JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

ARTICLE

pubs.acs.org/JAFC

Red and White Wines Inhibit Cholesterol Oxidation Induced by Free Radicals

Ling Tian,[†,#] Hua Wang,[†] Ahmed Moursy Abdallah,[§] Witoon Prinyawiwatkul,[#] and Zhimin Xu[*,#]

[†]College of Enology, Northwest A&F University, Shaanxi, Yangling 712100, China

[§]Department of Dairy and Food Sciences and Technology, Suez Canal University, Arish 41522, Egypt

[#]Department of Food Science, Louisiana State University Agricultural Center, Baton Rouge, Louisiana 70803, United States

ABSTRACT: The capabilities of two red (RW) and two white wines (WW) in inhibiting cholesterol oxidation were evaluated using a cholesterol emulsion (CE) system. Each RW or WW was mixed with CE at different (v/v) ratios. Cholesterol oxidation was accelerated by a free radical generator, 2,2′-azobis(2-methylpropionamidine) dihydrochloride (AAPH), at 37 °C. The major oxidation product, 7-ketocholesterol, was monitored to determine cholesterol stability in the CE system. At a ratio of 1:250 (RW/CE), 7-ketocholesterol production was not detected during 72 h of oxidation. At a 1:1000 ratio, the inhibition rate of each RW was maintained at 100% at 24 h but decreased afterward. Both WWs had 100% inhibition rate within 48 h at a ratio of 1:10. Also, the capabilities of catechin and resveratrol solutions (1 mg/mL) in inhibiting cholesterol oxidation were studied. Each of the wine polyphenolics showed a 100% of 7-ketocholesterol inhibition rate in 24 h at a ratio of 1:500 (solution/CE). However, the inhibition rate of resveratrol was lower than that of catechin at 48 or 72 h. The results demonstrated that red wine possesses great anti-cholesterol-oxidation capability, which may contribute to health benefits in preventing cardiovascular diseases. Catechin may play a more important role than resveratrol in inhibiting cholesterol oxidation.

KEYWORDS: cholesterol, wine, antioxidant, oxidation, catechin, resveratrol

INTRODUCTION

Many epidemiological studies have demonstrated that wine has health benefit functions of reducing blood platelet aggregation and preventing cardiovascular diseases.[1,2] Being different from other alcohol beverages, wine is rich in various polyphenolic compounds that possess antioxidation activity and may contribute to health benefits. Although anthocyanins and catechin are the major polyphenolic compounds in red wine, recently, resveratrol, which is released from the grape skin and seeds during the wine fermentation process, was reported to reduce the risk of atherosclerosis diseases.[2,3] Compared with anthocyanins, catechin and resveratrol are more bioavailable and found in the bloodstream without degradation after intake of red wine.[4]

Cardiovascular diseases have been confirmed to closely link to higher low-density lipoprotein (LDL) cholesterol level and cholesterol oxidation.[5] The oxidation of cholesterol is initiated by free radicals or active oxygen to produce a major cholesterol oxidation product, 7-ketocholerserol, and other compounds, such as 5,6-epoxycholesterol and 7-hydroxycholesterol.[6] The higher cholesterol level could lead to higher possibility of cholesterol oxidation, which produces toxic oxidation products that damage the macrophage and endothelial cells in blood vessels.[5] The malfunction of those cells directly affects cholesterol metabolism in the human body. The abnormal metabolism causes cholesterol to gradually deposit on the inside wall of blood vessels to form a plaque and, thus, increases the risk of cardiovascular disease.[7] Some clinical studies confirmed the relationship between elevated level of LDL cholesterol oxidation and increased risks of stroke disease or coronary heart disease.[8,9] The cholesterol oxidation products were found at a significant level in the plaque formed in the inside of blood vessel of cardiovascular disease patients.[10] For example, Takano et al. found that oxidized LDL within or outside the cell can induce the formation of foam cells, which[8] were ruptured afterward to release hydrophobic fragments that destroy the function of the biological membrane, therefore resulting in the atheroma. Thus, reducing LDL cholesterol oxidation could maintain the functionality of the cells associated with cholesterol metabolism and prevent the atheroma or plaque from being formed in blood vessels.

