wine is composed of phenols, carbonyls, hydrocarbons, acetals, lactones, sulphur and nitrogen compounds. The majority of the compounds in wine, 160 of which are esters, are present in concentrations ranging from 10^{-1} mg/L to 10^{-6} mg/L. Individually they play a small role, if any at all, in the human organoleptic perception (taste); collectively, their role may be significant (27). Red wine contains a high concentration and a wide variety of polyphenolic substances, most of which come from the extraction derived from the skin and seeds during the fermentation process. These compounds are responsible for the wine's bitterness, astringency and colour, as well as for providing potent antioxidant effects. As such, they are wine's main preservative, allowing for a long aging process (29).

Polyphenolic composition varies among different wines according to the type of grape used, vivification process used, type of yeast that participates in the fermentation, and whether grape solids are present in the maceration process. When the same type of grape is involved, phenolic content may differ depending on the type of soil, weather variations (temperature, rain and humidity) and other biological effects (fungi, insecticides and fertilizers) (33). Water deficit decreases the amount of flavanols and greatly increases the rate of loss during fruit ripening. Polyphenols also decrease as the fruit matures (34). On the other hand, exposure of the grape skins to sunlight strongly favours high levels of some flavonoids (35). Polyphenols are categorized as flavonoids and nonflavonoids. Among the flavonoids are the flavonols (quercetin and myricetin), flavanols or flavan-3-ols (catechin and epicatechin), and the anthocyanins. The nonflavonoids include the stilbenes (resveratrol), hydroxycinnamates (caffeic, caftaric and coutaric acids) and the hydroxybenzoates (29). The presence of ethanol and its solvent properties facilitate the process of polyphenol extraction.

A typical commercial bottle of red wine contains approximately 1.8 g/L of total polyphenols, while a typical bottle of white wine contains only approximately 0.2 g/L to 0.3 g/L of total polyphenols (18). Therefore, the total amount of polyphenols found in a glass of red wine is approximately 200 mg in comparison with only 30 mg in a glass of white wine (Figure 3). Flavonoids constitute the majority of the phenols in red wine. In typical wine making, approximately one-half of the phenolics are extracted during the maceration process. The amount extracted is strongly affected by the types of seed-extracting methods used and is higher with the use of extended maceration techniques. The amount of polyphenols in a wine decreases with prolonged storage due to the formation of insoluble polymers. This could also be attributed to some oxidation reactions (29).

Polyphenols have varying levels of antioxidant characteristics that depend on their chemical structures (36,37). The phenol group is a strong electron donor and is readily oxidized (29). In addition, red wine is rich in catechol-containing compounds that also have antioxidant activity, albeit less than polyphenols. For instance, although the hydroxyl groups on

TABLE 1
Putative mechanisms of the cardioprotective effects of red wine

1. Inhibition of LDL oxidation – free radical scavenging, metal ion chelation, antioxidant sparing, preservation of paraoxonase activity
2. Inhibition of SMC proliferation and vascular hyperplasia – arresting of cell cycle, inhibition of ICAM-1, VCAM-1, PDGF and MMP-9, apoptosis
3. Inhibition of platelet aggregation – inhibition of cyclo-oxygenase pathway and thromboxane B-2 synthesis, and potentiation of prostaglandin
4. Increased HDL – increase apolipoproteins A-1 and A-2, and C 20:5 (omega-3)
5. Vasorelaxation – eNOS expression and nitric oxide release

HDL High-density lipoprotein; eNOS Endothelial nitric oxide synthase; ICAM-1 Intracellular adhesion molecule 1; LDL Low-density lipoprotein; MMP-9 Matrix metalloproteinase 9; PDGF Platelet-derived growth factor; SMC Smooth muscle cell; VCAM-1 Vascular cell adhesion molecule 1. Adapted from reference 77

quercetin and catechin possess similar arrangements, quercetin inhibits low-density lipoprotein (LDL) oxidation to a greater extent, due to its double bond between carbons 2 and 3, and the 4-oxo structure in its C ring (38). Conversely, anthocyanins and polymerized tannins are very poor antioxidants (39). Although tannins are the most abundant of the wine polyphenols, they are not absorbed due to their large molecular size and thus impart no health effects, except perhaps in the gut. Given their control over the processing of grapes to reach a specific flavour, winemakers are ultimately the critical determinants of a wine's polyphenol content (29).

MECHANISMS OF ACTION

Moderate alcohol consumption has convincingly been associated with decreased cardiovascular mortality in epidemiological studies and meta-analyses. This decreased mortality has been attributed to changes in lipid profiles, decreased coagulation and increased fibrinolysis, inhibition of platelet aggregation, increased nitric oxide (NO) and antioxidant capacities of alcoholic beverages. Most of these laboratory and animal studies, as well as intervention trials in human volunteers, have revealed many interesting mechanisms that contribute to the cardioprotective effects of alcohol, red wine or red wine polyphenolic compounds (Table 1).

