

Original Research Article

Correlation of Metabolic and Morphological Effects of *Trigonella Foenum Graecum* (Fenugreek) in Liver and Skeletal Muscles of Alloxan Induced Diabetic Rats

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ABSTRACT

Background: Diabetes mellitus is going to be a major cause of mortality and morbidity in near future. Control of diabetes includes changes in lifestyle and diet along with administration of antidiabetic drugs. Many antidiabetic drugs may show side-effects or resistance for appropriate action. A suitable dietary ingredient may avoid these unwanted effects. *Trigonella foenum graecum* (Fenugreek) seems to be one of the most effective food ingredients having this anti-diabetic activity.

Objectives: of the study were to study various important metabolic effects of Fenugreek including its antidiabetic effect in non-diabetic as well as in diabetic rats.

Materials and Methods: This research included two study groups with Fenugreek administration, e.g., diabetic and non-diabetic groups; and two corresponding control groups. Serial blood glucose levels along with serum cholesterol, triglyceride, albumin and total protein levels were estimated at the end of study period. H & E, PAS stained sections and electron microscopic studies were carried out in pancreas, liver and skeletal muscles in all four study groups.

Results: Study showed statistically significant control of blood glucose and cholesterol levels in both the study groups as compared to control groups. Serum albumin levels also showed significant improvement in study group. These biochemical findings were well supported by microscopic and ultrastructural findings.

Conclusion: *Trigonella foenum graecum* (Fenugreek) reveals significant anti-diabetic effect and anti-cholesterol effect through its insulin-like action on insulin receptors in hepatocytes and skeletal muscles. Longer duration of study may reveal few more metabolic effects, possible side-effects and even long term effectiveness of its anti-diabetic action.

Key words: *Trigonella foenum graecum* (Fenugreek), Diabetes mellitus, Alloxan, Islet cells, Insulin receptors.

INTRODUCTION

Diabetes mellitus is one of the major health concerns all over the world. It is one of the commonest predisposing causes of morbidity and mortality associated with its complications. Most of these complications involve various important organs and structures like blood vessels, kidney, eyes,

nervous system and cardiovascular system. However, the predisposition to all these complications is directly proportionate to the degree and the chronicity of hyperglycemia.

The blood glucose levels are controlled with the balancing effects of hormones like insulin (hypoglycemic

effect), glucagon and other hormones from various endocrine tissues (hyperglycaemic effect). Amongst these hormones, insulin, which is secreted from β cells of islets of Langerhan of endocrine pancreas, plays the most important role in the pathogenesis of diabetes mellitus. While the deficit of this hormone is the pathogenesis of type I DM (IDDM), insulin resistance plays the key role in type II DM (NIDDM).

The major tissues in the insulin mediated glucose control in the body are liver and skeletal muscles. These tissues are the primary sites of storage of extra glucose in the form of glycogen (glycogenesis) as well as for conversion of glycogen to glucose when the body requires it (glycogenolysis). Liver is also the site of gluconeogenesis from other sources like lipids and proteins. Hence the major metabolic and pathogenic changes are expected to occur in these tissues, i.e., liver, skeletal muscles and pancreas.

There are a large number of synthetic drugs for the diabetes Type II ⁽¹⁾ which include:

- A. Sulfonylureas, which stimulate pancreas to secrete more insulin, thus helps in lowering blood glucose.
- B. Biguanides, which lower the glucose by reducing gluconeogenesis in liver.
- C. Alpha-Glucosidase Inhibitors - work by slowing down the digestion of foods high in Carbohydrate, such as rice, potatoes, bread, milk, and fruit.
- D. Thiazolidinediones potentiate action of insulin.
- E. Meglitinides stimulate more insulin secretion.
- F. D-phenylalanine Derivatives stimulate pancreas to make more insulin quickly for a short period of time immediately after meals.
- G. DPP-IV Inhibitors lower blood glucose by secretion of more insulin when it is needed, especially after meals. It also helps liver to store more glucose by gluconeogenesis.

