CHAPTER 4

Beneficial Health Properties of Psyllium and Approaches to Improve Its Functionalities

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Contents

Abstract

Psyllium is an excellent dietary source for both soluble and insoluble fibers and has been used in supplemental and food products for its beneficial health effects. The strong water-absorbing and gelling capacities have made it a great challenge to incorporate psyllium in foods at the level needed to claim health benefits on the label. This review is focused on the approaches to improve the functionality,

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sensory property, and bioactivity of psyllium. Also included is a brief summary of the health beneficial effects of psyllium, along with its possible adverse effects. The information may be useful for those in psyllium research and functional food development.

Key Words: Psyllium, Cholesterol lowering, Solid-state enzymatic reaction, Functionality.

I. INTRODUCTION

Psyllium is a mucilaginous material prepared from the seed husk of the plants of the *Plantago* genus including but not limited to *P. ovata*, *P. psyllium*, and *P. indica*, which grow in certain subtropical regions. Psyllium is a highly branched acidic arabinoxylan (Kennedy *et al.*, 1979). The xylan backbone has both (β1→4) and (β1→3) linkages. Other monosaccharides present in psyllium are D-galactose, D-rhamnose, D-galacturonic acid, 4-*O*-methyl-D-glucuronic acid, and 2-*O*-(2-D-galactopyranosyluronic acid)-L-rhamnose (Chan and Wypyszyk, 1988).

Psyllium has been investigated for its potential health benefits and its applications in food and other consumer products such as hair-setting lotions and drug delivery systems (Chan and Wypyszyk, 1988; Singh, 2007). Psyllium is well recognized for its laxative activity, cholesterol-lowering capacity, potential in reducing the risk of colon cancer and hyperglycemia, and possible application in the treatment of irritable bowel syndrome and in body weight control (Anderson *et al.*, 1990; Arjmandi *et al.*, 1992; Bijkerk *et al.*, 2004; Ganji and Kies, 1994; Hannan *et al.*, 2006; Hara *et al.*, 1996; Kang *et al.*, 2007; Marlett *et al.*, 2000; Park *et al.*, 1997; Pittler and Ernst, 2004). In addition to its beneficial health effects, psyllium also has functional contributions in foods or other consumer products. For instance, psyllium may be used as a deflocculant in paper and textile manufacture, an emulsifying agent, a binder or lubricant in meat products, and a carbohydrate-based fat replacer to be used in low fat/low total calorie foods (Haque and Morris, 1994).

However, the strong hydrophilic and gelling properties of psyllium make it a real challenge to incorporate psyllium in food/beverage formula at the level required to have a health claim on the label. A substantial amount of time is required for complete dispersal of psyllium in an aqueous system containing other ingredients including sugar even with vigorous agitation due to its water-absorbing and gelling capacities (Rudin, 1985). An unpleasant slimy mouth feeling is also related to these properties. Beverages are a preferred carrier of nutraceuticals. Adding a sufficient amount of psyllium into a beverage formula is impossible

due to its strong gel-forming capacity. Many previous studies have been conducted to improve its functional/biological/sensory properties to enhance its food and nonfood applications (Kumar and Verma, 2007; Yu and Perret, 2003b). This review summarizes the beneficial health properties of psyllium, and the approaches to improve its physicochemical and biological properties.

II. BENEFICIAL HEALTH EFFECTS OF PSYLLIUM

A. Hypolipidemic effects

The Division for Heart Disease and Stroke Prevention (DHDSP) of the Centers for Disease Control (CDC) classifies coronary heart disease (CHD) as the leading cause of death in the United States, and a major cause of disability. It costs billions of dollars to deal with this public health concern (Anderson *et al.*, 1990). Several factors influence the incidence of CHD. High blood cholesterol, or hypercholesterolemia, which is categorized as serum cholesterol levels above 240 mg/dl, has been conclusively linked to increased risk of CHD (Anderson *et al.*, 1988; Gupta *et al.*, 1994). Cholesterol causes plaque formation which narrows the blood vessels, and increases the risk of heart attacks. Serum concentrations of low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triacylglycerols (TG) are associated with the risk of CHD. Psyllium has been found to lower blood lipid levels and the risk of CHD in a number of previous studies (Anderson *et al.*, 1988, 2000a,b; Everson *et al.*, 1992; Ganji and Kies, 1996; Gupta *et al.*, 1994; Olson *et al.*, 1997; Pastors *et al.*, 1991; Roe *et al.*, 1988; Sola *et al.*, 2007; Sprecher *et al.*, 1993; Turley *et al.*, 1994).

A large number of *in vivo* studies using rats demonstrate the efficacy of the lipid-lowering activity of psyllium compared against different dietary fibers. Anderson *et al.* (1994) observed that feeding rats with a diet rich in soluble fiber significantly reduced their serum and liver cholesterol concentrations, compared to an insoluble fiber diet. They fed the rats with 10 different fibers, including psyllium, pectin, and guar gum. Cellulose, which has no significant hypocholesterolemic effect, was used as the control fiber. Test diets contained 60 g dietary fiber/kg diet, with 10 g cholesterol and 2 g cholic acid/kg diet. At this level of intake, over a period of three weeks, psyllium had the most impact on serum lipid levels, lowering serum and liver cholesterol concentrations by 34% and 53%, respectively, compared to the cellulose control. In another study, psyllium significantly reduced plasma and liver cholesterol concentrations in female rats fed a cholesterol-enriched diet (Terpstra *et al.*, 2000a). This reduced cholesterol level was accounted for by an observed 26% increase in fecal excretion of bile acids, primarily β-muricholic acid.

The results were based on a 3 g psyllium/100 g diet. Rats fed 10% psyllium diet (with 0.5% cholesterol) were found to have lower serum cholesterol levels, as well as higher HDL-cholesterol levels when compared with those fed with an equal amount of cellulose (Kritchevsky *et al*., 1995). The mechanisms involved in the cholesterol-modulating effect of psyllium fiber have been explored by various studies. Cholesterol 7α-hydroxylase is the key regulatory enzyme in the synthesis of bile acids, converting cholesterol to bile acids. The activity of this important rate-determining enzyme has been observed to increase in a dose-dependent manner when a psyllium-supplemented diet is fed to rats (Buhman *et al*., 2000; Matheson *et al*., 1995). The liver makes bile acids from cholesterol. Increased bile acid synthesis therefore implies increased removal of cholesterol from circulation, resulting in decreased liver and serum cholesterol levels. In Matheson *et al*. (1995), after 28 days of feeding the rats with a 5% psyllium supplemented diet, the activity of cholesterol 7α-hydroxylase increased twofold compared to the cellulose control at the same level of supplementation. Psyllium also reduced liver total cholesterol concentrations when cholesterol was added to the diet. Buhman *et al*. (2000) went further to explain from their results that the increase in the bile acid pool was achieved by the regulation of not only cholesterol 7α-hydroxylase, but also involved the regulation of ileal apical sodium-dependent bile acid transporter (ASBT) and 3-hydroxyl-3-methylglutaryl (HMG) CoA reductase mRNA levels. The antinutritional properties of dietary fiber are a concern, and some fibers have actually demonstrated this undesirable effect, both in human and animal studies. Results from the study by Perez-Olleros *et al*. (1999) showed no effect on macronutrient utilization by a 100 g psyllium fiber/kg diet in rats. They however observed a reduction in protein utilization compared to the cellulose control.

