Introduction

The French people have a lower mortality rate from cardiovascular disease than the other Nordic countries despite a high consumption of saturated fatty acids in the daily diet, which is namely the famous “French paradox”. Renaud and de Lorgeril (1) demonstrated that the consumption of red wine is a major cause of the “French paradox” and further confirmed that the protective effect of red wine consumption against cardiovascular heart disease (CHD) might be attributable, at least in part, to polyphenols, including catechins, epicatechin, gallic acid, ferulic acid, caffeic acid, anthocyanins, and resveratrol (2, 3). Yellow rice wine is one of the three ancient wines in the world (Shaoxing rice wine, beer, and grape wine) which is derived from Shaoxing, China. It is fermented from glutinous rice, wheat, and aspergillus yeast over 80 days (4). Yellow rice wine is also rich in polyphenols, which is mainly from glutinous rice and...
wheat, including catechin, epicatechin, rutin, quercetin, protocatechuic, chlorogenic acid, caffeic acid, syringic acid, ferulic acid, p-incense beans, and so on. The total phenolic content comes to 1.023 mg/ml, which can be comparable with polyphenol content in the red wine (4 – 6). In previous studies, we have observed that Chinese yellow wine could prevent the progression of early atherosclerotic lesions in vivo (7) and inhibit the activity of MMP-2 induced by homocysteine (HCY) in cultured rat vascular smooth muscle cells (VSMCs) (8). Atherosclerotic plaque area and matrix metalloproteinase-2 expression and activity significantly decrease in the yellow wine group (high fat diet + 3% rice wine) and red wine group (high fat diet + 3% red wine) compared to those in the control group (high fat diet + sterile water) and alcohol group (high fat diet + 3% alcohol) in vivo (7). We hypothesized that something in the yellow wine, possibly the yellow wine polyphenols compounds (YWPC), besides the alcohol may be responsible for the protective effect on the cardiovascular system.

The formation and progression of atherosclerotic lesions are lipid-driven chronic inflammatory processes associated with excessive vascular remodeling, which is mainly regulated by matrix metalloproteinases (MMPs) through degradation and synthesis of extracellular matrix (ECM) (9). The present study found that MMP-2 contributed to monocyte migration and macrophage proliferation into the intima, resulting in increased atherosclerotic plaque lesions (10, 11). Growing evidence suggested that MMP-9 deficiency reduced atherosclerosis progression or promoted a stable plaque phenotype in apoE−/− mice (11). These findings suggest strongly that inhibiting MMP-2 and MMP-9 production should have a protective effect against plaque growth and remodeling. The activity of MMPs is controlled by, an endogenous inhibitor, tissue inhibitors of metalloproteinases (TIMPs) (9).

Statins are a family of compounds that competitively inhibit 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), the rate-controlling enzyme in cholesterol synthesis (12). At present, rosuvastatin or atorvastatin has become the main compound among the statins used clinically for lipid lowering therapy to prevent cardiovascular disease (12, 13). Furthermore, recent investigations have found that statins have pleiotropic effects that besides lipid lowering, may directly or indirectly limit atherosclerosis progression. The pleiotropic effects of statins include relieving vascular inflammation, improving the function of endothelial cells, inhibiting the proliferation and migration of VSMCs, reducing the expression of MMPs, increasing the expression of TIMPs, and stabilizing atherosclerotic plaques (14 – 17). The dose of 10 mg/kg per day rosuvastatin is a common dosage in clinical practice (18) and has been widely used in animal studies. It has been found that this dose is effective in the prevention of atherosclerosis in the LDLR−/− mice (19). So we chose the dose of 10 mg/kg per day of rosuvastatin as the intervention dosage in the present study.

The present study was designed to investigate the effects of YWPC on the activity and expression of MMP-2, 9 and to evaluate the preventive effects against atherogenesis and compare them with those of rosuvastatin, further promoting our understanding of the protective effects of this compound on CHD. For this purpose, we used the LDLR−/− mice, which are a more physiologic model to study mechanisms involved in atherogenesis in comparison to Apo-E–deficient mice as demonstrated by previous studies (20). In this model an absence of functional low density lipoprotein (LDL) receptors leads to marked accumulation of cholesterol-rich very low-density lipoprotein (VLDL), intermediate density lipoproteins (IDL), and LDL in plasma and a secondary deposition of cholesteryl esters in macrophage foam cells along with massive atherosclerosis (21, 22).

