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Regulation of hepatic and mucosal 6-phosphofructo-1-kinase activity by trigonella foenum-graecum linn (fenugreek) seeds of streptozotocin-induced diabetic rats

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Abstract

Background: Trigonella foenum-graecum Linn. (fenugreek) can ameliorate hyperglycemia and dyslipidemia, however, the detailed mechanism is unclear. The present study aims to investigate the effect of fenugreek seeds water extract (FSE) on 6-phosphofructo-1-kinase (PFK-1) activity, a key enzyme of glycolysis, in the liver and small intestine of streptozotocin induced diabetic rats and its impact on plasma glucose and lipid concentrations.

Methods: 50 male Wistar rats were used in this study. The rats were divided into five groups with 10 rats in each group: normal control rats (Group1), streptozotocin-induced diabetic rats (Group2), streptozotocin-induced diabetic rats + Fenugreek seeds (0.5g/500 ml water) (Group3), streptozotocin-induced diabetic rats + Fenugreek seeds (1.0g/500 ml water) (Group4), streptozotocin-induced diabetic rats + insulin (Group5). Blood samples were then collected after the period of treatment for the analysis of glucose, total cholesterol, triacylglycerol and insulin concentration. PFK-1 for liver and intestinal mucosa was extracted and assayed.

Results: Diabetic rats showed significantly lower liver and intestinal mucosa PFK-1 activities (both at $P<0.05$) compared with control rats. Diabetic rats treated with FSE (1.0g / 500 ml water) showed a significant ($P<0.0001$) increase in the PFK-1 activity of liver and intestinal mucosa by 54% and 75% respectively. The plasma glucose concentrations of diabetic rats treated with 0.5g and 1.0g fenugreek / 500 ml water were significantly ($P<0.001$) decreased by 32% and 43%. In addition the concentrations of plasma total cholesterol and triacylglycerol were significantly (both at $P<0.0001$) decreased by 57% and 42%, respectively in rats treated with 1.0g fenugreek / 500 ml water, compared with non-treated diabetic rats.

Conclusions: These results may suggest that the in-vivo hypoglycaemic effect of FSE is mediated, at least in part, by the activation of PFK-1 in intestinal and liver cells.

Keywords: Diabetes, fenugreek seeds, glucose, lipids, PFK-1

Background

Diabetes mellitus (DM) is a progressive metabolic disorder affecting millions worldwide [1,2]. Individuals with this disease require medications to control their blood glucose. It is emerging as a global epidemic that imposes a tremendous burden on health economies mainly because of its devastating complications [3]. Systemic complications are the major cause of morbidity and mortality in patients with diabetes. These complications are divided into two groups, macrovascular and microvascular complications [4-6].

Although there are many classes of antidiabetic compounds are widely used with a good deal of success, these various medications do not address the needs of all diabetic patients, not to mention their adverse effects [7]. Phytotherapy or herbal medicine approaches have demonstrated many advantages in developing countries [8,9]. There are around 400 experimentally proven medicinal plants having antidiabetic properties but the complete mechanism of action is available only for about 100 plants. There are several medicinal plants whose extract modulate glycolysis, Krebs cycle, gluconeogenesis, HMP shunt pathway, glycogen synthesis and their degradation, cholesterol synthesis, metabolism and absorption of carbohydrates, and synthesis and release of insulin [8].

Among herbs reported to possess anti-diabetic properties, Trigonella foenum graecum (fenugreek). Fenugreek is widely used as a supplementary treatment for diabetes [10,11]. It causes dose-dependent reduction in blood glucose in normal and diabetic rats [12]. Human studies have shown that fenugreek causes reduction in blood glucose in type-1 and type diabetes-2 [10,13]. Preliminary reports suggested possible hypoglycemic effect of fenugreek seeds are related to high fiber content, high viscosity, inhibition of intestinal glycosidase activity [14], inhibition of glucagon release, increase in sensitivity to insulin [15], increase glucose-induced insulin secretion [16,17], potentiating insulin action [18], and inhibiting intestinal carbohydrate digestion and absorption [11]. Although, the anti-hyperglycemic effect of fenugreek has been shown in animal and human studies, the reports published so far on the hypoglycemic effect of fenugreek could not establish a direct relationship with glucose metabolism in diabetes mellitus.

