Rice bran oil, not fiber, lowers cholesterol in humans[1–3]

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ABSTRACT

Background: The cholesterol-lowering abilities of rice bran's fiber and oil apart from its fatty acid composition remain unclear.

Objective: The objective of the study was to assess the effects of defatted rice bran and rice bran oil in an average American diet on blood lipids in moderately hypercholesterolemic persons.

Design: Study 1 used a parallel-arm design. Twenty-six healthy volunteers consumed a diet with 13–22 g dietary fiber/d for 3 wk, and then 13 of the volunteers were switched to a diet with defatted rice bran to double the fiber intake for 5 wk. Study 2 was a randomized, crossover, 10-wk feeding study performed in 14 volunteers who consumed a diet with rice bran oil (1/3 of the total dietary fat) substituted for an oil blend that had a fatty acid composition similar to that of the rice bran oil. Serum lipids and factor VII were measured in both studies.

Results: Defatted rice bran did not lower lipid concentrations. In study 2, total cholesterol was significantly lower with consumption of the diet containing rice bran oil than with consumption of the control diet. Moreover, with consumption of the rice bran oil diet, LDL cholesterol decreased by 7% ($P < 0.0004$), whereas HDL cholesterol was unchanged.

Conclusions: Rice bran oil, not fiber, lowers cholesterol in healthy, moderately hypercholesterolemic adults. There were no substantial differences in the fatty acid composition of the diets; therefore, the reduction of cholesterol was due to other components present in the rice bran oil, such as unsaponifiable compounds. *Am J Clin Nutr* 2005;81:64–8.

KEY WORDS Rice bran fiber, rice bran oil, lipoproteins, phytosterols

INTRODUCTION

Rice bran, a coproduct of milled rice, and its oil may have cardiovascular health benefits. Human consumption of rice bran has been limited, primarily because of the rapid onset of rancidity in rice bran, but methods to stabilize rice bran and to extract its oil have been developed. Interest in rice bran grew from the determination that the inclusion of oat bran in the diet lowers serum cholesterol (1, 2). Studies of rice bran supplementation in humans found similar beneficial effects on lipoproteins (3–6). In a 10-wk controlled feeding trial, rice bran was as effective as oat bran in lowering blood cholesterol concentrations in men and women with moderately high blood cholesterol concentrations (7).

Rice bran contains 10–23% oil (8) and (unlike oat bran) negligible amounts of water-soluble β-glucans and larger amounts of insoluble dietary fiber. Because of these differences, it is believed that rice bran lowers cholesterol by a mechanism different from that of oat bran. Decreases in cholesterol were found in hypercholesterolemic subjects who replaced their usual cooking oils with rice bran oil (9) and in middle-aged and elderly subjects consuming a low-fat diet containing rice bran oil (10). Yet rice bran oil typically contains 20% saturated fatty acids and approximately equal amounts of oleic and linoleic fatty acids (11). Previous research showed the deleterious effects of saturated fatty acids on total cholesterol concentrations, and the fact that rice bran oil lowers cholesterol is contrary to these findings. Research now suggests that rice bran oil's cholesterol-lowering properties are explained by its unsaponifiable components more than by its fatty acid composition (12, 13). Attention has begun to focus on the components of rice bran oil, including phytosterols, triterpene alcohols, tocopherols, and tocotrienols, as possible hypocholesterolemic agents.

We examined further the cholesterol-lowering abilities of rice bran's fiber and oil apart from its fatty acid composition. This was accomplished with 2 well-controlled feeding studies designed to evaluate the effects of using defatted rice bran and rice bran oil in an average American diet on cardiovascular disease risk factors in men and women.

SUBJECTS AND METHODS

Subjects

For study 1, 27 healthy men and women were recruited in 2 cohorts. One woman was taking hormone replacement therapy, and the other women were premenopausal and not taking oral contraceptives. One man was dropped from the study after random assignment to the treatment diet because of an allergic reaction. Fourteen healthy men and premenopausal women (3 taking oral contraceptives) participated in study 2. The subjects' characteristics are shown in **Table 1**.