The health benefit of red wine in preventing cardiovascular diseases may be closely associated with its anti-cholesterol-oxidation activity. The capabilities of red and white wines in lowering cholesterol oxidation were determined in this study. The information could be valuable in explaining why consumption of grape wine is able to reduce the risk of cardiovascular diseases. Although the more readily bioavailable catechin and resveratrol are well recognized in preventing fatty acids oxidation, their capability or role in red wine in inhibiting cholesterol oxidation is very limited and needs to be evaluated as well.

The contents of polyphenolic antioxidants in red wine are variable and depend on the grape variety, vineyard location, cultivation system, climate, soil type, vine practices, harvesting time, and enological practices.[11] Resveratrol and catechin in red wine are in the ranges of 0.2−5.8 and 10−250 mg/L, respectively.[12] In this study, the capabilities of red and white wines and catechin and resveratrol in inhibiting cholesterol oxidation were determined using an emulsion system in which the cholesterol level was 100 mg/100 mL (approximately equivalent to the level in

Received: February 8, 2011
Revised: May 1, 2011
Accepted: May 12, 2011
Published: May 12, 2011

Table 1. Ratio of Control and Each Test Wine or Compound to the Cholesterol Emulsion

group	ratio (v/v)
red wine	1:250
	1:500
	1:1000
white wine	1:10
	1:50
	1:100
resveratrol (1 mg/mL)	1:500
catechin (1 mg/mL)	1:500

human blood fluid). A free radical reaction initiator, 2,2′-azobis-(2-methylpropionamidine) dihydrochloride (AAPH), was used to accelerate the cholesterol oxidation at 37 °C. The system could be an appropriate model to evaluate the capability of a compound or sample against cholesterol oxidation at relatively similar conditions in the human body. In general, the results presented in this study could reveal the relationship of red and white wines and their anti-cholesterol-oxidation activities. It would be helpful in fully understanding the mechanism of the health benefit function of wine and its major polyphenolics in preventing the risk of heart diseases.

MATERIALS AND METHODS

Materials. HPLC grade hexane, acetonitrile, methanol, and acetic acid were purchased from Fisher Chemicals (Fair Lawn, NJ). Isopropanol was from Mallinckrodt Co. (Paris, KY). Ethyl acetate was from EM Science (Gibbstown, NJ). Cholesterol, 7-ketocholesterol, resveratrol, catechin, AAPH, Tween 20, and formic acid (TFA) were purchased from Sigma-Aldrich (St. Louis, MO). Red wines, Merlot and Cabernet Sauvignon, and white wines, Chenin Blanc and Sauvignon Blanc, were obtained from a local market.

Preparation of Cholesterol Emulsion and Cholesterol Oxidation Reaction. Cholesterol emulsion (CE) was prepared using the method described in the study of Xu et al.[13] In this study, the concentrations of cholesterol and AAPH in the CE system were 1000 and 100 mg/L, respectively. After the emulsion solution had been prepared, it was immediately mixed with test sample in a 40 mL vial with a Teflon seal cap and homogenized using a sonication method. The ratios of added amounts of test sample to the emulsion are listed in Table 1. Each ratio had a control group in which test sample was replaced by the same amount of distilled water. Then, the vial was placed in a 37 °C water bath (PolyStat model 12050, Cole-Parmer Instrument Co, Chicago, IL) and continuously shaken at 200 rpm for 72 h to perform the oxidation reaction. At 0, 24, 48, and 72 h, 2.0 mL of the reaction solution was taken to determine the 7-ketocholesterol level in the CE system.

Determination of 7-Ketochesterol Using an HPLC Method. The sample taken was mixed with 2.0 mL of hexane and vortexed for 1 min. Then, it was centrifuged at 5000*g* for 10 min to separate hexane and aqueous layers. The hexane layer was added in a test tube containing 0.1 g of Na_2SO_4 at the bottom to remove any possible moisture, before it was transferred to an HPLC injection vial.

The oxidation product, 7-ketocholesterol, was analyzed using the HPLC method according to Xu et al.[13] The system included a Waters 2690 separation module, a silica normal phase column, a 996 photodiode array detector, and a Millennium chromatography station (Milford, MA). The mobile phase was a mixture of hexane and isopropanol (99%:1%) at a 1.5 mL/min flow rate. The wavelength for monitoring 7-ketocholesterol was set at 234 nm. The concentration was calculated using a calibration curve of 7-ketocholesterol standard.

