

Effects of Dietary Proso Millet on Cholesterol and Fatty Acid Metabolism in Rats Fed High Cholesterol Diets

Sung-Hee Cho^{1§}, Seung-Eun Jung¹, Hye-Kyung Lee¹ and Tae-Youl Ha²

¹Department of Food Science and Nutrition, Catholic University of Taegu-Hyosung, Kyungbuk 712-702, Korea

²Korea Food Research Institute, Rice Research Group, Kyonggi-do 463-420, Korea

ABSTRACT

To study the effect of proso millet (*Panicum milaceum*) on lipid metabolism, male Sprague-Dawley rats weighing 190 ± 8 g were fed six experimental diets for four weeks. The six diets based on AIN-76 composition consisted of one cholesterol-free (normal) and five 1% (w/w) cholesterol diets, i.e. control, two diets containing additional 0.3 and 0.6% (w/w) methanol extracts of proso millet and another two diets containing 15 and 30% (w/w) proso millet powder. There was no difference in weight gains between the groups but relative liver weights increased under the cholesterol diets. Plasma levels of total cholesterol and triglyceride (TG) decreased by 23–27% and by 37–52%, respectively, in the four proso millet diet groups compared to those of the normal and control groups. Whereas in the liver, only TG levels decreased in the proso millet diet groups. Fecal excretions of bile acid and cholesterol increased 5–10 times with cholesterol feeding and further increased with proso millet powder in the diets. They did not increase significantly with methanol extracts of proso millet. There was a significant increase in the activity of hepatic microsomal cholesterol 7 α -hydroxylase when feeding 1% cholesterol but proso millet in the diet, either as in the form of powder or methanol extract, appeared to have only slight additional effects, namely increases in enzyme activity. The activity of liver cytosolic glucose-6-phosphate dehydrogenase (G6PDH) tended to be reduced with high cholesterol diets and dropped markedly by 15% using additional proso millet powder. Those of the liver cytosolic malic enzyme had a similar tendency to those of G6PDH. The results indicate that certain active components in proso millet other than fiber have the potential to exert hypolipidemic effects via regulating cholesterol excretions and lipogenesis.

KEY WORDS: proso millet, cholesterol, triglyceride, cholesterol 7 α -hydroxylase, G6PDH

INTRODUCTION

Among plant foods, grains are particularly important to public health since they supply a considerable amount of energy and a few other nutrients to humans. Increased consumption of whole grain products has been recommended to prevent coronary heart disease (CHD) but it is only in recent years that an inverse relation was shown specifically between intakes of whole grain and CHD risk^{1,2}. The effects of the cereals are attributed mainly to dietary fiber, which plays a role in reducing serum cholesterol. With regard to types of dietary fiber, those with high content of water-soluble β -glucans are believed to decrease absorption of dietary lipids and increase fecal excretion of bile acids and neutral sterols through their viscosity in aqueous solutions. But there are other data suggesting that the hypocholesterolemic effect of cereal is not solely due to viscosity resulting from soluble fibers. Zhang *et al.*³ have shown that feeding brewer's spent grain that was low

in water-soluble β -glucan decreased plasma cholesterol and increased fecal steroid loss in human subjects with ileostomies. Reports from Topping *et al.*⁴⁻⁶ have supported the results of Zhang *et al.*³ and also conceded the findings of Qureshi *et al.*⁷ that lipid components from barley were involved in the hypocholesterolemic effects of cereals via inhibitory on hepatic 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (EC 1.1.1.34). In their subsequent works, Qureshi *et al.*^{8,9} have identified α -tocotrienol as one of the active constituents and later showed that α -tocotrienol is as potent as α -isomer in humans, although Pearce *et al.*¹⁰ have argued that α -isomer has much greater inhibitory activity toward cholesterol biosynthesis in HepG2 cell *in vitro*. It is well known that cereal grains contain various types of polyphenolic compounds other than tocotrienols.¹¹ Among them tannic acid and morin¹² have been reported to reduce serum levels of total cholesterol and triglyceride.