Eligible subjects were 18–50 y old and had total serum cholesterol concentrations between the 25th and 90th percentiles after adjustment for sex, age, and race (14); triacylglycerol concentrations < 90th percentile after adjustment for sex, age, and

TABLE 1
Baseline characteristics at screening of subjects in study 1 and study 2[1]

	Study 1 (n = 13 F, 13 M)	Study 2 (n = 7 F, 7 M)
Age (y)	32.9 ± 1.7	33.6 ± 2.8
BMI (kg/m^2)	24.3 ± 0.6	24.8 ± 0.7
Total cholesterol (mmol/L)	5.03 ± 0.12	5.33 ± 0.11
HDL cholesterol (mmol/L)	1.29 ± 0.08	1.19 ± 0.07
LDL cholesterol (mmol/L)	3.33 ± 0.15	3.65 ± 0.12
Triacylglycerols (mmol/L)	0.84 ± 0.08	1.00 ± 0.09

[1] All values are $\bar{x}$ ± SEM of subject's average of replicate measurements. To convert cholesterol values to mg/dL, divide by 0.02586; to convert triacylglycerol values to mg/dL, divide by 0.01129.

race; LDL concentrations < 4.91 mmol/L (190 mg/dL) and HDL concentrations > 0.65 mmol/L (25 mg/dL); and a body mass index (BMI; in kg/m^2) ≤ 30. Exclusion criteria included renal, hepatic, cardiovascular, endocrine, gastrointestinal, or other systemic disease; hypertension; pregnancy (for women); history of drug or alcohol abuse; smoking or other tobacco use; chronic use of prescribed medication; extreme dietary habits such as vegetarianism or severely low fat intakes; multiple food allergies; extreme levels of physical or athletic activities; and current weight-loss efforts.

The study protocol and consent form were approved by the Louisiana State University's Institutional Review Board. Written informed consent was obtained from all subjects, and all subjects received monetary compensation for their participation.

Experimental design

Study 1: defatted rice bran

All subjects began with consumption of a run-in diet for 3 wk and then were randomly assigned to either the control or intervention diet for an additional 5 wk. Assessment of outcome measures occurred at the end of the run-in period and at the end of the study. Blood samples were collected in triplicate on separate days to minimize the influence of biologic variability in these measures. In addition, a single measurement of blood lipids was taken 2 wk after the randomization. Body weight was measured twice a week throughout the study, and energy was adjusted to ensure weight stability.

The study 1 diets were a low-fiber control diet (control 1) and a high-fiber intervention diet containing defatted rice bran (DRB). The control 1 diet provided 13–22 g dietary fiber/d, varying with total energy, whereas the addition of DRB (56–94 g/d, varying with total energy level) to the intervention diet doubled the fiber content. Both diets provided 37% of total energy as fat. DRB was incorporated into muffins, cookies, and breads. A 4-d menu rotation was used to maintain variety throughout the study. The macronutrient composition of each diet (an average of the 4 menu plans, each at 2 different energy amounts), as determined by the Pennington Center's Food Analysis Laboratory, is shown in **Table 2**.

Study 2: rice bran oil

Study 2 used a randomized, double-blind, crossover design with two 5-wk diet periods. Assessment of outcome measures occurred at the end of each diet period. Blood samples were collected in triplicate on separate days to minimize the influence

TABLE 2
Chemical composition of the diets provided to subjects participating in study 1[1]

	Control diet	Defatted rice bran diet
Fat (% of energy)		
Total	36.6 ± 1.0	36.5 ± 1.2
Saturated	14.6 ± 0.4	14.5 ± 0.6
Polyunsaturated	10.6 ± 0.4	10.6 ± 0.4
Monounsaturated	11.4 ± 0.4	11.3 ± 0.4
Carbohydrate (% of energy)	51.3 ± 1.4	50.6 ± 1.3[2]
Protein (% of energy)	12.1 ± 0.6	12.9 ± 0.5[2]
Fiber (g)	16.6 ± 1.8	33.3 ± 4.7[3]

[1] All values are $\bar{x}$ ± SEM and reflect the average values of 4 menu plans at 2 energy levels (9205 and 12 552 kJ; 2200 and 3000 kcal).
[2,3] Significantly different from control diet (two-sample t test): [2] P < 0.05, [3] P < 0.002.

of biologic variability in these measures. Body weight was measured twice a week, and energy was adjusted to ensure weight stability.