Materials and Methods

Materials and reagents

YWPC in dry powder form from yellow rice wine (Shaoxing, China) were provided by national engineering and research center for traditional Chinese medicine (Shanghai, China). The procedures used to prepare and analyze YWPC have been described previously (4). Rosuvastatin was provided by Astrazeneca (Macclesfield, UK). Antibodies against MMP-2, 9 and TIMP-2 were purchased from Abcam (Cambridge, MA, USA), and antibodies against TIMP-1 were purchased from Abbiotec (San Diego, CA, USA). Anti-MMP-2, MMP-9, TIMP-1, and TIMP-2 and horseradish peroxidase–conjugated goat anti-mouse and goat anti-rabbit IgG antibody were purchased from Jackson Immunoresearch Laboratories (West Grove, PA, USA). Gelatin was purchased from Abcam (Cambridge, MA). The other reagents of immunoblot assay were purchased from Beyotime (Jiangsu, China). All other chemicals were of reagent grade or were of the highest grade commercially available.

Animals

Animal studies were treated in compliance with the Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of Wenzhou Medical University. Six-week-old male LDL-receptor–knockout (LDLR−/−) mice with the genetic background back-crossed ten generations into C57BL/6J (n = 40, body weight 20 – 25 g)
were obtained from Model Animal Research Center of Nanjing University (Nanjing, China). The LDLR−/− mice can spontaneously develop atherosclerosis with plaque size (20) and components similar to those of humans with a high fat diet, so these mice are a more physiologic model to study mechanisms involved in atherogenesis.

Methods

Mice were maintained on a 12 h light/dark cycle, in a temperature (25°C ± 2°C) and humidity (55% ± 3%) controlled environment. Forty mice were randomly divided into 5 groups (n = 8, each group). After one week of an adaptation, at age 7 weeks, the mice were fed an experimental high-fat diet containing 10% fat and 1.25% cholesterol for the entire study. YWPC and rosuvastatin were dissolved in drinking water as follows: group 1, high-fat diet (control group); group 2, high-fat diet plus 10 mg/kg per day YWPC; group 3, high-fat diet plus 10 mg/kg per day YWPC; group 4, high-fat diet plus 30 mg/kg per day YWPC; group 5, high-fat diet plus 50 mg/kg per day YWPC. They were allowed free access to food and water. Weights, fluid intake, and food consumption were monitored weekly throughout the study.

The Food and Drug Administration (FDA) recommend that daily moderate alcohol consumption is up to 12 – 24 g of alcohol/day, so 200 mL yellow wine of 12% ethanol per day is moderate drinking. Considering that the YWPC content of yellow wine was 1.0 mg/ml, the average person gets about 200 mg of YWPC a day. The concentration in the intake YWPC is 2.86 mg/kg in a 70-kg man. This translates into 26 mg/kg of YWPC in 20 – 25 g mice according to the coefficient of 9.1 (23). According to the previous experiments, treatment with polyphenols at a dose of 10 mg/kg per day attenuated the progression of atherosclerosis (24). In our experiment, we chose doses ranging from 10 to 50 mg/kg per day, and 30 mg/kg per day was used as a middle dose.

Plasma analysis

At the end of the 14-week experimental period, these mice were deprived of food for 12 h and sacrificed by inhalant 1.5% isoflurane anesthesia. Blood was drawn from the right ventricle into EDTA containing tube and then plasma was isolated by centrifugation at 2000 × g for 15 min at 4°C and stored at −80°C until analysis. Total serum cholesterol (TC), triacylglycerol (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels were measured by the standard enzymatic method, using a fully automatic clinical biochemical analyzer (Abbott Labs, Abbott Park, IL, USA).

Morphological and atherosclerotic lesion area of the aorta artery

After blood collection, the mice were perfused through the left cardiac ventricle with ice-cold phosphate buffered saline (PBS). After removal of the surrounding adventitial fat and fascia tissue, the aortas were opened longitudinally from the aortic root to the renal artery and fixed in formalin (10%) for 24 h. The aortas were then rinsed in 70% alcohol for 30 s, stained with Sudan IV for 15 min, differentiated in 80% alcohol for 20 min, and washed in running water for 1 h. The aortas were photographed by a digital camera connected to a dissection microscope. The extent of atherosclerosis was analyzed with Image-pro plus 6.0 (Media Cybernetics Inc., Bethesda, MD, USA). Data are reported as the percentage of the aortic surface covered by lesions (total surface area of the atherosclerotic lesions divided by the total surface area of the aorta) (25).

