Mol. Nutr. Food Res. 2005, *49*, 791 – 796 DOI 10.1002/mnfr.200500035

Bitter gourd (*Momordica charantia*) modulates activities of intestinal and renal disaccharidases in streptozotocin-induced diabetic rats

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During diabetes, structural and functional changes in the alimentary tract are known to take place resulting in increased absorption of intestinal glucose and alterations in the activities of brush border disaccharidases. Similar observations are also reported in the renal cortex. In the present investigation, we examined the effect of feeding bitter gourd fruit devoid of seeds on activities of intestinal and renal disaccharidases, *viz.*, maltase, sucrase, and lactase in streptozotocin-induced diabetic rats. Normal and diabetic rats were fed either with basal diet or a diet containing 10% bitter gourd powder. Specific activities of intestinal disaccharidases were significantly increased during diabetes, and supplementing bitter gourd in the diet clearly indicated amelioration in the activities of maltase and lactase during diabetes. However, a significant change was not observed with sucrase activity by feeding of bitter gourd. During diabetes, renal disaccharidase activities were significantly lower than those in the control rats. Bitter gourd supplementation was beneficial in alleviating the reduction in maltase activity during diabetes. However, not much change in the activities of sucrase and lactase was observed upon feeding. This positive influence of feeding bitter gourd on intestinal and renal disaccharidases clearly indicates their beneficial role in the management of diabetes, thus making diabetic animals more tolerant to hyperglycemia.

Keywords: Bitter gourd / Diabetes / Disaccharidase / Intestine / Renal

Received: March 10, 2005; revised: Arpil 19, 2005; accepted: April 21, 2005

1 Introduction

Diabetic patients are susceptible to a series of complications that cause morbidity and premature mortality. The disease hardly spares any organ of the body. Most patients with diabetes are at the risk of long-term complications, such as vision loss, renal failure, nerve damage, and heart disease. Prevention and control of complications associated with diabetes has become one of the key issues in biomedical research [1–3]. In this regard, disaccharidases play an important role. Disaccharidases are essential for terminal absorption of carbohydrates, specifically in conversion of disaccharides to readily absorbable monosaccharides. During diabetes structural and functional changes in the alimentary tract, namely intestinal hyperplasia, increase in intestinal glucose absorption, and alterations in the activities of brush border enzymes such as maltase, sucrase, and lactase, are known to take place. The ability of the intestine to increased monosaccharide absorption in diabetes can further complicate the pathophysiology of this disease. Similar changes are also visible to some extent in the renal cortex [4–9]. Although exogenous insulin and other medications can control many aspects of diabetes, management plays a key role in longevity and quality of life. Plants with medicinal value are used since centuries for better management of diabetes [10]. In this aspect, bitter gourd or karela or bitter melon (*Momordica charantia*), a member of the Cucurbitaceae family, commonly consumed as vegetable in India, is most widely studied with regard to its hypoglycemic effect [11, 12]. Although contradictory claims have been reported on the hypoglycemic effects of bitter gourd [13], our study with bitter gourd powder (10%) rich in dietary fiber was effective in controlling diabetes-related symptoms (submitted for publication). However, its potential effect on intestinal and renal disaccharidases during diabetes is unknown. The metabolic changes during digestion are accomplished with the aid of hydrolases in the gastrointestinal tract. Therefore, a study on alteration in the activ-

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Abbreviations: **BFC**, bitter gourd-fed control; **BFD**, bitter gourd-fed diabetic; **SFC**, starch-fed control; **SFD**, starch-fed diabetic; **STZ**, streptozotocin

ities of disaccharidases during diabetes and their modulation by feeding bitter gourd is important in understanding the mechanism regulating the progression of the diabetic status.

2 Materials and methods

2.1 Materials

Streptozotocin, maltose, sucrose, and lactose were obtained from Sigma-Aldrich (St. Louis, MO, USA). GOD/POD kit was obtained from Span Diagnostics Ltd (Surat, India). Fresh bitter gourd (*Momordica charantia*) procured from the local market was cleaned and the edible portion (devoid of seeds) was air-dried in an oven maintained at 37–40°C and powdered. All other chemicals used were of analytical grade.