To determine whether unsaponifiable components present in rice bran oil (RBO) affect lipid metabolism, the fatty acid composition of RBO was matched with that of an oil blend that was used in the control diet. The fatty acid profile of the RBO that was obtained for the second feeding study was determined. Then other oils were combined, chemically analyzed, and adjusted until the best match of the RBO's fatty acid profile was achieved. The oil blend was composed of peanut oil, olive oil, corn oil, canola oil, palm oil, and butter. The comparison of the control blend and RBOs for the major fatty acids and for the tocopherol, tocotrienol, and oryzanol contents is shown in **Table 3**.

Both diets were designed to provide 37% of total energy as fat. For the study 2 control diet (control 2), one-third of the total dietary fat was in the form of the oil blend, and for the RBO intervention diet, the oil blend was replaced with RBO. The oil blend or rice bran oil was incorporated into recipes for a 5-d menu rotation. Other fats were added to the diets so that the total diet would provide 15%, 17%, and 6% of energy as saturated, monounsaturated, and polyunsaturated fat, respectively. The total dietary cholesterol was ≈125 mg/1000 kcal. To keep the participants blinded to their diet assignment, the control 2 (oil blend)

TABLE 3
Comparison of the fatty acid profile and of the tocopherol, tocotrienol, and oryzanol content of the control oil blend and the rice bran oil used in study 2, as determined by chemical analysis

	Control oil blend	Rice bran oil
14:0 (g/100 g)	0.37	0.40
16:0 (g/100 g)	12.96	14.60
18:0 (g/100 g)	2.97	2.09
18:1 (g/100 g)	45.43	44.51
18:2 (g/100 g)	35.90	36.59
18:3n (g/100 g)	0.84	0.87
α-Tocopherol (µg/g)	108.4	180.0
α-Tocotrienol (µg/g)	34.4	218.0
γ-Tocopherol (µg/g)	127.5	38.0
γ-Tocotrienol (µg/g)	11.7	59.0
δ-Tocopherol (µg/g)	2.92	—
δ-Tocotrienol (µg/g)	—	—
Oryzanol (mg/g)	0.04	15.8

TABLE 4
Chemical composition of the diets provided to subjects participating in study 2[1]

	Control oil blend diet	Rice bran oil diet
Fat (% of energy)		
Total	38.4 ± 0.5	37.8 ± 0.3
Saturated	15.6 ± 0.2	15.7 ± 0.2
Polyunsaturated	7.0 ± 0.2	6.7 ± 0.1
Monounsaturated	15.8 ± 0.2	15.7 ± 0.2
Carbohydrate (% of energy)	47.1 ± 0.4	47.5 ± 0.5
Protein (% of energy)	14.5 ± 0.3	14.8 ± 0.3
Cholesterol (mg)	320.9 ± 14.6	366.4 ± 20.0[2]

[1] All values are $\bar{x}$ ± SEM and reflect the average values of 5 menu plans at 2 energy levels (9205 and 12 552 kJ; 2200 and 3000 kcal).

[2] Significantly different from control diet, $P < 0.002$ (two-sample t test).

diet was similar in appearance to the RBO intervention diet. The macronutrient composition of both diets (an average of the 5 menu plans, each at 2 different energy amounts), as determined by the Pennington Center's Food Analysis Laboratory, is shown in **Table 4**.