An inhibition rate of 7-ketocholesterol was used to express the capability of the test sample in inhibiting cholesterol oxidation. It was calculated according to the formula

$$\text{inhibition rate } (\%) = [(C_{ctr} - C_{trt})/C_{ctr}] \times 100$$

where C_{ctr} is the concentration of 7-ketocholesterol in the control group without test sample at a given sampling time and C_{trt} is the concentration of 7-ketocholesterol in the treatment group with test sample at a given sampling time.

Determination of Catechin and Resveratrol Using the HPLC Method. Catechin and resveratrol in the wines were quantified using an analytical HPLC system.[14] The HPLC system consisted of a Supelco (Bellefonte, PA) Discovery C18 column (i.d. 3 mm × 25 cm), a Waters 2690 separation module, a 996 photodiode array detector, and a Millennium32 chromatography manager. The mobile phase was a mixture of (A) 0.4% formic acid in water and (B) acetonitrile, with the percentage of A ramped from 100 to 55% in 60 min with a constant flow rate of 0.8 mL/min. The chromatograms obtained at wavelengths of 280 and 310 nm were used to quantify catechin and resveratrol, respectively. The concentration was calculated using the calibration curve obtained from catechin or resveratrol standard.

Statistical Analysis. The experiment for each ratio of test sample and its control group was independently performed three times. The means and standard deviations of the sample and control group inhibition rates were calculated, and the data were analyzed by one-way ANOVA to evaluate significant difference at $P < 0.05$ (SAS 9.1.3, Cary, NC).

RESULTS AND DISCUSSION

Cholesterol Oxidation in the Emulsion System. The cholesterol level in the emulsion system was 1000 mg/L, which is similar to a normal LDL cholesterol level (100 mg/100 mL) in the human body in this study.[15] Without AAPH catalyzing the oxidation, it was found that the major cholesterol oxidation product, 7-ketocholesterol, was generated to a detectable level in the emulsion after 36 h of incubation at 37 °C. With 100 mg/L AAPH, the cholesterol oxidation rate was increased approximately 3 times that without AAPH. The production of 7-ketocholesterol was 5.8 ± 0.4, 25.5 ± 5.6, and 63.7 ± 3.9 mg/L after 24, 48, and 72 h of oxidation, respectively. This is similar to the result of a previous study in which the concentration of 7-ketocholesterol increased to 0.3% of original cholesterol in a 24 h oxidation period.[13] However, heating is a more aggressive acceleration method to oxidize cholesterol than using AAPH free radical generator.[5] The concentration of 7-ketocholesterol was approximately 6% of cholesterol in 30 min of heating at 150 °C. Those studies suggested that cholesterol is as vulnerable as fatty acids and readily oxidized under attack by free radicals and reactive oxygen species.

The mechanism of cholesterol oxidation is similar to lipid autoxidation.[5] It is initiated by free radicals in the environment to produce cholesterol hydroperoxides, which are not stable and continue to be oxidized to cholesterol peroxides. Eventually, the peroxides predominately form 7-ketocholesterol and other minor oxidation products. Those cholesterol oxidation products are different from the products produced from fatty acid oxidation. These oxidation products are neither small nor volatile and will remain in the system after oxidation. It was confirmed that those oxidation products are toxic to the endothelial cells of blood

