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Evaluation of biochemical markers in type 2 diabetes mellitus with adjunct therapy of fenugreek seed aqueous extract

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Abstract
Background: *Trigonella foenum-graecum* seeds have been suggested to have potential anti-diabetic effects.
Aim: To study effects of fenugreek seeds aqueous extract on glycemic status, insulin resistance, homeostatic model assessment, safety parameters and antioxidant superoxide dismutase in Type 2 Diabetes Mellitus (T2DM) subjects and its correlation.
Methods: Randomized case-control study consisting of control (n=30), T2DM (n=30) and T2DM patients with adjunct therapy (n=30) of 1.32g fenugreek seeds aqueous extract for 3 months. Blood glucose, HbA1C, lipid profile, liver and kidney function tests were done using chemistry autoanalyzer. Insulin and C-peptide were done on chemiluminescence. Malondialdehyde and superoxide dismutase were analysed using spectrophotometer.
Results: Glucose, HbA1C and malondialdehyde were significantly lowered after 3 months in group receiving adjunct therapy. Insulin resistance, anthropometric and antioxidant status were improved while haemoglobin, alanine transaminase and renal functions remained unaltered.
Conclusion: Aqueous extract of fenugreek is effective and safe to control hyperglycemia in T2DM.

Keywords: fenugreek, HBA1C, homa, SOD, MDA, T2DM

Introduction
Diabetes mellitus is a clinical syndrome characterized by inappropriate hyperglycemia caused by a relative or absolute deficiency of insulin or by a resistance to the action of insulin at the cellular level [1]. It is a predominant public health concern, substantially causing morbidity, mortality, and long-term complications and remains an important risk factor for macro and micro vascular diseases like retinopathy, nephropathy, neuropathy, cardiovascular diseases etc. [2] At present, the treatment of diabetes mainly involves a sustained reduction in hyperglycaemia by the use of biguanides, thiazolidinediones, sulphonylureas, D-phenylalanine derivatives, meglitinides and a-glucosidase inhibitors in addition to insulin. However, due to unwanted side effects the efficacies of these compounds are debatable and there is a demand for new compounds for the treatment of diabetes (UKPDS Group, 1995; Moller, 2001) [3].
Antidiabetic plant medicines might provide an important source of new oral hypoglycemic compounds for development as pharmaceutical entities, or as simple dietary adjuncts to existing therapies. Although a botanical substitute for insulin seems unlikely, compounds that stimulate insulin biosynthesis and secretion, or promote peripheral glucose uptake and utilization, are realistic possibilities. Hence, plants have been suggested as a rich, as yet unexplored source of potentially useful anti-diabetic drugs [3, 4].
Fenugreek (Trigonella foenum-graecum), one of the oldest medicinal plants, is of Mediterranean origin and cultivated worldwide. Aqueous extracts of seeds and leaves of fenugreek have been widely used in diabetes treatment and shown to possess hypoglycaemic, anti-lipidimic and antioxidant properties activity. It has been reported to have action to correct insulin resistance, a basic etiological factor for development of non-insulin dependent diabetes mellitus and is nontoxic [4, 6, 7, 8, 9].
Fenugreek lowers lipids because it contains saponins that are transformed in the gastrointestinal tract into sapogenins. Fenugreek seeds contain 50% fiber (30% soluble fiber and 20% insoluble fiber) that can slow the rate of postprandial glucose absorption. In humans,

fenugreek seeds exert hypoglycemic effects by stimulating glucose-dependent insulin secretion from pancreatic beta cells, as well as by inhibiting the activities of α-amylase and sucrose enzymes involved in carbohydrate metabolism. Sapogenins which increase biliary cholesterol excretion that results lower serum triglycerides, total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) [8].