6-Phosphofructo-1-Kinase (PFK-1, EC.2.7.1.11) is a multi-subunit allosteric enzyme that has important consequences

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for several different aspects of cell metabolism as well as for systemic metabolic conditions such as diabetes. PFK-1 catalyzes the first reaction that commits glucose to the glycolytic pathway. In addition, the rate of th-e reaction catalyzed by PFK-1 is important in the regulation of the glycolytic flux [19,20]. On the other hand, diabetes has a complex and variable effect on PFK-1 activity depending on the organ examined. Hence, reduced PFK-1 activity was reported in the enterocytes [21], adipocytes [22], liver [23], heart atria [24], intestinal mucosa and placenta [25].

Therefore, this *in vivo* study was aimed to explain the mecha-nism of the anti-hyperglycemic effect of fenugreek by modulation of PFK-1, as a key enzyme in glycolysis, in the liver and small intestine of streptozotocin-induced diabetic rats.

Materials and Methods

Chemicals

All chemicals were of the analytical reagent grade and were obtained from BDH chemicals, Poole, Dorset, U.K. Streptozotocin (N-(Methylnitrosocarbamoyl)-α-D-glucosamine) was purchased from Sigma Chemical Co., Poole, Dorest, U.K., and used without further purification. Sagatal for anaesthetizing rats was obtained from May and Baker Ltd., Dagenham, England. The kits for glucose, total cholesterol and triacylglycerol determinations were obtained from Biosystem reagents and instruments, Costa Brava, Barcelona, Spain. The ELISA kit for the insulin measurements was purchased from DPG Instruments Gmbh, Germany. Mixtard insulin (Novo Nordisk A/S 2880 Bagsvaerd, Denmark) was purchased from local pharmacy without preparation.

Preparation of fenugreek seeds extract (FSE)

Fenugreek seed water extract was prepared as previously reported by Kassaian *et al.*, [13]. Fenugreek seeds were purchased from the local market, cleaned and dried. 0.5g and 1.0g of Fenugreek seeds left in 500ml water for 8 days. The water was transferred to the drinking bottle of rats.

Animals

50 Male Wistar rats (180-200g) used in this work were housed individually in an environment in which the temperature was maintained at a constant temperature 24 ± 1°C, with lighting for 12 hours each day. Rats were fed ad libitum on standard laboratory chow with free access to water. All procedures conformed to institutional standards of animal care and use. Animals were divided into five groups with 10 rats in each group as follow:

1. Normal control rats (Group 1).
2. Streptozotocin-induced diabetic rats (Group 2).
3. Streptozotocin-induced diabetic rats + Fenugreek seeds (0.5g/500 ml water) (Group 3).
4. Streptozotocin-induced diabetic rats + Fenugreek seeds (1.0g/500 ml water) (Group 4).
5. Streptozotocin-induced rats + insulin (Group 5).

Induction of Diabetes

Male wistar rats (groups 2-5) received a single i.p. injection of streptozotocin (65 mg/kg body weight) dissolved in citrate buffer, pH 4.5 immediately before use. Rats with serum glucose levels > 300 mg/dl, 48 hr after administration of streptozotocin were included in the study. The weight, food intake and blood glucose concentration of all groups were recorded.

Animals treatment with insulin or fenugreek

Insulin was purchased from the local pharmacy without purification. The effects of diabetes were reserved with 4 intramuscular injections of insulin (0.2ml/kg body weight). Insulin treatment in group 5 was started after 10 days of diabetes induction.

Fenugreek treatment in groups 3 and 4 was started 10 days after the induction of diabetes. The period of treatment was 30 days. The total experimental period was 40 days.

Collection of blood samples

Blood samples were collected retro-orbitally from the inner canthus of the eye under light sagatal anesthesia using capillary tubes, then plasma was separated by centrifugation at 3000 x g for 20 minutes and stored at -20°C until assayed for glucose, cholesterol, triacylglycerol and insulin concentration.