The exact mechanism of red wine's effects on the cardiovascular system has not been fully elucidated, but there are many pathways in which it is thought to have a role in preventing arteriosclerosis. These include increased antioxidant serum activity, increased resistance of LDL to peroxidation (16,20,32,36,40-45), increased levels of serum HDL cholesterol and enhanced serum paraoxonase activation. It is apparent that alcohol by itself affects cardiovascular events by influencing the levels of lipoproteins in the blood and decreasing the adhesiveness of platelets. High levels of HDL cholesterol are associated with low risks of cardiovascular morbidity and mortality. HDL cholesterol rises with the consumption of alcohol (7,37,46,47). Epidemiological studies have shown that those who consume alcohol moderately develop lower LDL cholesterol levels. High concentrations of LDL cholesterol have not been associated with a risk of CAD in men who consumed three or more drinks per day. In a controlled diet study of premenopausal women, consumption of alcohol over a three-month period was associated with an 8% decrease in LDL cholesterol, a 10% increase in HDL cholesterol and no change in lipoprotein(a) (37). Although alcohol increases the serum levels of HDL cholesterol, it also increases the serum level of triglycerides, which is a risk factor for CVD. However, it appears that the beneficial effects of red wine via polyphenols may counteract this increase in triglycerides.

Alcohol has a direct effect on the status of the coagulation system. A low plasma fibrinogen level is associated with a low risk of CAD, even when LDL cholesterol concentrations are elevated. Alcohol consumption is inversely correlated with fibrinogen levels (19). There is a positive association between moderate alcohol intake and plasma concentrations of plasminogen and endogenous tissue-type plasminogen activator antigen. Moderate consumption of alcohol also enhances postprandial fibrinolytic activity and inhibits platelet aggregation (48). An associated decrease in thromboxane A2 production has also been noted with consumption of alcohol. It is apparent that of the many factors that appear to account for a lower mortality in moderate consumers of alcohol, a substantial benefit may be derived from inhibited clot formation.

Polyphenols are components of wine, particularly red wine, that do not exist in spirits, and exist in low concentrations in beer and malt whiskey. They have been identified as antioxidants, antimutagens, chelators of catalytic metals and free radical scavengers. The antioxidant effects of these phenols counter the pro-oxidant activity of alcohol (23,24). In a crossover study by Micallef et al (49), red wine consumption was found to significantly increase total plasma antioxidant status in both younger and older volunteers. These subjects either consumed 400 mL/day of red wine for two weeks or abstained from alcohol for two weeks before crossing over to the other group; blood samples were obtained both before and after red wine consumption to evaluate the antioxidant status of the blood. This antioxidant effect is believed to be a result of both plasma urate levels and polyphenols (50). Wine polyphenols decrease platelet aggregation and adhesion to endothelium, increase HDL cholesterol independent of the alcohol content of wine and inhibit the oxidation of LDL cholesterol (24,51-54). These compounds inhibit the cyclo-oxygenase and lipo-oxygenase of platelets and macrophages, thereby inhibiting clotting and the inflammatory mediators in a developing atheroma.

Resveratrol has been found to inhibit intracellular adhesion molecule 1 and vascular cell adhesion molecule 1 expression, which promote the adhesion of macrophages to endothelium and their entry into the intima, which then initiates the atherosclerotic plaque (55). This is supported by another study by Sacanella et al (56) that showed decreased levels of cellular adhesion molecules and several inflammatory markers in healthy women volunteering for a crossover study. NO production is stimulated by exposure to red wine and other red grape products, but not white wine, independent of alcohol. A study by Gresele et al (57) noted that, in healthy volunteers, blood levels of NO increased with increased resveratrol levels. They also noted in vitro that washing platelets in 0.5 µmol/L resveratrol, a concentration comparable with drinking 300 mL of red wine, increased their NO production. NO probably influences hemostatic mechanisms such as platelet-vessel wall (collagen) interaction and promotes vasorelaxation.

DECREASED INCIDENCE OF CANCER AND OTHER HEALTH BENEFITS

Red wine consumption has been correlated with a decreased incidence of certain cancers and chronic pathologies. Carcinogens resulting from the combination of tobacco and alcohol use increases the risk of tumours to the oropharynx, larynx and esophagus sixfold compared with abstinence (58). Although the risk of esophageal squamous cell carcinoma more than doubled with beer and tripled with liquor consumption, drinkers of wine had a 40% reduction in risk for all forms of esophageal and gastric cancers (59). Another study suggested that those who drank more than 30% of their total intake as wine had an RR of 0.5 (60). This was confirmed by Vioque et al (61), who examined the risk factors present in Spanish patients with a pathological diagnosis of esophageal cancer and compared them with a frequency-matched selection of those without such a diagnosis. This study showed that any consumption of hard liquor increased the risk for esophageal cancer, while consumption of wine did not have such an effect (61). In vitro studies have shown that flavonoids suppress cancer cell growth and resveratrol inhibits cyclo-oxygenase-2 gene transcription, a factor favouring the growth of cancers. Anthocyanins have been shown to inhibit growth of tumours against cultured human colon cancer cells (HCT-15) and human gastric cancer cells (AGS) (62).