Cereals consumed in Korea are of various kinds and some of them have been reported to have hypocholesterolemic effects.^{13,14} But active materials other than dietary fibers for the effects have been rarely investigated. In our

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[§]To whom correspondence should be addressed.

recent work, we showed both *in vitro*⁵¹ and *in vivo*¹⁰ inhibitory effects of methanol extract of prosomillet on the activity of rat liver microsomal HMG-CoA reductase. In the present study, using rats fed a high cholesterol diet, we report hypolipidemic effects of prosomillet in the form of methanol extract and powder as well as changes in bile acid excretion and activities in hepatic cholesterol 7 α -hydroxylase and glucose-6-phosphate dehydrogenase.

MATERIALS AND METHODS

1. Animals and diets

Male Sprague-Dawley rats weighing about 190 \pm 8 g were obtained from Korea Research Institute of Bioscience and Biotechnology (Taejon, Korea) and acclimated to the facility for 1 week. The rats were divided into six groups, each group comprising 8–9 rats in stainless steel cages with wire mesh bottoms in an environment of constant temperature (22 \pm 1 $^{\circ}$ C) and lighting (light on, 08 : 00–20 : 00 h). They were allowed free access to test diets and water for 4 weeks. Food intake was measured daily and body weight every three days; feces were collected during the last week and kept frozen at –50 $^{\circ}$ C. The experiment was done under guidelines for animal experiments provided by the Catholic University of Taegu-Hyosung.

The six test diets were one cholesterol-free diet (normal) and five kinds of 1.0% (w/w) cholesterol diets, all of which were based on AIN-76 diet¹⁷ as shown in Table 1. Casein, cholesterol and vitamin and mineral mixtures (AIN-76) were purchased from Teklad Test Diets (Madison, WI, USA) and cellulose, DL-methionine, choline bitartrate and Na-taurocholate from Sigma-Aldrich Chemical (St. Louis, MO, USA). Corn starch, sucrose and lard were obtained from a local supermarket. The clean prosomillet harvested in Chung-buk, Korea were ground into 40 mesh powder and added to diet either as such or as methanol extract (MeOH-ext). The MeOH-ext was prepared using 80% methanol and ten times volume of prosomillet powder for 16 hours with continuous shaking. The resultant extract was filtered, concentrated under vacuum at 60 $^{\circ}$ C and finally freeze-dried to remove solvent before being added to the diets. The MeOH-ext was added to the prosomillet diets at levels of 0.3 or 0.6% (w/w) and prosomillet powder at levels of 15 or 30% (w/w), respectively. Contents of starch, cellulose and soybean oil in the prosomillet powder diets were adjusted as shown in Table 1. The contents of starch, protein, fat and fiber was 76.1%, 11.3%, 2.2% and 1.8%, respectively, in the prosomillet¹⁸ in order for all diets to have 20% protein,

Table 1. Composition of experimental diets (g/~1000 g Diet)

	Normal	Control	Prosomillet			
			0.3% MeOH- ext	0.6% MeOH- ext	15% Powder	30% Powder
Casein ^f	200	200	200	200	183	166
DL-Methionine ^h	3	3	3	3	3	3
Starch ^c	150	150	150	150	36	0
Sucrose ^f	450	450	450	450	450	372
Cellulose ^b	50	50	50	50	47	45
Lard ^c	100	100	100	100	97	93
Mineral mix ^a	35	35	35	35	35	35
Vitamin mix ^a	10	10	10	10	10	10
Choline ^h	2	2	2	2	2	2
Cholesterol ^g		10	10	10	10	10
Na taurocholate ^b		3	3	3	3	3
Prosomillet ^d						
MeOH-ext			3	6		
Powder					150	300
kcal/1000g	4100	4047	4035	4023	3996	3766

a: Teklad Test Diets, Madison, WI, USA

b: Sigma-Aldrich Chemical, St. Louis, MO, USA

c: Obtained from local mart

d: Harvested in Chung-buk, Korea

60% carbohydrate and 10% fat by weight. Since 2.8 g of the methanol extract was obtained from 100 g dry prosomillet powder, 15 and 30% (w/w) powder in the diets were assumed to have methanol extractable components at the level of 0.42 and 0.84% (w/w), which were slightly higher than two levels of MeOH-ext in the respective diets.

