Red wine: A drink to your heart

T.S. Mohamed Saleem, S. Darbar Basha

Department of Pharmacology, Annamacharya College of Pharmacy, New Boyanapalli, Rajampet - 516 126, Andhra Pradesh, India

Address for correspondence: Mr. T.S. Mohamed Saleem Department of Pharmacology, Annamacharya College of Pharmacy, New Boyanapalli, Rajampet - 516 126, Kadapa Dt., Andhra Pradesh, India.
Email: saleemcology@gmail.com

ABSTRACT

Mortality and morbidity are still high in cardiovascular disease (CVD). Myocardial ischemia reperfusion injury leading to myocardial infarction is one of the most frequent causes of the death in humans. Atherosclerosis and generation of reactive oxygen species through oxidative stress is the major risk factor for CVD. From the literature collection, it has been identified that moderate consumption of red wine helps in preventing CVD through several mechanisms, including increasing the high-density lipoprotein cholesterol plasma levels, decreasing platelet aggregation, by antioxidant effects, and by restoration of endothelial function. The aim of this review is to discuss the accumulating evidence that suggests that red wine possesses a diverse range of biological actions and may be beneficial in the prevention of CVD.

Key words: Alcohol, flavonoids, grape juice, polyphenols, resveratrol, wine research

INTRODUCTION

Since ancient times, cardiovascular disease (CVD) has become a known, life-threatening problem for the world. The risk factors and higher mortality from CVD have been proved without doubt from the well-developed countries of Western Europe, North America and East Asia, as well as for the vast majority of developing countries and even the large urban centers of sub-Saharan Africa. The highest majority of risk factors for this overall mortality are industrial exposure according to their profession, changing dietary habits, lifestyle and increasing obesity. Moreover, tobacco smoking is highly prevalent and risk factors for atherosclerosis tend to occur earlier in life, accounting for earlier presentation of CVD events. CVD is a leading cause of mortality and is responsible for one-third of the global deaths. Nearly 85% of the global mortality and disease burden from CVD is borne by low- and middle-income countries. In India, for example, approximately 53% of the CVD deaths are in people younger than 70 years of age; in China, the corresponding figure is 35%. The majority of the estimated 32 million heart attacks and strokes that occur every year are caused by one or more of the following cardiovascular risk factors – hypertension, diabetes, smoking, high levels of blood lipids and physical inactivity – and most of these CVD events are preventable if meaningful action is taken against these risk factors. The prevalence of coronary artery disease (CAD) in urban North India varies from 7% to 10% compared with 3% in USA. The CAD rates in South India are two-folds higher than that in North India, with Kerela reporting 14% in urban and 7% in rural Thiruvananthapuram.

A recent report from the World Health Organization (WHO) stated that mortality from CVD in countries of Sothern Asia, including India, Pakistan and Bangladesh, is not as high as that of Central Asian countries, but is significantly higher than that of East Asian countries.
Large variation, however, likely exists within these countries between the urban and nonurban populations.

Epidemiological studies have shown that consumption of foods and beverages rich in natural polyphenols, including those presented in grape fruit, vegetables, tea or red wine, is associated with lower incidence of CVDs and, especially, with ischemic heart disease. Moderate wine consumption markedly decreased the cardiovascular and cerebrovascular ischemic events, which has been proven by many epidemiological studies. Red wine may exert its effect by different mechanisms, such as the ability to raise the high-density lipoprotein (HDL) levels, to increase the antioxidant plasmatic potential, to improve endothelium-dependent vasodilation and to inhibit platelet aggregation and leukocyte adhesion. Particularly, nonalcoholized red wine has a protective mechanism due to its active components like polyphenols, quercetin and resveratrol. The protective mechanism of these components was already proven by many human and animal studies. The present review is aimed at compiling data based on the reported works on red wine and the promising active principles of red wine to prevent CVDs.