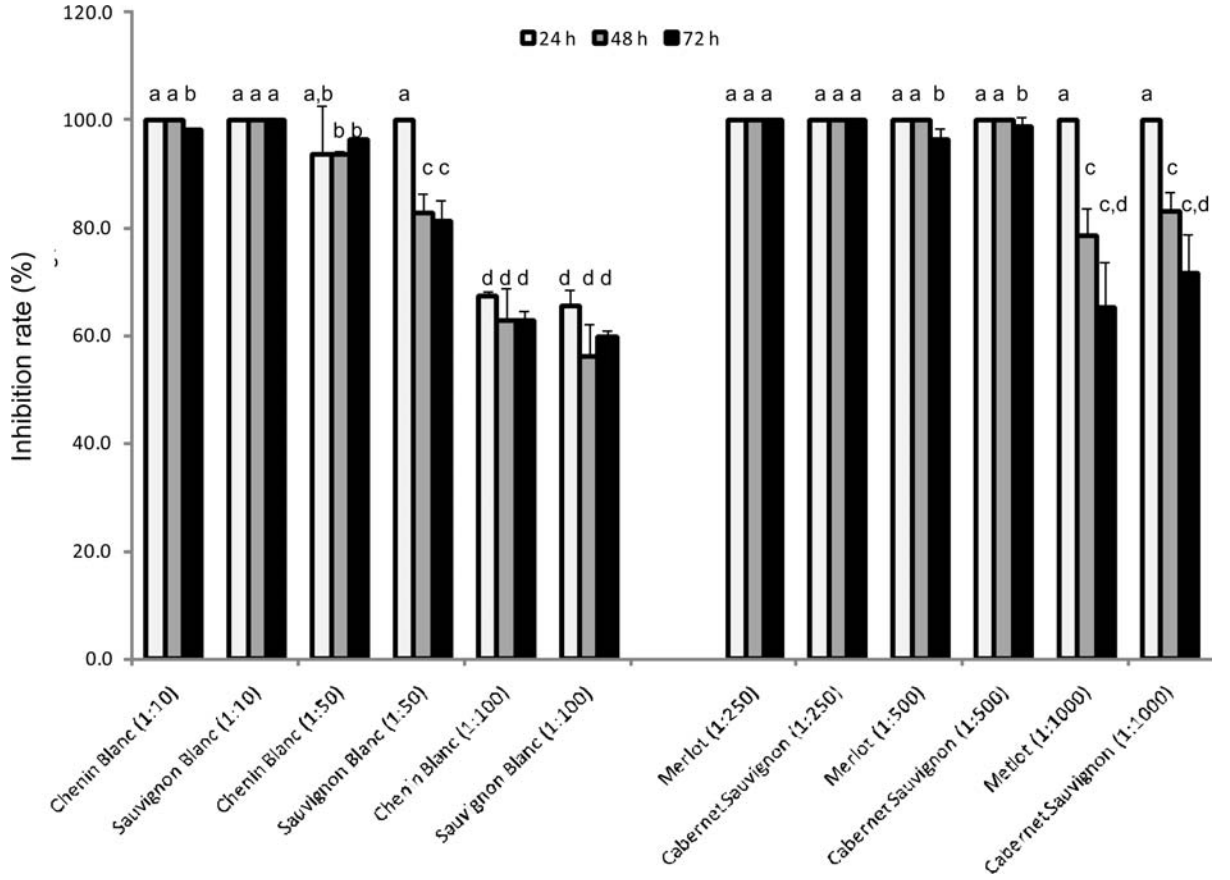

Figure 1. Inhibition rate of Chenin blanc, Sauvignon blanc, Merlot, and Cabernet Sauvignon in preventing cholesterol oxidation at different adding ratios and oxidation time intervals. Bars with different letters on top are significantly different in inhibition rate ($P < 0.05$).

vessel and largely deposit in the plaque of cardiovascular disease patients.[9] As the LDL cholesterol level of those patients could be >200 mg/dL, which is 2 times higher than the level in the emulsion of this study, the oxidation of cholesterol could be severe if there are not adequate free radical scavenging antioxidants in the bloodstream. Furthermore, the CE model used in this study could be an economical and fast tool to evaluate the capability of different antioxidants against cholesterol oxidation at a condition relatively similar to the human body. An effective antioxidant evaluated by this model should be a good candidate and selected for further study, such as cell culture or in vivo studies, to evaluate their effectiveness in preventing cardiovascular and other epidemiological diseases associated with cholesterol oxidation.

Capabilities of White and Red Wines in Inhibiting Cholesterol Oxidation. The capabilities of two white (WW) and two red wines (RW) in inhibiting 7-ketocholesterol production at different adding ratios are shown in Figure 1. No 7-ketocholesrterol was detected in 48 h of oxidation for white wines at a 1:10 ratio or for red wines at a 1:500 ratio in the emulsion. After 72 h of oxidation, 7-ketocholesterol inhibition rate was remained at 100% in Sauvignon Blanc white wine at a 1:10 ratio and in both of the red wines at a 1:250 ratio. The inhibition rates of the two white wines dropped to 60−70% during 72 h of oxidation when the adding ratio was decreased to 1:100. For the red wines, the inhibition rate decreased to 70−80% after 48 h of oxidation when the adding ratio was as low as 1:1000. The results demonstrated that red wine was much more efficient than white wine in inhibiting cholesterol oxidation. However, the two red or two white wines in this study had similar antioxidant activities in inhibiting cholesterol oxidation (Figure 1).