According to Yeh *et al*, level of evidence produced by these studies is not optimal (on Jadad scale and ADA criteria). They have recommended that further studies are warranted and until more definitive studies are done, clinicians should remain cautious, yet open - minded, regarding adjunctive use of these supplements [2]. Our study was designed to evaluate efficacy and safety of fenugreek in type 2 diabetic patients on anti-diabetic adjunct fenugreek therapy. In addition to hypoglycemic (Fasting glucose and HbA1c), antilipidimic properties (lipid profile) and antioxidant properties by superoxide dismutase (SOD) were also analyzed. We have studied it's mechanism of action by levels of serum insulin, C- peptide levels and 'HOMA Insulin Resistance 2' a computer model [10, 11].

Material and Methods

Study was undertaken in Department of Biochemistry, Grant government medical college and Sir J. J. groups of Hospitals, Mumbai in 30 control and 126 subjects of T2DM as per American Diabetes Association criteria with age sex matched between 30 and 60 years (12). Six did not tolerate fenugreek (skin rash, abdominal discomfort, vomiting etc.), ten dropped out for health reasons: e.g. surgical procedures, medical conditions (unrelated to fenugreek treatment), twenty did not turn up for follow up. Approval of the ethical committee of the institute was obtained for the study. Informed consent was taken from the subjects. Subjects with serious hepatic or renal impairment, hypertensive, cardiovascular co–morbidities psychiatric disorders human immuno-deficiency virus infection, pregnancy, addicts i.e. drugs, alcohol and tobacco were excluded from studies.

Randomized case control study consists of control (n=30), T2DM (n=30) and T2DM patients with adjunct therapy (n=30). Diabetic subjects were on anti-diabetic treatment and T2DM patients with adjunct therapy received additional 1.32gm aqueous extract of fenugreek seeds. Initially small doses were given to the patients as adjunct therapy and doses were increased slowly with careful monitoring for side effects including risk of hypoglycaemia for 3 months.

Baseline and 3 months follow up study was done for glucose, insulin, C-peptide, malondialdehyde (MDA), SOD, lipid profile, haemoglobin, alanine transaminase (ALT) and renal function tests which were estimated using chemiluminescence (Immulite 1000), fully automated chemistry analyser (Olympus AU-400) and spectrophotometer Jasco-V670. Clinical history, blood pressure, anthropometric measurements - height, weight, hip and waist measurements, BMI was also measured [13, 22].

Homeostatic model (HOMA 2) is a method for assessing β – cell function and insulin resistance (IR) from basal (fasting) glucose and insulin or C- peptide concentrations. HOMA2, the correctly solved computer model, has nonlinear solutions [10, 11]. Statistical analysis was done using Mini-tab 17 software with 95% confidence interval and two-sided correlation among groups was done.

Plant extract

Aqua soluble extract of fenugreek tablets were supplied by FDA approved ayurvedic manufacturer Sheetal Medicare. Fenugreek seeds purchased from local market were certified by botanist. Material was tested and certified as per Agmark standards for pesticides, fertilizers, toxins and heavy metals residues. Seeds were washed, dried, powered and decoction was prepared from which tablets were made by the standard procedure in text book of Indian medicine, 'Sharangdhar Samhita' [14]. Aqueous extract of Fenugreek was made in 1:10 ratio. Gum Acacia was used as binder and filler. One tablet contained 330 mg extract. 1.32gm extract was equivalent to 13.2gm Fenugreek seed powder. Our optimum dose was 4 tablets/day. During the 1st week only 1 tablet/day was administered 5-10 minutes before breakfast. In the 2nd week, 2 tablets/day were given each before breakfast and dinner. The dosage was further increased in the 3rd week with a total of 4 tablets/day, 2 tablets before breakfast and 2 tablets before dinner.

