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Hypolipidemic Effects of Modified Psyllium Preparations

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The hypolipidemic effects of two solid-state enzymatically modified psyllium preparations were compared to that of the original psyllium husks in hamsters. Hamsters were ad libitum fed 0.2 wt % cholesterol diets formulated to contain 12% cellulose or 5% cellulose plus 7% raw or enzymatically modified psyllium preparations. Psyllium additions to the diet did not significantly alter food consumption or the weekly mean hamster weight over the 5 weeks of feeding. However, the total weight gained over 35 days of feeding of modified psyllium Y-26-4, one of the modified psyllium preparations, was significantly lower, 48, 47, and 32% than that for the cellulose, raw psyllium, and modified psyllium Y-24-3 groups, respectively. At 35 days, psyllium feeding significantly reduced plasma total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol by 50−100% in comparison to cellulose feeding, with no significant differences between the psyllium preparations. Fecal dry weight was unaffected by dietary treatment. At days 29−31, fecal bile acid excretion was significantly increased by 30−70% with all three psyllium diets, with no significant differences between psyllium preparations. These results suggest that improving the functional properties of psyllium by solid-state enzymatic procedures, such that its incorporation into food products is feasible, does not alter psyllium-mediated hypolipidemic effects.

KEYWORDS: Psyllium; *Plantago*; hypolipidemic, modified psyllium

INTRODUCTION

Psyllium is a mucilaginous material prepared from the seed husk from the plants of *Plantago* genus and is an excellent source of both soluble and insoluble fibers. Previous studies have shown that psyllium exhibits several health beneficial properties, including cholesterol-lowering, laxative, gastric hypoacidity, and perhaps weight control effects (*1*−*4*). However, the strong water absorbing and gelling properties of psyllium make it a challenge to manufacture food and beverage products that contain psyllium at the level necessary to assert a health claim on the product label. To be able to utilize psyllium in foods or other consumer products, it is necessary to improve its physicochemical properties, while retaining its beneficial health properties.

Several physical and mechanical techniques have been employed to improve the physicochemical and functional properties of psyllium. These included granulating and coating psyllium to improve its water-dispersibility (*5*, *6*) and preparing extrudes of psyllium blended with other food ingredients (*7*) to reduce its water-uptaking capacity. In 2001, Yu and others disclosed a conventional enzymatic procedure to modify the chemical and molecular structures of psyllium. The enzymatic modification improved the gelling and water-absorbing capacities of psyllium (*5*). The procedure proved to be impractical for preparation of improved psyllium fibers in commercial scale, due to its requirement of a lyophilization step to remove moisture at the end of the reaction. To overcome this disadvantage, solid-state enzymatic procedures have been developed in our laboratory (*8*−*10*). The psyllium preparations prepared through the solid-state enzymatic reactions exhibited reduced water-absorbing and gelling abilities (*8*−*10*). Since changes in the chemical and molecular structure may alter the hypolipidemic properties and capacity of the psyllium preparation, it is necessary to evaluate the hypolipidemic potential of the modified psyllium preparations, in comparison to raw psyllium, to establish their utility for incorporation into commercial food products. Therefore, the present study was conducted to examine and compare the modified psyllium preparations with the original psyllium and cellulose for their effects on plasma lipids and fecal bile acids excretion. The modified psyllium preparations were also investigated and compared with the original psyllium and cellulose for their effects on hamster growth and food consumption.

MATERIALS AND METHODS

Psyllium husks (95% purity, 40 mesh) were kindly provided by the Bio-Products Co. (Joliet, IL), the xylanase (Shearzyme 500L) and Viscozyme L used in the solid-state enzymatic preparation of modified psylliums were provided by Novo Nordisk Biochem North America,

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Table 1. Hamster Diet Composition

component	g/kg
casein	200.0
sucrose	49.5
corn oil	50.0
coconut oil	50.0
cholesterol	2.0
cornstarch	318.0
dextrin	116.0
dyetrose	29.0
mineral mix	35.0
$CaHPO_4$	15.0
Vitamin mix	10.0
DL-methionine	3.0
choline bitartrate	2.5
fiber components[a]	120.0

[a] Fiber components: the cellulose diet contained 120.0 g/kg cellulose. Psyllium diets were constructed by substituting 70 g/kg of the appropriate psyllium (original, Y-26-4, or Y-24-3) for 70 g/kg cellulose. Vitamin and mineral mixtures are described in Rutten and de Groot (*11*).