2. Biochemical analysis

After 4 weeks of the experimental diets the rats were anesthetized with ether, blood was drawn from abdominal *vena cava* into heparinized tube and plasma was prepared by centrifugation and stored at –50 $^{\circ}$ C before lipid determination. The liver was excised after removing blood by passing saline through portal vein, blotted dry and one part of it quickly frozen in liquid nitrogen for subsequent measurements of lipids. Another part of the liver was homogenized and subjected to differential centrifugation to prepare microsomal fractions which were stored under –70 $^{\circ}$ C before measuring enzyme activities.

Plasma total cholesterol, HDL-cholesterol and triglyceride were measured by using enzymatic kit (Shinyang Chemical Co. Seoul, Korea). Hepatic lipids were extracted by the method of Folch *et al.*¹⁹ Cholesterol²⁰ was measured colorimetrically, and triglyceride was measured by using the enzymatic kit (Shinyang Chemical Co.) with the aid of detergent, triton X-100.²¹ Bile acid from dry feces was extracted by the method of Crowell and Macdonald²² and determined by using enzymatic kit (Sigma).

Activity of cholesterol 7 α -hydroxylase was measured using incorporation of liposome solubilized cholesterol isotope ([4-14C] cholesterol, Amersham, Buckinghamshire, England) into microsomal preparations²³⁾ but azolectin for liposome was prepared from phosphatidylcholine.¹⁶⁾ Activities of glucose-6-phosphate dehydrogenase and malic enzyme in cytosol were measured by recording NADP reduction.²¹⁾²⁵⁾

3. Statistical analysis

Data were analyzed by analysis of variances and group differences were considered statistically significant at $p < 0.05$ by Tukey's test.

RESULTS

1. Growth and liver weight

As shown in Table 2, there was no significant difference in feed efficiencies among the six experimental groups, although feed efficiency was somewhat lower in rats fed 30% prosmillet powder. Relative liver weights were higher in the five high-cholesterol fed groups than the normal group fed a cholesterol-free diet. However, increases in body and liver weights were smaller in the group fed a diet containing 30% prosmillet powder compared to the control and the other three prosmillet groups.

2. Effects of dietary prosmillet on plasma and liver lipids and fecal excretion of bile acid

Table 3 shows plasma lipid levels of experimental groups. Levels of total cholesterol were increased 2.8 times with the 1% cholesterol diet (control) compared to the normal cholesterol-free diet. But the cholesterol levels were reduced significantly (23–27%) with diets containing 0.3% and 0.6% methanol extract of prosmillet and 30% prosmillet

Table 2. Effects of dietary prosmillet on growth of rats on high cholesterol diet

	Initial body weight (g)	Body weight gain (g)	Feed efficiency (g/100 g diet)	Relative liver weight (g/100 g bw)
Normal	197.3 \pm 3.7 ^{NS}	116.5 \pm 4.2 ^{NS}	22 \pm 2 ^{NS}	2.67 \pm 0.56 ^b
Control	193.0 \pm 3.5	127.0 \pm 2.4	25 \pm 1	4.02 \pm 1.01 ^a
MeOH-ext				
0.3%	190.5 \pm 2.8	130.1 \pm 1.9	23 \pm 2	4.17 \pm 1.98 ^a
0.6%	193.5 \pm 3.1	120.3 \pm 4.8	25 \pm 2	4.20 \pm 0.60 ^a
Powder				
15%	187.9 \pm 2.7	120.9 \pm 5.0	24 \pm 2	4.15 \pm 1.00 ^a
30%	188.9 \pm 3.2	111.8 \pm 2.5	19 \pm 2	3.80 \pm 0.44 ^{ab}

Mean \pm SE of 8 rats per group

Values in the same column not sharing common superscript letters are significantly different at $p < 0.05$ by Tukey's test

powder, while they tended to decrease in the group fed 15% prosmillet powder. Plasma levels of HDL-cholesterol and HDL-cholesterol/total cholesterol ratios decreased, on the other hand, in the control and four prosmillet groups but they did not differ among these five groups. Plasma triglyceride levels, which tended to be higher in the control group with the 1% cholesterol diet, was significantly (37–52%) lower in the four prosmillet groups than in the control group.

Hepatic cholesterol and triglyceride concentrations were elevated about 1.5 and 2.5 times respectively using the 1% cholesterol diet, as shown in Table 4. In contrast to those observed in plasma, cholesterol levels in the liver were not reduced in all prosmillet groups compared with the control group, although they exhibited a tendency to decrease. Liver triglyceride levels were significantly (15–21%) reduced only in groups fed 0.3% prosmillet methanol extract and 15% prosmillet powder.