For both studies, the subjects were provided with all foods for the duration of the study. On weekdays, subjects were required to consume breakfast and dinner under supervision at the Pennington Biomedical Research Center dining facility, and weekday lunches and snacks and all weekend meals were packaged for take-out. Subjects were initially assigned a total energy level to maintain body weight, and energy adjustments were made as needed to attempt to maintain weight within 2 kg of each person's initial value. They were not allowed to take vitamin or mineral supplements during the study. Each participant completed a daily food diary to assist with compliance assessment; in this diary, they recorded study foods not eaten, nonstudy foods eaten, and beverages consumed.

Laboratory analyses

Total cholesterol and triacylglycerol concentrations were measured on a Synchron CX5 automated chemistry analyzer (Beckman, Brea, CA). HDL cholesterol was measured as cholesterol on the CX5 after precipitation of lower-density lipids by using dextran sulfate (DML, Dallas). LDL cholesterol was calculated by using the Friedewald equation (15) and by assuming that triacylglycerols were within normal limits. Serum apolipoproteins A1 and B were measured on an Array analyzer (Beckman) employing reagents supplied by the manufacturer. Factor VII activity was measured by using an ACL 3000+ coagulation instrument (Instrument Laboratory, Lexington, MA). The interassay CVs for these assays are ≈7%.

Statistical analysis

For study 1, lipids, apolipoproteins, and factor VII were analyzed with the help of a mixed model. Sex, diet, and time and their interactions were treated as fixed effects to compare the effects on the outcome variables of DRB with those of the control diet. The measurements at the end of the run-in period and BMI were included as covariates. The covariance matrix included a variance component for subject and one for subject × time to take into account the repeated nature of the observations in a subject. To allow for comparisoin of the response under treatment and the

run-in measurements, the difference between the treatment response and the run-in measurement was analyzed in the same manner as described above.

Similarly, in study 2, sex and diet and their interactions were considered fixed effects in the two-way mixed-model analysis of the primary endpoints. In this study, the covariance matrix was modeled by using the random effects subject and subject × diet to accommodate the repeated measurements. BMI was included as a covariate.

Because the triacylglycerol data were not normally distributed, statistical analysis was performed on log-transformed values. All tests were nondirectional or two-sided and were based on adjusted means predicted by the model (least-squares means). Statements concerning the significance of tests were based on a type I error rate of 0.05. All statistical analyses were performed by using SAS software (version 8.2; SAS Institute, Cary, NC).

RESULTS

Study 1: defatted rice bran

Of the 27 subjects enrolled, 26 completed the entire study. The one subject who dropped out had only run-in period data, which was not taken into account in the analysis. The mean (±SEM) age of the subjects was 32.9 ± 1.7 y, and their mean BMI was 24.3 ± 0.6 (Table 1). Body weight did not change during the study (data not shown). All participants consumed the control diet during run-in and thus are sampled from one population. They subsequently were randomly assigned to the separate treatment groups—control or DRB. Thus, the fixed-effects model included the end-of-run-in level of response variable as a covariate to account for any possible differences that might have existed. On the basis of this model, lipid and lipoprotein concentrations and factor VII activity in response to the diets are shown in **Table 5**. Unexpectedly, after 5 wk, LDL cholesterol and apolipoprotein B were higher in the subjects consuming the DRB than in those consuming the control diet. Despite the change in LDL cholesterol, total cholesterol was not significantly changed by either diet. All other cardiovascular disease risk factors that we measured were unchanged.

Study 2: rice bran oil

At enrollment, the average age of the subject was 33.6 ± 2.8 y, and the average BMI was 24.8 ± 0.7 (Table 1). At enrollment, the subjects' total cholesterol was 5.33 ± 0.11 mmol/L, HDL was 1.19 ± 0.07, LDL was 3.65 ± 0.12 mmol/L, and triacylglycerol was 1.00 ± 0.09 mmol/L. All subjects enrolled completed the study.