Inc. (Franklinton, NC). Male Golden Syrian hamsters, 80−100 g, were obtained from Charles River Laboratories (Wilmington MA). Hamster diets were formulated by Dyets Inc. (Bethlehem, PA). Reagents for plasma cholesterol, triglyceride, and high-density lipoprotein (HDL) cholesterol concentration determinations, NAD, and 3α-hydroxysteroid dehydrogenase (*Pseudomonas testosteroni*) were obtained from Sigma-Aldrich (St. Louis, MO). All other chemicals and solvents were the highest commercial grade and used without further purification.

Preparation of Modified Psylliums. Details of the preparation of modified psylliums have been described previously (*8*, *9*). Enzyme (Shearzyme or Viscozyme) was mixed into 600 g of psyllium powder to start the solid-state enzymatic reaction. The final concentrations were 48 and 19 units of Shearzyme (xylanase) and Viscozyme (multienzyme complex containing cellulose, hemicellulase, xylanase, arabinase, and β-glucanase activities) per gram of psyllium, respectively. The reaction was carried out at ambient temperature and terminated by microwave inactivation of the enzyme. The final product of the solid-state reaction was obtained after grinding the material through a 20 mesh sieve. The modified psyllium preparations were stored in airtight glass containers at ambient temperature. The Viscozyme modified psyllium preparation was designated as Y-26-4, and the Shearzyme preparation was designated as Y-24-3. Soluble and insoluble fiber contents of psyllium preparations were determined according to a previously described procedure (*8*).

Hamster Diets. Diets were a modification of the Rutten and de Groot purified hamster diet (*11*, *12*), and the composition of the diets is shown in **Table 1**. All diets contained 2 g of cholesterol/kg of diet. The control (cellulose) diet was formulated with 120 g of cellulose/kg of diet. The three psyllium diets, raw (unmodified), Y-26-4, and Y-24-3, were formulated by substituting 70 g/kg of the appropriate psyllium preparation for 70 g/kg cellulose. Diets were fed in a pellet form.

Animal Feeding and Tissue Sampling. All animal procedures were approved by Colorado State University Animal Care and Use Committee. Male Golden Syrian hamsters were obtained at 80−100-g body weight and were housed individually in polycarbonate cages in an animal care facility, 22−24 °C, 40−50% relative humidity, with 12 h light/dark cycle. Animals were fed rodent stock diet (Harlan Teklad, Indianapolis, IN) ad libitum for 2 days. A group of five animals was fasted for 12 h and anesthetized with halothane, and blood was obtained by cardiac puncture for analysis of basal cholesterol, triglyceride, and HDL cholesterol concentration. Remaining hamsters were assigned to four groups of nine animals each, and each group was ad libitum fed one of four diets; cellulose, raw psyllium, psyllium Y-26-4, or psyllium Y-24-3 (**Table 1**). Tap water was provided ad libitum. Animals were weighed weekly, and 24-h food consumption was measured on days 4−5, 21−22, and 33−34. On day 29, hamsters were individually housed in metabolic cages and feces were collected for 48 h. On day 35, animals were fasted overnight and blood was obtained by cardiac puncture under halothane anesthesia. Blood was collected in EDTA treated tubes and plasma prepared by centrifugation.

Plasma Lipoprotein Cholesterol and Triglyceride Analyses. Total plasma cholesterol was determined spectrophotometrically by the cholesterol esterase and cholesterol oxidase method (*13*, *14*). Plasma triglycerides were measured by spectrophotometric determination of glycerol liberated by lipoprotein lipase treatment of plasma (*15*). For high-density lipoprotein (HDL) cholesterol measurement, plasma low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL) were precipitated by phosphotungstic acid and magnesium chloride (*16*) and the cholesterol concentration of supernatant HDL determined by the cholesterol esterase and oxidase method, as described above (*13*, *14*). VLDL cholesterol (mg/dL) was calculated according to the Friedewald (*17*) equation as triglycerides (mg/dL)/5. LDL cholesterol was calculated according to the equation total cholesterol − HDL cholesterol − triglycerides/5.