Table 2. Concentrations of Catechin and Resveratrol in Four Wines

wine	catechin (mg/L)	resveratrol (mg/L)
Chenin Blanc	10.6	0.3
Sauvignon Blanc	11.0	0.3
Merlot	140.6	0.7
Cabernate Sauvignon	132.5	1.0

The antioxidant capacity of red wine has been observed in a number of biological studies. Fuhrman et al.[16] reported that consumption of red wine with meals reduced the susceptibility of human plasma and low-density lipoprotein to lipid peroxidation. Some phenolic substances that exist in red wine, but not in white wine, were suggested to be responsible for the antioxidant activity.[2] The effect of the nonalcoholic fraction of red wine and white wine on the total-trapping antioxidant parameters (TRAP) and the total plasma levels of polyphenolics in human subjects was evaluated by Serafini et al.[17] The results showed that the alcohol-free fraction in red wine also caused significant increases in plasma TRAP values and polyphenolics concentrations in 50 min after ingestion, whereas white wine had no effects on either of the plasma values. Carluccio et al.[18] reported red wine antioxidant polyphenolics at a nutritionally relevant concentration transcriptionally inhibited endothelial adhesion molecule

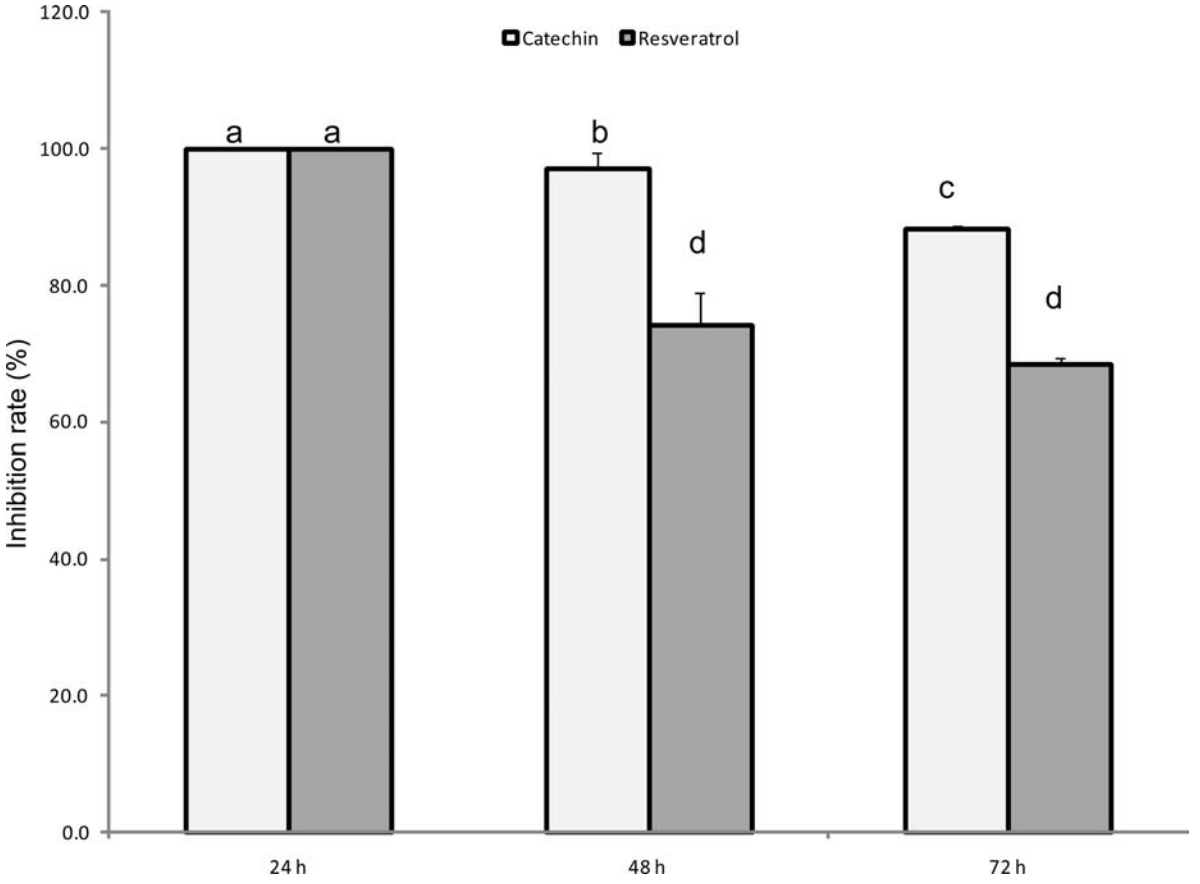

Figure 2. Inhibition rate of catechin (1 mg/mL) and resveratrol (1 mg/mL) in preventing cholesterol oxidation at the adding ratio of 1:500 to cholesterol (1000 mg/L) emulsion at 24, 48, and 72 h of oxidation time. Bars with different letters on top are significantly different in inhibition rate ($P < 0.05$).