Result

Table 1: Anthropometric parameters in Healthy Control, T2DM (DM) and Adjunct T2DM (ADJ DM)

Anthropometric Parameters	Control	DM	ADJ DM
	Mean ± SD	Mean ± SD	Mean ± SD
Age (Years) Baseline	42.43 ± 7.15	53.7 ± 7.28	48.6 ± 10.52
Age (Years) after 3 Months	42.43 ± 7.15	53.7 ± 7.28	48.6 ± 10.52
Height (cm) Baseline	167.33 ± 9.3	163.2 ± 10.23	165.13 ± 5.26
Height (cm) after 3 Months	167.33 ± 9.3	163.2 ± 10.23	165.13 ± 5.26
Weight (kg) Baseline	64.8 ± 9.82	69.86 ± 13.58	64.43 ± 10.6
Weight (kg) after 3 Months	64.8 ± 9.82	70.46 ± 13.33	62.4 ± 10.38
BMI Baseline	21.63 ± 3.02	26.25 ± 3.78	23.56 ± 3.71
BMI after 3 Months	21.63 ± 3.02	26.5 ± 3.69	22.83 ± 3.65
W/H Ratio Baseline	0.99 ± 0.16	0.89 ± 0.06	0.91 ± 0.08
W/H Ratio after 3 Months	0.99 ± 0.16	0.87 ± 0.16	0.88 ± 0.06
Hb% Baseline	13.75 ± 1.59	11.63 ± 1.18	12.4 ± 1.8
Hb% after 3 Months	13.73 ± 1.58	11.91 ± 1.12	12.27 ± 1.79

Table 2: Values of different parameters in Healthy control, T2DM and Adjunct T2DM groups at baseline and after 3 Months

Parameters	Control	DM	ADJ DM
	Mean ± SD	Mean ± SD	Mean ± SD
FBS (mg/dl) Baseline	82.3±11.712	271.7 ± 57.47	257 ± 42.19
FBS (mg/dl) after 3 Months	----	266.5 ± 52.6	197 ± 38.83
Insulin (U/ml) Baseline	5.07 ± 0.91	9.66 ± 5.53	18.6 ± 6.17
Insulin (U/ml) after 3 Months	----	9.85 ± 5.31	14.96 ± 4.13
C-peptide (ng/ml)Baseline	5.33 ± 1.17	1.93 ± 1.59	3.98 ± 1.12
C-peptide (ng/ml)after 3 Months	----	2.09 ± 1.44	3.46 ± 0.93
HbA1C (%) Baseline	4.35 ± 0.46	10.35 ± 1.04	9.96 ± 0.85
HbA1C (%)after 3 Months	----	7.8 ± 1.04	5.86 ± 0.41
HOMA Baseline	0.96 ± 0.13	3.52±1.12	3.36±1.35
HOMA after 3 Months	----	3.53±1.11	2.32 ±0.69
Cholesterol (mg/dl) Baseline	155.16 ± 24.28	201.46 ±22.49	216.43 ± 18.32
Cholesterol(mg/dl) after 3 Months	----	202.03 ± 18.6	182.13 ± 15.19

TG(mg/dl) Baseline	90.56 ± 21.09	159.4 ± 30.03	192.13 ± 18.74
TG(mg/dl) after 3 Months	----	154.73 ± 27.42	158.36 ± 14.96
HDL(mg/dl) Baseline	52.7 ± 1.62	32.92 ± 5.63	40.7 ± 4.04
HDL(mg/dl) after 3 Months	----	32.4 ± 3.98	50.96 ± 3.89
LDL(mg/dl) Baseline	94.08 ± 25.18	137.77 ± 19.29	147.03 ± 16.66
LDL(mg/dl) after 3 Months	----	137.77 ± 14.69	116.36 ± 13.52
MDA(nmol/ml) Baseline	4.28 ± 0.49	7.11 ± 1.28	6.98 ± 0.9
MDA(nmol/ml) after 3 Months	----	5.31 ± 0.41	4.43 ± 0.45
SOD (U/gHb) Baseline	826 ± 62.23	541 ± 49.29	527.7 ± 97.54
SOD(U/gHb) after 3 Months	----	533.33 ± 42.76	751 ± 85.12
Urea (mg/dl) Baseline	37.57±1.59	26.57±4.42	33.93 ± 3.71
Urea (mg/dl) after 3 Months	----	26.07±4.33	34.37 ± 3.62
Creatinine(mg/dl) Baseline	1.15±0.17	0.94±0.21	0.95 ± 0.18
Creatinine (mg/dl) after 3 Months	----	0.92±0.19	0.94 ± 0.19
ALT (IU/L) Baseline	33.14±5.63	22.87±4.41	28.47 ± 5.24
ALT (IU/L) after 3 months	----	22.40±4.35	28.33 ± 5.05