RED WINE: A POTENT ANTIOXIDANT

For many years, the emphasis has been on the relationship between serum total cholesterol levels and the risk of CVD. However, the focus has recently shifted to oxidative stress induced by reactive oxygen species (ROS) and nitrogen-reactive species as important key players in the etiology and pathogenesis of various chronic diseases, including CVD. Antioxidant nutrients are believed to slow down the progression of atherosclerosis due to their ability to inhibit the damaging oxidative processes. Epidemiological and prospective studies have shown that consumption of antioxidant vitamins such as vitamin E and β-carotene could reduce the risk of CVD. Clinical trials also suggest a reduced risk of CVD with vitamin E supplementation. The protective effect of vitamin E can be ascribed to its antioxidant properties. Observations that men and women with CVD show lower levels of circulating antioxidants have led scientists to support the proposed protective role of antioxidants in the prevention and management of CVD. Red wine-active principles like red wine polyphenols, resveratrol and quercetin have experimental cardioprotective properties and may counter one of the mechanisms underlying its antioxidant potential. The cardioprotective properties of individual red wine components are discussed below.

Red wine polyphenols

Many research and epidemiological studies have shown that intake of polyphenols as grape juice and red wine is associated with a reduced risk of CVD. The most active polyphenol present in red wine is flavonoids, and it is important due to its putative antioxidant properties. The cardiovascular benefits of red wine flavonoids are explained in the French Paradox phenomenon as well as in the Mediterranean diet.

Several studies have documented a protective role of moderate wine consumption (15.5–31 g alcohol/day) in both vascular and nonvascular diseases. Different mechanisms may be responsible for these beneficial effects, including increases in the HDL-cholesterol plasma levels, decreased platelet aggregation, antioxidant effects and restoration of endothelial function by flavonoids. Numerous cross-sectional, observational and controlled studies reveal a range of red wine effects on the different aspects related to CVD. In a recent research, it has been reported that red wine elicits different metabolic, autonomic and endothelial responses among individuals with hypercholesterolemia or arterial hypertension and healthy controls. Chronic administration of moderate amounts of red wine has been associated with a protective effect on the cardiovascular system. Impaired endothelium-dependent relaxation in both animals and humans is playing a major role in the development of CVD, such as atherosclerosis and hypertension. Generation of ROS is one of the factors for endothelium dysfunction, particularly superoxide anions, which reduce the bioavailability of nitric oxide (NO). Although red wine polyphenols have antihypertensive properties, the possibility that they prevent the oxidative stress-induced endothelial dysfunction remains to be determined. In one research, it has been...
reported that intake of red wine polyphenols prevents Angiotensin (Ang) II-induced hypertension and endothelial dysfunction. Prevention of vascular nicotinamide adenine dinucleotide phosphate (NADPH) oxidase induction and preservation of arterial NO availability during Ang II administration likely contribute to this effect.\[19]\ Red wine polyphenols and a grape skin extract also reduced the blood pressure in \( \text{N}^\circ -\text{nitro-L-arginine methyl ester (L-NAME)} \) and desoxytocicosterone acetate (DOCA) salt-induced hypertensive rats.\[25,30]\ In another study, it has been reported that chronic administration of red wine polyphenols brings about a reduction in blood pressure and vascular dysfunction through reduction in vascular oxidative stress.\[29]\ Inflammation plays a vital role in the pathogenesis of atherosclerosis, which is a known risk factor for CVD. High levels of fibrinogen and C-reactive protein (CRP), both markers of inflammation, are associated with a risk of developing CVD. In one randomized controlled crossover trial, it has been reported that red wine consumption markedly decreases the level of fibrinogen, but it does not have any effect on the CRP level.\[29]\ The effects of short-term oral administration of red wine polyphenolic compounds (20 mg/kg/day for 7 days) on the hemodynamics, ex vivo cardiac responsiveness and ischemia reperfusion injury were investigated in rats. From this study, it has been concluded that short-term treatment with red wine polyphenols decreases blood pressure and cardiac responsiveness and protects against posts ischemic infarction via decreased oxidative stress. All the above effects of red wine polyphenols are sensitive to NO synthase inhibition, which implies an involvement of the NO-dependent pathway. This study suggests a basis for the beneficial effects of red wine against CVD.\[8]\ The same research group already reported that the in vivo cardiovascular action of red wine and also the oral administration of red wine polyphenols was able to produce a decrease in blood pressure in normotensive rats.\[9,29]\ This hemodynamic effect was associated with an enhanced endothelium-dependent relaxation and induction of the expression of inducible NO synthase and cyclooxygenase 2 within the arterial wall. Moreover, red wine polyphenols accelerated the regression of blood pressure and improved the structural and functional cardiovascular changes, including cardiac fibrosis, in hypertensive rats.\[25,30]\ In another study, it has been reported that red wine polyphenolic compounds exert a powerful protective effect on the endothelial cells from the injury caused by carbon tetrachloride (CCl4). This effect was documented by decreased endothelium, with corresponded to the diminished endothelial cell swelling and detachment evaluated by histology of the vascular intima.\[31]\ The endothelium-protective effect may be one of the key factors that contribute to the preventive action of red wine on CVDs. Hozumi et al.\[32]\ reported that daily intake of red wine polyphenols may benefit patients with or without CVD by increasing the coronary microcirculation. In patients with CAD, 250 ml of de-alcoholized Greek red wine decreased the arterial stiffness and improved the augmentation index, as derived from arterial wave reflection patterns. A similar dose of de-alcoholized red wine decreased the adverse post-smoking arterial wave reflections and lessened the rise in systolic blood pressure. Brachial artery flow-mediated vasodilation was improved by 250–500 ml of de-alcoholized red wine.\[33]\ Several epidemiological studies suggest that moderate alcohol intake, especially red wine, decreases cardiac mortality due to atherosclerosis. The alcohol effect is described by a J curve, suggesting that moderate drinkers may benefit while abstainers and heavy drinkers are at higher risk.\[34]\ Wine drinkers have higher HDL levels than that of nonwine drinkers. The ingestion of red wine is associated with an increase in the antioxidant activity in the serum, an increase in apolipoprotein A-1 and a decrease in the atherogenic agent lipoprotein (a), mainly due to the presence of flavonoids and stilbenes. It has been further suggested that this increase in the antioxidant activity in patients regularly drinking red wine may be the primary factor inhibiting LDL oxidation, which, in turn, reduces atherosclerotic complications.