2.2 Animals, diet, and induction of diabetes

The present study was approved by the Institutional Animal Ethical Committee. Male Wistar rats (OUTB-Wistar IND cftri) weighing between 120 and 130 g were taken for the study from the Institute Animal House Facility. The animals were placed individually in stainless-steel cages and had free access to water and diet. Rats were divided into two groups of diabetic rats (14 rats/group) and two groups of age matched normal rats (6 rats/group). One group received a basal diet and the second group received bitter gourd devoid of seeds in powder form, incorporated at 10% level at the expense of an equivalent amount corn starch in AIN-76 basal diet containing 63.5% corn starch, 20% protein, 10% fat, 3.5% AIN-76 mineral mix, 1% AIN-76 vitamin mix, and 0.2% choline chloride and stored at 4°C [14]. Refined groundnut oil was used as a source of fat. Rats were rendered diabetes by a single intra-peritoneal injection of streptozotocin (STZ, 55 mg/kg body weight in freshly prepared 0.1 M citrate buffer, pH 4.5) and control rats received citrate buffer only. STZ-injected rats had access to glucose water (5%) for two days [15].

2.3 Collection and analysis of blood and urine

Urine was collected two days prior to the sacrifice, under a layer of toluene by keeping the rats in metabolic cages for a period of 24 h. Rats were fasted overnight and the blood was collected in tubes containing heparin (20 U/mL blood), either from the retro-orbital plexus during the experiment (under mild anesthesia to check the diabetic status after STZ injection) or from the heart at the time of sacrificing to measure fasting blood glucose. The content of reducing sugar present in the urine was measured by dinitrosalicylic acid method [16], while the glucose level in the plasma was measured by the glucose oxidase method using a commercially available kit.

2.4 Intestinal and kidney homogenate

Rats were sacrificed under ether anesthesia and the small intestine and kidney were harvested. The intestinal lumen was flushed with ice-cold saline to free from food particles and cut open. Mucosa was scrapped using a glass slide and homogenized in 0.9% saline. Similarly, the kidney was homogenized in 0.9% saline and centrifuged at 3000 rpm for 10 min at 4°C. The supernatant obtained was used for disaccharidase assays.

2.5 Disaccharidase assay

The assay was carried out by determining the specific activities of sucrase, maltase, and lactase, which was correlated to the amount of glucose released from sucrose, maltose, and lactose, respectively, at 37°C in maleate buffer (0.2 M, pH 6.0) at different time intervals as described by Dahlquist [17]. The amount of protein in the samples was determined by Lowry's method [18].

2.6 Statistical analysis

Results are expressed as mean values ± SEM. Differences in mean values were analyzed using Student's *t*-test and analysis of variance (ANOVA). Significance is defined as $p < 0.05$. Statistical tests were carried out with graph pad PRISM statistical software package.

3 Results

Diabetes was induced in male Wistar rats by injecting STZ in citrate buffer. Rats were maintained on experimental diet for a period of 45 days. Initially 6 rats as control and 14 diabetic rats were taken. Diabetic rats were grouped to the uniform average diabetic status, after measuring fasting blood glucose taken from retro orbital plexus. In the diabetic groups 7 rats were considered, which were diabetic with respect to fasting blood glucose and urine sugar, after excluding the rats which did not develop diabetes and rats which died during the course of the experiment. The experiment was terminated when the mortality was about to set in, which was initially in the starch-fed diabetic group (SFD). The rats were sacrificed at the end of the experimental period under ether anesthesia. The diabetic status was evaluated by measuring urine volume, urine sugar, and fasting blood glucose at the end of the experiment.

3.1 Effect of bitter gourd on urine volume, urine sugar, and fasting blood glucose in control and diabetic rats

Excretion of urine was monitored. Both the control groups (starch-fed control/bitter gourd-fed control, SFC/BFC) excreted 12 – 14 mL of urine/day (Table 1) during the experiment and polyuria condition prevailed in the SFD and was 75.6 mL of urine/day. Bitter gourd incorporation in the diet showed significant reduction in urine excretion during diabetes, and treated rats (BFD) excreted 46.7 mL of urine/day, which was statistically significant when compared to diabetic controls (SFD). Similarly, normal rats (SFC/BFC) excreted reducing sugar in milligram quantities (Table 1). The SFD rats excreted 6.86 g reducing sugar/day, which was much higher than normal values. At the same time, bitter gourd-fed diabetic rats excreted around 3.68 g reducing sugar/day, which was statistically significant compared to diabetic rats (SFD) indicating the beneficial effect of bitter gourd in controlling excretion of reducing sugar in diabetic rats. Fasting blood glucose was measured in plasma at the end of the experiment in the blood drawn by puncturing the heart. The control rats, both starch-fed control (SFC) and bitter gourd-fed control (BFC), had fasting blood glucose of 105 – 110 mg/dL (Fig. 1). The increase in fasting blood glucose level was clearly visible in starch-fed diabetic (SFD) rats, which was about 340 mg/dL. Supplementing bitter gourd in the diet significantly reduced the fasting blood glucose level by about 30%, clearly indicating its hypoglycemic influence during diabetes (Fig. 1).

