Chinese Journal of Physiology 54(2): 79-86, 2011
DOI: 10.4077/CJP.2011.AMM006

Nephro-Protective Effects of a Ginger Extract on Cytosolic and Mitochondrial Enzymes against Streptozotocin (STZ)-Induced Diabetic Complications in Rats

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Abstract

Diabetes is characterized by elevated blood glucose levels and disturbed homeostasis of metabolic enzymes in whole-body. This study aimed to investigate the effect of ginger administration on altered blood glucose levels, intra- and extra-mitochondrial enzymes and tissue injuries in streptozotocin (STZ)-induced diabetic rats. Wistar strain rats (n = 30) were equally divided into 5 groups: normal control (NC), ginger treated (Gt, 200 mg/kg b.w. orally/30 days), diabetic control (DC, 50 mg/kg b.w.), diabetic plus ginger treated (D + Gt) and diabetic plus glibenclamide treated (D + Gli) groups. We found highly elevated blood glucose levels in the diabetic group, and the glucose levels were significantly ($P < 0.001$) lowered by ginger administration. Activities of intra- and extra-mitochondrial enzymes such as glucose-6-phosphate dehydrogenase (G6PD), succinate dehydrogenase (SDH), malate dehydrogenase (MDH) and glutamate dehydrogenase (GDH) were significantly ($P < 0.01$) decreased in the kidneys of the diabetic rats, while this was significantly reversed by 30 days of ginger treatment. We also observed consistent renal tissue damages in the diabetic rats; however, these injuries recovered in the ginger-treated diabetic rats as shown in histopathological studies. In this study, we demonstrated that an ethanolic extract of ginger could lower the blood glucose levels as well as improve activities of intra- and extra-mitochondrial enzymes in diabetic rats. Our results suggest that ginger extracts could be used as a nephro-protective supplement particularly to reverse diabetic-induced complications.

Key Words: diabetes, ginger, mitochondrial enzymes, blood glucose, kidney

Introduction

Diabetes is a major threat to global public health, and the numbers of diabetic patients are rapidly increasing world-wide. According to a projection of the International Diabetes Federation (IDF), the number would increase from 240 million (2007) to 380 million in 2025. Apart from this, more than 60%

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Received: January 15, 2010; Revised: May 5, 2010; Accepted: May 31, 2010.
 ISSN : 0304-4920. http://www.cps.org.tw

of the world population with diabetes will come from Asia (8, 27). Among Asian countries, India is a capital with 35 million diabetic patients (28). In Taiwan, diabetes-related deaths have been ranked as fifth among other causes since 1998 (20). It has already been established that chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction and eventually failure of organs, especially the kidneys, nerves, heart, eyes and blood vessels (10, 13). Kidney disease is usually attributed to metabolic consequences of abnormal glucose regulation and impaired energy metabolic enzymes (4).

Mitochondria are one of the most important cell organelles in diabetes research because of its crucial role as a regulator of energy balance (33). Various NAD/NADP-linked enzymes are intricately involved in the maintenance of the reduced redox state in mitochondria in order to provide the reducing power to generate ATP *via* oxidative phosphorylation (14, 16). There is a huge understanding between cytosolic and mitochondrial enzymes to maintain the favorable conditions to regulate various biological functions. However, it is not surprising that activities of various cytosolic and mitochondrial enzymes are altered with diabetes, and this has been previously reported (21).

Herbs and spices are generally considered safe and proved to be effective against various human ailments. In India and other developing countries, a large number of herbal drugs has been used to treat several diabetic complications. Among the most common spices used, *Zingiber officinale*, commonly known as ginger, is one of the important herbal medicines in India, China and other countries. Earlier studies have reported the pharmacological effects of ginger rhizomes includes anti-diabetic, antimicrobial, antipyretic, antiulcer, cardiotonic, antihypertensive, antihyperlipidamic, anti-oxidant and anti-inflammatory properties (1, 11, 18, 32).

However, the impact of ginger ethanolic extract on altered cytosolic and mitochondrial enzymes in diabetic condition is poorly understood. The present study aimed to analyze the fate of cytosolic and mitochondrial enzyme activities with ginger supplementation in diabetic rats. Additionally, we also evaluated nephro-protective effects of ginger against Streptozotocin (STZ)-induced renal cell damages in the rat.