**RESVERATROL**

Interest in this compound has expanded in recent years, when numerous epidemiological studies showed an inverse correlation between red wine consumption and incidence of CVDs. Accumulating evidence indicates that resveratrol may confer a protective action on the cardiovascular system. The cardiovascular benefits of resveratrol may relate to protecting the heart cells from ischemia reperfusion injury, inhibiting platelet aggregation and decreasing plasma triglycerides and cholesterol
accumulation in the aorta. Furthermore, it can also relax the coronary arteries. It seems likely that resveratrol might be partly responsible for the cardiovascular benefits associated with wine consumption.\[10,33\] Resveratrol is a potent vasodilator and, in several researches, it has been reported that the vasorelaxant properties of resveratrol might be due to NO-mediated relaxation.\[36\] Novakovic et al.\[37\] reported that resveratrol induces relaxation of the human internal mammary artery (HIMA) rings without endothelium. It seems likely that 4-AP- and margatoxin-sensitive K+ channels located in the vascular smooth muscle mediated the relaxation of HIMA produced by resveratrol. In addition, the vasodilator effect of resveratrol through NO-mediated endothelium-dependent relaxation in spontaneous hypertensive rats was also reported.\[37\] A separate experiment showed that chronic resveratrol administration enhanced the endothelium-dependent vasodilation in ovariectomized, stroke-prone, spontaneously hypertensive rats.\[38\]

Resveratrol shortened the duration of action potential in papillary muscles in normal guinea pig and also decreased the maximal velocity of phase 0 depolarization in partially depolarized papillary muscles. In addition, resveratrol inhibited delayed-after depolarization and triggered activity induced by ouabain and high Ca\textsuperscript{2+} in the papillary muscle of guinea pigs in a dose-dependent manner.\[39-44\] In another research, it was found that resveratrol inhibited the spontaneous discharges of neurons in the CA1 area of rat hippocampal slices. These effects were likely due to a decrease of calcium influx.\[45\] Zheng et al.\[46\] reported that resveratrol decreased the intracellular calcium concentration in rat cardiac myocytes. The inhibition of voltage-dependent Ca\textsuperscript{2+} channel and tyrosine kinase and alleviation of Ca\textsuperscript{2+} release from the sarcoplasmic reticulum (SR) are possibly involved in the effects of resveratrol on rat ventricular myocytes. Intake of resveratrol as red wine also increases the production of platelet-dependent NO and, in this way, it decreases the proinflammatory pathway of p38MAPK thus inhibiting ROS production and, ultimately, platelet function. This activity may contribute to the beneficial effects of moderate wine intake on ischemic CVD.\[11\]