3. Fecal excretions of bile acid and cholesterol

Fecal excretions of bile acid and cholesterol were three to five times higher in the control group fed 1% cho-

Table 3. Effects of dietary prosmillet on concentrations of plasma cholesterol and triglyceride of rats on high cholesterol diet

	Total cholesterol (mg/100 mL)	HDL-cholesterol (mg/100 mL)	HDLc/TChol	Triglyceride (mg/100 mL)
Normal	86.4 \pm 6.6 ^c	45.1 \pm 2.0 ^a	0.522 \pm 0.06 ^a	34.1 \pm 7.5 ^{ab}
Control	238.9 \pm 20.1 ^a	19.4 \pm 2.4 ^b	0.081 \pm 0.06 ^b	42.6 \pm 6.8 ^a
MeOH-ext				
0.3%	172.7 \pm 6.8 ^b	16.5 \pm 1.5 ^{bc}	0.096 \pm 0.06 ^b	20.4 \pm 2.4 ^b
0.6%	184.5 \pm 7.2 ^b	13.6 \pm 1.1 ^c	0.074 \pm 0.06 ^b	26.9 \pm 6.0 ^b
Powder				
15%	199.8 \pm 11.2 ^{ab}	18.3 \pm 1.5 ^{bc}	0.092 \pm 0.06 ^b	22.1 \pm 3.4 ^b
30%	174.6 \pm 13.5 ^b	15.7 \pm 1.9 ^{bc}	0.090 \pm 0.06 ^b	23.5 \pm 2.8 ^{ab}

Mean \pm SE of 8 rats per group

Values in the same column not sharing common superscript letters are significantly different at $p < 0.05$ by Tukey's test

Table 4. Effects of dietary prosmillet on concentrations of liver cholesterol and triglyceride of rats on high cholesterol diet

	Cholesterol (mg/g liver)	Triglyceride
Normal	1.90 \pm 0.31 ^b	14.82 \pm 1.24 ^c
Control	27.88 \pm 4.39 ^a	37.91 \pm 4.8 ^a
MeOH-ext		
0.3%	22.88 \pm 4.02 ^a	32.06 \pm 2.97 ^b
0.6%	24.42 \pm 2.25 ^a	34.31 \pm 4.10 ^{ab}
Powder		
15%	25.06 \pm 3.68 ^a	29.97 \pm 3.19 ^b
30%	25.28 \pm 3.20 ^c	35.62 \pm 3.15 ^{ab}

Mean \pm SE of 8 rats per group

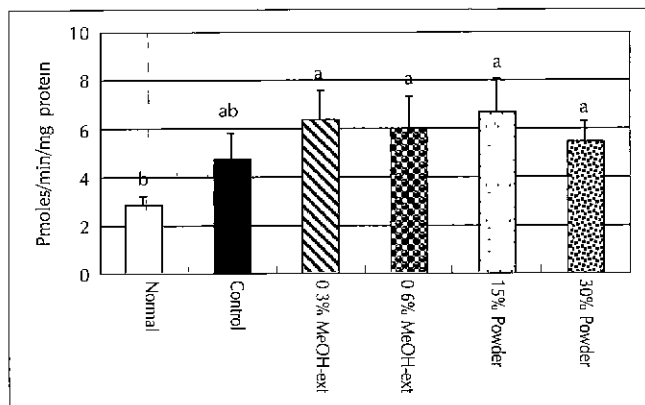
Values in the same column not sharing common superscript letters are significantly different at $p < 0.05$ by Tukey's test

Table 5. Effects of dietary prosomillet on fecal excretions of bile acids and cholesterol of rats on high cholesterol diets