expression in a cell culture model. Another study also showed that the serum antioxidant capacity (SAOC) after ingestion of red wine was much higher than that of white wine; the red wine treatment's SAOC was increased by 18% after 1 h and by 11% after 2 h, but the white wine produced 4 and 7% increases, respectively.[19] Those results are in agreement with the findings of this study, in which the CE model showed that the red wine had 50 times higher capability than white wine in inhibiting cholesterol oxidation. One portion of the red wine could significantly protect 500 portions of the emulsion having a cholesterol level equivalent to the bloodstream from free radical oxidation stress. With such a low ratio, it is suggested that if not all polyphenolic antioxidants, for example, in 50 mL of red wine, are absorbed by the bloodstream after consumption, a small fraction of the absorbed polyphenolics from the red wine may be adequate to increase the antioxidant capacity of the blood in retarding cholesterol oxidation. White wines are generally made from the free running juice without grape mash, having no contact with the grape skins.[20] The lower antioxidant activity of the white wines compared with the red wines could be due to lower antioxidant polyphenolics content.

Capabilities of Catechin and Resveratrol in Inhibiting Cholesterol Oxidation. Although a positive correlation of the antioxidant capacity of red wine and its polyphenolics content was concluded,[2,18] the correlation is not always equal for individual polyphenolics in red wine. It was reported that their molecular structure rather than the amount is much more important for the antioxidant activity.[21] Pignatelli et al.[22] also reported that the antioxidant capability of red wine may be dependent upon a synergism among polyphenolics. Ghiselli et al.[23] found that the anthocyanin fractions from Italian red wine could inhibit low-density lipoprotein oxidation and platelet aggregation, which are the two main causes in the pathogenesis of atherosclerosis. Another study found that, actually, plasma concentrations of anthocyanins were much lower after they were consumed.[24] Most of the anthocyanins in red wine were found in the urine but not in the bloodstream within the first 3 h of ingestion.[24] However, catechin, a major polyphenolic compound in red wine, can be absorbed in the human plasma after red wine is consumed.[25] Resveratrol was also found to reach the highest level in the blood only 10 min after consumption.[25] Compared with anthocyanins, catechin or resveratrol is more bioavailable in the bloodstream and absorbed without degradation.[4]

The concentrations of catechin and resveratrol in the four wine samples are listed in Table 2. Catechin in Merlot and Cabernet Sauvignon red wine was 140.6 and 132.5 mg/L, respectively. Both white wines contained only 10.6−11.0 mg/L of catechin. Resveratrol in the red and white wines (<1.0 mg/L) was much lower than catechin. The results were similar to those of other studies that reported catechin and resveratrol in red wine in a range of 10−250 and 0.2−5.8 mg/L, respectively.[12] Figure 2 shows the 7-ketocholesterol inhibition rate of catechin and resveratrol in reducing cholesterol oxidation in the emulsion

system. The oxidation product was not detected in 24 h of oxidation when 1 mg/mL of catechin or resveratrol solution was mixed with the cholesterol emulsion at the ratio of 1:500 (Figure 2). However, the inhibition rate of catechin remained higher after 48 h of oxidation, compared with that of resveratrol, which decreased to 74% (Figure 2). The inhibition rate of resveratrol continuously dropped to 68% after 72 h of oxidation, whereas that of catechin still was at 88% (Figure 2). Recently, a study showed that resveratrol as a potent antioxidant could protect the heart from ischemia and/or reperfusion injury and inhibit apoptotic cell death as well as release and/or generate inflammatory mediators.[9] It was suggested that the heart can be protected by free radical scavenging and lipid peroxidation inhibition.[2] However, resveratrol may not be the major antioxidant in red wine in protecting cholesterol against free radical attack due to relatively lower concentration and antioxidant activity, compared with catechin. Catechin was also found to delay the degradation of endogenous α-tocopherol and β-carotene by inhibiting most lipid oxidation in plasma.[26] Therefore, catechin in red wine may play an important role in enhancing the antioxidant activity in the human bloodstream after ingestion due to its higher antioxidant activity and bioavailability.