Table 1. Effect of bitter gourd on urine volume and urine sugar in control and diabetic rats

Groups	Urine volume (mL/day)	Urine sugar (g/day)
SFC	13.54 ± 0.57	0.03 ± 0.001
SFD	75.64 ± 2.84[a)]	6.86 ± 0.49[a)]
BFC	12.6 ± 1.07	0.03 ± 0.003
BFD	46.7 ± 2.45[b)]	3.68 ± 0.21[b)]

SFC, starch-fed control; SFD, starch-fed diabetic; BFC, bitter gourd-fed control; BFD, bitter gourd-fed diabetic. Values are mean ± SEM of 6 rats in control and 7 rats in diabetic groups.
a) Statistically significant when compared to SFC ($p < 0.05$)
b) Statistically significant when compared to SFD ($p < 0.05$)

3.2 Effect of bitter gourd on activities of intestinal maltase, sucrase, and lactase in control and diabetic rats

The specific activities of intestinal disaccharidases, *viz.*, maltase, sucrase, and lactase, were measured in control and diabetic rats (Table 2). In the intestine, a twofold increase in maltase activity was observed in starch-fed diabetic rats (SFD) when compared to control rats (SFC). Bitter gourd in the diet (BFD) showed a significant decrease in the maltase activity during diabetes when compared to starch-fed diabetic rats (SFD). There was a significant increase in sucrase activity in SFD rats compared to control rats. However, bitter gourd feeding during diabetes (BFD) did not show a significant change in intestinal sucrase activity. During diabetes (SFD), a significant increase in lactase activity was observed compared to its control (SFC). An effective reduction in the intestinal lactase activity was observed by feeding bitter gourd in the diet, indicating a beneficial role of bitter gourd during diabetes.

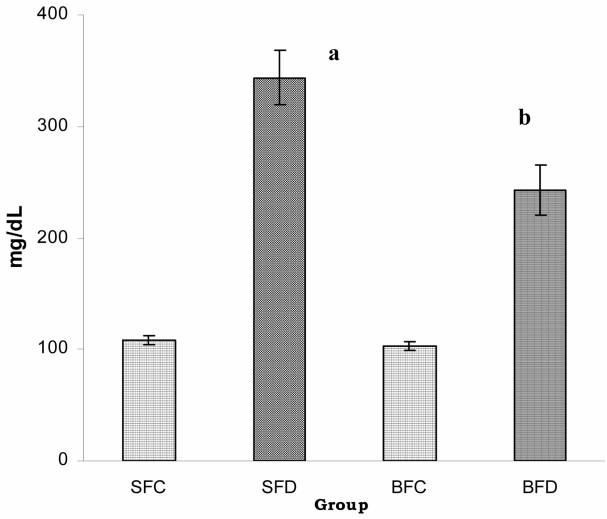

Figure 1. Effect of bitter gourd on fasting blood glucose in control and diabetic rats. Abbreviations and foot note as in Table 1.

Table 2. Effect of bitter gourd on activities of intestinal maltase, sucrase, and lactase in control and diabetic rats

Groups	Maltase	Sucrase	Lactase
	(*n* moles of product formed/mg of protein/min)		
SFC	457.4 ± 16.3	27.8 ± 2.1	2.43 ± 0.3
SFD	905.6 ± 29.7[a)]	62.0 ± 1.9[a)]	3.45 ± 0.2[a)]
BFC	466.6 ± 6.9	29.0 ± 0.2	1.97 ± 0.4
BFD	732.0 ± 44.7[b)]	57.2 ± 1.3[NS]	2.27 ± 0.2[b)]

Abbreviations and foot note as in Table 1. NS, not significant statistically when compared to SFD ($p < 0.05$)

3.3 Effect of bitter gourd on activities of renal maltase, sucrase, and lactase in control and diabetic rats

Renal disaccharidases showed considerable variation in the specific activities during diabetes (Table 3). A significant

Table 3. Effect of bitter gourd on activities of renal maltase, sucrase, and lactase in control and diabetic rats

Groups	Maltase	Sucrase	Lactase
	(*n* moles of product formed/mg of protein/min)		
SFC	192.5 ± 8.7	2.03 ± 0.03	3.36 ± 0.09
SFD	100.9 ± 3.3[a)]	1.16 ± 0.03[a)]	2.66 ± 0.17[a)]
FFC	190.0 ± 2.6	1.90 ± 0.03	3.68 ± 0.28
FFD	122.6 ± 3.7[b)]	1.46 ± 0.04[NS]	2.98 ± 0.20[NS]

Abbreviations and foot note as in Table 1. NS, not significant statistically when compared to SFD ($p < 0.05$)

decrease in all three enzyme activities during diabetes (SFD) was observed when compared to their controls (SFC). The renal maltase activity in SFD rats was decreased when compared to the control. By feeding bitter gourd, a marginal yet statistically significant increase in the maltase activity was observed in the diabetic rats (BFD) when compared to the diabetic controls (SFD). The specific activities of renal sucrase and lactase decreased during diabetes (SFD) compared to their control (SFC). However, further supplementation with bitter gourd had no additive effect on renal sucrase and lactase activities (Table 3).