Materials and Methods

Animals

Wistar strain male albino rats, aged 6 months and weighing 180 ± 20 g, were obtained from the Indian Institute of Science, Bangalore. The rats were housed in clean polypropylene cages having 6 rats per cage and maintained under temperature controlled room (25 ± 2°C) with a photo-period of 12 h light and 12 h dark cycle. The rats were fed with a standard rat pellet diet and water *ad libitum*. This study was approved by the Institutional Animal Ethics Committee (Regd. No. 438/01/a/CPCSEA /dt.17.07. 2001) in its resolution number 15 /IAEC/SVU/2001/ dt.4.03.2008.

Chemicals

All chemicals used in the present study were Analar Grade (AR) obtained from the following scientific companies: Sigma (St. Louis, MO, USA), Fisher (Pittsburgh, PA, USA), Merck (Mumbai, India), Ranbaxy (New Delhi, India) and Qualigens (Mumbai, India).

Induction of Diabetes

The animals were fasted overnight and diabetes was induced by a single intraperitoneal injection of a freshly prepared streptozotocin (STZ) solution (50 mg/kg body weight, dissolved in 0.1 M cold citrate buffer, pH 4.5). After injection, rats had free access to food and water, and given a 15% glucose solution to drink overnight to counter hypoglycemic shock. The rats were considered as diabetic if their blood glucose values reached above 250 mg/dl on day 3 after STZ injection. The blood glucose levels were measured by using Accucheck Glucometer (Roche, Germany). In addition to increased blood glucose levels, we also observed other diabetic symptoms including marked elevation in polyuria and frequent urination during the course of the study. After diabetes confirmation, rats were allowed for 7 days to acclimatize to diabetic conditions, and rats with hyperglycemia (blood glucose > 250 mg/dl) were chosen for the study. Ginger treatment was started on day 8 after STZ injection which was also considered as the first day of treatment and continued further for 30 days.

Preparation of Ginger Ethanolic Extract

Fresh rhizomes of *Zingiber officinale* were purchased from the local market and allowed to air dry. Two kilograms of air-dried rhizomes was mechanically milled into fine powder and was extracted in cold percolation with 95% ethanol for 24 h. The extract was recovered and 95% ethanol was further added to the ginger powder and the extraction was continued. This process was repeated three times. The three extracts were pooled, filtered, and the filtrate was concentrated to dryness under reduced pressure in a rotary evaporator. After that, the obtained ethanolic

Table 1. Effect of oral administration of ginger. Changes in the body and kidney weights in normal control and diabetic rats

Groups	Body weight (g)		Kidney weight (g)
	Day-1	Day-30	Day-30
Normal control (NC)	195 ± 9.66	215 ± 14.28	1.55 ± 0.06
Ginger treated (Gt)	200 ± 7.07	190 ± 8.01	1.50 ± 0.06
Diabetic control (DC)	187 ± 2.73	150 ± 6.83*	1.70 ± 0.04
Diabetic plus ginger treated (D + Gt)	185 ± 6.3	190 ± 4.08†	1.49 ± 0.04
Diabetic plus glibenclamide (D + Gli)	190 ± 3.12	205 ± 2.07†	1.52 ± 0.02

All the values are means ± SD of six individual observations. Values are significant compared to normal control (*$P <$ 0.01) and diabetic control ($^{\dagger}P < 0.01$).

extract was allowed to air-dry and finally the dark-brown and gelatinous substance was weighed. Without any further purification, the ethanolic extract was used for the experiments. Dose equivalent to 200 mg of the extract per kg body weight was calculated and suspended in a 2% Tween-80 (v/v) solution for the experiments as per the study of Bhandari *et al*. (5).

Grouping of Animals

Rats of the same age group (6 months) were divided into 5 groups, six rats in each group, and were treated as follows:

(I) *Normal Control (NC)*: This group of rats were fed on normal diet and received vehicle solution (2%, Tween-80) for equivalent handling.
(II) *Ginger Treated (Gt)*: This group of rats received ginger ethanolic extract *via* orogastric tube daily for a period of 30 days with the dose of 200 mg/kg body weight.
(III) *Diabetic Control (DC)*: STZ was injected intraperitonially (50 mg/kg body weight) for induction of diabetes in the rats.
(IV) *Diabetic plus Ginger Treated (D + Gt)*: After diabetic confirmation test, this group of rats received ginger ethanolic extract as described in group II for a period of 30 days.
(V) *Diabetic plus Glibenclamide Treated (D + Gli)*: In this group, diabetic rats were treated with the standard diabetic drug, Glibenclamide (600 µg/kg body weight), for the same period as in group IV. This group was maintained for better comparison of the nephro-protective effect of ginger against diabetic-induced complications.