Western blotting analysis

Aorta protein extracts were prepared by homogenizing 100 mg of aorta in 500 µl radio-immunoprecipitation assay buffer (RIPA Lysis Buffer; Beyotime, Jiangsu, China) containing freshly dissolved protease inhibitors (1 mM phenylmethanesulfonyl fluoride, PMSF; Beyotime). Homogenates were centrifuged at 12, 000 × g for 10 min at 4°C. The supernatant was collected and assayed for protein concentrations using the BCA method (BCA Protein assay kit, Beyotime). The supernatant was mixed with 5 × SDS sample buffer and heated in a boiling water bath for 5 min. Denatured protein (30 µg total proteins for MMPs, 50 µg total proteins for TIMPs) was subjected to SDS-PAGE on a 10% (for MMP-2 and MMP-9) or 12% (for TIMP-1 and TIMP-2) polyacrylamide gel and transferred to PVDF blotting membranes. After the transfer, membranes were blocked with blocking buffer for 1 h at room temperature and then incubated with the respective primary antibody overnight at 4°C. After being washed with TBS-T (3 times for 10 min), the membranes were incubated with horseradish peroxidase–linked secondary antibody at room temperature for 1 h. Finally, antigen was detected by using the standard chemical luminescence method (Beyotime). The membranes were exposed to Kodak X-Omat AR film (Eastman Kodak Co., Rochester, NY, USA). Finally, the films were scanned on a densitograph and measured using Quantity One 4.4 (Bio-Rad, Hercules, CA, USA).

Gelatin zymography analysis

The activity of MMP-2 and MMP-9 in the supernatants was assessed by zymography. Equal amounts (30 µg) of total protein extracts were mixed with 5 × SDS sample buffer without a reducing agent and loaded onto the
SDS-PAGE gel (8% polyacrylamide gel containing 0.1% gelatin). After electrophoresis, the gels were washed at room temperature for 30 min × 2 in a solution containing 2.5% Triton X-100 to remove the SDS and then incubated in renaturation buffer (pH 7.5, 50 mM Tris-HCl, 10 mM CaCl2, 0.02% NaN3) for 42 h at 37°C. The gels were stained for 2 h with 0.1% Coomassie blue R-250 in 10% glacial acetic acid / 45% methanol and then destained with 10% glacial acetic acid / 45% methanol. Gelatinolytic activity was visualized as clear bands against the blue background of the stained gelatin. The strength of each band was quantified by means of densitometric scanning using a digital camera and measured using Quantity One 4.4 (Bio-Rad).

**Statistical analyses**

Results are presented as the mean ± S.D. The statistical significance of differences between groups was determined by one-way analysis of variance (ANOVA) followed by Tukey’s Studentized Range (HSD) post-hoc test for multiple comparisons. A value of $P < 0.05$ was considered significant.

**Results**

**Serum cholesterol levels**

After the mice were treated for 14 weeks with YWPC or rosuvastatin, there were no significant differences in food intake, water intake, and body weight in the 5 groups. The levels of plasma TC, LDL-C, and TG in the rosuvastatin group were significantly compared to those in the control group. YWPC at 10, 30, and 50 mg/kg per day significantly decreased the plasma TC and LDL-C levels compared with those in the control group. YWPC tended to decrease the serum TG level, although the effect was not significant. The levels of plasma TC, LDL-C, and TG were each significantly different between the YWPC groups and the rosuvastatin intervention group. There was no significant difference in the level of plasma HDL-C among the groups (Table 1).

**Plaque area**

Their aortas were analyzed for the extent of atherosclerosis. Extensive atherosclerotic lesions were observed proximal to the aortas in LDLR−−/− mice, especially in the control group (Fig. 1). Yellow wine polyphenolic compounds reduced the lesion area: even the lowest dose (10 mg/kg per day) reduced the lesion area by 18.51% compared with the control group. Similarly, 30 and 50 mg/kg per day YWPC reduced the lesion area by 40.09% and 38.42%, respectively; and stronger inhibition, 74.14%, was observed in the rosuvastatin group.