Preparation of tissue extracts

Rats were anaesthetized with 35 mg pentobarbitone sodium (Sagatal: May & Baker Ltd, Dagenham)/kg body weight given intraperitoneally and fresh tissues (liver and intestinal mucosa) were removed and immediately frozen in liquid nitrogen until use. Tissues were then homogenized with Tris-chloride extraction buffer pH 8.0 (50mM Tris-HCl, 30mM KF, 5mM β-mercaptoethanol, 1mM EDTA, 100mM $(NH_4)_2SO_4$, 1mM PMSF dissolve in 1ml ethanol and 1mg/10ml trypsin inhibitor) and then the homogenates were centrifuged at 70000 x g for 20 minutes at 4°C. The supernatants were used for the assays of PFK-1.

Enzyme assays

The activity of PFK-1 under optimal conditions at pH 8.0 was assayed as described previously [26]. The regulatory properties at pH 7.0 were determined as described by Hussey *et al.*, [27].

Results

Effect of FSE on PFK-1 activity

The food intake of streptozotocin-induced diabetic rats was significantly decreased ($P<0.0001$) on the first two days after the injection of streptozotocin and it had returned back to normal by the third day. Therefore, plasma glucose concentrations and PFK-1 activity were measured 30 days after induction of diabetes (unpublished results).

Figure 1A shows the fructose-6-phosphate (F-6-P) saturation curve of liver PFK-1 measured under suboptimal conditions in the presence of 2.5mM ATP at pH 7.0. It appears that in diabetic

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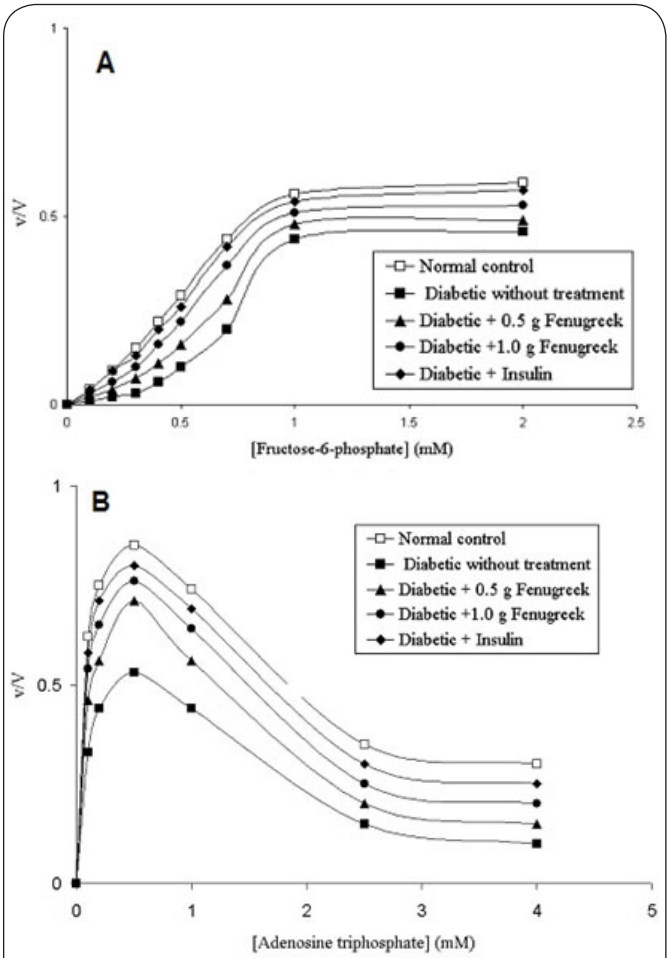

Figure 1. Effect of Fenugreek seeds on the regulatory properties of PFK-1 of rat liver. (A) Dependence of PFK-1 activity on fructose 6-phosphate concentration in the presence of 2.5mM ATP at pH 7.0. (B) Dependence of PFK-1 activity on ATP concentration in the presence of 0.5mM fructose 6- phosphate. Significant differences between control and all other group were made by ANOVA ($P < 0.0001$).