Biochemical Assays

After completion of 30 days of treatment, all the animals were sacrificed by cervical dislocation and kidney tissues was excised at 4°C. The tissues were washed with ice-cold saline and were immediately immersed in liquid nitrogen and stored at -80°C for further biochemical analysis. Activities of selected cytosolic enzymes were assayed: glucose-6-phosphate dehydrogenase (G6PD) activity was assayed by the method of Lohr and Waller (15), and lactate dehydrogenase (LDH) activity was monitored by the method of Nachlas *et al*. (19) as modified by Prameelamma and Swami (22) with slight modifications. Mitochondrial enzymes including succinate dehydrogenase (SDH) and malate dehydrogenase (MDH) were also assayed by the modified version of Nachlas *et al*. (19). The activity of another important enzyme, glutamate dehydrogenase (GDH), was determined by the method of Lee and Lardy (14). All enzymatic assays in this study were performed using the crude homogenate of kidney.

Blood samples were collected from all the rats before sacrifice and blood glucose levels were estimated. Body weights before and after treatment and kidney weights immediately after sacrifice were recorded.

Histopathological Studies

The kidney tissue was washed with ice-cold saline immediately after isolation and then fixed in 10% formalin solution. Sections of 3 µm thickness were stained with hematoxylin and eosin (HE) for histopathological examination.

Statistical Analyses

The data were analyzed by using SPSS (Version 13.5; SPSS Inc., Chicago, IL, USA) and M.S. Office Excel Software for the significance of the main effects and along with their interactions. One way analysis of variance (ANOVA) was carried out with Dunnett's multiple comparison test and differences were considered significant at $P < 0.05$.

Table 2. Effect of oral administration of ginger on blood glucose in normal control and diabetic rats

Groups	Blood glucose (mg/dL)	
	Day 1	Day 30
Normal control (NC)	81 ± 1.41	94 ± 2.8
Ginger treated (Gt)	83 ± 1.47	88 ± 1.87
Diabetic control (DC)	253 ± 3.53*	269 ± 15.6*
Diabetic plus ginger treated (D + Gt)	259 ± 4.09*	138 ± 5.84*†
Diabetic plus Glibenclamide (D + Gli)	260 ± 1.79*	91 ± 3.71†

All the values are means ± SD of six individual observations. Values are significant compared to normal control (*$P <$ 0.01) and diabetic control (†$P < 0.01$).

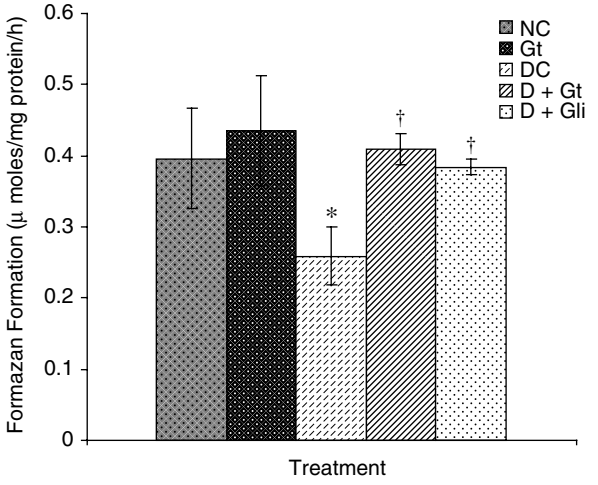

Fig. 1. Effect of oral administration of ginger (Gt) on glucose-6-phosphate dehydrogenase (G6PD) activity in normal and diabetic rats. Values are significant compared to normal control (NC, *$P < 0.01$) and diabetic control (DC, †$P <$ 0.01).