Fecal Bile Acid Analyses. Fecal collections during 48 h, days 29−31, were lyophilized, pulverized using pestle and mortar, and weighed. Dry feces, approximately 2 g, were hydrolyzed by autoclaving in 25.0 mL of 1.25 M KOH at 18 psi and 121 °C for 3 h. Cooled hydrolysates were extracted with two 50-mL portions of diethyl ether to remove nonsaponifiable components and acidified to pH 2 using 12 M hydrochloric acid (*18*). The acidified solution was extracted with two 50-mL portions of diethyl ether. Pooled ether extracts were evaporated using a rotary evaporator and redissolved in 5.0 mL of ethanol, and total fecal bile acids were determined enzymatically using 3α-hydroxysteroid dehydrogenase (*18*). Assay solutions, 1.5-mL final volume, contained 0.85 mL of 0.1 M sodium pyrophosphate, pH 10.8, 0.5 mL of 5.0 mM NAD^+, 0.1 mL of a 10-mg/mL solution of 3α-hydroxysteroid dehydrogenase solution and 0.05 mL of ethanolic fecal bile acid extract. Assay samples were incubated at 26 °C for 1 h, and absorption was read at 340 nm. Blanks contained 0.05 mL of ethanol in place of ethanolic fecal bile acid extracts. Bile acids were determined as μmoles 3α-hydroxysteroid based on the molar extinction coefficient of NADH at 340 nm.

Statistical Analysis. Data are reported as mean ± SEM. Data were analyzed by analysis of variance (ANOVA) using SPSS for Windows (SPSS Inc., Chicago, IL). Comparisons between treatment groups were determined using the least significant difference method when ANOVA results were statistically significant ($p < 0.05$).

RESULTS

Weight Gain and Food Consumption. Growth of hamsters is shown in **Figure 1**. There were no significant differences in weekly mean hamster weight over the 5 weeks of feeding. However, total weight gained over the 35 days of feeding for the Y-26-4 group was significantly lower, 48, 47, and 32%, than that for the cellulose, raw psyllium, and Y-24-3 groups, respectively (**Figure 2**).The 24-h food consumption measured at four time points throughout the experiment (see methods) was not significantly different among the four diet groups (data not shown). These data suggest the potential application of Y-26-4, the Viscozyme treated psyllium, in controlling body weight.

Plasma Lipids. Hamster plasma total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, and plasma triglyceride concentrations of 5 animals, 12-h fasted, following 2 days of rodent stock diet feeding (before assignment to diet groups) were normal, with the following mean ± SEM concentration values (mg/dL): total cholesterol, 101.3 ± 8.4; HDL cholesterol, 44.6 ± 4.4; LDL cholesterol, 52.5 ± 8.3; triglycerides, 22.0 ± 3.3; VLDL cholesterol, 4.4 ± 0.7. At day 35, all three psyllium diets significantly reduced plasma total cholesterol and LDL cholesterol concentrations by 47−59% in comparison to the cellulose group, and there were no significant differences between the psyllium preparations (**Figure 3**). At day 35, the three psyllium diets significantly reduced HDL cholesterol by approximately 100% (**Figure 3**), without any significant differences between the three psyllium preparations.