In conclusion, the capability of red wine in inhibiting cholesterol oxidation was much higher than that of white wine. In the model of this study, the capability of red wine was 50 times higher than that of white wine. The higher polyphenolic antioxidants in red wine may lead to the greater antioxidant activity. Compared with anthocyanins, catechin and resveratrol are more readily absorbed in the bloodstream without degradation after ingestion. Although resveratrol was reported to have the function of reducing the risk of cardiovascular diseases in several studies, its level in red wine is 10−20 times lower than that of catechin. In this study, catechin also demonstrated a higher antioxidant capability than resveratrol. It is suggested that catechin rather than resveratrol may significantly contribute to the antioxidant capability of red wine in retarding cholesterol oxidation. On the basis of the results of this study, it may be assumed that if the catechin level in a red wine is 150 mg/L, consuming 60−70 mL of a red wine containing >10 mg of catechin would be very helpful in inhibiting the oxidation of LDL cholesterol of a healthy person for 24 h without consideration of other antioxidants and metabolism factors. This study establishes that moderate red wine consumption is beneficial to health. It also demonstrated that the health beneficial function may be directly contributed by the antioxidant activity of wine polyphenolics.

AUTHOR INFORMATION

Corresponding Author

*Postal address: 111 Food Science Building, LSU, Baton Rouge, LA 70803. Phone: (225) 578-5280. Fax: (225) 578-5300. E-mail: zxu@agcenter.lsu.edu.

REFERENCES

(1) De Lange, D.; Van Golden, P.; Scholman, W.; Kraaijenhagen, R.; Akkerman, J.; Van De Wiel, A. Red wine and red wine polyphenolic compounds but not alcohol inhibit ADP-induced platelet aggregation. *Eur. J. Intern. Med.* **2003**, *14*, 361–366.

(2) Das, S.; Santani, D. D.; Dhalla, N. S. Experimental evidence for the cardioprotective effects of red wine. *Exp. Clin. Cardiol.* **2007**, *12*, 5–10.

(3) Fan, E.; Zhang, L.; Jiang, S.; Bai, Y. Beneficial effects of resveratrol on atherosclerosis. *J. Med. Food* **2008**, *11*, 610–614.

(4) Forester, S. C.; Waterhouse, A. L. Metabolites are key to understanding health effects of wine polyphenolics. *J. Nutr.* **2009**, *139*, 1824S–1831S.

(5) Chien, J.; Wang, H.; Chen, B. Kinetic model of the cholesterol oxidation during heating. *J. Agric. Food Chem.* **1998**, *46*, 2572–2577.

(6) Cui, Y.; Watson, D.; Girman, C.; Shapiro, D.; Gotto, A.; Hiserote, P.; Clearfield, M. Effects of increasing high-density lipoprotein cholesterol and decreasing low-density lipoprotein cholesterol on the incidence of first acute coronary events (from the Air Force/Texas coronary atherosclerosis prevention study). *Am. J. Cardiol.* **2009**, *104*, 829–834.

(7) Hausenloy, D.; Yellon, D. Targeting residual cardiovascular risk: raising high-density lipoprotein cholesterol levels. *Postgrad. Med. J.* **2008**, *84*, 590.

(8) Takano, T.; Itabe, H.; Mori, M.; Kimura, J.; Nakagami, K.; Sato, R.; Hashita, R.; Yagyu, Y.; Mineo, C.; Amanuma, K. Molecular pathology in atherosclerosis: the mechanism how cholesteryl ester accumulates in atheromatous aorta. *Yakugaku Zasshi* **2008**, *128*, 1383–1401.

(9) Dohadwala, M. M.; Vita, J. A. Grapes and cardiovascular disease. *J. Nutr.* **2009**, *139*, 1788S–1793S.

(10) Carpenter, K. Good COP, bad COP: an unsolved murder. Are dietary cholesterol oxidation products guilty of atherogenicity? *Br. J. Nntr.* **2002**, *88*, 335–338.