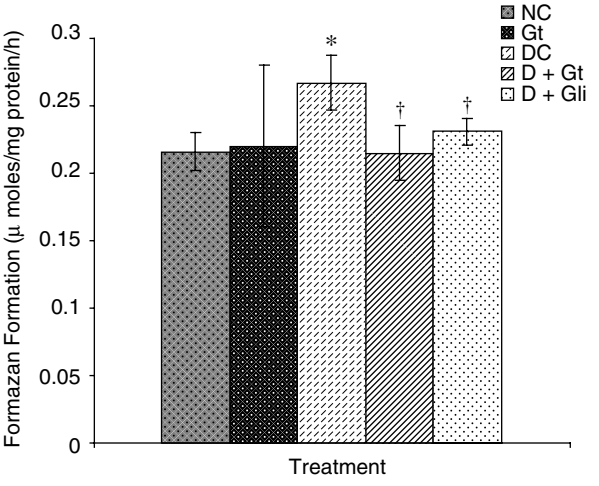

Fig. 2. Effect of oral administration of ginger (Gt) on lactate dehydrogenase (LDH) activity in normal and diabetic rats. Values are significant compared to normal control (NC, *$P < 0.01$) and diabetic control (DC, †$P <$ 0.01).

Results

Effects of Ginger Extract on Body Weight Changes and Blood Glucose Levels

Body weight was significantly ($P < 0.01$) decreased from day 1 to day 30 in the diabetic group compared to the normal control rats. The decreased body weight in diabetic rats were significantly regained on receiving ginger extract and also by glibenclamide treatment than that of diabetic untreated rats. No significant changes in kidney weights were observed in this study (Table 1). The blood glucose levels in STZ-injected diabetic rats were drastically increased from the baseline (Table 2). This increase of blood glucose was almost three-fold higher even after 30 days compared to the control rats. However, it was found that the elevated blood glucose levels in diabetic rats dropped significantly ($P < 0.01$) after 30-day ginger administration. Glibenclamide, which has been used as a standard diabetic drug to compare the beneficial effects of ginger extract, showed significant ($P < 0.01$) decrease in blood glucose levels and this was almost equal to the normal control rats.

Effects of Ginger Extract on Cytosolic and Mitochondrial Enzymes

Renal G6PD activity in diabetic rats was significantly ($P < 0.01$) decreased compared to the normal control rats. However, diabetic rats treated with ginger for a 30-day period resulted in marked increase in G6PD activity which was almost parallel with glibenclamide treatment (Fig. 1).

LDH activity was significantly ($P < 0.01$) increased in the diabetic controls compared to the normal control rats. Similar to the glibenclamide treatment, oral administration of ginger extract to the diabetic rats significantly decreased the LDH activity compared with that of the diabetic control rats. Nevertheless, no

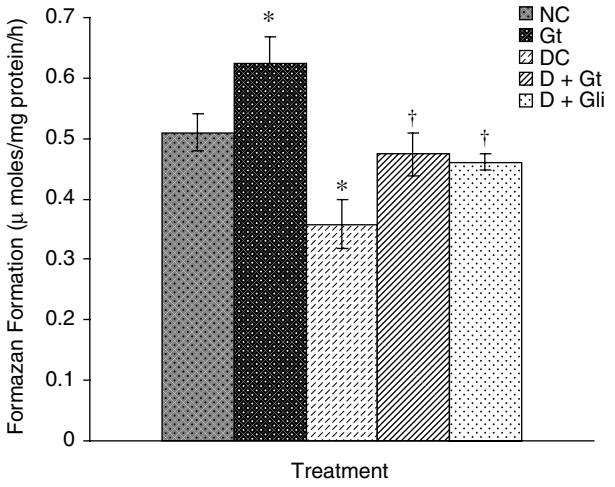

Fig. 3. Effect of oral administration of ginger (Gt) on succinate dehydrogenase (SDH) activity in normal and diabetic rats. Values are significant compared to normal control (NC, $^{*}P < 0.01$) and diabetic control (DC, $^{\dagger}P < 0.01$).

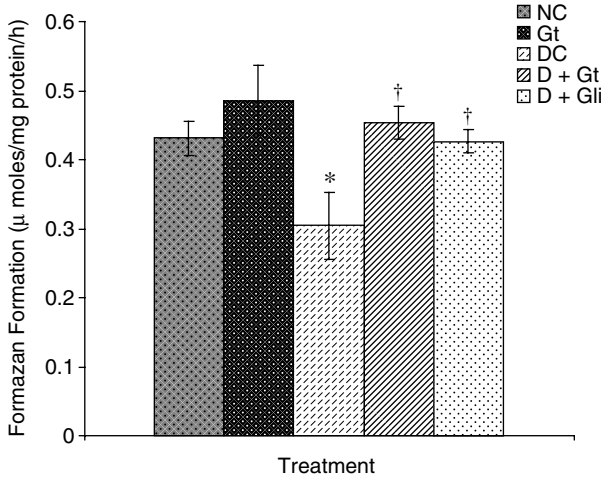

Fig. 4. Effect of oral administration of ginger (Gt) on malate dehydrogenase (MDH) activity in normal and diabetic rats. Values are significant compared to normal control (NC, $^{*}P < 0.01$) and diabetic control (DC, $^{\dagger}P < 0.01$).

difference in LDH activity was noticed with ginger alone treatment when compared to the normal control rats (Fig. 2).