Resveratrol may exert a protective effect against cell death through many signaling pathways. Hwang et al.\[47\] reported that resveratrol may exert a protective effect on damage to heart muscle through modulation of the AMP-activated kinase (AMPK) signaling pathway. Resveratrol induced a strong activation of AMPK and inhibited the occurrence of cell death caused by treatment with H\textsubscript{2}O\textsubscript{2}. Under the same conditions, inhibition of AMPK using dominant negative AMPK constructs dramatically abolished the effect of resveratrol on cell survival in H\textsubscript{2}O\textsubscript{2}-treated cardiac muscle cells. These results indicate that resveratrol-induced cell survival is mediated by AMPK in H\textsubscript{9}c\textsubscript{2} cells, and may exert a novel therapeutic effect on oxidative stress induced in cardiac disorders.

Ray et al.\[48\] reported that resveratrol can ameliorate myocardial ischemia reperfusion injury. In this research, they found that administration of resveratrol to the rat provides cardioprotection by decreasing the oxidative stress generated in the ischemic-reperfused myocardium. The antiischemic effect of resveratrol in another study states that the resveratrol-treated hearts showed better functional recovery at reperfusion and significant vasodilation, but no variation in high-energy phosphates. This suggests that long-term moderate resveratrol consumption could play an important role in late cardioprotective effects.\[49\] A preliminary study carried out by the same research group reported that 10 min of resveratrol infusion (10 μM) in Langendorff-perfused rat hearts caused a 40% decrease in the baseline phosphorylation potential without affecting contractility. The level of effluent adenosine was increased by 68%, and paralleled a 50% increase in coronary flow. They suggested that an increase in the adenosine bioavailability is involved in resveratrol-mediated cardioprotection.\[49\]

The dose-dependent activity of resveratrol was evaluated by Das et al.\[50\] by using the ischemic myocardium in rats. The results thus indicate that at, lower doses, resveratrol exerts survival function by upregulating the antiapoptotic and redox proteins Akt and Bcl-2, while at higher doses, it potentiates a death function by downregulating the redox proteins and upregulating the proapoptotic proteins.

In another study, it has been reported that resveratrol prevents leukocyte recruitment and endothelial barrier disruption induced by a number of superoxide-dependent proinflammatory stimuli, including ischemia and reperfusion, hypoxanthine and xanthine oxidase (HX/XO) or platelet activating factor. These salutary effects appear to be related to the antioxidant properties of resveratrol and contribute to the cardioprotective actions associated with the consumption of red wine.\[51\]

The protective role of resveratrol in ischemia reperfusion injury is well defined by many researchers. The mitochondrial permeability transition pore (mPTP) opening has been proposed to play an important role in myocardial ischemia/reperfusion injury. The mPTP remains closed during ischemia but opens at the onset of reperfusion, and
modulation of the mPTP opening at early reperfusion can protect the heart from reperfusion injury. Because resveratrol protects the heart through a NO-dependent mechanism, and NO has been demonstrated to prevent the mPTP opening, it is possible that resveratrol could modulate the mPTP opening at reperfusion.\textsuperscript{[53]}

**QUERCETIN**

Quercetin is one of the most important flavonoids present in red wine. The antioxidant and protective mechanisms in various ischemic conditions were proved by many researches. It has been reported that quercetin inhibited thrombocyte aggregation\textsuperscript{[53]} and had an antihypertensive effect through vasodilator action on the vascular smooth muscles.\textsuperscript{[54]} The studies that focused on the antioxidant efficiency of flavonoids against ischemia/reperfusion (I/R) injury have demonstrated that quercetin possesses robust protective effects in renal, cerebral and hepatic I/R models.\textsuperscript{[55-57]} Quercetin was also demonstrated to improve the contractile function of the left ventricle in experimental myocardial infarction with subsequent 24-h reperfusion.\textsuperscript{[58]} Ikizier et al. reported that quercetin has the capacity to protect the myocardial tissue against global ischemia and reperfusion injury. In instances where the molecule is administered for the purpose of acute therapy, this cardioprotective effect of a significant degree can be observed, and the protective action might be due to its antioxidant and cytoprotective actions.