In contrast to the synthetic drugs, there are natural herbs or products which may show

hypoglycemic effects but with minimal side effects or possibly without any side effects. The following are some of natural herbs which were studied experimentally:

- A. Fenugreek Seeds, ⁽²⁾ leaves ⁽³⁾ and oil. ⁽⁴⁾
- B. Cherries ⁽⁵⁾
- C. Other: Dried leaves of agrimony (*Agrimonia eupatoria*), alfalfa (*Medicago sativa*), blackberry (*Rubus fruticosus*), celandine (*Chelidonium majus*), eucalyptus (*Eucalyptus globulus*), Lady's mantle (*Alchemilla vulgaris*), lily of the valley (*Convallaria majalis*); seeds of coriander (*Coriandrum sativum*); dried berries of juniper (*Juniperus communis*); bulbs of garlic (*Allium sativum*) and roots of liquorice (*Glycyrrhiza glabra*). ⁽⁶⁾
Abrus precatorius L. (Fabaceae),
Wattakaka volubilis (Asclepiadaceae),
Solanum viarum, Flax seeds and date palm leaves ⁽⁷⁾

Trigonella foenum graecum (Fenugreek) has been used routinely as Ayurvedic and Chinese medicine for numerous indications, including labor induction, aiding digestion, and as a general tonic to improve metabolism and health. Some preliminary animal and human trials suggest possible hypoglycemic and antihyperlipidemic effects of oral administration. ⁽⁸⁾

This study was aimed to find the metabolic effects along with morphological changes in pancreas, liver and skeletal muscles of Alloxan induced diabetic rats in comparison to non diabetic rats. The metabolic parameters determined were blood glucose, serum triglyceride, serum cholesterol, serum albumin and total proteins levels. The morphological changes in the tissues were studied by routine paraffin processed and Haematoxylin & eosin (H/E) stained sections in light microscopy, Periodic Acid Schiff reaction with diastase (PAS-D) for glycogen, and ultrastructural changes by Electron microscopy. All these findings were integrated together to understand the mechanisms of possible protective effects of

Trigonella foenum graecum in controlling the blood glucose levels.

MATERIALS AND METHODS

Project design: This research project was an experimental module with comparative study of specifically defined animal groups to derive the role and utility of *Trigonella foenum graecum* in the treatment of Diabetes mellitus.

In this study 20 Male Wistar rats, with body weight of 150-200 grams were divided into 4 groups as follows:

Group 1	Rats without induced Diabetes and without Trigonella foenum graecum supplement	Normal Control
Group 2	Rats without induced Diabetes but with Trigonella foenum graecum supplement	Study group-Normal
Group 3	Rats with induced Diabetes but without Trigonella foenum graecum supplement	Diabetic control
Group 4	Rats with induced Diabetes and with Trigonella foenum graecum supplement	Study group-Diabetic

Diabetes was induced in rats of Group 3 and 4 by intra peritoneal injection of 120 mg/kg Alloxan after fasting of 36 hours. (9,10) *Trigonella foenum graecum* (Fenugreek) supplement (8) was started in rats of study groups (2 and 4), after confirmation of induction of diabetes in the Alloxan treated rats. The duration of the *Trigonella foenum graecum* supplement was 30 days with daily dose of supplement.

All the rats were sacrificed at the end of 30 days and the blood sample were collected after cardiac puncture in Plain bulb. Serum was separated after complete clotting of the blood. Serum samples were analysed for Lipids (Cholesterol and Triglycerides), total proteins and serum albumin levels by spectrophotometric method.

Sacrificed rats were dissected to sample out following tissues:

- Pancreas (Tail part) ,
- Skeletal muscle (thigh region), and
- Liver (Right lobe)

These tissues were fixed in:

- 10 % buffered Formalin (for Paraffin processing and light microscopic morphology study by Haematoxylin and eosin - H/E stain);
- 2 % Glutaraldehyde (for Electron microscopy); and
- Carnoy's solution (for PAS-D special stain for demonstration of Glycogen)

Statistical analysis of all the biochemical variables was carried out in different groups by paired sample T test using SPSS version 16. These findings were utilized to understand various hypothesis of mechanism of actions of *Trigonella foenum graecum* in diabetic and non-diabetic groups in comparison to the corresponding controls.