Lipid and apolipoprotein concentrations and factor VII activity in response to the 2 diets are shown in **Table 6**. There was a significant effect of diet on total cholesterol, LDL cholesterol, and apolipoprotein B. Total cholesterol was lowest on the diet containing RBO, because of the lower concentration of LDL cholesterol; HDL cholesterol did not change. Triacylglycerol and factor VII were unchanged.

DISCUSSION

Evidence from these 2 well-controlled feeding studies shows that it is the RBO, and not the fiber, that lowers blood lipids in men and women with borderline high total cholesterol. Rice bran

TABLE 5
Lipid and apolipoprotein concentrations and factor VII activity in study 1[1]

	Run-in diet (n = 26)	Control diet (n = 13)	Defatted rice bran diet (n = 13)
Total cholesterol (mmol/L)	5.01 ± 0.12	4.84 ± 0.17	5.21 ± 0.26
HDL cholesterol (mmol/L)	1.32 ± 0.08	1.44 ± 0.14	1.22 ± 0.09
LDL cholesterol (mmol/L)	3.25 ± 0.13	3.04 ± 0.16	3.53 ± 0.25[2]
Triacylglycerols (mmol/L)[3]	0.93 ± 0.08	0.76 ± 0.09	0.99 ± 0.12
Apolipoprotein A-1 (g/L)	1.36 ± 0.05	1.43 ± 0.11	1.32 ± 0.05
Apolipoprotein B (g/L)	0.95 ± 0.04	0.88 ± 0.05	1.00 ± 0.07[4]
Factor VII (%)	81.69 ± 3.31	80.92 ± 5.58	85.49 ± 5.23

[1] All values are $\bar{x}$ ± SEM of each subject's average of replicate measurements taken at end of diet periods. To convert cholesterol values to mg/dL, divide by 0.02586; to convert triacylglycerol values to mg/dL, divide by 0.01129.

[2,4] Significantly different from control diet (two-sided t tests for pairwise comparison): [2]$P = 0.0204$, [4]$P = 0.0299$.

[3] Statistical analyses performed on log-transformed values; no significant difference was found.

fiber and oil did not affect triacylglycerols or factor VII activity. During the first study, 26 men and women completed a parallel-arm feeding study comparing a control diet with a diet containing DRB. Between the run-in diet and the RBO, there were no decreases in total, LDL, or HDL cholesterol. During study 2, 14 men and women completed a 10-wk crossover study evaluating the isoenergetic substitution of RBO for an oil blend in a reference diet designed to provide 37% of energy as fat. The oil blend or RBO provided one-third of the total fat. The oil blend was designed to have a fatty acid profile similar to that of the RBO. Predictive equations (16) show that the variations in fatty acids between the control oil blend and the RBO would have a minimal effect on blood lipids. Total, LDL, and HDL cholesterol would increase by only 0.01, 0.007, and 0.003 mmol/L, respectively. Instead, the RBO diet lowered total and LDL cholesterol significantly more than did the control diet, but the effect of the 2 diets on HDL cholesterol was similar. Changes in apolipoprotein B followed changes in LDL. Because there were no substantial differences in the fatty acid composition of the diets, the reduction in cholesterol was likely due to other components present in the RBO.

Another approach to examining the cholesterol-lowering abilities of RBO sterols separate from the fatty acid composition was reported by Lichtenstein et al (10) in humans and by Wilson et al

TABLE 6
Lipid and apolipoprotein concentrations and factor VII activity at the end of study 2[1]

	Control oil blend diet (n = 14)	Rice bran oil diet (n = 14)
Total cholesterol (mmol/L)	5.22 ± 0.15	4.95 ± 0.14[2]
HDL cholesterol (mmol/L)	1.22 ± 0.06	1.22 ± 0.07
LDL cholesterol (mmol/L)	3.57 ± 0.15	3.30 ± 0.14[3]
Triacylglycerols (mmol/L)[4]	0.93 ± 0.11	0.93 ± 0.08
Apolipoprotein A-1 (g/L)	1.32 ± 0.05	1.34 ± 0.05
Apolipoprotein B (g/L)	1.03 ± 0.05	0.97 ± 0.04[5]
Factor VII (%)	103.48 ± 3.66	101.48 ± 4.38

[1] All values are $\bar{x}$ ± SEM of each subject's average of replicate measurements. To convert cholesterol values to mg/dL, divide by 0.02586; to convert triacylglycerol values to mg/dL, divide by 0.01129.