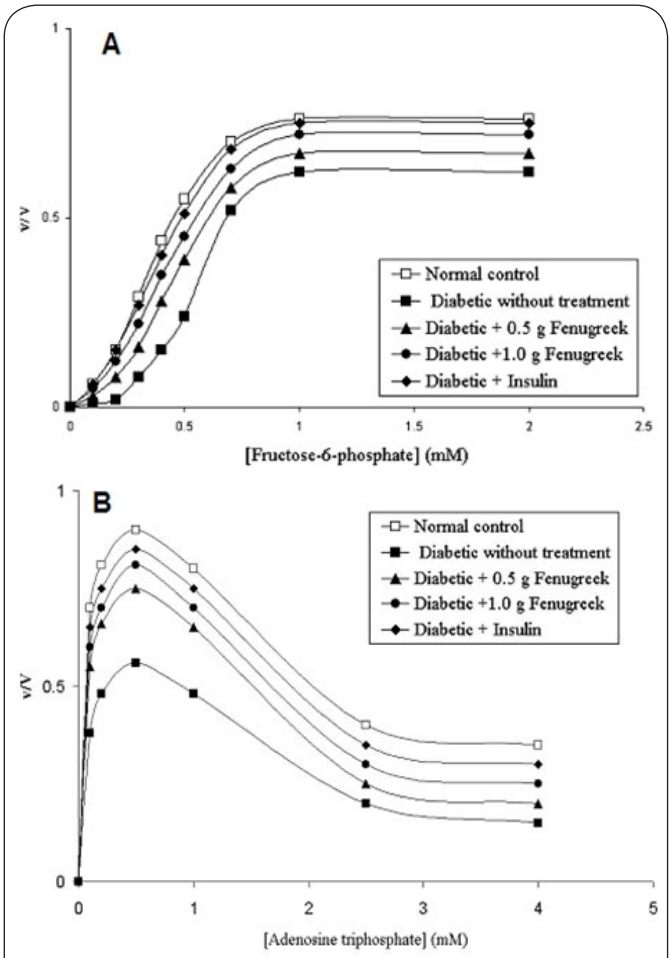

Figure 2. Effect of Fenugreek seeds on the regulatory properties of PFK-1 of rat intestinal mucosa. (A) Dependence of PFK-1 activity on fructose 6-phosphate concentration in the presence of 2.5mM ATP at pH 7.0. (B) Dependence of PFK-1 activity on ATP concentration in the presence of 0.5mM fructose 6-phosphate. Significant differences between control and all other groups were made by ANOVA ($P < 0.0001$).

rats without treatment the curve is displaced to higher F-6-P concentration. The apparent K_m value of the enzyme in the diabetic rats was 0.7 mM compared with 0.5 mM in normal control rats. The Fenugreek-treated rats showed a decrease in K_m value of the enzyme compared with diabetic rats but this K_m value was still higher than that in normal rats. This increase in Km is a reflection of an increased susceptibility to inhibition by ATP (**Figure 1B**).

Figure 2A shows the F-6-P saturation curve of intestinal mucosa PFK-1 measured under suboptimal conditions in the presence of 2.5mM ATP at pH 7.0. The enzyme showed a sigmoidal velocity curve in all groups; however the sigmoidicity in F-6-P saturation curve was higher in diabetic rats without treatment. The apparent K_m value of the enzyme in the diabetic rats was 0.5 mM compared with 0.35 mM in normal control rats. The Fenugreek-treated rats showed a decrease in K_m value of the enzyme compared with diabetic rats but this K_m value was still higher than that in normal rats. The ATP inhibition curve at 0.5mM F-6-P of PFK-1 from rat intestinal mucosa is presented in a (**Figure 2B**). The enzyme of the diabetic rats was more susceptible to inhibition by ATP. This increase in susceptibility to ATP inhibition is reflected in an increase in K_m for F-6-P. The administration of insulin reversed the effects of streptozotocin induced diabetes on the regulatory properties and on the total activities of liver and intestinal mucosal PFK-1 (**Figure 3**).

Effect of FSE on blood glucose concentration

Table 1 shows the anti-hyperglycemic effect of Fenugreek on the blood glucose levels of diabetic rats. Control rats did not show any significant variation in the blood throughout the experimental period. Administration of streptozotocin (STZ)