Objectives of the study included:

1. Assessment of metabolic effects of *Trigonella foenum graecum* on carbohydrate, lipid and protein metabolisms in diabetic and non-diabetic rats.
2. Determination of histological and ultrastructural changes in pancreas, liver and skeletal muscles of all study groups and interpret the effects of *Trigonella foenum graecum* in diabetes.
3. Estimation and comparison of various changes of in four groups and correlate between biochemical and microscopic changes.
4. To find out the most statistically significant changes in the study group in comparison to the control groups.
5. To find out the possible mechanisms of actions of *Trigonella foenum graecum* (Fenugreek) in the treatment of DM.

RESULTS AND STATISTICAL ANALYSIS

During the period of 30 days after development of Alloxan induced diabetes in group 3 and group 4, weekly estimations of blood glucose levels were done with glucometer. The average blood glucose levels in the four groups were as follows: (Table-1)

Table-1: Average blood glucose levels in four groups at the end of each week

Group	Week 0	Week 1	Week 2	Week 3	Week 4
Group 1 (Normal controls)	125.5	122	124	121.5	121.25
Group 2 (Normal with Fenugreek)	108	110	115.5	116	115.75
Group 3 (Diabetic controls)	418.75	569	609.75	637	678.5
Group 4 (Diabetic with Fenugreek)	492.75	380.5	302.75	248	231

Table-2: Paired T - test results for blood sugar level comparison amongst four groups

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Group 1 Non-Diabetic Non Fenugreek - Group 2 Non-Diabetic Fenugreek	-9.80	9.32	2.08	-14.16	-5.44	-4.70	19	.000154
Pair 2	Group 3 Diabetic Non-Fenugreek - Group 4 Diabetic Fenugreek	251.60	211.69	47.33	152.52	350.67	5.32	19	.000039

Table-3: Paired T - test results for serum cholesterol level comparison amongst four groups

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Group 1 Non-Diabetic Non Fenugreek - Group 2 Non-Diabetic Fenugreek	-.40	0.16	0.08	-0.66	-0.14	-4.90	3	.016
Pair 2	Group 3 Diabetic Non-Fenugreek - Group 4 Diabetic Fenugreek	1.48	0.096	0.05	1.32	1.63	30.81	3	.000075

Table-4: Paired T - test results for serum Triglyceride level comparison amongst four groups

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Group 1 Non-Diabetic Non Fenugreek - Group 2 Non-Diabetic Fenugreek	-.138	0.17	0.09	-0.41	0.13	-1.63	3	0.202
Pair 2	Group 3 Diabetic Non-Fenugreek - Group 4 Diabetic Fenugreek	-0.01	0.03	0.014	-0.06	0.04	-0.71	3	0.530

Table-5: Paired T - test results for serum Total protein level comparison amongst four groups

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Group 1 Non-Diabetic Non Fenugreek - Group 2 Non-Diabetic Fenugreek	2.88	5.51	2.75	-5.89	11.64	1.04	3	0.373
Pair 2	Group 3 Diabetic Non-Fenugreek - Group 4 Diabetic Fenugreek	-0.50	5.81	2.91	-9.75	8.75	-1.72	3	0.874

Table-6: Paired T - test results for serum Albumin level comparison amongst four groups

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Group 1 Non-Diabetic Non Fenugreek - Group 2 Non-Diabetic Fenugreek	-7.95	4.26	2.13	-14.72	-1.17	-3.73	3	0.034
Pair 2	Group 3 Diabetic Non-Fenugreek - Group 4 Diabetic Fenugreek	-10.99	2.90	1.45	-15.60	-6.37	-7.58	3	0.005

When evaluated by paired sample T test using SPSS version 16, these values showed statistically significant reduction in the blood sugar levels of rats treated with Fenugreek in both diabetic and non-diabetic groups, in comparison to those without Fenugreek (p value < 0.0005). (Table-2)

Paired T - test showed strong significance ($p=0.000075$) in reduction of serum cholesterol levels in diabetic group treated with Fenugreek. The non-diabetic group also showed significantly reduced serum cholesterol levels with administration of Fenugreek ($p=0.016$) (Table-3)

However, the statistical results were not significant for triglycerides levels in both diabetic and non-diabetic groups with administration of Fenugreek in these two groups (p value 0.530 and 0.202 respectively) (Table-4)

Similarly, the test was not significant for total protein levels in both groups treated with Fenugreek with p values of 0.373 and

0.874 for non-diabetic and diabetic groups respectively. (Table-5)

Serum albumin levels were significantly improved with Fenugreek in diabetic group ($p = 0.005$), but it showed less significant change in non-diabetic group with Fenugreek ($p= 0.034$) as compared to respective control groups. (Table-6)

Paraffin processed and Haematoxylin & eosin (H/E) stained sections from pancreatic tail, right lobe of liver and skeletal muscles were studied in all the four groups.