Table 3: Correlations among various parameters at Baseline (B) and after 3 Months (aft 3M)

Parameters	Control / DM		Control / ADJDM		DM / ADJDM	
	r-value	p-value	r-value	p-value	r-value	p-value
FBS (mg/dl) B/B	-0.126	0.507	-0.140	0.459	-0.024	0.900
FBS (mg/dl) B/aft 3M	0.011	0.953	-0.187	0.323	0.028	0.885
HbA1c (%)B/B	-0.180	0.341	0.130	0.494	-0.170	0.370
HbA1c (%)B/aft 3M	0.037	0.846	0.038	0.843	-0.108	0.569
Insulin (U/ml) B/B	0.070	0.712	0.136	0.475	-0.117	0.537
Insulin (U/ml) B/aft 3M	0.240	0.201	0.150	0.430	-0.141	0.459
C-peptide (ng/ml) B/B	0.315	0.090	-0.108	0.570	-0.270	0.149
C-peptide (ng/ml) B/aft 3M	0.191	0.311	-0.040	0.836	-0.137	0.471
Cholesterol (mg/dl) B/B	-0.023	0.902	-0.110	0.561	-0.030	0.873
Cholesterol (mg/dl) B/aft 3M	-0.095	0.618	-0.041	0.830	0.18	0.340
TG (mg/dl) B/B	0.422	0.020	-0.187	0.324	-0.083	0.662
TG (mg/dl) B/aft 3M	0.239	0.204	-0.279	0.136	-0.098	0.606
HDL (mg/dl) B/B	0.079	0.677	-0.251	0.181	-0.084	0.659
HDL (mg/dl) B/aft 3M	0.027	0.886	-0.241	0.200	0.100	0.59
LDL (mg/dl) B/B	-0.113	0.551	-0.077	0.686	-0.071	0.710
LDL (mg/dl) B/aft 3M	-0.100	0.599	0.076	0.691	-0.201	0.288
MDA (nmol/ml) B/B	0.273	0.145	-0.056	0.768	-0.132	0.486
MDA (nmol/ml) B/aft 3M	-0.221	0.241	-0.086	0.653	-0.114	0.549
SOD (U/gHb) B/B	0.152	0.423	-0.133	0.484	-0.053	0.781
SOD (U/gHb) B/aft 3M	0.282	0.130	-0.125	0.510	-0.066	0.730

Table 4: Correlations of Control FBS with FBS, HbA1c, Insulin and C-peptide of DM and ADJDM groups at baseline and after 3 months

Parameters		R-value	P-value
Control / DM (B/B)	FBS / FBS	-0.126	0.507
	FBS/ HbA1c	0.050	0.792
	FBS/ Insulin	0.201	0.286
	FBS/ C-peptide	0.388	0.034
	HbA1c/HbA1c	-0.124	0.523
Control / DM (B/aft 3M)	FBS/ FBS	-0.079	0.677
	FBS/ HbA1c	-0.051	0.787
	FBS/ Insulin	0.205	0.276
	FBS/ C-peptide	0.395	0.031
	HbA1c/HbA1c	-0.178	0.354
Control / ADJDM (B/B)	FBS/ FBS	-0.140	0.459
	FBS/ HbA1c	0.053	0.781
	FBS/ Insulin	0.100	0.598
	FBS/ C-peptide	-0.333	0.072
	HbA1c/HbA1c	0.304	0.109
Control / ADJDM (B/aft 3M)	FBS/ FBS	-0.243	0.195
	FBS/ HbA1c	-0.335	0.071
	FBS/ Insulin	0.071	0.708
	FBS/ C-peptide	-0.123	0.519
	HbA1c/HbA1c	-0.403	0.030
ADJDM / ADJDM (B/B)	BSL / HbA1c	-0.118	0.534
ADJDM / ADJDM (B/aft 3M)	BSL / HbA1c	0.061	0.750
	BSL / BSL	0.926	0.000
	HbA1c /HbA1c	-0.204	0.279
ADJDM / ADJDM (aft 3M/aft 3M)	BSL / HbA1c	0.087	0.646

