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Hypocholesterolemic Effects of a Flavonoid-Rich Extract of *Hypericum perforatum* L. in Rats Fed a Cholesterol-Rich Diet

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In a previous study, a flavonoid-rich extract of *Hypericum perforatum* L. (FEHP) was prepared and its antioxidant activity was determined by a series of models in vitro. In this study, the hypocholesterolemic effects of FEHP in rats fed a cholesterol-rich diet were tested. Forty Wistar rats fed a standard laboratory diet or a cholesterol-rich diet for 16 weeks were used. The serum lipid levels, as well as malondialdehyde (MDA) and activity of superoxide dismutase (SOD) and catalase (CAT) in serum and liver, were examined. Cholesterol-rich diet induced hypercholesterolemia was manifested in the elevation of serum lipid levels such as total cholesterol (TC), total triglycerides (TG), and low density lipoprotein cholesterol (LDL-C). Administration of middle-dose (75 mg/kg of BW/day) and high-dose (150 mg/kg of BW/day) FEHP significantly lowered the serum levels of TC, TG, and LDL-C, while increasing the serum level of high density lipoprotein cholesterol (HDL-C). Also, the content of MDA in serum and liver decreased significantly after oral administration of FEHP compared with those of rats fed a cholesterol-rich diet. In addition, FEHP increased the activity of SOD in serum and liver, but the activity of CAT was significantly elevated only in liver. These results suggested that the hypocholesterolemic effects of FEHP might be due to its abilities to lower serum TC, TG, and LDL-C levels as well as to slow the lipid peroxidation process and to enhance the antioxidant enzyme activity.

KEYWORDS: ***Hypericum perforatum* L.; flavonoids; hypocholesterolemic; serum lipid levels; malondialdehyde; antioxidant enzymes**

INTRODUCTION

Flavonoids, possessing a three-ring structure containing two aromatic (A and B rings) and a central oxygenated heterocyclic moiety (C ring), are polyphenolic compounds, and they distribute widely in the plant kingdom. Over 8000 individual compounds of flavonoids have been described to date, and the number is constantly increasing (*1*, *2*). Flavonoids have been reported to exhibit a wide range of biological effects such as anti-inflammatory activity and antiallergenic, antiviral, anticarcinogenic, and cardioprotective action (*3*−*5*).

Atherosclerosis, the principal contributor to the pathogenesis of myocardial and cerebral infarction, is known to be one of the leading causes of morbidity and mortality worldwide (*6*). Elevated plasma concentration of cholesterol, especially low-density lipoprotein (LDL), is recognized as a leading cause in the development of atherosclerosis (*7*). Epidemiological studies have revealed an association between increased consumption of antioxidant-rich vegetables and fruits and a decreased risk of coronary heart disease (CHD) (*8*). Flavonoids from various sources have been reported to prevent LDL oxidation in vitro and show markedly hypolipidemic activity in vivo, suggesting the effectiveness of flavonoids for the prevention and treatment of atherosclerosis (*9*−*11*).

Hypericum perforatum L. (HPL) has been used traditionally as an antidepressant for the treatment of mild to moderate depression (*12*, *13*). Phytochemical analysis of HPL shows that it is a rich source of flavonoids, and much of its antioxidant activities are attributed to these compounds. However, research on this plant has focussed mainly on its antidepressant activity. In our previous study, a flavonoid-rich extract of *Hypericum perforatum* L. (FEHP) was prepared and its antioxidant activity was determined by a series of models in vitro (*14*). Therefore, in the present study, we investigated the hypocholesterolemic effects of this flavonoid-rich extract by observing its effects on serum lipid levels and antioxidant enzyme activity in rats fed a cholesterol-rich diet.

MATERIALS AND METHODS

Preparation of FEHP. FEHP was prepared from *Hypericum perforatum* L. as previously reported (*14*).