Several hamster feeding studies indicate that psyllium reduces plasma cholesterol concentrations by primarily increasing fecal bile acid excretion (Terpstra *et al*., 2000b; Trautwein *et al*., 1998, 1999). Both Terpstra *et al*. (2000b) and Trautwein *et al*. (1998) attributed the observed increase in fecal bile acid excretion to an increase in the ratio of the secondary bile acid deoxycholic acid to lithocholic acid. Trautwein *et al*. (1999) observed that in addition to lowering plasma concentrations of cholesterol, psyllium also reduced plasma levels of TG to an extent similar to that induced by cholestyramine, an effective pharmacological intervention in the regulation of cholesterol levels. Psyllium has been observed to enhance the cholesterol-lowering activity of cholestyramine in hamsters (Daggy *et al*., 1997; Turley *et al*.,1994). Combining psyllium and cholestyramine in a diet (5% psyllium and 0.5% cholestyramine) increased total bile acid excretion by as much as 79% (Daggy *et al*., 1997). Turley *et al*. (1994) observed a dose-dependent increase in sterol loss in a combination of psyllium with a low dose of cholestyramine. It appears from the data reviewed that

psyllium, in hamsters, exerts a greater hypocholesterolemic effect on liver cholesterol concentrations than serum cholesterol levels (Table 4.1).

The hypocholesterolemic effects of psyllium in guinea pigs are similar to the other animals already discussed. An increase in fecal bile acids of as much as threefold was observed when guinea pigs were fed with a diet containing at most 10 g psyllium/100 g diet, compared to the cellulose control (Romero *et al.*, 2002). Plasma triglycerides and LDL cholesterol were also 34% and 23% lower in the same study. Lecithin cholesterol acyltransferase (LCAT) and cholesterol ester transfer protein (CETP) activities were significantly affected. Fernandez *et al.* (1995) suggested from their results that psyllium lowered plasma cholesterol levels by inducing cholesterol 7α-hydroxylase and HMG CoA reductase, and suppressing acyl CoA cholesterol acyltransferase (ACAT) activities. Upregulation of apolipoproteins B and E receptors was also observed to be influenced by psyllium intake, contributing to the lower plasma cholesterol levels. Increased secretion of apolipoprotein B and upregulation of LDL receptors might also contribute to the reduced plasma cholesterol concentrations induced by psyllium (Fernandez *et al.*, 1997). Some studies suggest that the metabolic response to the cholesterol-lowering effect of psyllium in guinea pigs may be gender dependent (Fernandez *et al.*, 1995; Roy *et al.*, 2000). Under low cholesterol intake conditions, both male and female guinea pigs exhibited similar responses in their plasma cholesterol concentrations to dietary psyllium supplementation (Fernandez *et al.*, 1995). However, under stressed hormonal conditions (as induced in this study by ovariectomization to mimic menopause in the female subjects), the psyllium diet exhibited a diminished hypocholesterolemic effect (Roy *et al.*, 2000). In addition to lowering cholesterol and other blood lipid concentrations, psyllium has been shown to exhibit a potential antioxidant effect (Vergara-Jimenez *et al.*, 1999).

Psyllium has been evaluated in human subjects for its effectiveness in the control of mild to moderate hyperlipidemia. In pilot human studies, it lowered serum cholesterol levels by 5–20% with daily psyllium doses from 3.5 to 24 g (Gupta *et al.*, 1994). The study conducted by Gupta *et al.* (1994) showed that two daily doses of 3.5 g psyllium significantly reduced total serum cholesterol (19.7%), LDL-cholesterol (23.7%), and triglycerides (27.2%) in patients with non-insulin-dependent diabetes mellitus (NIDDM). Everson *et al.* (1992) found psyllium to lower LDL-cholesterol in 50% of hypercholesterolemic men. Their study also concluded that the cholesterol-lowering effect of psyllium was due primarily to its stimulation of bile acid synthesis. This might be achieved by promoting the regulatory enzyme that catalyzes the conversion of cholesterol to bile acids. Some studies have examined the hypocholesterolemic effect of psyllium when it was used as an adjunct to diet therapy in controlling hyperlipidemia (Anderson *et al.*, 2000a; Bell *et al.*, 1990; Gupta *et al.*, 1994;

TABLE 4.1 Effect of dietary psyllium on plasma and liver cholesterol concentrations in hamsters[a]

Number per group	Days on diet	Cholesterol in diet (%)	Psyllium in diet (%)	Fat in diet (%)	Plasma cholesterol (mmol/l)		Decrease (%)	Liver cholesterol (μmol/g)		Decrease (%)	References
					Cellulose	Psyllium		Cellulose	Psyllium		
8	21	0.2	5	10	8.84	6.52	26	42.9	15.8	63	Daggy *et al.* (1997)
10	28	2	20	NR	6.81	2.83	58	ND	ND	–	Leng-Peschlow (1993)
12	35	0.4	5	5	9.72	6.69	31	107.3	114.0	–6	Trautwein *et al.* (1993)
10	35	0.12	8	20	5.54	2.96	47	92.8	10.5	89	Trautwein *et al.* (1998)
16	28	0.1	7.5	10	10.30	3.15	69	42.9	6.7	84	Turley *et al.* (1991)
8/10	17	0	7.5	4.6	3.20	2.11	34	6.5	5.2	19	Turley *et al.* (1994)
8	18	0.1	7.5	10	8.61	4.11	52	20.0	6.2	69	Turley and Dietschy (1995)
14	56	0.1	3	10	5.72	4.21	26	25.6	15.0	41	Terpstra *et al.* (1998)

ND, not determined; NR, not reported. Table adapted from Terpstra *et al.* (2000b).
[a] Statistical significance was $P<0.05$ in all studies except Trautwein *et al.* (1993).