(11) Ribereau-Gayon, P. *Handbook of Enology*; Wiley: Bordeaux, France, 2006; Vol. 1, pp 191−194.

(12) Gu, X.; Kester, A.; Zeece, M. Capillary electrophoretic determination of resveratrol in wines. *J. Agric. Food Chem.* **1999**, *47*, 3223–3227.

(13) Xu, Z.; Hua, N.; Godber, J. Antioxidant activity of tocopherols, tocotrienols, and γ-oryzanol components from rice bran against cholesterol oxidation accelerated by 2,2′-azobis(2-methylpropionamidine) dihydrochloride. *J. Agric. Food Chem.* **2001**, *49*, 2077–2081.

(14) Jang, S.; Xu, Z. Lipophilic and hydrophilic antioxidants and their antioxidant activities in purple rice bran. *J. Agric. Food Chem.* **2009**, *57*, 858–862.

(15) Cholesterol levels: what numbers should you aim for? http://www.mayoclinic.com/health/cholesterol-levels/CL00001 (accessed Jan 24, 2011).

(16) Fuhrman, B.; Lavy, A.; Aviram, M. Consumption of red wine with meals reduces the susceptibility of human plasma and low-density lipoprotein to lipid peroxidation. *Am. J. Clin. Nutr.* **1995**, *61*, 549–554.

(17) Serafini, M.; Maiani, G.; Ferro-Luzzi, A. Alcohol-free red wine enhances plasma antioxidant capacity in humans. *J. Nutr.* **1998**, *128*, 1003–1007.

(18) Carluccio, M. A.; Siculella, L.; Ancora, M. A.; Massaro, M.; Scoditti, E.; Storelli, C.; Visioli, F.; Distante, A.; De Caterina, R. Olive oil and red wine antioxidant polyphenols inhibit endothelial activation: antiatherogenic properties of Mediterranean diet phytochemicals. *Arterioscler. Thromb., Vasc. Biol.* **2003**, *23*, 622–629.

(19) Seigneur, M.; Bonnet, J.; Dorian, B.; Benchimol, D.; Drouillet, F.; Gouverneur, G.; Larrue, J.; Crockett, R.; Boisseau, M. R.; Ribereau-Gayon, P. Effect of the consumption of alcohol, white wine and red wine on platelet function and serum lipids. *J. Agric. Food Chem.* **1990**, *5*, 215–222.

(20) Fuhrman, B.; Volkova, N.; Suraski, A.; Aviram, M. White wine with red wine-like properties: increased extraction of grape skin polyphenols improves the antioxidant capacity of the derived white wine. *J. Agric. Food Chem.* **2001**, *49*, 3164–3168.

(21) Di Majo, D.; La Guardia, M.; Giammanco, S.; La Neve, L.; Giammanco, M. The antioxidant capacity of red wine in relationship with its polyphenolic constituents. *Food Chem.* **2008**, *111*, 45–49.

(22) Pignatelli, P.; Ghiselli, A.; Buchetti, B.; Carnevale, R.; Natella, F.; German, G.; Fimognari, F.; Di Santo, S.; Lenti, L.; Violi, F. Polyphenols synergistically inhibit oxidative stress in subjects given red and white wine. *Atherosclerosis* **2006**, *188*, 77–83.

(23) Ghiselli, A.; Nardini, M.; Baldi, A.; Scaccini, C. Antioxidant activity of different phenolic fractions separated from an Italian red wine. *J. Agric. Food Chem.* **1998**, *46*, 361–367.

(24) Cao, G.; Muccitelli, H. U.; Sanchez-Moreno, C.; Prior, R. L. Anthocyanins are absorbed in glycated forms in elderly women: a pharmacokinetic study. *Am. J. Clin. Nutr.* **2001**, *73*, 920–926.

(25) De Lange, D.; Van Golden, P.; Scholman, W.; Kraaijenhagen, R.; Akkerman, J.; Van De Wiel, A. Red wine and red wine polyphenolic compounds but not alcohol inhibit ADP-induced platelet aggregation. *Eur. J. Intern. Med.* **2003**, *14*, 361–366.

(26) Levites, Y.; Amit, T.; Youdim, M.; Mandel, S. Involvement of protein kinase C activation and cell survival/cell cycle genes in green tea polyphenol (−)-epigallocatechin 3-gallate neuroprotective action. *J. Biol. Chem.* **2002**, *277*, 30574.