Table 5: Correlation between Control, T2DM and Adjunct therapy T2DM groups

Fasting Parameters after 3 months of treatment	Control/DM r-value	Control/ADJDM r-value	DM/ADJDM r-value
FBS (mg/dl)	0.83	0.95	0.92
Insulin (U/ml)	0.89	0.97	0.9
HOMA	0.81	0.98	0.83
C-peptide (ng/ml)	0.82	0.97	0.86
HbA1C (%)	0.63	0.72	0.62
Cholesterol (mg/dl)	0.95	0.96	0.98
SOD (U/g Hb)	0.78	0.79	0.8

Discussion

Fenugreek and other traditional plants are currently being investigated for their potential as a source of new hypoglycaemic compounds for the treatment of diabetes [2]. In the present study, anthropometric study was done in control, DM, Adjunct DM group with age and sex matched. The base line levels of blood glucose, serum cholesterol, TG, LDL and MDA were high and lower levels of HDL, SOD were seen in T2DM and adjunct T2DM as compare to control group (Table No 1, 2) [4, 6, 7, 15]. Ibrahim Shaikh *et al* 2015 and many other studies suggest that these effects may be due to sapogenins, which increase biliary cholesterol excretion in the faeces, in turn leading to lowered serum cholesterol levels. The lipid

lowering effect of fenugreek might also be attributed to its estrogenic constituent, indirectly increasing thyroid hormone thyroxine (T4) [8, 16, 17, 18]. Insulin and C-peptide were analysed to calculate HOMA IR in all three groups. Liver function test, Kidney function test were done and they show normal levels in all groups [19]. Adjunct group received Fenugreek treatment along with routine treatment of diabetes patients who tolerated fenugreek extract in tablet form. Both DM and adjunct group were compared after 3 months and group taking fenugreek tables showed improvement in biochemical parameters, anthropometric as well as HOMA IR (Table No 1, 2). The correlations among same and different parameters in different groups at baseline and after 3 months are shown in Table 3, 4. There was better improvement in HbA1C as a marker of diabetic control in Adjunct T2DM group after 3 months treatment of aqueous extract of Fenugreek seed tablet Gupta *et al* [7]. They have demonstrated that a dialyzed aqueous extract of fenugreek seeds possesses hypoglycemic properties and that it stimulates insulin signalling pathways in adipocytes and liver cells. Fenugreek induces a rapid, dose–dependent stimulatory effect on cellular glucose uptake by activating cellular responses that lead to glucose transporter (GLUT4) translocation from intracellular space to plasma membrane. Their results also indicated that fenugreek contains factor(s) that might act independently of insulin to enhance glucose transporter-mediated glucoseuptake [5, 20, 21]. The control, T2DM and Adjunct T2DM after 3 months have good positive correlation showing improvement in fenugreek supplementation (Table 5) as effective and safe to control hyperglycemia by stabilizing glucose homeostasis, glycemic status, dislipidimias and antioxidant SOD status [23].

Conclusion

Aqueous extract of fenugreek seeds possesses hypoglycaemic and hypolipidemic properties, this effect is shown by HbA1c, insulin and C peptide in Type 2 diabetes. This action is mainly attributed to decreased insulin resistance i.e. HOMA. This study concludes that fenugreek seed extract adjunct supplementation along with routine diabetic treatment will help to control glycemic status instead of only diabetic treatment. Thus, the activity of natural compounds like fenugreek may be suitable for the development of novel anti-diabetic drugs.

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