Olson *et al*., 1997; Wolever *et al*., 1994). Wolever *et al*. (1994) concluded that psyllium mixed with foods had a greater influence on serum cholesterol levels than when it was taken alone. Considering that one of the proposed mechanisms of psyllium action might be interfering with lipid absorption (Anderson *et al*., 1990; Wolever *et al*., 1994), it makes sense that it has an increased effect on total cholesterol levels when taken with food. When a psyllium-enriched cereal was administered together with a low-fat diet in hypercholesterolemic adults, the combination resulted in an improved blood lipid profile (Olson *et al*., 1997). Stoy *et al*. (1993) recorded modest increases in the total cholesterol and LDL-cholesterol-lowering effect of a standard low-fat, low-cholesterol diet, when the diet was administered together with a ready-to-eat psyllium cereal. In another study, a psyllium-enriched cereal, as part of a step-1 diet, reduced total cholesterol and LDL-cholesterol by an additional 5.9% and 5.7%, respectively, compared to the 3.8% reduction by the step-1 diet alone in patients with mild to moderate hypercholesterolemia (Bell *et al*., 1990). The step-1 diet is the introductory diet recommended by the National Heart, Lung, and Blood Institute's National Cholesterol Education Program (NCEP) for patients with high cholesterol. The step-1 diet contains not more than 30% fat (as a percentage of total calories), with no more than 10% as saturated fat, and less than 300 mg/day cholesterol (American Heart Association, http://www.americanheart.org/presenter.jhtml?identifier=4764). A study in hypercholesterolemic children revealed a 7% reduction in LDL-cholesterol concentrations when subjects on a low-fat diet were fed a psyllium-enriched cereal (Davidson *et al*., 1996). The hypocholesterolemic effect of psyllium has been found to persist in long-term use. In a 26-week, placebo-controlled study, subjects with hypercholesterolemia were treated with 5.1 g psyllium two times a day, and showed 4.7% and 6.7% reductions in serum total cholesterol and LDL-cholesterol concentrations, respectively (Anderson *et al*., 2000b). In another long-term study, a 5.3% reduction in LDL-cholesterol, effected by treating hypercholesterolemic patients with 10.2 g psyllium seed husk, persisted throughout the 24-week treatment period (Davidson *et al*., 1998).

In summary, all these data suggest, conclusively, that psyllium does lower serum and liver cholesterol concentrations, and may increase HDL-cholesterol levels. Psyllium appears to have a greater influence on LDL-cholesterol levels than on total serum cholesterol and triglyceride concentrations (Table 4.2). The significance of this hypocholesterolemic behavior in reducing the risk of CHD is still being debated. A meta-analysis conducted by Brown *et al*. (1999) concludes that, within the practical range of intake (3 g), dietary fiber, including psyllium, lowers total and LDL-cholesterol by ≈0.13 mmol/l, which they considered only a small contribution in the dietary intervention against hypercholesterolemia. The precise mechanisms involved are still under investigation.

TABLE 4.2 Hypocholesterolemic effect of psyllium in humans

Number of subjects	Status of subjects	Type of diet	Psyllium (g/day)	Decrease (%)			References
				TC	LDL-C	TG	
26	Mild to moderate hypercholesterolemia	Normal (<300 mg cholesterol)	10.2	14.8	20.2	12.7	Anderson *et al.* (1988)
24	NIDDM[a] with hyperlipidemia		7	19.7	23.7	27.2	Gupta *et al.* (1994)
37	Primary hypercholesterolemia	High fat	10.2	5.8	7.2	NR	Sprecher *et al.* (1993)
81		Low fat	10.2	4.2	6.4		
28	CVD[b]	Low saturated fat	10.5	3.76	6.9	2.79	Sola *et al.* (2007)
248	Hypercholesterolemia	Step 1 diet	10.2	4.7	6.7	NR	Anderson *et al.* (2000b)

NR, not reported; TC, total cholesterol; LDL-C, LDL cholesterol; TG, triglycerides.
[a] Non-insulin-dependent diabetes mellitus.
[b] Cardiovascular diseases.

Some researches suggest that psyllium binds to and reduces the reabsorption of bile acids in the small intestine in a fashion similar to bile acid-binding resins like cholestyramine, increasing its excretion (Everson *et al*., 1992; Turley *et al*., 1994; Wolever *et al*., 1994). Another mechanism proposed is that psyllium fiber reduces fat absorption by interfering with digestive enzyme activity and/or altering the absorptive surface of the small intestine (Anderson *et al*., 1990). Reduced rate of carbohydrate absorption (Wolever *et al*., 1994), interference in hepatic cholesterol metabolism by short chain fatty acids (SCFAs) produced by bacterial fermentation of psyllium in the colon (Wolever *et al*., 1994), and influencing hormonal (insulin and glucagon) control of lipid metabolism (Anderson *et al*., 1990) are some other mechanisms that explain the CHD risk-reducing effect of psyllium. These mechanisms are however not necessarily mutually exclusive (Wolever *et al*., 1994).

B. Reducing hyperglycemia

Water-soluble fibers are well known for their potential in moderating postprandial glucose and insulin concentrations in non-insulin-dependent diabetic patients if taken with meals (Hannan *et al*., 2006; Pastors *et al*., 1991). Psyllium is traditionally used in India for treatment of diabetes and has been evaluated in animal models and human pilot studies for its effectiveness in reducing hyperglycemia and the possible mechanisms involved in this beneficial activity (Anderson *et al*., 1999; Hannan *et al*., 2006; Song *et al*., 2000). A recent rat feeding study (Hannan *et al*., 2006) evaluated the hot-water extractable components of *P. ovata* for their potential in reducing hyperglycemia at a daily dose level of 0.5 g/kg body weight/day. It was found out that the psyllium preparation was able to significantly inhibit the rise of blood glucose level induced by the oral intake of glucose or sucrose, with no alteration in fasting levels of blood glucose and insulin status. The administration of psyllium also reduced sucrose absorption in the gastrointestinal tract, decreased intestinal glucose absorption during the 30 min of perfusion, and increased gastrointestinal motility, while it had no effect on disaccharidase activity. It was concluded that the psyllium preparation may reduce hyperglycemia by suppressing intestinal glucose absorption. In an earlier study, psyllium was able to enhance blood glucose disposal or improve insulin sensitivity by significantly increasing the skeletal muscle plasma membrane GLUT-4 protein expression without phosphatidylinositol 3 (PI3)-kinase activation in stroke-prone spontaneously hypertensive rats (Song *et al*., 2000). Insulin enhances glucose uptake into skeletal muscle by transporting GLUT-4, a glucose transporter, from the intracellular membrane to the plasma membrane through PI3-kinase activation.

A number of human pilot studies indicated the potential for application of psyllium in improving postprandial glycemic index and insulin sensitivity (Anderson *et al.*, 1995 , 1999; Sierra *et al.*, 2002; Ziai *et al.*, 2005). For instance, the addition of psyllium in the diet was shown to reduce postprandial serum glucose and insulin concentrations in hypercholesterolemic men (Anderson *et al.*, 1995), and in type-2 diabetic human subjects (Pastors *et al.*, 1991; Sierra *et al.*, 2002). In 1999, Anderson and others reported that psyllium at a level of 5.1 g/day and twice a week for 8 weeks resulted in 11% and 19% reduction of all-day and postprandial glucose concentrations after lunch in men with type-2 diabetes (Anderson *et al.*, 1999). This observation was supported by a later study in which psyllium intake significantly decreased fasting plasma glucose (Ziai *et al.*, 2005). It needs to be pointed out that conflicting results were obtained for the possible residual effect of psyllium intake after the second meal in type-2 diabetic human subjects (Anderson *et al.*, 1999; Clark *et al.*, 2006; Pastors *et al.*, 1991). In addition, these previous studies suggest that addition of psyllium to a conventional diet is a safe approach for improving the glycemic index (Anderson *et al.*, 1999; Ziai *et al.*, 2005), and may not adversely affect the bioavailability of dietary minerals and vitamins (Sierra *et al.*, 2002).