Since diabetes was induced by Alloxan, group 3 and group 4 showed marked reduction in size of Islets of Langerhan as compared to group 1 and group 2. Fenugreek administration did not cause any significant morphological changes when compared with sections of pancreas in respective control groups. (Figure 1-A and 1-B)

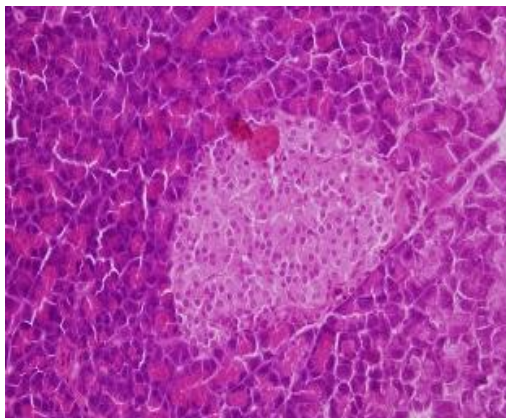


Figure 1-A: Normal Islet cells seen in non-diabetic group 2 (X 40 magnification)

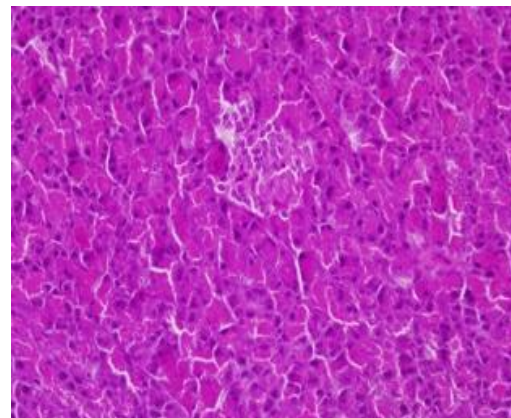


Figure 1-B: Loss of Islet cells in diabetic rats of group 1 and rats of group 3 and 4 (X 40 magnification)

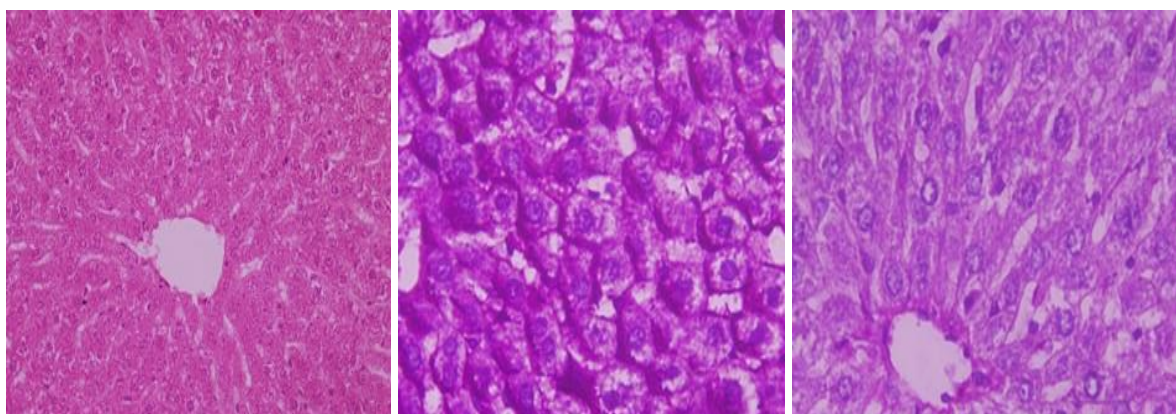


Figure 2: A) H & E stained of liver of group 1 rat (X 80 magnification); B) PAS positive amorphous material in hepatocytes (x 100 magnification); C) Same section showing negative reaction after treatment with diastase (x 100)