Animals and Diets. Forty male Wistar rats weighing 125 ± 6 g at the beginning of this study was purchased from Shanghai Laboratory Animal Center of Chinese Academy of Sciences (Shanghai, China). All of the rats were initially fed a standard laboratory diet (Shanghai Laboratory Animal Center; the diet compositions are shown in **Table 1**) for at least 7 days after delivery to our laboratory in order to accustom

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Table 1. Compositions of the Experimental Diets

standard lab diet	%	cholesterol-rich diet	%
crude protein	22.31	standard lab diet	87.8
fat	5.43	lard oil	10
fiber	4.30	cholesterol	2
moisture	9.80	sodium cholate	0.1
ash	6.06	propylthiouracil	0.1
calcium	1.30		
phosphorus	0.80		
Lys	1.34		
Met + Cys	0.81		

the rats to our experimental conditions. After 1 week of acclimatization, the rats were randomly divided into five experimental groups. They were housed identically in polypropylene cages (four in each cage) in an air-conditioned room (24 ± 2 °C) under a 12 h light/12 h dark cycle with free access to food and water. Water was allowed ad libitum. The rats in the control group were fed a standard laboratory diet (normal group, NG); the rats in the hypercholesterolemic group were fed a cholesterol-rich diet (hypercholesterolemic group, HCG). At the same time, the rats in three other groups were treated with FEHP at a dose of 25 mg/kg of body weight (BW)/day (low-dose FEHP treated group, LDG), 75 mg/kg of BW/day (middle-dose FEHP treated group, MDG), and 150 mg/kg of BW/day (high-dose FEHP treated group, HDG) while being fed the cholesterol-rich diet. FEHP was dissolved in water and given orally to rats by an orogastric tube. During the 16 weeks feeding period, all animals used were handled according to the guidelines of the Chinese government for the care and use of laboratory animals.

Measurement of Body Weight and Serum Lipid Levels. Diet intake was measured daily and body weight (BW) was recorded before the start of the treatment and every 1 week. After the rats were deprived of food overnight, blood samples were collected from the venous plexus of fundus of eyes and centrifuged at a speed of 4000*g* (3 min, 4 °C) to obtain serum. Serum was stored at −80 °C until serum lipids were analyzed. Concentrations of total cholesterol (TC), total glycerides (TG), and high density lipoprotein cholesterol (HDL-C) in serum were determined by enzymatic colorimetric methods using commercial kits (Shanghai Rongsheng Biotech. Co. Ltd., Shanghai, China). Low density lipoprotein cholesterol (LDL-C) was accomplished according to the procedures outlined earlier (*15*).

Evaluation of Malondialdehyde (MDA) and Enzyme Activity in Serum and Liver. At the end of 16 weeks, the rats were sacrificed by cervical dislocation. The livers, kidneys, and spleens were rapidly removed, cleaned of adhering matters, blotted on filter paper, and weighed. The organ:BW was calculated and expressed as percentage. The livers were homogenized with ice-cold saline (1:10, w/v), and the homogenates were centrifuged (4000*g*, 10 min, 4 °C).The homogenate supernatants were analyzed for MDA and activity of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) using commercial kits (Nanjing Jiancheng Bioengineering Institute, Nanjing, China). The protein content of supernatants was determined by the method of Lowry et al. (*16*).

Statistical Analysis. The data were expressed as the mean ± standard deviation (SD) of eight rats in each group, and statistical comparisons were made with Student's test. p values of <0.05 were considered to be significant.

RESULTS

The daily diet intake of the rats did not differ among the groups during the feeding period (**Figure 1**). In addition, there was no significant difference in body weight among rats fed the standard laboratory diet and rats fed the cholesterol-rich diet (**Figure 2**). As shown in **Figure 3**, the ratios between organs (liver, kidney, spleen) and body weight did not show any significant difference among the groups at the end of the experiment.

According to the statistical evaluation, at the beginning of this study, all experimental groups did not differ from the normal group in serum lipid concentrations ($p > 0.05$ in all cases, data not shown). **Figure 4** shows the serum lipid levels at the end of the experiment. After 16 weeks of feeding, the TC, TG, and LDL-C concentrations of rats in HCG showed a significant increase compared with those of rats fed the standard laboratory

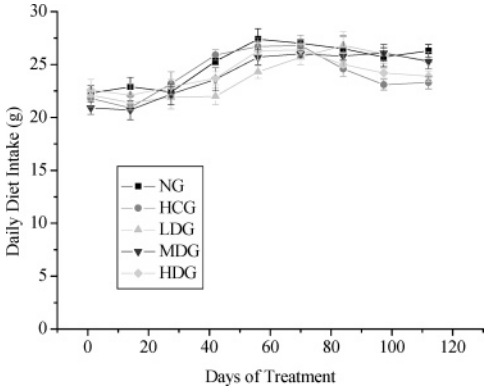

Figure 1. Daily diet intake of rats fed standard laboratory diet or cholesterol-rich diet during the 16-week feeding period. NG, normal group; HCG, hypercholesterolemic group; LDG, low-dose FEHP treated group (25 mg/kg of BW/day); MDG, middle-dose FEHP treated group (75 mg/kg of BW/day); HDG, high-dose FEHP treated group (150 mg/kg of BW/day). Values are expressed as means ± SD of eight rats per group.