![Morphology of the aorta artery of the 5 groups.](image)

**Fig. 1.** Morphology of the aorta artery of the 5 groups.

### Table 1. Effects of rosuvastatin and 10, 30, and 50 mg/kg per day YWPC on plasma lipid concentration in LDLR−−/− mice treated with high-fat diet after 14 weeks

<table>
<thead>
<tr>
<th>Group</th>
<th>TG (mmol/L)</th>
<th>TC (mmol/L)</th>
<th>LDL-C (mmol/L)</th>
<th>HDL-C (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvs</td>
<td>2.76 ± 0.67†</td>
<td>14.32 ± 2.45*</td>
<td>9.59 ± 1.81*</td>
<td>5.57 ± 0.67</td>
</tr>
<tr>
<td>Control</td>
<td>4.52 ± 0.93</td>
<td>30.73 ± 2.92</td>
<td>22.99 ± 3.50</td>
<td>5.03 ± 0.65</td>
</tr>
<tr>
<td>YWPC 10 mg/kg per day</td>
<td>4.17 ± 0.77*</td>
<td>25.28 ± 2.46*</td>
<td>18.98 ± 2.17*</td>
<td>5.21 ± 0.41</td>
</tr>
<tr>
<td>YWPC 30 mg/kg per day</td>
<td>3.75 ± 0.77*</td>
<td>18.26 ± 2.89*</td>
<td>13.47 ± 1.94*</td>
<td>5.48 ± 0.92</td>
</tr>
<tr>
<td>YWPC 50 mg/kg per day</td>
<td>3.86 ± 0.90*</td>
<td>20.09 ± 3.48*</td>
<td>15.23 ± 2.58*</td>
<td>5.36 ± 0.72</td>
</tr>
</tbody>
</table>

Data are expressed as the mean ± S.D. *$P < 0.05$ vs. rosuvs, †$P < 0.01$ vs. control, ‡$P < 0.05$ vs. YWPC (10 mg/kg per day). Rosuvs, rosuvastatin.
group. Yellow wine polyphenolic compounds and rosuvastatin significantly reduced the atherosclerosis lesion area (Fig. 2).

**Effects of YWPC on MMP-2 and MMP-9 protein expression and activity**

MMPs degrade the vascular ECM, which have been involved in atherosclerotic plaque growth and instability, leading to an increased risk of cardiovascular events. In order to determine the impact of YWPC supplementation on MMP-2 and MMP-9, we analyzed their protein expression by western blotting and activity, by gelatin zymography. The results demonstrated that YWPC at 10, 30, and 50 mg/kg per day significantly inhibited MMP-2, 9 activity and protein expression when compared to the control group. Rosuvastatin, used as a positive control, also significantly inhibited MMP-2 and MMP-9 activity and protein expression in comparison with the control group and YWPC groups. (Figs. 3, 4)

**Effects of YWPC on TIMP-1 and TIMP-2 protein expression**

The physiological activities of MMPs are related closely to that of their specific endogenous tissue inhibitors of metalloproteinase. We further examined protein expression of TIMP-1 and TIMP-2, the key inhibitors of MMP-9 and MMP-2. We found that the expression of TIMP-1 and TIMP-2 in mice treated with 10, 30, and 50 mg/kg per day YWPC increased significantly in comparison with the control group, which was enhanced more in the rosuvastatin group when compared to the control group and YWPC groups (Fig. 5).

**Discussion**

Many epidemiological studies have demonstrated that moderate consumption of polyphenol-rich foods, such as fruits and vegetables, tea, and red wine, is associated with a reduction in overall mortality, especially the reduced risk of coronary heart disease (CHD). Yellow wine is also a rich source of polyphenolic compounds. However the regulative effects of yellow wine on CHD have not been completely evaluated yet. Therefore, we planned this study to examine the potential beneficial effects of YWPC from yellow wine in LDLR−/− mice fed a high-fat diet. The dose level of YWPC to rats is comparable to human exposure, and the effect of rosuvastatin was tested for comparison.

Studies have found that a high level of plasma choles-
terol is a risk factor contributing to the incidence and severity of CHD. The present study showed that dietary YWPC at levels of 10, 30, and 50 mg/kg per day reduced circulating total cholesterol and LDL cholesterol levels as well as the rosuvastatin in LDLR−/− rats compared with that in the control group. There was no statistically significant difference between YWPC at 30 and 50 mg/kg per day. We speculated that a maximum beneficial effect of YWPC on blood lipids was gained at a dose of 30 mg/kg per day and then the lipid-lowering effect reached a plateau. The lipid effects cannot be attributed to differences in food or energy intake. It was consistent with other investigations that showed a hypocholesterolic effect in rats fed diets containing phenolic compounds derived from red wine or tea (26, 27). The mechanism by which polyphenols decrease the cholesterol level may be through their interaction with cholesterol carriers and transporters present across the brush border membrane, which inhibits the absorption of cholesterol and bile.