H & E as well as Periodic Acid Schiff reaction with diastase stains were performed on microscopic sections from liver. Both of these stains showed normal morphology of liver with normal amounts of glycogen in hepatocytes (in PAS stain) in group 1 and group 2. (Figure 2- A, B, C). Group 4 showed significant fatty change by H & E stain, while PAS stain showed marked reduction in the amount of glycogen in hepatocytes. (Figure 3-A, B). Group 3 (diabetic rats with Fenugreek administration) showed decreased fatty

change (in H & E sections) and more amount of glycogen (in PAS stain). (Figure 4- A, B). Diastase reaction was used to confirm the glycogen demonstrated in PAS stain.

H & E stained sections of skeletal muscles did not show any significant microscopic features. However, PAS stain with diastase treatment showed presence of glycogen in group 1, group 2 and group 4. Glycogen was conspicuously decreased in group 3 cases. (Figure 5- A,B, C)

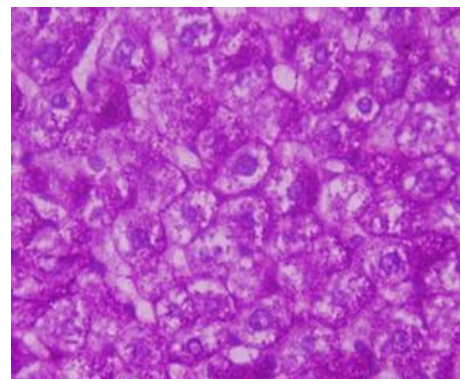
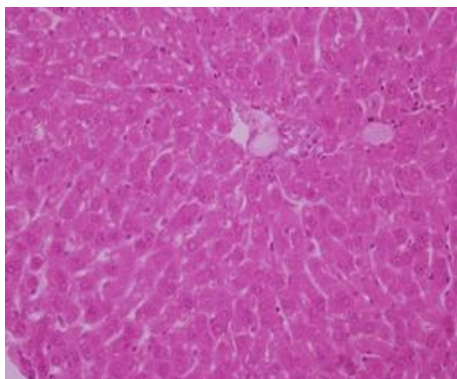


Figure 3: A) H & E stained section showing minimal fatty change in group 3 rats (x 40); B) PAS stained section revealing significant fatty change and marked reduction in glycogen stores. (x 100)

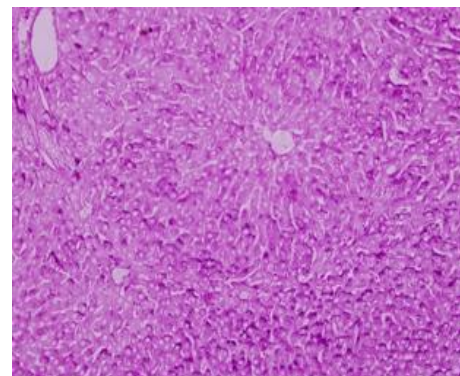
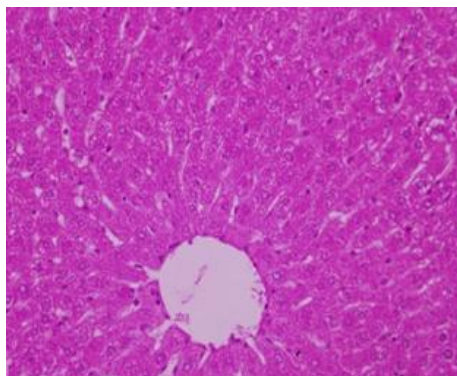


Figure 4: A) H & E stained section showing decreased fatty change in group 4 rats (x 40); B) PAS stained section revealing minimal fatty change and focal areas showing glycogen stores. (x 40)