C. Cancer prevention

Psyllium has been implicated in the prevention of cancer, particularly colon and breast cancers (Morita *et al.*, 1999; Nakamura *et al.*, 2004, 2005). The mechanism of this observation is not clearly understood, but various theories have been put forward. Psyllium intervention in colon cancer is thought to be due to its fermentation in the distal colon by the *in vivo* bacterial flora, converting this soluble fiber into SCFAs (Morita *et al.*, 1999). These SCFAs include acetate, propionate, and *n*-butyrate. Research by Morita *et al.* (1999) suggested that psyllium might slow down the fermentation of high amylase corn starch, making it possible for fermentation of the starch to take place in the distal colon, which is the common site of colon cancer. The presence of SCFA, specifically *n*-butyrate, has been associated with slowing the reduction of proliferation of cancer cells and induction of differentiation of mucosa cells.

Five different combinations of psyllium and wheat bran, with comparative levels of wheat bran to psyllium of 12% and 0%, 8% and 2%, 6% and 3%, 4% and 4%, and 0% and 6%, were evaluated and compared for their effects on chemically induced mammary tumorigenesis in F344 rats (Cohen *et al.*, 1996). After 19 weeks on the treatment diets, rats on 1:1 (wheat bran/psyllium) had the lowest rate of mammary tumorigenesis, and rats on the other combined fiber diets or on the psyllium-alone diet had an intermediate rate of tumorigenesis. Rats on a diet with higher level

of psyllium had lower fecal estrogen excretion, although rats on different diets had no differences in their circulating estrogens or urinary estrogen excretions. In addition, suppression of bacterial β-D glucuronidase activity was observed with psyllium intake (Cohen *et al.*, 1996). The relationship between bacterial β-D glucuronidase activity and mammary tumor development was not clear, and other phytochemicals such as phytates, isoflavonoids, and protease inhibitors may contribute to the overall anticarcinogenesis activity.

D. Laxative effect

Psyllium fiber has long been used as a laxative. It absorbs water in the large intestine and swells, increasing fecal bulk (http://www.hort.purdue.edu/newcrop/afcm/psyllium.html). It also increases bowel movement by stimulating contraction of the colon walls. In a study involving 15 healthy adults, it was found out that a component of psyllium, unlike other viscous fibers, was not fermented in the colon (Marlett *et al.*, 2000). It formed a gel that acted as a lubricant, facilitating propulsion of colon contents. This resulted in bulkier stools with higher moisture content. The results of this study were based on 15 g/day of psyllium husk. Another study examined the laxative effect of psyllium in subjects suffering from chronic idiopathic constipation (McRorie *et al.*, 1998). The subjects were treated with psyllium and docusate for 2 weeks following a 2-week placebo control phase. At the end of the study, psyllium was found to have a more efficacious laxative effect than the docusate, increasing stool water content significantly over the period of the study. The stool softening effect was observed to increase as the study progressed, suggesting that continued use of psyllium may increase its laxative effect. The study showed that psyllium was a better stool softener than docusate in patients suffering from idiopathic constipation.

E. Possible effects on gastrointestinal system

Psyllium has been investigated for its possible influence on the gastrointestinal system (Bijkerk *et al.*, 2004; Cavaliere *et al.*, 2001; Satchithanandam *et al.*, 1996). In 2004, Bijkerk and others reviewed the available information and concluded that psyllium might play a role in treatment of irritable bowel syndrome and irritable bowel syndrome-related constipation (Bijkerk *et al.*, 2004). They also suggested performing additional clinical studies for investigating the effect and tolerability of psyllium use in primary care. It was believed that the beneficial effects of psyllium in treatment of irritable bowel syndrome were associated with its anticonstipation activity. Interestingly, psyllium has also been shown to slow down the gastric emptying time and colon transit, which may benefit the

consumers with diarrhea and pain (Washington *et al.*, 1998) and those using pancreatic lipase inhibitor for its antiobesity effect (Cavaliere *et al.*, 2001). Diarrhea and abdominal cramping were reported side effects for orlistat, a pancreatic lipase inhibitor for treatment of obesity.

F. Possible adverse effects

Many previous studies detected the possible adverse effects of psyllium intake, although others demonstrated that psyllium is generally safe for human consumption. Psyllium may alter nutrient and drug absorption, reduce food intake or appetite suppression, decrease caloric availability, increase bloating and flatulence, cause abdominal pain, and elicit anaphylactic symptoms (Lantner *et al.*, 1990; Roe *et al.*, 1988; Stevens *et al.*, 1987). The allergic symptoms of psyllium exposure including oral intake has been reviewed and discussed briefly by Lantner *et al.* (1990). The effects of psyllium intake on mineral absorption have been evaluated in a number of previous studies (Asvarujanon *et al.*, 2004; Heaney and Weaver, 1995; Luccia and Kunkel, 2002a,b). In 2002, psyllium was shown to reduce calcium bioavailability and induce undesirable changes in bone composition in weanling Wistar rats (Luccia and Kunkel, 2002b), though an *in vitro* study showed that psyllium had no binding of exogenous calcium (Luccia and Kunkel, 2002a). This observation was in contrast to that observed in an earlier human study, which concluded that a commercial form of psyllium preparation at typical therapeutic levels had little practical effect on the availability of co-ingested calcium (Heaney and Weaver, 1995). It was also reported that the viscosity and fermentability of psyllium might be associated with its capacity in suppressing mineral absorption. A reduction in viscosity and fermentability may decrease its inhibitory effects on calcium, magnesium, and zinc absorption. In addition, psyllium may slow down intestinal gas transition and increase gas production, which is associated with the pronounced gaseous symptoms such as bloating and uncomfortable abdominal distension (Gonlachanvit *et al.*, 2004).

III. APPROACHES TO IMPROVE THE FUNCTIONALITY, SAFETY, AND BIOLOGICAL ACTIVITY OF PSYLLIUM

A. Physical and mechanical approaches

It has been a continuous effort to improve the physicochemical, functional, sensory, and biological properties of psyllium for promoting its food utilization and enhancing its safety. It is a great challenge to disperse psyllium in water or aqueous solutions even with vigorous agitation

because of its extremely strong water-absorbing capacity. Several approaches have been investigated for their potential in improving the water dispersibility of psyllium powder. The first approach was to use psyllium with a wide range of particle sizes (Rudin, 1985). However, these psyllium preparations were not sufficiently more dispersible than the commonly used forms with uniform particle sizes. Changes of particle size distribution also could not improve the adverse sensory impact of psyllium in food formulations. Powell and Patel (1982) disclosed that coating psyllium granules with polyvinylpyrrolidone, polyethylene glycol, or their combination may substantially improve its water dispersibility. Addition of polyvinylpyrrolidone may reduce the granule friability. Coating was carried out in an anhydrous solvent system containing ethanol and methanol (Powell and Patel, 1982). Later in 1985, Rudin disclosed that agglomeration of psyllium in water could be prevented or reduced by coating psyllium particles with a food-grade emulsifier (Rudin, 1985). The coating might be accomplished by blending the emulsifier, psyllium, and cereal bran in pure ethanol, followed by evaporation of the solvent in air at ambient temperature. It was proposed that the food-grade emulsifier might consist of a mixture of monoglycerides, diglycerides, sodium stearyl lactylate, hydrophilic ethoxylated sorbitan monoesters, maltodextrin, lecithin, and a combination of them (Rudin, 1985).