![Fig. 4](image.png)

**Fig. 4.** Effects of rosuvastatin and 10, 30, and 50 mg/kg per day YWPC on MMP-2 (A) and MMP-9 (B) activity. Protein extracts from the aortic arch of LDLR−/− mice treated with high-fat diet after 14 weeks. They were examined by gelatin zymography assay. Data are expressed as the mean ± S.D. *P < 0.01 vs. control, *P < 0.05 and **P < 0.01 vs. rosuv, *P < 0.05 vs. YWPC (10 mg/kg per day). Rosuvs, rosuvastatin.

![Fig. 5](image.png)

**Fig. 5.** Effects of rosuvastatin and 10, 30, and 50 mg/kg per day YWPC on TIMP-1 (A) and TIMP-2 (B) protein production in the aorta isolated from LDLR−/− mice treated with high-fat diet after 14 weeks. They were analyzed by western blotting and normalized with the housekeeping gene β-actin. Data are expressed as the mean ± S.D. *P < 0.01 vs. control, *P < 0.05 and **P < 0.01 vs. rosuv, *P < 0.05 vs. YWPC (10 mg/kg per day). Rosuvs, rosuvastatin.
acid (27, 28). In our study, YWPC and rosuvastatin tended to increase the serum HDL-C level, although the effect was not significant. HDL plays an important anti-atherogenesis role by mediating reverse cholesterol transport (RCT) to promote cholesterol efflux from macrophages and transporting the cholesterol to the liver (29). Several studies have shown that both polyphenols and rosuvastatin could enhance HDL-mediated cholesterol efflux via up-regulation of ABCA1 protein expression and reduce atherosclerosis (29 – 31).

In addition, increasing evidence demonstrated that the dietary polyphenols had the capacity to reduce LDL susceptibility to oxidation which could operate to benefit atherosclerosis (32). The activity of polyphenols for protecting LDL from oxidation could be attributable, at least in part, to both binding to the LDL particle against metal-catalyzed oxidation and scavenging property of free radicals (33), whereas the reduction of oxLDL by rosuvastatin is due to the anti-oxidative properties, which are correlated with the reducing equivalent donating property or direct hydroxyl radical-scavenging activity (34). Thus, additional research is necessary to determine the inhibitory effect of YWPC on LDL oxidation.

The development of atherosclerotic lesions is a chronic inflammatory process that is characterized by excessive vascular remodeling with accumulation of cells and lipids within the intimal layer of the pathological artery (35). ECM is the main composition which constitutes blood vessel wall. Remodeling of ECM, including its degradation and synthesis, is in dynamic balance in the organism. MMPs are a family of proteolytic enzymes that participate in the degradation of components of the ECM, resulting in atherosclerotic plaque formation and vulnerability (36). Studies in mice have suggested that different members of the MMP family may exert different effects on atherogenesis. In particular, MMP-2 and MMP-9 have been identified as major proteinases degrading most collagen in atherosclerotic plaque lesions during atherosclerotic lesion formation and instability, leading to an increased risk of cardiovascular events (36, 37). Therefore, the inhibition of MMP-2 and MMP-9 is considered to be an important target for therapeutic intervention. Previous findings have pointed out that polyphenols prevent effectively the expression of MMP-9 in endothelial cells and the Ang II–induced expression of MMP-2 in vivo (38, 39). In our investigation, we demonstrated that the activities and expressions of both MMP-2 and MMP-9 were reduced by YWPC and rosuvastatin. These data suggested that YWPC have a distinct effect on MMP-2 and MMP-9 activities and expressions that may be related with a limited atherosclerotic effect.