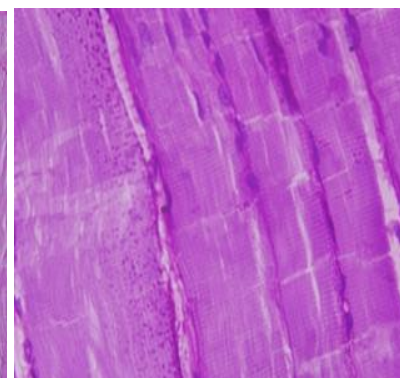
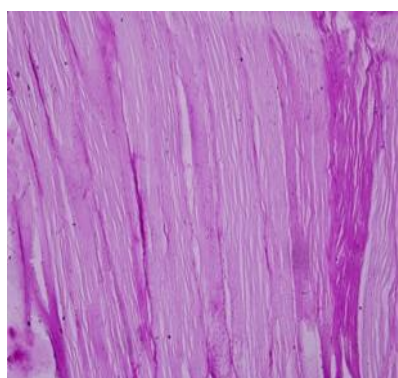
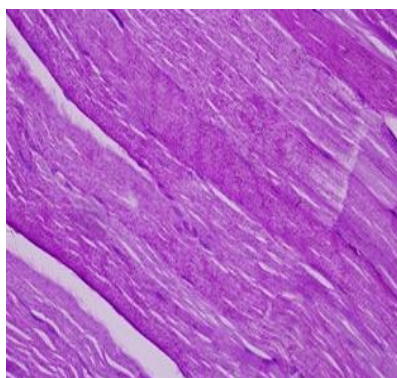


Figure 5 : A) PAS stained section showing glycogen granules in skeletal muscle fibres in group 1 and 2 (x 100); B) PAS stained section revealing loss of glycogen stores in group 3 (x 100); C) PAS stained section showing regaining of glycogen granules in skeletal muscle fibres in group 4 (x 100)

Liver tissue was also subjected to electron microscopic studies which showed following ultrastructural changes (Figure 6- A, B, C, D):