**CONCLUSION**

CVDs are now a current major problem in causing mortality in both Western and developing countries. Oxidative stress associated with atherosclerosis and endothelium-dependent vascular inflammation plays a major role in the development of CVD. Red wine contains antioxidative components like resveratrol, proanthocyanidine, quercetin, etc. and these active components exert protective functions like free radical scavenging effects, decreasing the oxidative stress and reducing the inflammatory atherosclerotic lesion in both animals and humans, which is evident in this review. From these findings, it has been concluded that red wine as a diet supplement might be beneficial for cardiovascular risk factors.

**REFERENCES**

1. Tarik M, Ramahi. Cardiovascular disease in the Asia Middle East Region: Global trends and local implications. Asia Pac J Public Health 2010;22:83.
2. Boni A, Lorenzoni R, Lazzari M, Gemignani C, Bovenzi F. Cardiovascular risk management: An overview. Curr News Cardiol 2007;9:407-16.
3. Reddy KS, Yusuf S. Emerging of cardiovascular disease in developing countries. Circulation 1998;97:596-601.
4. Reddy KS. Cardiovascular disease in India. World Hlth Stat 1993;46:101-7.
5. Desteefano F, Merri TK, Anda RF. Trends in coronary heart disease in the United States, 1980 through 1989. Arch Intern Med 1993;153:2489-94.
6. Begum R, Singh RB. Prevalence of CAD and its risk factors in urban population of South and North India. Acta Cardiol 1995;53:227-40.
7. Kutty RV, Balakrishnan KG, Jayashree AK, Thomas J. Prevalence of CAD in rural population of Thruvanthapuram, Kerela, India. Int J Cardiol 1993;39:59-70.
8. WHO-World Health Organization. World Health Statistics 2009. Available from: http://www.who.int/whosis/whostat/2009/en/index.html. [accessed on 2010 Feb 20].
9. Ranaivo HR, Diebolt M, Andriantsitohaina R. Wine polyphenols induce hypotension, and decrease cardiac reactivity and infarct size in rats: Involvement of nitric oxide. Br J Pharmacol 2004;142:671-8.
10. Pechanova O, Rezzani R, Babal P, Bernatova I, Andriantsitohaina R. Beneficial effects of Provinols\textsuperscript{™}. Cardiovascular system and kidney. Physiol Res 2006;55:17-30.
11. Gresele P, Pasquale P, Anna MM, Giuseppe G, Andrea G, Stefania M, et al. Resveratrol, at concentrations attainable with moderate wine consumption, stimulates human platelet nitric oxide production. J Nutr 2008;138:1602-8.
12. Ames BN, Gold I, Willer WC. Causes and prevention of cancer. Proc Natl Acad Sci USA 1995;92:5258-65.
13. Parthasarathy S. Mechanisms by which dietary antioxidants may prevent cardiovascular diseases. J Med Food 1998;1:45-51.
14. Stephens NG, Parsons A, Schofield PM, Kelly F, Cheeseman K, Mitchinson MJ. Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). Lancet 1996;347:781-6.
15. Heller FR, Descampes O, Hondejkijn JC. LDL oxidation: Therapeutic perspectives. Atherosclerosis 1998;137:S25-31.
16. Andrade AC, Cesena FH, Consolim-Colombo FM, Coimbra SR, Benjó AM, Krieger EM, et al. Antithrombotic effect of polyphenols in experimental models: A mechanism of reduced vascular risk by moderate wine consumption. Ann NY Acad Sci 2002;957:174-88.
17. De Gaeta no G, De Curtis A, di Castelnuovo v, Donati MB, Iacovi ello L, Rotond o S. Antithrombotic effect of polyphenols in expert mental models: A mechanis m of reduced vascular risk by moderate wine con-sumption. Am NY Acad Sci 2002;957:174-88.
18. Sarr M, Chataigneau M, Martinin S, Schott C, Jasser EL, Min-Ho O, et al. Red wine polyphenols prevent angiotensin II-induced hypertension and endothelial dysfunction in rats: Role of NADPH oxidase. Cardiovascular Research 2006;71:794-802.
19. Mombaulli JV, Vanhoutte PM. Endothelial dysfunction: From physiology to therapy. J Mol Cell Cardiol 1999;31:61-74.
20. Taddel S, Virdis A, Ghidioni L, Magagna A, Pasini AF, Garbin U. Effect of calcium antagonist or beta blockade treatment on nitric oxide-dependent vasodilatation and oxidative stress in essential hypertensive patients. J Hypertens 2001;19:1379-86.
21. rajagopalan S, Kurz S, Munzel T, Tarpey M, Freeman BA, Griendling KK. Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADPH/NADPH oxidase activation. Contribution to alterations of vasomotor tone. J Clin Invest 1996;97:1916-23.
22. Miller FJ, Gutterman DD, Ris o CD, Heistad DD, Davidson BL. Superoxide production in vascular smooth muscle contributes to oxidative stress and impaired relaxation in atherosclerosis. Circ Res 1998;82:1298-305.
23. Pagano PJ, Clark JK, Cifuentes-Pagano ME, Clark SM, Callis GM, Quinn MT. Localization of a constitutively active, phagocyte-like NADPH oxidases in rabbit aortic adventitia: Enhancement by angiotensin II. Proc Natl Acad Sci USA 1997;94:14483-8.
24. Berntoiva I, Pechanova O, Babal P, Kysela S, Svrtrina S, Andriantsitohaina R. Wine polyphenols improve cardiovascular remodeling and vascular function in NO-deficient hypertension. Am J Physiol Heart Circ Physiol 2002;282:H1942-8.
25. Soares de Moura R, Costa Viana FS, Souza MA, Kovary K, Guedes DC, et al. Antihypertensive, vasodilator and antioxidant effects of vinifera grape-skin extract. J Pharm Pharmacol 2002;54:151-20.