Wine has also been shown to have bactericidal properties against multiple organisms, including *Escherichia coli*, *Salmonella*, *Shigella* and *Helicobacter pylori* (63). Brenner et al (64) reported that the adjusted odds of an *H pylori* infection in those who drank 50 g to 75 g of alcohol each week was one-third that of those who drank less or abstained completely. A prospective cohort study by Aldoori et al (65) indicated that intake of alcohol was not associated with development of peptic ulcer, and that the OR for moderate alcohol consumption was lower than in those who rarely drank. Antiviral properties have also been proposed. Decreased susceptibility to clinical colds was found in nonsmokers who consumed alcohol, with greater alcohol consumption related to a greater reduction in susceptibility to respiratory infection. Smokers were not protected from respiratory infection at any level of alcohol intake (66).

Protection against the formation of stones in the biliary system and the urinary tract has been reported. Consumption of alcohol is associated with a decreased risk of gallstone formation, 10% to 50% less than that for abstainers (67). Regarding nephrolithiasis, analysis of 45,289 men in the Health Professionals Follow-up Study (68) showed that increasing fluid intake decreased the risk of stone formation. The decrease in risk of stone formation varied according to the type of beverage – caffeinated coffee by 10%, decaffeinated coffee by 10%, tea by 14%, beer by 21% and wine by 39%. In a similar study of 81,093 women in the Nurse's Health Study (69), the results of fluid intake and the influence of beverage type were comparable.

An analysis of alcohol and age-related macular degeneration from the National Health and Nutrition Examination Survey-1 (NHANES-1) (70) showed that there was a significant negative association between alcohol consumption and age-related macular degeneration; this was particularly significant for wine.

Multiple studies show a direct correlation between the consumption of alcohol and the preservation of bone density in men and women of the older population. In most of these studies, the type of alcoholic beverage was not analyzed, but in one study there was a trend showing wine to be more protective than other beverages (71). There was a lower incidence of bone fractures in the elderly who consumed moderate amounts of alcohol (72).

Studies have shown cognitive function to be better in moderate drinkers compared with abstainers or abusers (73). In a prospective cohort study involving 3767 residents near Bordeaux (France) who were older than 65 years of age, moderate wine drinkers were shown to have a reduced OR of 0.18 for Alzheimer's disease and dementia compared with nondrinkers (74). Fourteen thousand middle-aged adults in the Atherosclerotic Risk in Communities (ARIC) study (75) showed that moderate drinkers had higher cognitive scores than nondrinkers. In the Framingham Heart Study (55,76), subjects were given cognitive tests, and it was noted that female moderate drinkers performed better than abstainers; this correlation was weaker for men.

CONCLUSION

Regular and moderate consumption of red wine, perhaps one or two drinks a day with meals, should be encouraged. As discussed, this would lead to a decreased incidence of CVD as well as other pathologies such as hypertension, peptic ulcer disease, respiratory infections, cholelithiasis, nephrolithiasis, macular degeneration, Alzheimer's disease and even cancer. It may even improve our cognitive function. However, sound clinical judgment should be used in determining whether alcohol consumption is an appropriate recommendation for each patient, taking into account factors such as contraindications with other medications. It is also important that a distinction be made between moderate use of alcohol and its abuse. Let us keep in mind that there is a small portion of the population that may be prone to addiction, or fail to moderate consumption, and therefore may present a hazard to society via acts of violence, accidents, and spousal, child and elder abuse, as well as incurring detrimental effects on their own health. Maintaining a healthy diet and lifestyle should not be a choice but a responsibility. For this reason, by all means, we must maintain an organized life with a healthy diet, regular exercise and adequate sleep. Dietary and lifestyle habits proven to be beneficial by the medical community or society must be sought. In these terms, the regular consumption of red wine in a moderate fashion, one to two drinks a day (one-half to one glass), constitutes a solution, to some extent, to the grave public health problem of CVD as well as for some other chronic illnesses, including cancer.

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ACKNOWLEDGEMENTS: Individuals who contributed significantly to the research or preparation of the manuscript may be acknowledged. When this is done, the letter of transmittal should indicate that all those named have given their permission.

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