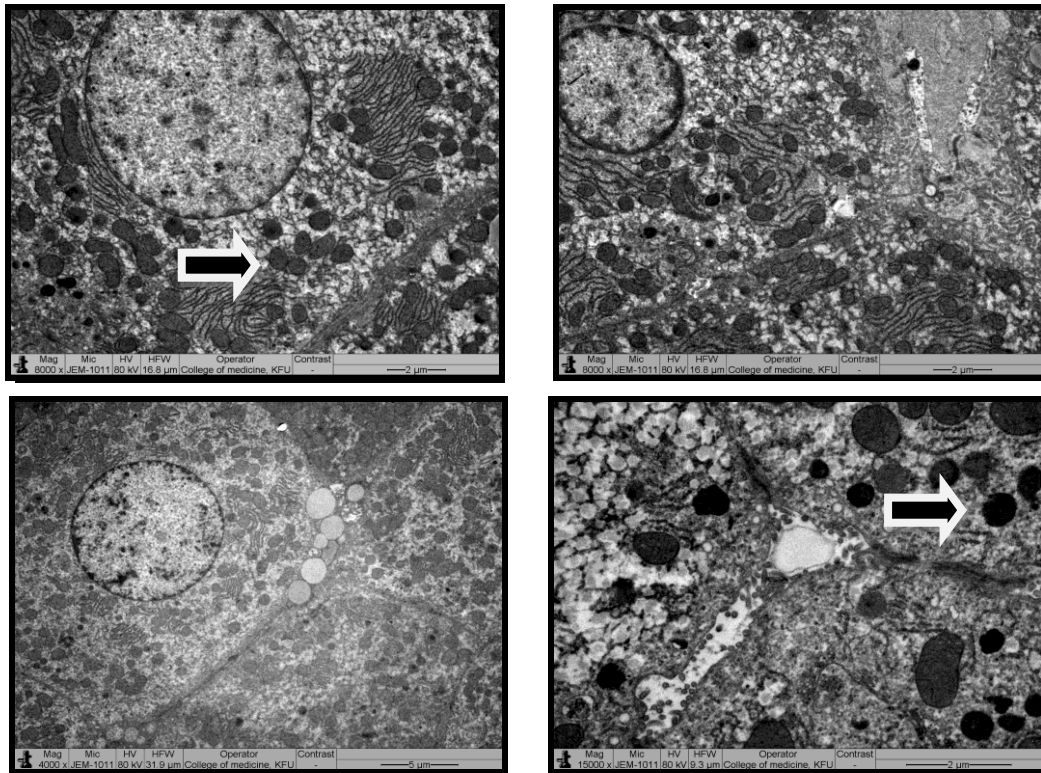


Figure 6-A) This EM photograph shows the normal glycogen rosettes in the hepatocytes in normal control group (Arrow); Figure 6-B) The glycogen rosettes are similar in morphology in the hepatocytes of non-diabetic rats treated with Fenugreek indicating no much difference in their morphology. Figure C shows markedly reduced number of glycogen rosettes in the hepatocytes of diabetic rats (group 3), while figure D shows presence of large and irregular glycogen rosettes in the hepatocytes of diabetic rats treated with Fenugreek (Arrow). (Group 4)

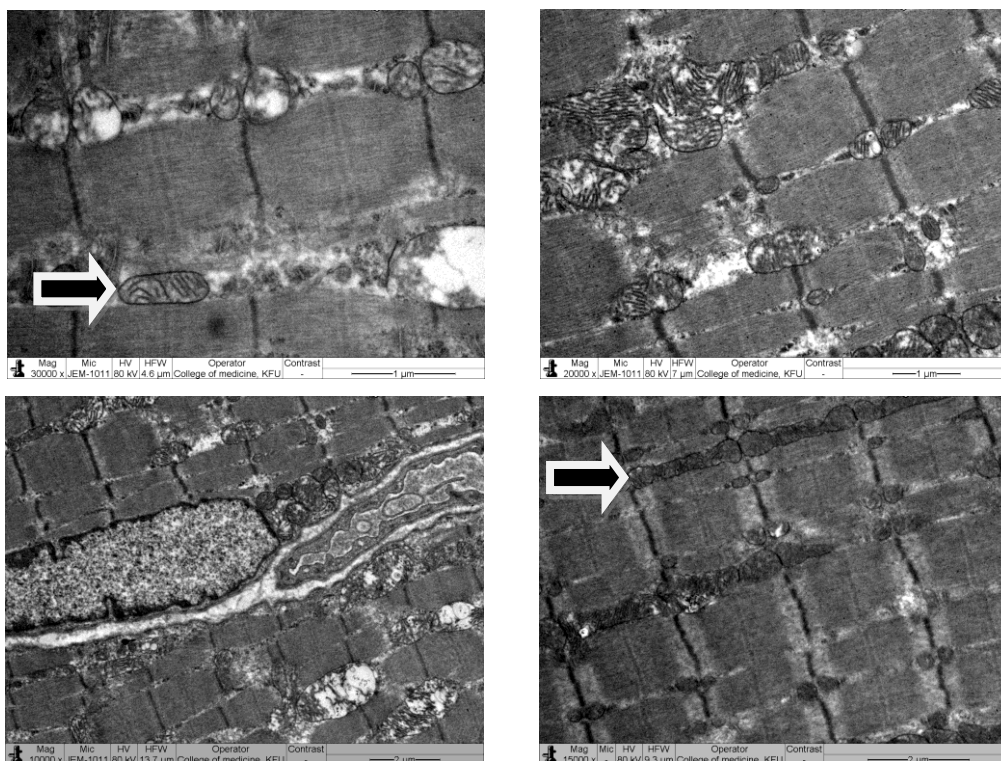


Figure 7-A) This EM photograph shows normal mitochondria in the myocytes in normal control group (Arrow); Figure 7-B) Mitochondria are normal in morphology but show increased number in the myocytes of non-diabetic rats treated with Fenugreek. Figure 7-C shows markedly reduced number of mitochondria in the myocytes of diabetic rats (group 3), while figure D shows presence of many mitochondria in the myocytes of diabetic rats treated with Fenugreek (Arrow). (Group 4)

Electron microscopic studies from skeletal muscles showed increased number of mitochondria in both study groups treated with Fenugreek as compared to corresponding controls. Mitochondria showed marked quantitative and morphological changes in diabetic rats. (Figure 7 - A, B, C, D)