26. Rush JW, Quadrilatero J, Levy AS, Ford RJ. Chronic resveratrol enhances endothelium-dependent relaxation but does not alter eNOS levels in aorta of spontaneously hypertensive rats. Exp Biol Med 2007;232:814-22.

27. Lopez-Sepulveda R, Rosario J, Miguel R, Maria JZ, Manuel S, Manuel GG, et al. Wine polyphenols improve endothelial function in large vessels of female spontaneously hypertensive rats. Hypertension 2008;51:1088-95.

28. Rutterstol I, Berge KE, Braaten O, Lars E, Terje R, Sandvik L. A daily glass of red wine: Does it affect markers of inflammation? Alcohol Alcoholism 2005;40:102-5.

29. Diebolt M, Bucher B, Andriantsitohaina R. Wine polyphenols decrease blood pressure, improve NO vasodilation, and induce gene expression. Hypertension 2001;38:159-65.

30. Babal P, Danihel L, Černa A, Janega P, Andriantsitohaina R, Pechnova O. Red Wine polyphenols prevent endothelial damage induced by CCl4 administration. J Nutr Res 2006;55:245-51.

31. Hozumi T, Sugioka T, Shimada K, Kim SH, Kuo MY, Miyake Y, et al. Beneficial effect of short term intake of red wine polyphenols on coronary microcirculation in patients with coronary artery disease. Heart 2006;92:681-2.

32. Opie LH, Lecour S. The red wine hypothesis: From concepts to protective signalling molecules. Eur Heart J 2007;28:1683-93.

33. Da Luz PL, Coimbra SR. Wine, alcohol and atherosclerosis: Clinical evidences and mechanisms. Braz J Med Bio Res 2004;37:1275-95.

34. Wu JM, Wang ZR, Hsieh TC, Bruder JL, Zou JG, Huang YZ. Mechanism of endothelium independent vascular relaxation but does not alter eNOS levels in aorta of spontaneously hypertensive rats. Exp Biol Med 2007;232:814-22.

35. Chen CK, Pace-Asciak CR. Vasorelaxing activity of resveratrol and quercetin of spontaneously hypertensive rats. Hypertension 2008;51:1088-95.

36. Saleem and Basha.: Red wine: A drink to your heart

Source of Support: Nil, Conflict of Interest: None declared.