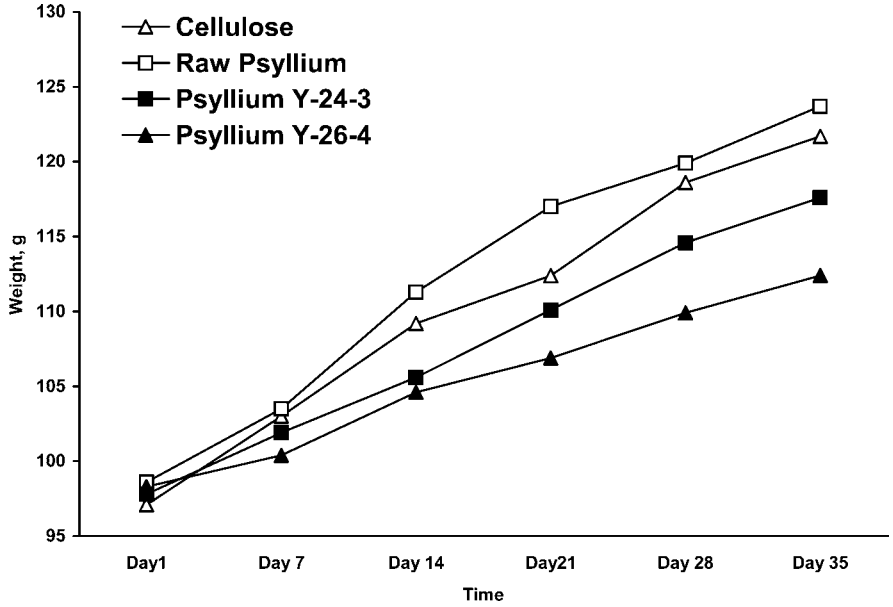

Figure 1. Growth of hamsters. Values are means. Pooled standard errors: day 1, 8.6; day 7, 13.5; day 14, 18.5; day 21, 20.6; day 28, 21.5; day 35, 21.5. Psyllium Y-24-3 (xylanase treated) and Psyllium Y-26-4 (Viscozyme treated) are the two solid-state enzymatically modified psyllium preparations. Raw psyllium represents the original psyllium without any treatment.

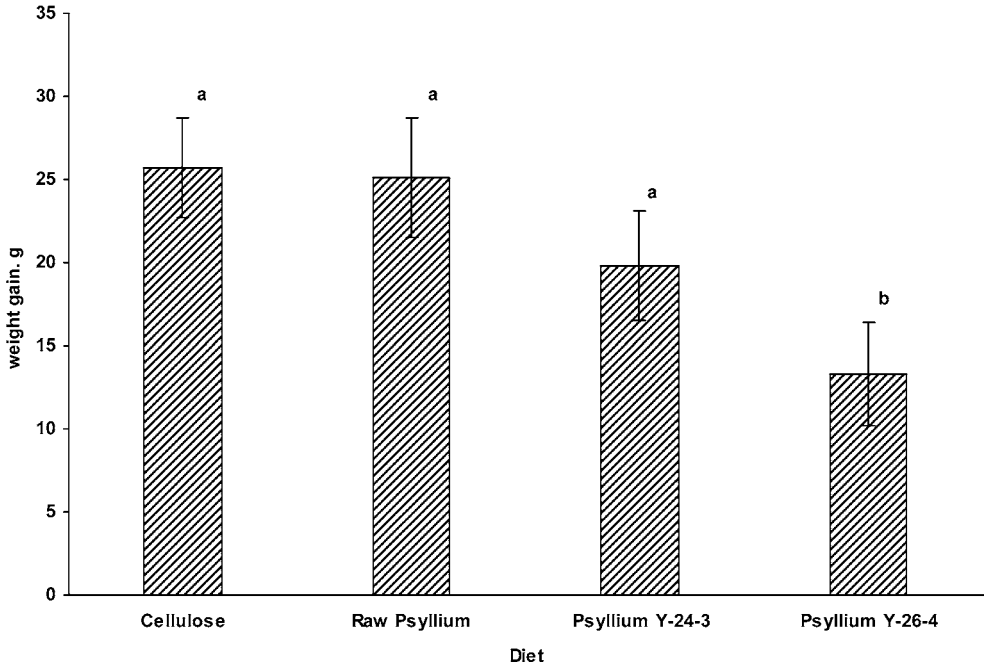

Figure 2. Total body weight gained over the 35 days of feeding. Values are Mean ± SEM (vertical bars) for nine animals per group. Within each response parameter, values not sharing common letter superscripts are significantly different, $P < 0.05$. For explanation of the psyllium groups, see **Figure 1**.