	Fecal bile acid	Cholesterol	Bile acid + Cholesterol
mg/day			
Normal	11.18 ± 1.32 ^c	11.50 ± 1.20 ^c	22.68 ± 1.70 ^c
Control	51.22 ± 3.26 ^{ab}	92.70 ± 15.33 ^b	143.9 ± 15.49 ^b
MeOH-ext			
0.3%	56.13 ± 2.88 ^{ab}	109.68 ± 4.97 ^{ab}	165.8 ± 13.85 ^{ab}
0.6%	48.72 ± 2.90 ^b	104.52 ± 8.15 ^{ab}	151.4 ± 11.47 ^{ab}
Powder			
15%	59.56 ± 2.10 ^a	118.90 ± 4.28 ^a	178.51 ± 8.50 ^a
30%	61.55 ± 9.30 ^a	114.09 ± 9.20 ^{ab}	175.62 ± 24.25 ^a

Mean ± SE of 8 rats per group

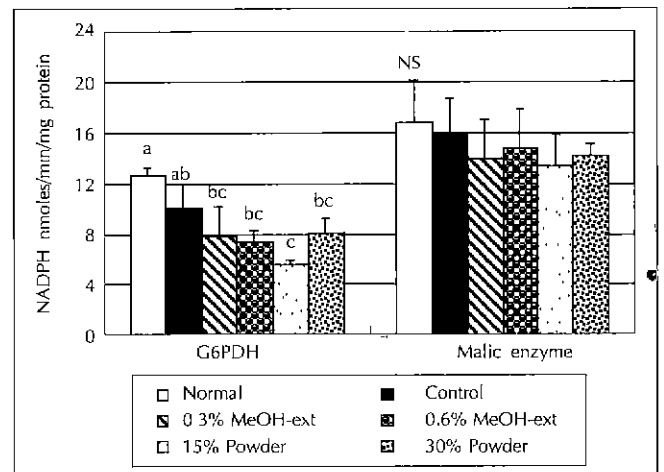
Values in the same column not sharing common superscript letters are significantly different at $p < 0.05$ by Tukey's test

**Fig. 1.** Changes in activities of hepatic cholesterol 7 α -hydroxylase of rats on high cholesterol diets by prosomillet extract and powder. 1 pmoles of [¹⁴C] cholesterol into [¹⁴C] 7 α -hydroxycholesterol/min/mg microsomal protein, Mean ± SE of 8 rats per group, Different alphabet letters in cholesterol 7 α -hydroxylase activities denotes significant difference among groups.

lesterol than in the normal group fed a cholesterol-free diet, as seen in Table 5. Feeding 0.3 and 0.6% prosomillet methanol extract did not significantly increase excretions of either bile acid or cholesterol but 15 and 30% prosomillet powder did, although bile acid and cholesterol excretions tended to be higher in the two groups fed prosomillet methanol extract than the control group.

4. Hepatic activities of cholesterol 7 α -hydroxylase and lipogenic enzymes

As shown in Fig. 1, there was a significant increase in the activity of liver microsomal cholesterol 7 α -hydroxylase when using 1% cholesterol in the diets for the control and four prosomillet groups. But neither prosomillet methanol extract nor powder in the diet further elevated the level of enzyme activity, although there were increasing tendencies of the enzyme activities in the four prosomillet groups compared with the control.

**Fig. 2.** Changes in activities of hepatic lipogenic enzymes of rats on high cholesterol diets by prosomillet extract and powder.

Mean ± SE of 8 rats per group, Different alphabet letters in the same enzyme activities denotes significant difference among groups, NS, not significant.

The activities of liver cytosolic glucose-6-phosphate dehydrogenase (G6PDH) and malic enzyme are shown in Fig. 2. G6PDH activities were significantly (20–40%) reduced and malic enzyme activities appeared also to be lowered by dietary cholesterol. Methanol extract of prosomillet or powder in the diets seemed to suppress the activities of both enzymes further.

DISCUSSION

In the present study, hypocholesterolemic effect was clearly shown by either methanol extract of prosomillet or by prosomillet powder, whereas the effect was not observed in the previous study using cholesterol-free diets.¹⁶ This means that prosomillet can exert a cholesterol-lowering effect above a certain level of plasma cholesterol. The present experimental conditions were comparable to those of many other studies^{23,26,28} in which test materials exerted hypocholesterolemic effects only in diet-induced hypercholesterolemia. The hypotriglyceridemic effect of a prosomillet diet without added cholesterol¹⁶ was more pronounced in the present study using 1% cholesterol in the diet.