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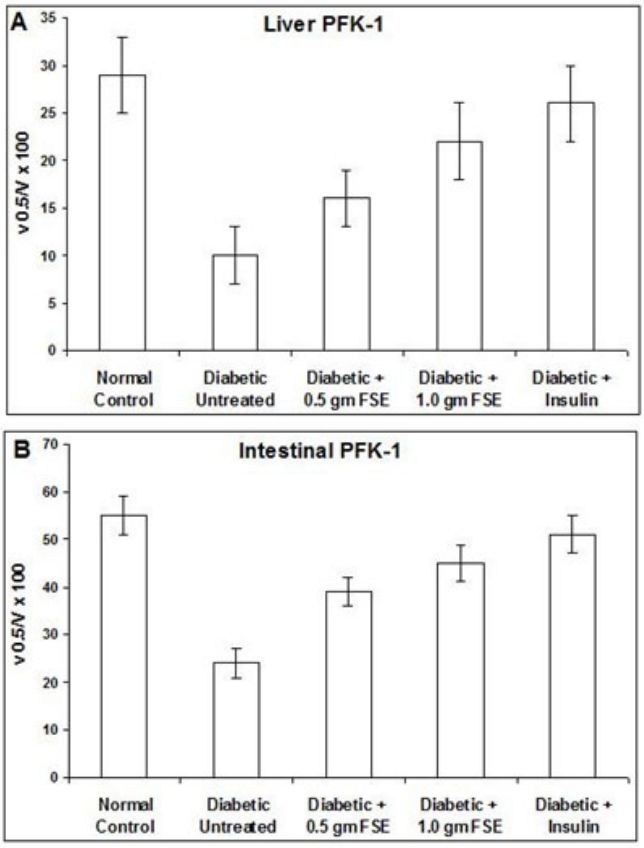

Figure 3. PFK-1 activity in intestinal mucosa and liver in the different studied groups.
v0.5= velocity of PFK-1 at 0.5mM F6P and 2.5 mM ATP at pH 7.0, V= Maximum activity of PFK-1 at pH 8.0

Table 1. The effect of fenugreek seeds administration (30 days) on glucose level (mg/dl) in STZ (65/kg) diabetic rats.

Category	0 day (n)	10th day (n)	25th day (n)	40th day (n)
Normal control (Group 1)	76.40 ± 1.74	78.20 ± 2.22	82.20 ± 0.80	83.57 ± 1.77
Diabetic without treatment (Group 2)	76.60 ± 0.81	331.40 ± 1.02*	326.20 ± 1.85	328.84 ± 5.04
Diabetic + 0.5g fenugreek (Group 3)	78.10 ± 1.76	325.40 ± 7.03*	293.40 ± 1.42*	220.66 ± 1.49*
Diabetic + 1.0g fenugreek (Group 4)	78.50 ± 1.72	330.70 ± 3.73*	270.10 ± 0.91*	189.23 ± 0.70*

Results are presented as mean ± SEM. Significant differences between control and all other groups were made by ANOVA (*P < 0.0001), where (n) is the number of rats.

(65mg/kg) led to a significant elevation of more than 4-fold in blood glucose levels (P<0.0001) in all 4 groups (*i.e.*, Group 2-5) compared to control group (Group 1), which was maintained over a period of 5 weeks. A daily treatment with 0.5g Fenugreek seeds per 500 ml water (Group 3), started 10 days after the induction of diabetes, led to a significant decrease in plasma glucose concentration by 10% on 25th day and 32% on 40th day of the experiment, respectively (P<0.0001), compared to diabetic rats without treatments (group 2). Whereas treatment with 1.0g Fenugreek seeds/ 500 ml water (Group 4) led to decrease in blood sugar levels by 18% and 43% on 25th day and 40th day of the experiment, respectively (P<0.0001), compared to group 2.

Table 2. The plasma concentrations of total cholesterol, triacylglycerol and insulin.

Category	Total cholesterol mg/dl	Triacylglycerol mg/dl	Insulin mg/dl
Normal control (Group 1)	108.56 ± 7.07	126.50 ± 9.65	59.36 ± 1.06
Diabetic without treatment (Group 2)	162.85 ± 5.76*	284.77 ± 7.47	18.78 ± 1.29
Diabetic + 0.5g fenugreek (Group 3)	115.53 ± 2.22*	207.74 ± 5.59*	45.41 ± 1.17*
Diabetic + 1.0g fenugreek (Group 4)	69.64 ± 4.22*	166.31 ± 5.14*	50.54 ± 1.81*
Diabetic + insulin (Group 5)	95.08 ± 6.70*	145.31 ± 11.70*	108.38 ± 3.15*

Results are presented as mean ± SEM. Significant differences between control and all other groups were made by ANOVA (*P < 0.0001), where (n) is the number of rats.