4 Discussion

Appropriate nutritional management is essential for restoring and maintaining a good metabolic state. In this context the diet remains a cornerstone in diabetic management. The beneficial effect of bitter gourd in countering increase in urine volume, urine sugar, and fasting blood sugar during diabetes could be mainly attributed to dietary fibers (DFs) or it could be due to its bioactive components. A recent review on bitter gourd by Grover and Yadav [19] showed that bitter gourd contains 48.1% DFs (16.6% soluble and 31.5% insoluble DFs). DFs are well known to facilitate slow absorption of glucose along the passage through the gastro-intestinal tract [20]. The role of fermentation products of DFs in the form of short-chain fatty acids (butyrate) is also to be considered in the amelioration of the diabetic status [21]. Karunanayeke *et al.* [22] have reported the insulin secretgouge effect of bitter gourd. Khanna *et al.* [23] demonstrated the hypoglycemic activity of polypeptide-p and Baldwa *et al.* [24] reported on plant insulin from bitter gourd. Contrary to these positive results of bitter gourd, Platel and Srinivasan [25] found that 0.5% freeze-dried bitter gourd powder had no beneficial effect during diabetes. Chandrashekar *et al.* [26] reported that bitter gourd did not have a hypoglycemic effect. Our earlier results with dried bitter gourd powder at 10% level clearly showed a positive effect on diabetes in terms of glycemic and diabetic nephropathy status (submitted for publication).

Diabetes frequently results in severe metabolic imbalances and pathological changes in many tissues. In the small intestine this causes significant changes in the morphology and functions of the mucosa [27, 28]. Luminal membrane upregulation in large segments of intestinal villi appear to be responsible for the alterations in glucose uptake and transport in STZ-induced diabetic rats [29]. This could be due to increased disaccharidases activities. Increased intestinal disaccharidase activities have been reported in human diabetics [6–8]. The changes in the specific activities of intestinal and renal maltase, sucrase, and lactase observed in our present study during diabetes were similar to those previously reported [15, 30]. However, in our studies bitter gourd was not effective in significantly inhibiting sucrase activity. Dietary carbohydrates are also known to stimulate specific sucrase activity during diabetes [31]. Our studies showed an increase in lactase activity during diabetes. It has been observed that under insulin-dependent diabetes mellitus (IDDM) increased lactase and sucrase activities in the small intestine are suppressed by insulin administration [32–34].

The presence of disaccharidase activities in subcellular fractions of the rat kidney cortex probably reflects an involvement in the digestion or transport of sugar across the membranes [35]. A decrease in renal disaccharidase activity was observed during diabetes [36–38]. The renal maltase activity in diabetic rats was significantly lower than that in control rats (Table 3). Bitter gourd at 10% level was effective in countering the decrease in maltase activity during diabetes. However, a significant change was not observed in sucrase and lactase activities (Table 3). In kidneys, the distribution of maltase is associated with the plasma membrane, while that of lactase may be due to the hydrolysis of lactose by β-galactosidase present in rat kidney lysosome [39]. However, the role of other disaccharidases in the kidney remains undefined.

The data presented clearly exhibit the beneficial role of bitter gourd during diabetes. Increase in the specific activity of intestinal disaccharidases could be one of the reasons for higher sugar levels in the blood and urine during diabetes. This increase in the sugar level was ameliorated considerably by feeding of bitter gourd in the diet. The decrease in the activities of renal disaccharidase (maltase) was alleviated by incorporating bitter gourd in the diet. Alleviation of the diabetic status as indicated by urine sugar, urine volume, and fasting blood glucose in the treated groups is further substantiated by the alleviation of altered activities of intestinal and renal disaccharidases. Our data clearly provided an experimental evidence to demonstrate that bitter gourd powder at 10% level in the diet controlled progression of the diabetic status by modulating the activities of intestinal and renal disaccharidases as one of the mechanisms in STZ-induced diabetic rats.

The research fellowships received by AKS from Council of Scientific and Industrial Research, New Delhi and GSK from University of Mysore are gratefully acknowledged. The authors thank for the financial assistance from Department of Science and Technology, New Delhi, India (DST/SP/SO/HS-56/2002). The authors are thankful to Dr. K. Sambaiah for useful suggestions and discussions.

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