[2,3,5] Significantly different from oil blend diet (F tests using a mixed model): [2]$P = 0.0036$, [3]$P = 0.0004$, [5]$P = 0.0054$.

[4] Statistical analyses performed on log-transformed values.

(13) in cynomologus monkeys. Moderately hypercholester-olemic men and women consumed diets enriched in rice bran, canola, corn, and olive oils at 20% of total energy. The subjects had similar plasma total and LDL-cholesterol concentrations after the consumption of the diets containing rice bran, canola, and corn oils, even though the fatty acid distributions differed. The RBO diet was richer in sterols, tocotrienols, and oryzanol than the 3 other diets. In the study of cynomologus monkeys, the fatty acid compositions of experimental oil blends used in the diets were similar except for higher total saturates in an RBO blend, higher total monounsaturates in a canola oil blend, and higher total polyunsaturates in a corn oil blend. Despite the differences in fatty acids, the diet containing the RBO blend reduced serum LDL-cholesterol concentrations significantly more than did the diets containing the other oil blends. In both studies, the changes in total and LDL cholesterol observed with consumption of the RBO diet represented a greater improvement than was predicted on the basis of the fatty acid composition of the diets. HDL-cholesterol concentrations were not decreased by the RBO. These observations parallel the results reported in the current study. Together, the results from the 2 studies provide evidence that the cholesterol-lowering capabilities of RBO can be attributed to the compounds it contains whose effects surpass those of its fatty acid composition.

Other investigators of rice bran have implicated the unsaponifiable compounds as being responsible for its cholesterol-lowering properties. The amounts present in commercial RBO are dependent on the refining process (17). The most notable compound is γ-oryzanol, a ferulate ester of triterpene alcohols (12). Major components of the triterpene alcohols are cycloartenol and 24-methylene cycloartanol. Also notable are the phytosterols campesterol and β-sitosterol, which are found at relatively high amounts in RBO. When the plant sterols from RBO were incorporated into margarine and provided at 2.1 g/d to normolipidemic men and women, total cholesterol decreased by 5% and LDL cholesterol decreased by 9% (18). The investigators postulated that the effect was due to the β-sitosterol and other 4-desmethylsterols and not to the 4,4'-dimethylsterols, such as cycloartenol and 24-methylene cycloartanol. The β-sitosterol structure is more similar to that of cholesterol than is that of the 4,4'-dimethylsterols, and it may be more effective than the 4,4'-dimethylsterols in inhibiting cholesterol absorption in the small intestine. This is further supported by Weststrate and Meijer (19),

who found no effect on cholesterol concentrations of an RBO margarine that contained more 4,4'-dimethylsterols and less 4-desmethylsterols.

RBO also is rich in tocotrienols; the major components are the β- and γ-tocotrienols (12). It is postulated that tocotrienols, especially γ-tocotrienols, lower cholesterol through the inhibition of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in endogenous cholesterol synthesis (20). Two studies have reported that a tocotrienol-rich fraction of rice bran, when taken in combination with an American Heart Association Step 1 diet, lowers serum total and LDL-cholesterol concentrations in hypercholesterolemic persons (21, 22). However, these effects of tocotrienols have been questioned, and confirmation is needed (20).

Our results confirm previous findings of the total and LDL-cholesterol–lowering effects of RBO in humans. By matching the fatty acids of the RBO with a control oil blend, we showed that the effect of RBO on serum cholesterol concentrations is due to the unsaponifiables present in it and not to its fatty acid profile. RBO that contains these compounds could become an important functional food with cardiovascular health benefits. ▣

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