Effect of FSE on blood lipids

Table 2 shows the plasma concentrations of total cholesterol, triacylglycerol and insulin. The plasma concentrations of total cholesterol and triacylglycerol increased significantly to 50% and 125%, respectively in diabetic rats without treatment group (Group 2) as compared with normal control group (Group 1). Fenugreek-treated rats with 0.5g (Group 3) and 1.0g (Group 4) FSE showed a significant decrease by 29% and 57%, respectively (P<0.0001) in plasma total cholesterol concentration and by about 27% and 42%, respectively (P<0.0001) in plasma triacylglycerol concentration as compared with diabetic rats without treatment group (Group2). The plasma concentrations of glucose, total cholesterol and triacylglycerol return to the normal in insulin-treated rats.

On other hand all the 3 groups (Group 3-5), showed a significant increase (P<0.0001) in plasma insulin concentration as compared with diabetic rats without treatment group (Group2).

Discussion

This study attempted to elucidate the hypoglycemic mode of action of fenugreek through investigating the regulatory properties of the rate-limiting enzyme of glycolytic pathway, PFK-1 in the liver and small intestine of streptozotocin-induced diabetic rats.

Diabetic rats showed a significant reduction in the maximum activities of liver and mucosa PFK-1 by 44% and 50% respectively, in comparison to the normal control rats. These reductions in PFK-1 activity were measured 30 days after the induction of diabetes since the daily food intakes of

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the diabetic animals were found to be significantly reduced in the first two days but returned to normal by the third day. Therefore, semi-starvation, which is known to be associated with the induction of diabetes [28], cannot be responsible for the changes in the properties of PFK-1 reported here.

The PFK-1 reduced activity in diabetic rats was reversed by supplying the animals with fenugreek seed water extract. An increase in the maximum activities of liver and mucosa PFK-1 in the 1.0g fenugreek treated rats (54% and 75% increase, respectively) implies that cellular entry of glucose was facilitated by fenugreek, which in turn stimulated the activity of PFK-1. This glucose influx could either be due to an insulin releasing or direct insulinomimetic effect of fenugreek. Since streptozotocin-induced diabetes is an insulin deficient model, the probability of insulinomimetic effect seems more probable, which is in agreement with the report by Vats *et al*., [29]. Such a possibility is also supported by our finding that the maximum activities of rat liver and mucosa PFK-1 were increased by 64% and 91%, respectively.

The enhancement in PFK-1 activity in liver and intestinal mucosa denotes that stimulation of glucose uptake and disposal by glycolysis could be occurred. In this regard, we found that oral administration of fenugreek seeds water (0.5g and 1.0g fenugreek seeds/ 500ml water) have significantly decreased plasma glucose concentrations by 18% and 43% respectively ($P < 0.0001$).

Although glucose receptor/transporter was not estimated in the present study, the increased glycolysis must be met by increasing glucose supply that is primarily mediated by two members of the facilitative glucose transporter family [30]. Therefore, there is a possibility that fenugreek seed extract may bring about some of its effects through increasing the expression of glucose transporter especially GLUT4 as previously reported [31].

Regarding the plasma lipids, the present results show a significant decrease in plasma total cholesterol (29% and 57% decrease, respectively), confirming the hypocholesterolemic effects of fenugreek seeds or extracts. This result is in agreement with previously reported data [32,33]. Moreover, the present results show a significant decrease in plasma triacylglycerol concentration (27% and 42% decrease, respectively), which is in agreement with previous reports [34,35] .

Conclusions

Collectively, our study indicates that fenugreek seed water extract exert overall improvement in the carbohydrate metabolism and total lipid content of tissues. In conclusion, the current work provides a novel mechanism for the antidiabetic/ insulin mimetic effects of fenugreek seeds, through enhancing glycolysis by activation of its rate limiting enzyme and primary site of regulation, PFK-1.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

NMA conducted lab work, analysis and drafted the manuscript under the direction of SMK. MAZ assisted with analysis and writing of the manuscript. SMK conceptualised the study and assisted with analysis and writing of the manuscript.

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