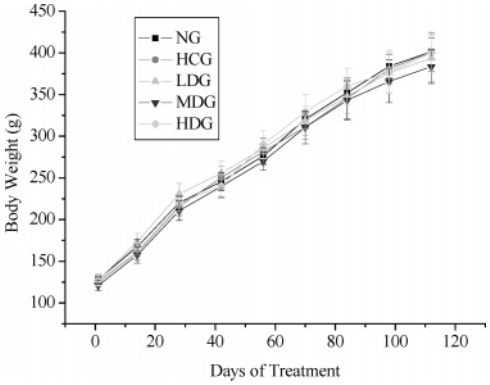

Figure 2. Growth curves of rats fed standard laboratory diet or cholesterol-rich diet during the 16-week feeding period. NG, normal group; HCG, hypercholesterolemic group; LDG, low-dose FEHP treated group (25 mg/kg of BW/day); MDG, middle-dose FEHP treated group (75 mg/kg of BW/day); HDG, high-dose FEHP treated group (150 mg/kg of BW/day). Values are expressed as means ± SD of eight rats per group.

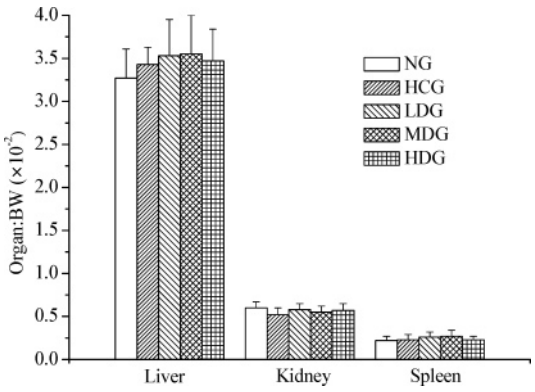

Figure 3. Ratios between organs (liver, kidney, spleen) and body weight of rats fed standard laboratory diet or cholesterol-rich diet for 16 weeks. BW, body weight; NG, normal group; HCG, hypercholesterolemic group; LDG, low-dose FEHP treated group (25 mg/kg of BW/day); MDG, middle-dose FEHP treated group (75 mg/kg of BW/day); HDG, high-dose FEHP treated group (150 mg/kg of BW/day). Values are expressed as means ± SD of eight rats per group.