In 1993, a mechanical procedure was developed to prepare a novel psyllium preparation, psyllium nuggets (Wullschleger *et al*., 1993). Psyllium was first blended with selected combinations of wheat bran, corn bran, oat bran, different flours, sugar, high fructose corn syrup, gums, salts, and food-grade acids. The resulting blends were subjected to extrusion under certain conditions. The extruded nuggets can be used to make ready-to-eat cereal products with an improved flavor and texture. The nuggets and the ready-to-eat cereal products were reported to retain their cholesterol-lowering activities (Wullschleger *et al*., 1993). However, the resultant psyllium preparation was not evaluated for its water-absorbing and gelling properties. The resultant psyllium preparations also may not be safe for consumers who have the restricted intake of sugar and salt.

Changing the pH or adding one or more food-grade acids with or without a coating could delay the gelling rate of psyllium and improve its dispersibility in liquids (Barbera, 1993, 1995; Barbera and Burns, 1993). It was disclosed that several food-grade acids such as citric, ascorbic, malic, succinic, tartaric, and phosphoric acids, as well as monopotassium phosphate and the mixture of these acids could reduce the gelling capacity of psyllium and improve the sensory properties of the final food formulation containing the psyllium preparation (Barbera, 1993). It was also reported that maltodextrin coating combined with food-grade acid (s) with or without sugar was able to improve the mixability and

dispersibility of psyllium in liquids (Barbera, 1993, 1995). The food-grade acids could be citric, malic, succinic, ascorbic, tartaric, or phosphoric acids, or monopotassium phosphate and mixture of them at a level not less than 0.5% in a final psyllium preparation (Barbera, 1995). Both maltodextrin and sugar may further alter the behavior of psyllium during food formulation and processing.

A physical approach was also applied to reduce the allergenicity of psyllium and psyllium-containing food products (Wullschleger, 1993). Psyllium was subjected to a thermal treatment under certain pressure and moisture content for a predetermined time period to destroy the allergenic proteins. The preferred treatment conditions included a temperature of 245–265 °F, pressure range of 14–20 psi, and a time period between 55 and 75 min. This procedure may eliminate up to 100% of the allergenicity of psyllium.

In summary, there have been several physical/mechanical means developed to improve the functionality, safety, and sensory properties of psyllium. These previous investigations have indicated the possibility to improve the physicochemical, sensory, biological properties of psyllium for its optimal applications in foods. However, none of them could sufficiently solve the strong gelling and extreme water-uptake problems of psyllium.

B. Conventional enzymatic approaches

Enzymatic approaches have been developed to improve the functionality and safety of psyllium (Allen *et al.*, 2004; Nielsen, 1993; Yu, 2003a,b; Yu and Perret, 2003a,b; Yu *et al.*, 2001). Psyllium exposure could lead to asthma, allergic rhinitis, and anaphylaxis (Lantner *et al.*, 1990; Nielsen, 1993). It was noted that the allergenic proteins in psyllium husks were water extractable. An enzymatic procedure was developed to treat psyllium husks with selected proteases in aqueous slurry to eliminate the allergenic protein fractions mainly by hydrolytic reactions (Nielsen, 1993). This procedure did not generate any toxic decomposition products or cause any undesirable changes in functionalities of psyllium. The procedure was easily performed, involving the preparation of the psyllium slurry, addition of the protease, enzymatic reaction at a pH close to the optimal pH of the proteolytic enzyme for a selected time period, and followed by inactivation of the enzyme (Nielsen, 1993). Suitable proteases include but are not limited to trypsin, chymostrypsin, and pronase E at a final concentration ranging from 100 to 2000 IU per liter of slurry at about 37 °C. The possible effects of the protease treatment on the functionality of psyllium were not reported in this invention disclosure.

Enzymatic procedures were also developed to improve the functionality of psyllium (Yu, 2003a,b; Yu and Perret, 2003a,b; Yu *et al.*, 2001). In 2001,

it was disclosed that carbohydrase treatment of a psyllium slurry might be able to reduce its water-absorbing and gelling capacity, thereby improving its functionality during food formulation and processing (Yu *et al.*, 2001). The potential effective carbohydrases included xylanases, cellulases, hemicellulases, arabanases, pentosansases, β-glucanases, and the various combinations of these enzymes. The enzymatic reaction might be conducted in water or a buffer with a pH value close to the optimal pH of the selected carbohydrase(s). The modified psyllium preparations were shown to have reduced gelling capacity measured as gel hardness and adhesiveness. The enzyme-treated psyllium was able to reduce serum total and LDL cholesterol levels, and serum triglycerides in male Golden Syrian hamsters (Yu *et al.*, 2001). The disadvantage of this enzymatic procedure was the requirement of a freeze-dry procedure to remove moisture from the enzyme-treated psyllium. The involvement of the freeze-dry step limited the possibility to scale this procedure up for commercial production of the psyllium-derived food ingredients with improved functionality. However, the results from this invention disclosure supported the hypothesis that (a) change of chemical/molecular structures of psyllium may alter its functional characteristics and its biological activity; (b) breaking of the xylan backbone may result in a reduced gelling capacity and improvement of the gel properties, associated with an improved dispersive effect and decreased water-absorbing capacity; and (c) psyllium preparations with reduced gelling and water-absorbing capacities may retain their health beneficial properties. In other words, the biological activity is not completely determined by the same structural factor(s) responsible for its water-absorbing/gelling properties.

C. Solid-state enzymatic procedures

Later in 2003, a solid-state enzymatic procedure was developed to reduce the water-absorbing and gelling capacities of psyllium (Yu, 2003a,b; Yu and Perret, 2003a,b; Yu *et al.*, 2003). In a typical solid-state enzymatic reaction, original psyllium was mixed with the enzyme and the solid reaction mixture is kept at ambient temperature until the inactivation of the enzyme, which terminates the reaction (Fig. 4.1 comparing solid and liquid reactions). The resulting solid mixture is the modified psyllium product with about 100% total yield. No chemical was added to the reaction mixture and no chemical waste is generated from the reaction. This ''solid-state'' procedure involves a limited amount of water in the enzymatic reaction and requires no additional step after enzyme inactivation for removing moisture content in the modified psyllium preparations, and thus can be easily scaled up for commercial production, whereas the product from the conventional liquid phase enzymatic reaction was a rubbery gel and required a freeze-drying step to remove