Nishizawa and Fudamoto²⁹ reported that feeding mice protein from prosomillet at a level of 25% increased HDL-cholesterol. In the present study, the 30% prosomillet powder diet contained only 3% protein from prosomillet and methanol extract diets had no prosomillet protein. Therefore, the fact that HDL-cholesterol levels relative to total cholesterol (HDL/TChol) were higher in prosomillet diet groups than in the control group may have to be ex-

plained by factors other than protein.

Extracts from green tea,³⁰ garlic,³¹ pepper,³² persimmon leaf,³³ some parts of plants used in oriental medicine,²⁸ and a few types of cereals⁶⁰⁽¹³⁾⁽¹⁴⁾ have been reported to show hypolipidemic action in animals. However, most of the extracts were prepared using hot water or more hydrophilic solvents such as ethanol and ethyl acetate.

In the present study, prosomillet extract was extracted with 80% methanol, but hexane extractable components comprised 55.6% of the total when a second extraction was carried out using several kinds of solvents serially.³⁴ Moreover, it was the hexane extractable fraction that inhibited rat liver microsomal hydroxymethyl glutaryl CoA reductase.¹⁶ Therefore, the effective components for hypolipidemic action by prosomillet in the present study are more likely to be lipophilic, although hydrophilic components cannot be excluded. Qureshi *et al* reported the hypocholesterolemic effects of various lipid soluble fractions from barley⁷ and later concluded that one of major active materials was α -tocotrienol.⁸⁹ Recently, Gerhardt and Gallo³⁵ reported that full-fat rice bran containing minimal soluble fiber reduced LDL-cholesterol by 13.7% when added to the prudent diet of hyperlipidemic adults but they have not identified the active components.

Among lipophilic plant components, β -carotene and lycopene have been shown to reduce LDL-cholesterol level in humans and been related to suppression of cholesterol-synthesis and augmentation of LDL receptor activity in macrophage.³⁶ Capsaicin of red pepper³⁷ as well as tannic acid and morin¹² were earlier recognized to have a hypotriglyceridemic effect. It is not elucidated which components in methanol extract of prosomillet exerted the lipid lowering effect.

Intake of dietary fiber from grains have been reported to increase fecal bile acid excretion.⁴ In the present study, fecal excretions of both bile acid and cholesterol were highest in the two prosomillet powder groups, although amounts of total dietary fiber were adjusted to be same in all six experimental diets. Different types of dietary fiber from prosomillet may have influenced the increase in fecal bile acid excretion, even though minute in quantity (6–10% of total dietary fiber). But prosomillet methanol extract devoid of the special type of fiber also seemed to increase the fecal excretion of bile acid and cholesterol. This indicates that certain constituents present in the extract were responsible for the effect, the mechanism of which probably differs from that of dietary fiber. The mechanism appears to be related to the activity of hepatic cholesterol 7α -hydroxylase. The enzyme activity was not significantly

enhanced by any of the prosomillet diets, but the activity positively correlated with the sum of fecal bile acid and cholesterol excretions, although correlation was weak ($r = 0.32$, $p = 0.056$). As for barley, however, both lipid and water soluble fractions were shown to decrease the activity of cholesterol 7α -hydroxylase.⁷⁸ The hypocholesterolemic effect by prosomillet is therefore due to enhanced activity of cholesterol 7α -hydroxylase as well as decreased *de novo* synthesis of cholesterol,¹⁶ although the latter may have been considerably suppressed by dietary cholesterol in the present study. Low activities of G6PDH and malic enzyme may play a role in reducing serum and liver levels of triglyceride in groups fed prosomillet, either as methanol extract or as powder, as observed in previous study using a cholesterol-free diet.¹⁶ The present results can be compared with those of Qureshi *et al.*,⁷ which showed the different effects on the activity of the fatty acid synthetase of two active compounds isolated from petroleum extracts of barley powder.

It is concluded that prosomillet contains potential hypolipidemic component(s), apart from dietary fiber and probably different from those found in barley.⁷⁸ Hexane extractable constituents of prosomillet, comprising more than half of total methanol extract of prosomillet, are likely to have active materials. They were composed of six different components separated by thin layer chromatography (unpublished observation).

Identification of active component(s) derived from them needs to be done and other polar components that were 28% of total methanol extract also have to be examined to shed light on the hypolipidemic effect of prosomillet in a future study.

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