The activity of the mitochondrial marker enzyme SDH was significantly ($P < 0.01$) decreased in the diabetic rats. In this study, we demonstrated that the decreased SDH activity in diabetic rats was ameliorated by ginger extract treatment. This increased SDH activity in ginger extract-treated diabetic rats was similar with that of glibenclamide-induced augmentation. We also found increased SDH activity with ginger alone treatment compared to the normal control group (Fig. 3).

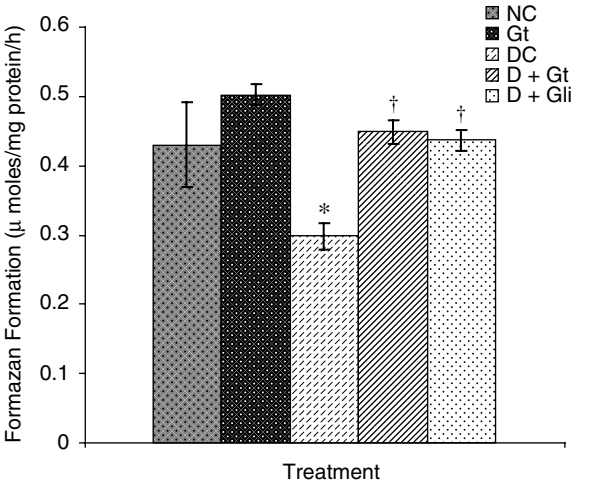

Fig. 5. Effect of oral administration of ginger (Gt) on glutamate dehydrogenase (GDH) activity in normal and diabetic rats. Values are significant compared to normal control (NC, $^{*}P < 0.01$) and diabetic control (DC, $^{\dagger}P < 0.01$).

Fig. 4 demonstrates that renal MDH activity in the diabetic rats was significantly ($P < 0.01$) decreased compared to the normal control rats whereas the activity of MDH was increased in ginger and glibenclamide supplemented diabetic groups compared to the diabetic control group. When compared, the ginger extract and glibenclamide treatments showed the same results regarding restoration of MDH and SDH activities against diabetes-induced depletion.

STZ injection resulted in a significant ($P < 0.01$) drop in the activity of GDH in the diabetic group as compared to the normal control rats. Interestingly, we found increased GDH activity by 30-day ginger treatment in diabetic rats compared with that of pathogenic diabetic control rats. Ginger extract mediated improvement in GDH activity was equal with that of glibenclamide-mediated improvement in diabetic treated rats (Fig. 5).

Effect of Ginger Extract on Histopathological Changes

Fig. 6 illustrates the pathological changes in the kidney of a diabetic rat including severe tubular degeneration, degeneration of glomeruli, focal necrosis of tubules, cystic dilatation of tubules and fatty infiltration. The above mentioned pathological symptoms were reduced in ginger-treated diabetic rats. The histological picture of ginger treated diabetic rats showed restoration of glomeruli, tubules and renal cells.

Discussion

Cytosolic and mitochondrial enzymes such as, G6PD, LDH, SDH, MDH and GDH plays a crucial role in maintenance of favorable physiological con-