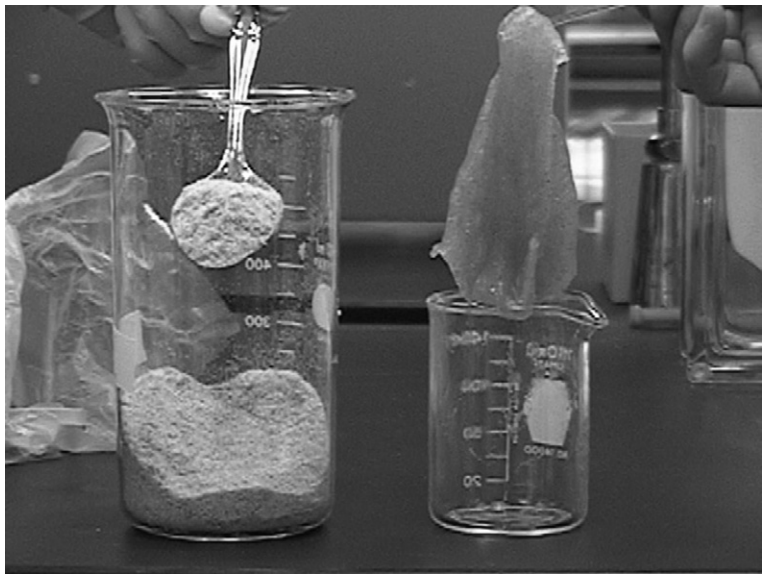

FIGURE 4.1 Psyllium products from solid (left) and liquid (right) enzymatic reactions. (Adapted from Yu, 2003b.)

moisture (Fig. 4.1 comparing solid and liquid reactions) (Yu, 2003a,b; Yu and Perret, 2003a,b; Yu *et al.*, 2003). A number of food-grade enzymes have been evaluated for their potential to improve psyllium functionality under the solid-state reaction conditions including Shearzyme 500L with xylanases activity, Pentopan Mono BG with pentosannase activity, and Viscozyme L with a combined activity of cellulase, hemicellulases, xylanases, arabanases, and β-glucanase. All three food-grade enzyme preparations are commercially available and may be obtained from Novo Nordisk Biochem North American, Inc. (Franklinton, NC).

The modified psyllium samples were evaluated and compared to original psyllium for their water-absorbing capacity and gelling properties, as well as their fiber contents. The water absorption capacity was determined following a protocol described previously (Elizalde *et al.*, 1996). In brief, all samples were equilibrated in a low relative humidity (RH) chamber for 48 h. Then, samples were transferred into a high RH chamber and exposed to moisture for a preselected time period. The dry matter and the absolute amount of absorbed water were determined. All three tested food-grade enzymes were able to dose-dependently reduce the water-absorbing capacity of psyllium, although their effectiveness on a per enzyme concentration basis differed (Yu and Perret, 2003a,b). Viscozyme L at levels of 19.2 and 36 units/g of psyllium significantly decreased the water-absorbing capacity of psyllium, and a 49% reduction

in the rate of water absorption was detected in the psyllium sample treated with Viscozyme L at a level of 36 units/g of psyllium under the experimental conditions (Fig. 4.2). The enzyme-treated psyllium samples were evaluated and compared with the original raw psyllium for their surface structures using a scanning electron microscope (SEM) technique. SEM analysis showed that solid-state enzyme treatment resulted in a smoother surface on the psyllium particles as compared to original raw psyllium and the control which went through the solid-state reaction without enzyme added (Fig. 4.3). It was suggested that solid-state enzymatic treatment reduced the total surface area which may partially explain the reduced water absorption rate of these modified psyllium preparations (Yu and Perret, 2003a,b; Yu *et al.*, 2003).

The gelling properties of the modified psyllium under the solid-state enzymatic reaction conditions were evaluated using a TA-XT2 texture analyzer (Texture Technologies Corp., Scarsdale, NY) (Boune and Comstock, 1981; Paraskevopoulou and Kiosseoglou, 1997; Pons and Fiszman, 1996). A known amount of psyllium was mixed into water with agitation. After incubation at room temperature for 3 h, gel samples were subjected to a double compression test (Yu and Perret, 2003a,b; Yu *et al.*, 2003). Shearzyme 500L and Viscozyme L were more effective than Pentopan Mono BG in reducing the gelling capacity of psyllium on a per same enzyme concentration basis (Yu and Perret, 2003a,b; Yu *et al.*, 2003).

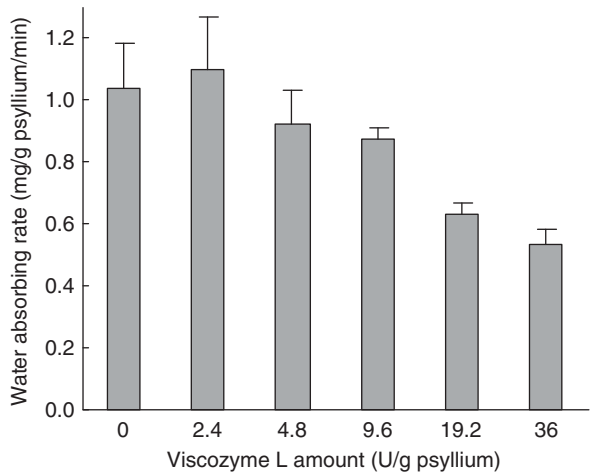

FIGURE 4.2 Effects of Viscozyme L on water uptaking capacity of psyllium. 0, 2.4, 4.8, 9.6, 19.2, and 36 represent the final Viscozyme L concentrations of 0, 2.4, 4.8, 9.6, 19.2, and 36 units/g of psyllium in the solid-state reactions, respectively. Means are reported and the vertical bars represent the standard deviation of each data point ($n = 3$). (Adapted from Yu *et al.*, 2003).

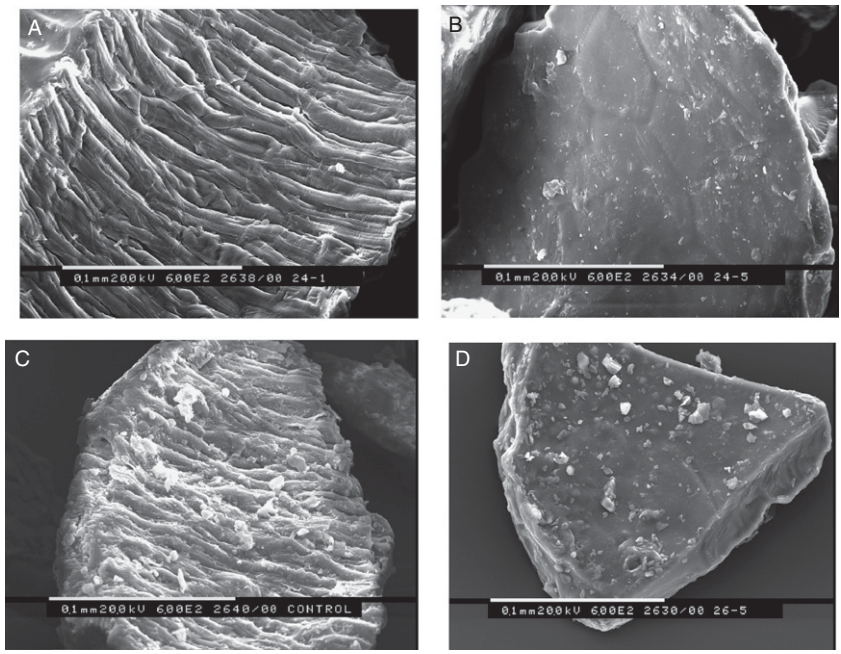

FIGURE 4.3 Surface structures of psyllium preparations determined by SEM. (A) Psyllium treated with 0 enzyme, (B) psyllium treated with 120 units of Shearzyme 500 L, (C) raw psyllium, and (D) psyllium treated with Viscozyme L at a level of 30 units/g psyllium, under the experimental conditions (A and B are adapted from Yu, 2003b, while C and D are adapted from Yu *et al.*, 2003).