Plasma triglycerides and VLDL cholesterol concentrations were not different between the cellulose and psyllium fed groups (**Figure 3**). Since there were no differences in the hypolipidemic effects among the three psyllium fed groups, these results suggest that solid-state enzymatic modification does not alter the cholesterol-lowering activity of psyllium.

Fecal Bile Acid Excretion. Fecal dry weight was not affected by diet (data not shown). There were no significant differences in fecal bile acids excretion (days 29−31), measured as 3α-hydroxysteroids, between the three psyllium diets. In comparison to the cellulose diet, the three psyllium diets significantly increased fecal bile acid excretion by 30−42% when expressed as micromoles of fecal bile acids excreted in 48 h and by 40−68% when expressed as micromoles of bile acids excreted per gram of dry feces (**Figure 4**).

DISCUSSION

Cardiovascular disease (CVD) is the leading cause of death in the United States, and accounts for the major portion of health care costs (*19*). Elevations in plasma and LDL cholesterol are major risk factors for coronary heart disease (*20*, *21*). Both dietary and pharmacological approaches to lowering blood cholesterol and LDL cholesterol have been extensively investigated, and studies of primary and secondary prevention of coronary artery disease have established the benefits of lowering total and LDL cholesterol concentrations in blood (*19*, *22*).

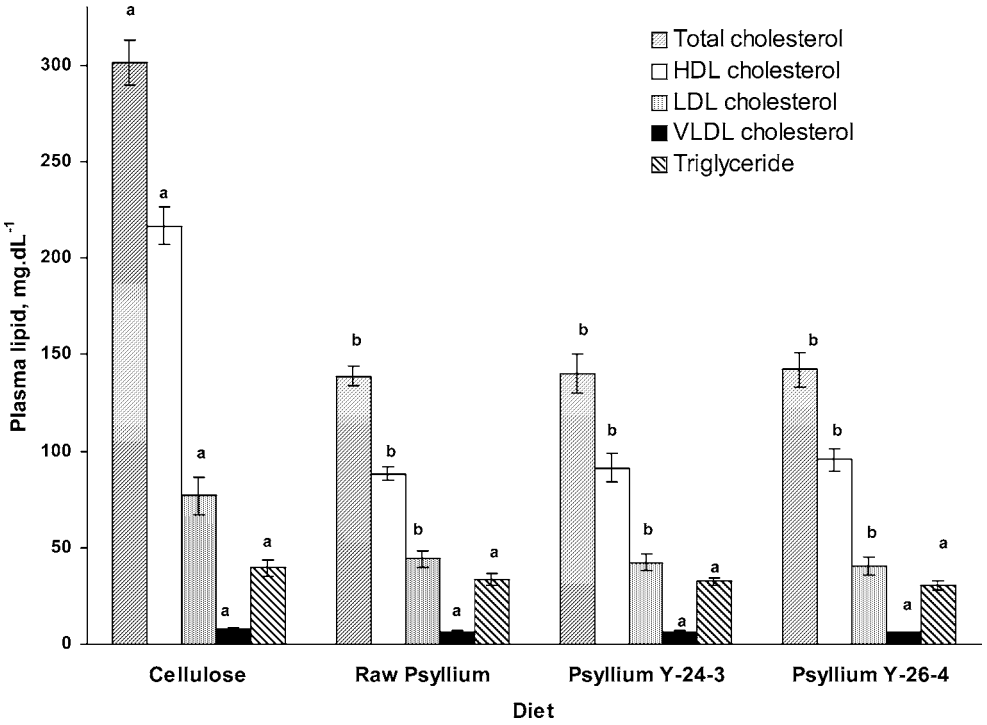

Figure 3. Plasma lipid concentrations at day 35. Values are mean ± SEM (vertical bars) for nine animals per group. Within each response parameter, values not sharing common letters are significantly different, $P < 0.05$. For explanation of the psyllium group, see **Figure 1**.