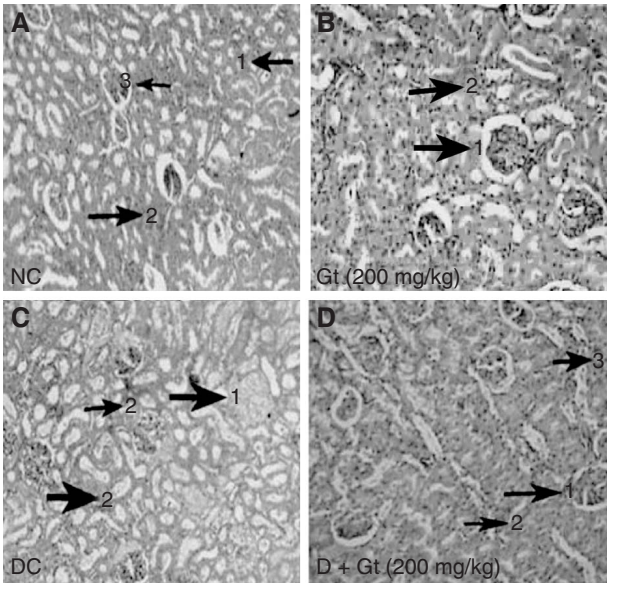

Fig. 6. Histopathological observations in the kidney of normal control (NC), ginger treated (Gt), diabetic control (DC) and combination of diabetic and ginger treated (D + Gt) rats. Arrows shows specific identification in each microphotograph. (A) Normal control (NC) rat kidney showing normal architecture with normal tubules (1) normal renal parenchyma (2) and normal glomeruli (3). (B) Ginger-treated (Gt) kidney showing normal glomeruli (1) and normal tubules (2). (C) Diabetic control (DC) kidney showing pathological signs like degenerated glomeruli (1), severe tubular degeneration and focal necrosis of tubules (2). (D) Diabetic plus ginger treated (D + Gt) rat's kidney showing restored glomeruli (1), tubules (2) and renal parenchyma (3).

ditions in the cell. Fluctuations in these enzyme activities during pathological conditions like diabetes leads to severe physiological malfunctions in the kidney (6). In this study, we found that the decreased G6PD, SDH, MDH and GDH activities in diabetic rats were significantly reversed to normal enzyme activity levels by 30 days of ginger oral administration. Here, for the first time we demonstrated improved activities of mitochondrial marker enzymes (SDH and MDH) from the diabetic-induced worsen conditions by ginger ethanolic extract supplementation. We also found that the architecture of damaged renal cells due to diabetic conditions recovered by ginger treatment in diabetic rats.

In the present study, elevated blood glucose levels in STZ-induced diabetic rats confirmed abnormalities of glucose levels which might be due to destruction of pancreatic β-cells by STZ (34). Our results clearly showed that ethanolic extract of ginger effectively lowered the blood glucose levels in diabetic rats. However, it should be noted that blood glucose levels in ginger-treated diabetic rats did not reach normal levels at the dose used in the present study. Higher dosages or longer periods of treatment might be required to bring about such levels. We speculate that hypoglycemic action of ginger may be due to an increase in pancreatic secretion of insulin from β-cells or release of bound insulin (2). Further experiments are required to investigate this regard. Predictable decrease in blood glucose levels by glibenclamide treatment indicates the efficiency of anti-diabetic properties of the drug. Decrease in body weight was found in STZ-injected group after 30 days. This was probably due to dehydration and excessive breakdown of tissue proteins, and protein wasting due to unavailability of carbohydrate as an energy source (12, 23). Weight loss during diabetes is also related to urinary glucose excretion because cells begin to use glucose. Ginger treatment of the diabetic rats produced increased body weight compared to untreated diabetic rats. This could be due to lowering of glucose levels, polyurea and ginger can also prevent osmotic degradation. The regained body weights were similarly noticed in glibenclamide-treated diabetic rats.

G6PD is extra-mitochondrial in location and is highly specific for NADP as an electron acceptor. In the present investigation, decreased G6PD activity was noticed in the kidney of diabetic rats. Similar to our findings, previous studies also demonstrated lower G6PD activity in diabetic tissues (24). Shibib *et al*. (26) reported that the hyperglycemia decreases HMP shunt enzyme activities in diabetic animals. The decreased activity of G6PD affects the concentration of NADPH in the cells, thus, increases oxidative stress leading to diabetic complications (31). In our study, increased G6PD activity with ginger supplementation to the diabetic rats may help to overcome diabetes-associated complications. Recovery of G6PD in ginger-treated diabetic rats may be due to its antioxidant property and/or through its pharmacological compounds like zingerone, gingerol and phytochemicals (7, 11).

The results of the present study showed that the kidney LDH activity was significantly higher in diabetic rats. Increased LDH activity in diabetic rats has been reported by Zappacosta *et al*. (36) and Ramachandran *et al*. (24). During diabetic condition, excessive accumulation of pyruvate may result in higher LDH activity. Excessive pyruvate is converted into lactate for which LDH is needed and, therefore, the activity of LDH may be increased due to less insulin availability in diabetes (9). Ginger supplementation to the diabetic rats resulted in decreased LDH activity. The confined LDH activity by ginger was parallel with the anti-diabetic drug glibenclamide treatment. Ginger compounds like 6-gingerols and oleoresins might inhibit LDH activity and decrease LDH activity

in ginger-treated diabetic rats. Ansari *et al.* (3) reported decreased LDH activity by ginger supplementation in isoproterenol (ISO)-treated rats.