Shearzyme 500 L and Viscozyme L were able to dose-dependently reduce the gelling capacity of psyllium. Figure 4.4 presents the effects of Viscozyme L on gelling properties of modified psyllium. Compared to the original psyllium, Viscozyme L treatment dose-dependently reduced the heights of all four peaks and altered the shape of the two negative peaks, indicating that the modified psyllium formed a weaker gel and might have reduced sliminess and less coating effects on sensory receptors in the mouth. Taking into account the water-absorbing and gelling properties of the modified psyllium, the solid-state enzymatic procedure may serve as an effective approach for improving the functionality and sensory properties of psyllium for promoting its food applications.

It is well accepted that the soluble fiber is the primary contributor for the beneficial health effects of psyllium especially the cholesterol-lowering activity, while the insoluble fiber may also have a contribution. The effects of solid-state enzymatic treatment on fiber contents were investigated for the modified psyllium. Shearzyme 500 L, Viscozyme L, and Pentopan Mono BG treatments all caused loss of soluble fiber under

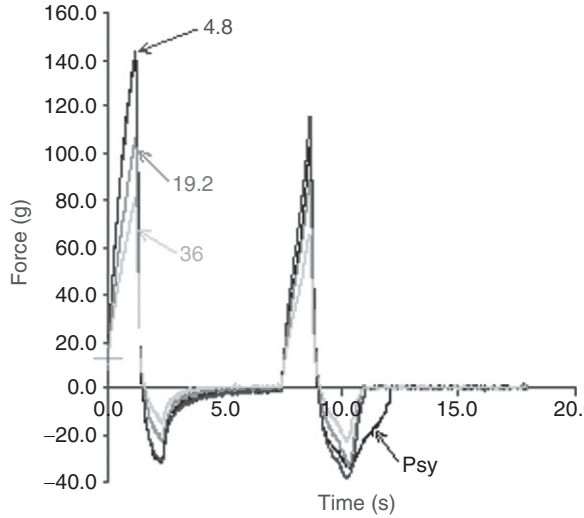

FIGURE 4.4 Effects of Viscozyme L treatment on gelling properties of psyllium. 4.8, 19.2, and 36 represent the final Viscozyme concentrations of 4.8, 19.2, and 36 units/g psyllium in the solid-state reaction mixtures, respectively, and Psy represents the original psyllium sample. The setting time was 3 h for all gel samples (redrawn from Yu *et al.*, 2003).

the solid-state enzymatic reaction conditions, but had no influence on insoluble fiber contents (Fig. 4.5) (Yu and Perret, 2003a,b; Yu *et al.*, 2003). A higher enzyme concentration was associated to a lower soluble fiber content in the modified psyllium products, although doubling the enzyme level did not result in doubled reduction in soluble fiber (Yu and Perret, 2003a,b; Yu *et al.*, 2003). It was also noted in these previous studies that the loss of soluble fiber under the solid-state reaction conditions was less than that under the liquid state enzymatic reaction conditions (Yu and Perret, 2003b). It was proposed that other chemical reactions such as isomerization or acceptor reaction may occur under the solid-state reaction conditions with the limited amounts of free water molecules available (Yu and Perret, 2003b).

The potential synergistic effect between enzymes on psyllium functionality was tested using Pentopan Mono BG and Shearzyme 500 L under the solid-state reaction conditions (Yu and Perret, 2003a). Pentopan Mono BG and Shearzyme 500 L exhibited synergistic effect in reducing the water-absorbing capacity of psyllium, but not in altering the gelling properties of psyllium. Addition of Shearzyme 500 L in the Pentopan Mono BG reaction resulted in further loss of soluble fiber from the psyllium preparation. These data warrant further investigation to develop enzyme combinations for improving functionality, sensory properties, and health benefits of psyllium.

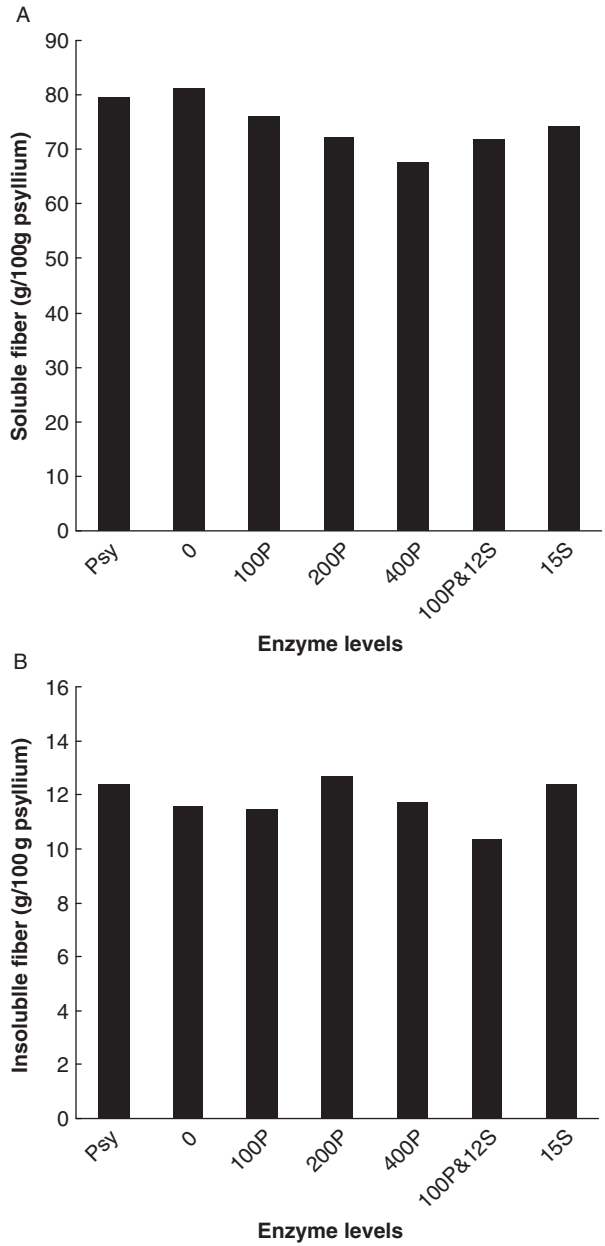

FIGURE 4.5 Effects of solid-state enzyme treatment on (A) soluble fiber and (B) insoluble fiber contents in psyllium. P, the Pentopan Mono BG; S, the Shearzyme 500 L from Novo Nordisk Ferment Ltd. (Switzerland); 100P, 100 units of P; 12S, 12 units of S; and Psy stands for the commercial psyllium husks, the starting material for the solid-state enzymatic reaction (re-drawn from Yu and Perret, 2003a).