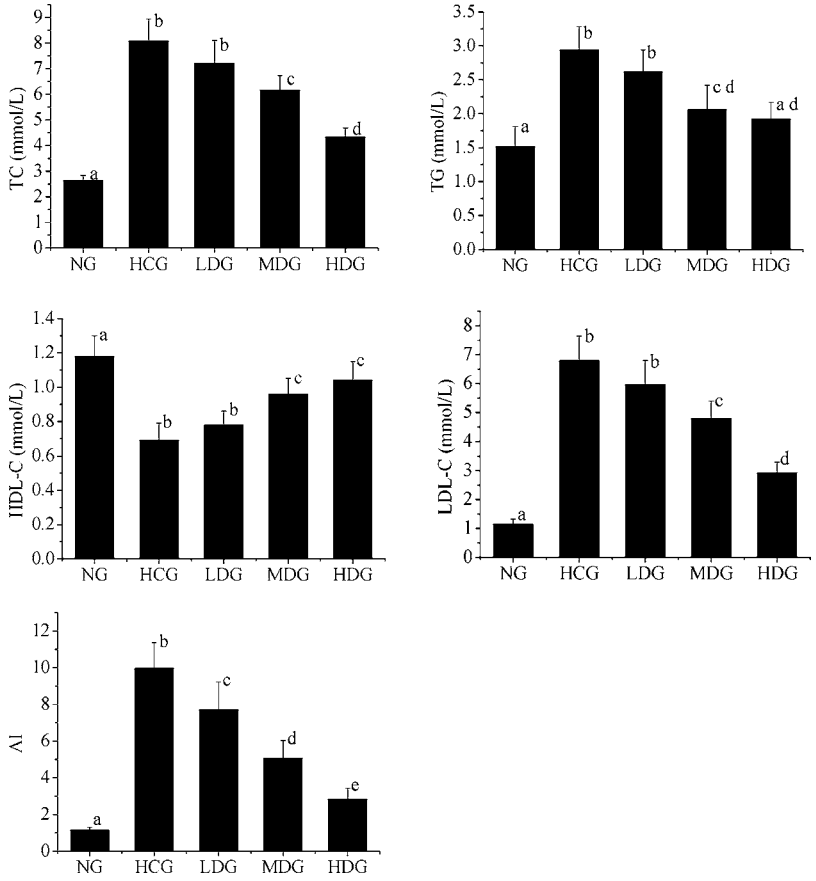

Figure 4. Effects of FEHP on serum lipid levels of rats fed cholesterol-rich diet for 16 weeks. FEHP, flavonoid-rich extract of *Hypericum perforatum* L.; NG, normal group; HCG, hypercholesterolemic group; LDG, low-dose FEHP treated group (25 mg/kg of BW/day); MDG, middle-dose FEHP treated group (75 mg/kg of BW/day); HDG, high-dose FEHP treated group (150 mg/kg of BW/day); TC, total cholesterol; TG, total glycerides; LDL and HDL are low- and high-density lipoprotein; AI, atherogenic index, AI = LDL-C/HDL-C. Values are expressed as means ± SD of eight rats per group. Bars not sharing common letter superscripts are significantly different ($p < 0.05$).

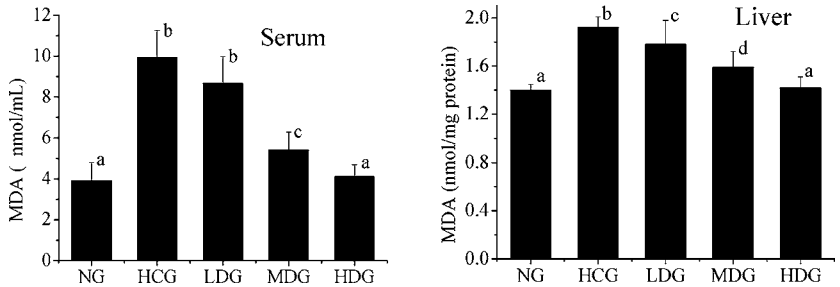

Figure 5. Effects of FEHP on MDA level in serum and liver of rats fed cholesterol-rich diet for 16 weeks. FEHP, flavonoid-rich extract of *Hypericum perforatum* L.; MDA, malondialdehyde; NG, normal group; HCG, hypercholesterolemic group; LDG, low-dose FEHP treated group (25 mg/kg of BW/day); MDG, middle-dose FEHP treated group (75 mg/kg of BW/day); HDG, high-dose FEHP treated group (150 mg/kg of BW/day). Values are expressed as means ± SD of eight rats per group. Bars not sharing common letter superscripts are significantly different ($p < 0.05$).

diet ($p < 0.01$). However, a decrease of HDL-C concentration of rats in HCG was observed ($p < 0.05$). Rats orally treated with FEHP had lower concentrations of TC, TG, and LDL-C than those of rats in HCG, and the serum lipid level reducing activity increased more as the oral dose increased; in particular, the administration of FEHP at doses of 75 and 150 mg/kg of BW/day reduced the TC, TG, and LDL-C levels by 23.6%, 46.3%, 29.9%, and 34.7%, 29.5%, 57.0%, respectively. Although the concentration of HDL-C in FEHP-treated rats never exceeded that of rats fed the standard laboratory diet, the concentration of HDL-C of rats in MDG and HDG increased significantly compared with those of rats in HCG ($p < 0.05$). The atherogenic index (AI) was significantly reduced in a dose-dependent manner by orally administrating FEHP.

As shown in **Figure 5**, when serum and liver MDA concentrations of rats in HCG were compared with those obtained from NG, a significant increase was observed. On the other hand, the middle dose and high dose of FEHP-treated rats showed a remarkable decrease in the concentration of MDA in serum and liver as compared with the rats fed the cholesterol-rich diet.