TIMPs are a family of specific endogenous inhibitors of MMPs whose activity correlates with decreased MMP activity in atherosclerotic plaques and plays a key role in maintaining the balance between the particular units of ECM (40). There are currently 4 known TIMPs — TIMP 1 to TIMP 4. Each TIMP member operates with different inhibition efficiencies against the different MMPs. It has been demonstrated that TIMP-1 binds and slows activation of the latent form of MMP-9, whereas TIMP-2 binds and regulates activation of MMP-2 (41). In order to investigate the mechanism underlying inhibition of MMP secretion, we mainly detected the expressions of TIMP-1 and TIMP-2 protein. The results of western blot analysis showed that with respect to the control group, the protein expression of TIMP-1 and TIMP-2 was significantly higher in both the YWPC and rosuvastatin groups. The plausible mechanism mediating this beneficial effect of rosuvastatin may be through statin-induced increase in nitric oxide bioavailability, as endothelial nitric oxide synthase gene transfer has been demonstrated to decrease MMP activities and increase TIMP-2 secretion (42), whereas YWPC inhibition against the transcription and expression of MMP-9 gene may be attributed to the downregulation of activator protein-1 (AP-1) and nuclear factor-nB (NF-nB), which could also up regulate the expression of TIMP (43). This result is in agreement with an earlier study in which polyphenols increase the expression of TIMP-1 and TIMP-2 (44). Therefore, the prevention of MMP activation by YWPC is likely to be mediated by the increase of TIMP level, thus weakening the ECM degradation that occurs in atherosclerotic arteries. In the present study, we found a reduction of the plaque lesion area in animals treated with YWPC and rosuvastatin. Based on the studies above, it is possible to conclude that YWPC decreases the activity of MMP-9 and MMP-2 protein and increase the expression of TIMP-1 and TIMP-2 to alleviate atherosclerotic lesion.

On the other hand, MMP and TIMP also act as key fibrogenic factors, which are important for hepatic fibrosis progression (45). The development of hepatic fibrosis can be prevented by polyphenols via a modulation of MMP-2 activity (46). Furthermore, polyphenols consumption has been shown to be inversely correlated with liver damage (47) and markers of liver function such as alanine aminotransferase (ALT) and aspartate transaminase (AST) (48). However, Galati et al. (49) found that administration of tea polyphenols resulted in a significantly increased level of plasma ALT level in mice, indicative of liver injury. Liver is an important organ participating in phenolics metabolism. We are planning future studies to identify the potential biological effects of YWPC on biomarkers of liver function.
Diet is a cornerstone in the prevention of cardiovascular disease. In general, the effects of red wine polyphenols have been conducted at doses ranging between 20 and 40 mg/kg for 1 – 4 week in vivo. In our experiments, 3 different concentrations of YWPC were used for 14 weeks. The results showed that all 3 doses of YWPC are adequate to produce sufficient circulating concentrations of compounds which are able to relieve atherosclerosis. At present, statin is the main way for the prevention of atherosclerotic disease including coronary heart disease in the clinic, but it seems impractical to apply statins to people for prevention of CHD because of economic status, side-effects of medicine, and compliance reasons. In our study, the YWPC exhibits similar effects compared with rosuvastatin, suggesting that regular and moderate yellow wine drinking could provide a safe, effective, convenient, and affordable way to lower the risk of CHD.

There are some limitations in the present study as well. Since YWPC is a mixture of different polyphenolic compounds, it is not certain which single polyphenol or family of polyphenolic components are responsible for the observed effects, and the bioavailability of polyphenols is not known, so further studies need to be done. In addition, we evaluated the expression of MMPs and TIMPs at the 14th week, but it is a dynamic balance that should be further studied dynamically during the development of atherosclerotic lesions. It has been postulated that the presence of ethanol in red wine improves the bioavailability of the polyphenols in vivo, possibly by preventing the precipitation of the polyphenolic tannins in the digestive tract (50, 51). So a comparative study on the respective roles of a yellow wine polyphenolic extract, ethanol, or both should be further evaluated to clarify the protective mechanism of yellow wine.

In conclusion, we demonstrated that YWPC decreased plasma TC and LDL-C concentration, inhibited expression of MMP-2 and MMP-9 and enhanced expression of TIMP-1 and TIMP-2, and limited the progression of atherosclerosis in LDLR-deficient mice exposed to a high-fat diet. We presume that the polyphenols from yellow wine prevent the development of atherosclerosis, at least in part, by decreasing blood lipid and inhibiting the MMP-2 and MMP-9 expression and increasing the TIMP-1 and TIMP-2 expression. These results could contribute to the explanation of the protective effect of yellow wine on CHD.

Acknowledgments

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References

45 Leroy V, Monier F, Bottari S, Trocme C, Sturm N, Hilleret MN,