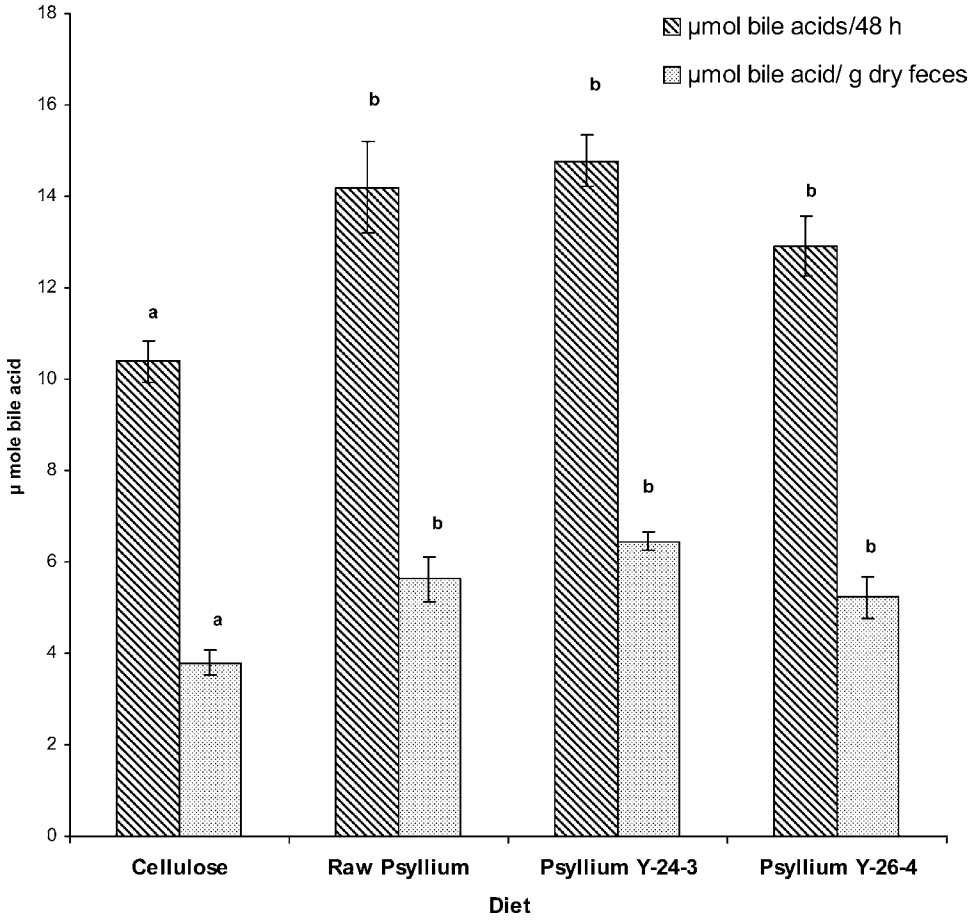

Figure 4. Fecal bile acid excretion. Fecal bile acids were measured as 3α-hydroxysteroids. Values are mean ± SEM (vertical bars) for nine animals per group. Within each response parameter, values not sharing common letters are significantly different, $P < 0.05$. For explanation of the psyllium group, see **Figure 1**.

Dietary recommendations for reducing the risk of cardiovascular disease have been recently modified by the American Heart Association (*23*). While reductions in blood total and LDL cholesterol through changes in dietary fat type intake remain

Table 2. Fiber Composition of Psyllium Preparations[a]

sample ID	enzyme concn (units/g psyllium)	soluble fiber (g/100 g psyllium)	insoluble fiber (g/100 g psyllium)
psyllium	N/A	79.6	12.4
Y-24-3	48 (Shearzyme)	77.4	3.1
Y-26-4	19 (Viscozyme)	75.9	13.2

[a] Y-24-3 and Y-26-4 represent the modified psyllium preparations through solid-state enzymatic reactions, whereas psyllium represents the original psyllium without any treatments. Shearzyme and Viscozyme were obtained from Novo Nordisk Biochem. North America, Inc (Franklinton, NC).

the main emphasis, these recommendations do recognize that fiber intakes also reduce LDL cholesterol.