SOD activity and CAT activity in serum and liver after treatment with the cholesterol-rich diet and FEHP for 16 weeks are illustrated in **Figure 6**. Serum and liver SOD and CAT activities of rats in HCG were significantly lower than those of rats in NG. Oral administration of middle dose and high dose of FEHP significantly increased the SOD activity compared with those of rats fed the cholesterol-rich diet. Also, the hepatic CAT

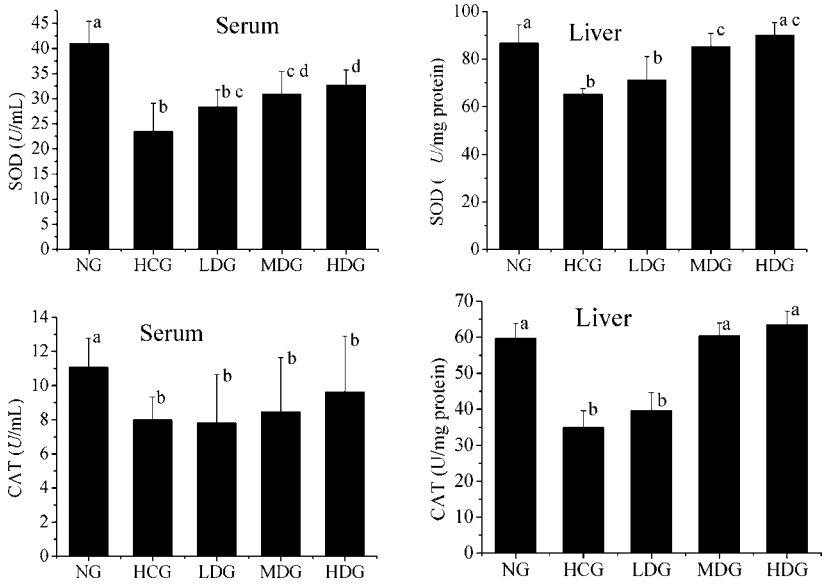

Figure 6. Effects of FEHP on antioxidant enzyme activity in serum and liver of rats fed cholesterol-rich diet for 16 weeks. FEHP, flavonoid-rich extract of *Hypericum perforatum* L.; SOD, superoxide dismutase; CAT, catalase; NG, normal group; HCG, hypercholesterolemic group; LDG, low-dose FEHP treated group (25 mg/kg of BW/day); MDG, middle-dose FEHP treated group (75 mg/kg of BW/day); HDG, high-dose FEHP treated group (150 mg/kg of BW/day). Values are expressed as means ± SD of eight rats per group. Bars not sharing common letter superscripts are significantly different ($p < 0.05$).

activity of rats in MDG and HDG significantly increased compared with that of rats in HCG by 73.2% and 81.7%, respectively, while the activity of CAT in serum was not influenced by the presence of FEHP since there was no significant difference between rats in HCG and rats treated with FEHP.

DISCUSSION

In our study, Wistar rats fed a cholesterol-rich diet for 16 weeks were used to study the effects of FEHP on serum lipid levels and antioxidant enzyme activity in serum and liver. The cholesterol-rich diet contained sodium cholate, which is reported to improve the adsorption and accumulation of cholesterol in vivo, and propylthiouracil, which can inhibit the synthesis of thyroxin and reduce the consumption of lipids (*17*).

The results of the diet intake, growth, and ratios between organs and BW after 16-week feeding showed no significant difference among all groups, suggesting that neither the cholesterol-rich diet nor FEHP had an adverse effect on the growth of rats. The rats in HCG had higher concentrations of TC, TG, and LDL-C in serum than those of NG, indicating that the hypercholesterolemic model was successfully established.

Most of cholesterol is an essential structure element of biological membranes, the rests is transited through blood or functions as the starting material for the synthesis of bile acid, steroid hormones, and vitamin D. However, increased concentration of serum cholesterol increases the risk of developing CHD (*18*). The present study demonstrated that rats fed a cholesterol-rich diet showed a higher concentration of serum TC compared with rats fed a standard laboratory diet, while oral administration of FEHP reduced the high level of TC. The reduction of TC induced by FEHP might be attributed to its inhibition of HMG CoA reductase activity or increased excretion of fecal bile acid and cholesterol. Although we did not determine the activity of HMG CoA reductase and the output of feces, similar effects were observed in flavonoids from other sources (*19*). Davignon et al. have reported that decreased plasma TG concentration was associated with a lower risk of CHD (*20*). In our study, the consumption of FEHP could significantly lower the serum TG level. This reduction might be related to the decreased triglyceride adsorption as well as increased excretion of TG via feces. A similar result was obtained by Shukla et al. (*21*).