DISCUSSION

The study was conducted with two control groups (non-diabetic control and diabetic control) and the effects of Fenugreek supplement were also studied in two similar study groups. This has helped us find the effects of Fenugreek in diabetic as well as in non-diabetic rats. The hypoglycemic activity of *Trigonella foenum graecum* (fenugreek seeds) in experimental animals and humans being has been well documented. It has been shown to reduce fasting and postprandial blood glucose levels in diabetic patients. These actions might be either due to decreased intestinal absorption of glucose or due to activation of insulin receptors caused by some component in Fenugreek extract. ⁽¹¹⁾ However, it was not clear whether the improvement in glucose tolerance is due to the effect of fenugreek on the absorption or metabolism of glucose. It's possible role in the increased peripheral utilization of glucose by the tissue due to either increased insulin receptor number or activity is being considered. Changes in the enzyme levels of glucose metabolism and ultrastructural changes in hepatocytes play important role in this activity. ⁽¹²⁾

In our study diabetes was induced with administration of Alloxan, which causes destruction of islet cells of pancreas as seen in the histology. ⁽⁹⁾ The biochemical, histological and ultramicroscopic changes seen in cases treated with Fenugreek suggest insulin-like actions. Since pancreas showed loss of islet cells, these actions are not due to increased production or release from islet cells. Hence it proves that the effects of

Fenugreek are due to insulin-like actions in the tissues. ⁽²⁾ Our study has well documented this hypothesis from ultramicroscopic and histological findings of increased glycogen stores in hepatocytes and skeletal muscles with Fenugreek administration.

Since insulin resistance is the main pathology of NIDDM, the effect of *Trigonella foenum graecum* on the insulin receptors of peripheral tissue like hepatocytes and skeletal muscles will be more important for the study. This extra-pancreatic mode of action showed significant changes in a study carried out on rabbits which suggested increased sensitivity of the insulin receptors. ⁽¹²⁾ One of the recent studies with daily oral administration of *Trigonella foenum graecum* to type 2 diabetic rats for 28 d showed decreased serum glucose, increased liver glycogen content and enhanced total antioxidant status. Serum insulin and insulin secretion were not affected. Increased insulin action was thought to be caused by inhibition of carbohydrate digestion and absorption, and enhancement of peripheral insulin action. ⁽¹³⁾ A study by Jayadev Raju et al demonstrated that fenugreek seed powder improves glucose homeostasis in alloxan diabetic rat tissues by reversing the altered glycolytic, gluconeogenic and lipogenic enzymes. ⁽¹⁴⁾ The hypoglycemic effect was observed to be slow but sustained, without any risk of developing severe hypoglycemia. ⁽¹⁵⁾

Our study incorporates all the metabolic, microscopic and ultramicroscopic studies, thus proving the peripheral mechanism of actions of *Trigonella foenum graecum* in the causation of hypoglycemia. Fenugreek not only causes control of hyperglycemia, but it also decreases serum cholesterol levels and increases serum albumin levels. These effects were seen in diabetic as well as in non-diabetic study group. In addition it helped in reducing fatty change in hepatocytes in diabetic cases. All these

effects of Fenugreek may help us to develop this food ingredient as one of the effective drug or adjunct in the treatment of NIDDM. It can also be used as a preventive measure to delay onset of hyperglycemia in hereditary predisposed cases of diabetes mellitus or in cases of obesity.

Study did not show statistical significance for total protein and triglyceride levels in both study groups. This can be attributed to short period of study. Longer duration of study might show significant changes in these parameters also. Such study may also help us to find out possible side effects of Fenugreek. Similarly, resistance to action of antidiabetic drug as seen in other therapeutic drugs can also be evaluated for chronic fenugreek administration with longer duration studies.

CONCLUSION

Trigonella foenum graecum (Fenugreek) reveals significant anti-diabetic effect and anti-cholesterol effect through its insulin-like action on insulin receptors in hepatocytes and skeletal muscles. It also has anti-cholesterol activity, which may help to decrease predisposition to cardiac diseases. Longer duration of study may be helpful in identification of more metabolic effects, possible side-effects and even long term effectiveness of its anti-diabetic action. Since Fenugreek can be used as a dietary ingredient, it can be used to decrease the blood glucose levels in diabetics without the possibility (or with least possibility) of having side-effect of hypoglycemia in non-diabetic cases. It can also be considered as one of the best adjunct in the treatment of diabetes mellitus. More studies for longer duration with specific extract of fenugreek are indicated to derive this information.

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