Psyllium, rich in soluble fiber, exhibits hypolipidemic effect in both animal feeding and human studies (*5*, *24*−*27*). In 2002, Marlett and Fischer evaluated the fractions of psyllium seed husks for their effects on stool output and blood cholesterol in rats, and concluded that the poorly fermented gel-forming fraction of the psyllium husk was more effective in holding moisture in stools and increasing bile acid excretion. In the present study, enzymaticly modified psyllium preparations, Y-24-3 and Y-26-4, were compared to the original psyllium and cellulose for their effects on plasma lipid concentrations and fecal bile acids excretion (**Table 2**). In contrast to Marlett and Fischer's observation, neither Y-24-3 nor Y-26-4 differed from the original psyllium in their effectiveness in promoting bile acid excretion, although both of them had weaker gelling and water-holding capacities than the original psyllium (*8*, *9*), indicating that the gel-forming capacity may not be the sole factor contributing to the overall hypolipidemic potency of psyllium husks.

The mechanisms involved in the biological actions of psyllium were investigated. Buhman and others (*26*) reported that the hypocholesterolemic effects of psyllium feeding in rats were due to increased fecal excretion of bile acids and total sterols. In addition, this increased bile acid excretion was associated with increased hepatic cholestertol 7α-hydroxylase activity, the rate controlling step of bile acid synthesis, and increased cholesterol 7α-hydroxylase mRNA abundance (*26*). Bile acids are the primary excretory route for cholesterol from the body, and increased conversion of cholesterol to bile acids is considered a potential mechanism for hypocholesterolemic effect of dietary fibers. In another study, diets rich in psyllium seeds reduced plasma triglycerides and LDL cholesterol by modulating hepatic and bile acid metabolism in guinea pigs (*27*). Diets enriched with psyllium reduced the activities of lecithin cholesterol acyltransferase and cholesterol ester transfer protein, enzymes involved in the remodeling of lipoproteins (*28*). In addition, both 3-hydroxy-3-methylglutaryl CoA reductase, the rate controlling step of cholesterol synthesis, and 7α-hydroxylase activities were elevated in the guinea pigs fed psyllium diets (*27*). The results from the present study showed no difference in plasma lipids and bile acid excretion between the three psyllium preparations. However, psyllium-fed groups showed a significant plasma cholesterol lowering and a significant enhancement of fecal bile acid excretion, in comparison to the cellulose group. These data suggest that the solid-state enzymatic modification is a practical means to improve the functionality of psyllium without reducing its hypocholesterolemic potency. Since the modified psyllium preparations, prepared by solid-state enzyme treatments, may retain the same monosugar composition but may differ in the arrangements of monosugar molecules, including branching and molecule folding (*8*−*10*), we propose that the mechanisms involved in their biological actions should be similar to that for the original psyllium.

Interestingly, one of the modified psyllium preparations, Y-26-4, significantly reduced the body weight gain in 35 days as compared to the other psyllium groups and the cellulose group, although no significant differences in weekly mean hamster weight over the 5 weeks of feeding were observed. This suggests the potential for developing novel psyllium preparations to control weight through solid-state enzymatic modification. Obesity and overweight condition is associated with the increased risk of morbidity from a number of diseases, including coronary heart disease, stroke, hypertension, type II diabetes, gallbladder disease, and certain cancers (*29*). It is well accepted that chemical and molecular structures determine the physicochemical and biological activities of a chemical compound. Psyllium preparation Y-26-4 had reduced gelling and water-uptaking capacities as compared to the original psyllium, suggesting the changes in their chemical and molecular structures. Additional research is required to further investigate the relationship between the structural changes and the potential of the psyllium in controlling both weight.

In conclusion, the two enzymatically modified psyllium preparations have hypolipidemic and bile acid excretion effects that are not different from the original psyllium husks. One of the modified psyllium preparation also showed potential for reducing body weight gain. These results suggest that solid-state enzymatic modification is a practical means to improve the physicochemical properties of psyllium husks without altering their hypolipidemic capacity. The solid-state enzymatic modification may also lead to novel psyllium preparations that can be included in food products with potential application of reducing circulating lipids and prevention of overweight and obesity.

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