It is widely accepted that elevations in plasma LDL are major risk factors for CHD (*7*). The relationship between LDL and atherosclerosis and the suggestion that the pathological process could be reversed by reducing the serum LDL have been reported by other researchers (*22*). When there is excessive LDL in the blood, it is deposited in the blood vessel walls and becomes a major component of atherosclerotic plaque lesions. In our study, the high concentration of LDL-C induced by hypercholesterolemia was significantly reduced by orally administrating FEHP. Our results indicated that FEHP might be a candidate for the treatment of atherosclerosis by lowering serum LDL-C.

Another risk factor for developing atherosclerosis is the reduced HDL, since HDL facilitates translocation of cholesterol from peripheral tissue like arterial walls to liver for catabolism. The increase in HDL may slow the atherosclerosis process (*23*). Our results showed that the FEHP-supplemented diet increased the concentration of serum HDL-C when compared with the cholesterol-rich diet, even though FEHP failed to increase serum HDL-C level to the normal level. Atherosclerotic index (AI), defined as the ratio of LDL-C and HDL-C, is believed to be an important risk factor of atherosclerosis. Since LDL-C was significantly suppressed and administrating FEHP resulted in increased HDL-C, the value of AI was significantly decreased. This decrease in AI was another positive change after FEHP treatment.

MDA, the product of lipid peroxidation, which reacts with thiobarbituric acid and forms a red compound that shows maximum absorbance at 532−535 nm, is an index of the level of oxygen free radicals. A decrease in lipid peroxidation leads to the reduction of atherosclerosis caused by hypercholesterolemia (*24*). The content of MDA in rats fed the cholesterol-rich diet was elevated 2 times than that of rats fed the standard laboratory diet, suggesting that hypercholesterolemia could

enhance the process of lipid peroxidation. A possible explanation may lie in the finding that hypercholesterolemia could elevate the cholesterol content of platelets, polymorphonuclear cells, leukocytes, and endothelial cells. This initiates a series of reactions, which may lead to the generation of oxygen free radicals, thus speeding up the course of lipid peroxidation (*25*, *26*). Our results demonstrated that oral administration of FEHP prevented the cholesterol rich diet induced elevation of MDA and resulted in a significantly decreased content of MDA in both serum and liver. The ability of FEHP to suppress the lipid peroxidation may partially be attributed to the antiradical activities of the flavonoid components known to act by free radical scavenging or chain-breaking mechanisms (*14*). The obtained data suggested that FEHP might be capable of lowering or slowing down oxidative-stress-related lipid peroxidation.

A cholesterol-rich diet brings about remarkable modifications in the antioxidant defense mechanisms. Studies have shown that hypercholesterolemia diminishes the antioxidant defense system and decreases the activity of SOD and CAT, thus elevating the lipid peroxide content (*27*). In the present study, the activities of SOD and CAT in serum and liver of rats in HCG were significantly decreased compared with those of rats in NG. Administration of FEHP to the rats fed the cholesterol-rich diet significantly elevated the activities of SOD in serum and liver by 31.6%, 39.3%, and 30.5%, 38.0% at doses of 75 and 150 mg/kg of BW/day, respectively. Those results suggested that FEHP could improve the efficiency of superoxide anion to hydrogen peroxide due to the increased SOD activity, which catalyzes dismutation of superoxide anion into hydrogen peroxide. FEHP also increased the activity of CAT in liver, which in turn detoxifies hydrogen peroxide and converts lipid hydroperoxides to nontoxic substances.

In conclusion, the present study demonstrated that FEHP had very pronounced hypocholesterolemic effects. It could significantly lower the concentrations of serum TC, TG, and LDL-C, and elevate the serum HDL-C level. It decreased the content of MDA in serum and liver, while it also significantly increased the activity of SOD both in serum and in liver and the activity of CAT in liver. These results suggest that the hypocholesterolemic effects of FEHP might be due to its abilities to lower serum TC, TG, and LDL-C levels as well as to slow the lipid peroxidation process and to enhance the antioxidant enzyme activity.

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