SDH, a marker enzyme for mitochondria, is usually far greater in activity than the other enzymes in both developing and adult animals. In the present study, renal SDH activity was significantly decreased in the diabetic rats. Our findings are similar with the study of Pannerselvam and Govindaswamy (21) who reported decreased SDH activity in alloxan-induced diabetic rats. Decreased SDH activity in diabetic condition affects succinate-fumarate conversion, which indicates depressed oxidative metabolism in mitochondria. It has been suggested that the diabetogenicity of STZ is dependent on the inhibition of activity of citric acid cycle enzymes like SDH (6, 25). The interesting finding in this study is that the SDH activity was ameliorated by ginger treatment in diabetic rats. This might be due to the influence of some compounds like shagoals, zingeberone and phenols that are present in ginger. Increased SDH activity in ginger-treated diabetic rats indicates better utilization of energy yielding intermediates by the TCA cycle, thus, suggesting increased mitochondrial oxidative potential and energy synthesis, utilization of carbohydrates and fats as substrates. Yemitan and Izegbu (35) reported improved SDH activity against chemically induced stress condition with ginger pretreatment in rats.

MDH plays an important role in the TCA cycle as SDH. Remarkable decrease in renal MDH activity in diabetic rats indicates irregularity in the TCA cycle and ultimately affects other mitochondrial enzymes. Decreased MDH activity in diabetic rats was also reported by Pannerselvam and Govindaswamy (21). Decrease in MDH activity in diabetic rats suggests decreased utilization of malate. Reduced TCA cycle intermediates in diabetic condition may be responsible for the decrease in MDH activity. Diabetes conditions decrease expression of genes involved in carbohydrate and energy metabolism through effects on known pathways such as glycolysis, TCA cycle and oxidative phosphorylation (17). However, ginger treatment of diabetic rats showed increased MDH activity.

In this study, the activity of GDH significantly decreased in the kidney of diabetic rats suggesting that regulation of ammonia levels in the kidney is affected in the diabetic condition. Telushkin *et al.* (30) reported the decreased GDH activity in the brain of diabetic rats. The decrease in GDH activity may be due to disturbances in energy metabolism, impairment of glutamate and activation of lipid peroxidation in the kidney (29). However, diabetic rats treated with ginger for 30 days exhibited increased GDH activity. The increased activity might be due to synchronization of energy metabolism and elevation of glutamate in the cells by ginger administration. The restored activities of mitochondrial enzymes and GDH by ginger treatment confirmed the protective role of ginger against diabetes complications since ginger administration showed similar upturn with standard anti-diabetic drug glibenclamide.

The histopathological studies of the kidney in this investigation provided additional evidence that damaged renal cells recovered with ginger treatment. The photographs revealed severe degeneration of tubular and glomeruli, focal necrosis of tubules, cystic dilatation of tubules and fatty infiltration in diabetic control rats. These pathological conditions might be associated with increased diuresis and renal hypertrophy in the diabetic rats. Here, we demonstrated that injury to cells in the diabetic rats recovered by a 30-day ginger treatment. In a recent study, Uz *et al*., (32) demonstrated reduced histological features in the kidney of ischemia/reperfusion rats by dietary ginger supplementation. In our study, nephroprotective effects of ginger ethanolic extract were observed in the images that glomeruli appeared to be restored, tubules appeared to be regenerated and less fatty infiltration was found.

From these findings it is concluded that extract of ginger from *Zingiber officinale* rhizome could be effective like the anti-diabetic drug glibenclamide in preventing the diabetic-induced disturbances in renal cytosolic and mitochondrial enzymes. This was shown by improved activities of metabolic enzymes and recovered renal cells from injuries by ginger treatment in the diabetic rats. These results could further suggest that possible use of ginger as a nutraceutical supplement to cope with diabetic-induced detrimental effects and to protect renal cells from damages.

Acknowledgments

This study was supported by the University Grants Commission (UGC), New Delhi, F. No. 36-225/2008 (SR).

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