In addition, modified psyllium preparations under the solid-state reaction conditions were evaluated for their hypolipidemic effects using hamsters (Allen *et al.*, 2004). Original psyllium was included as the positive control, and cellulose was used as a fiber control. Hamsters were fed 0.2 wt.% cholesterol diets with 12% cellulose or 5% cellulose plus 7% original or enzymatically modified psyllium preparations. During 5 weeks of feeding period, psyllium addition did not reduce total food intake. Both modified psyllium preparations were as effective as the original psyllium in reduction of the total plasma, LDL, and HDL cholesterol, but cellulose did not cause similar reductions under the same experimental conditions (Fig. 4.6). These psyllium preparations also exhibited similar effects in enhancing the bile acid extraction. Interestingly, one of the modified psyllium preparation was able to significantly reduce the total body weight gain over the 35 days of feeding (Fig. 4.7), suggesting its potential utilization in body weight control (Allen *et al.*, 2004). These previous studies indicate that solid-state enzymatic treatments may be an effective approach to improve not only the functionality but also the biological activity of psyllium, and additional research

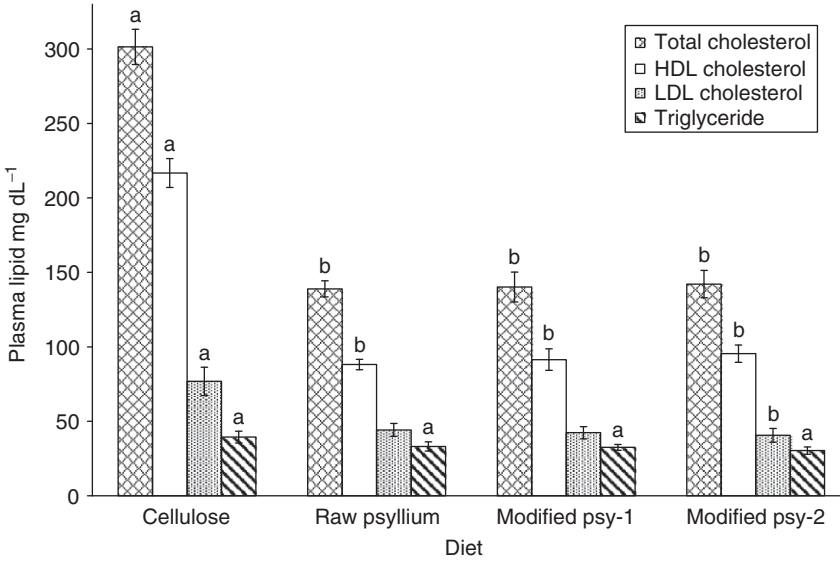

FIGURE 4.6 Effect of solid-state enzyme treatment on hypolipidemic activities of psyllium. Plasma lipid concentrations in hamsters were measured at day 35. Values are mean ± SEM (vertical bars) for nine animals per group. Within each response parameter, values not sharing common letters are significantly different, $P<0.05$. Modified Psy-1 and modified Psy-2 represent the two modified psyllium preparations using the Viscozyme L and the Shearzyme 500 L, respectively, under the solid-state reaction conditions (re-drawn from Allen *et al.*, 2004).

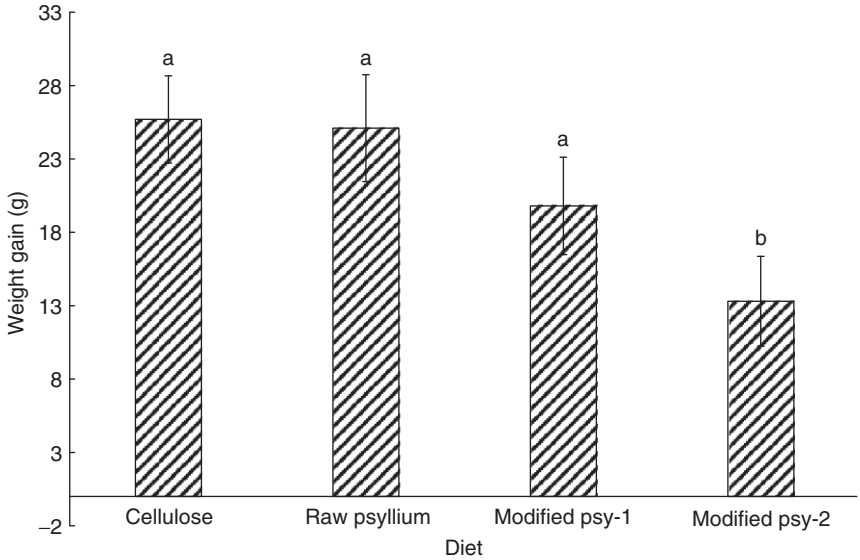

FIGURE 4.7 Comparison of enzymatically modified psyllium with cellulose and original raw psyllium for their effects on body weight gain in hamsters. Total body weights gained over the 35 days of feeding are reported. Values are mean ± SEM (vertical bars) for nine animals per group. Values not sharing common letters are significantly different, $P<0.05$. Modified Psy-1 and modified Psy-2 represent the two modified psyllium preparations using the Viscozyme L and the Shearzyme 500 L, respectively, under the solid-state reaction conditions (re-drawn from Allen *et al.*, 2004).

involving more food-grade enzymes is requested to further explore the opportunity. Additional research is also required to further investigate the relationships between the chemical/molecular structures and the physicochemical/health-benefit properties of psyllium.

D. Chemical modification of psyllium

Grafting and networking may modify the mechanical, chemical, and functional properties of polymers and enhance their utilization for some purposes, such as for water treatment (Kumar and Verma, 2007; Mishra *et al.*, 2003). Psyllium derivatives were prepared by grafting acrylonitrile onto psyllium molecules using a ceric ammonium nitrate and nitric acid system (Mishra *et al.*, 2003). The resulted grafted psyllium samples were not soluble in commonly used solvents or their combinations. In 2007, methacrylic acid derivatives of psyllium were prepared using ammonium persulfate as initiator and cross-linked using *N*,*N*-methylenebisacrylamide as the crosslinker (Kumar and Verma, 2007). The modified psyllium

showed different swelling and thermal degradation behaviors with the possible application in water treatment. These research activities suggest the potential of improving psyllium functionality and biological activity through chemical modifications, although these two grafted psyllium preparations were mainly for nonfood uses.

Chemical methods have also been developed to eliminate the allergenicity of psyllium (Ndife, 1993). The alkaline treatment, including aqueous sodium hydroxide or potassium hydroxide, at a ratio of 2–20 g of psyllium weight per 100 ml alkali with a concentration of 0.1–0.5 N for 10–60 min, might significantly decrease the allergenicity of psyllium.

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