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CLINICAL EVALUATION FENUGREEK SEED EXTRACT IN PATIENTS WITH TYPE-2 DIABETES: AN ADD-ON STUDY IN 154 PATIENTS

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ABSTRACT

Diabetes is an epidemic disease and is considered as the major cause of mortality and morbidity across globe. The global increase in the prevalence of diabetes is due to the combination of causes such as population growth, aging, unplanned fast urbanization and an increase in obesity and physical inactivity. Addition of fenugreek seed extract in the diet may reduce blood sugar and urine sugar levels along with improvement in glucose tolerance in type-2 diabetic patients. The present study was an add-on, randomized, double blind, placebo controlled study to evaluate the efficacy and safety of the standardized fenugreek seed extract as furostenolic saponins. It included the oral administration of Fenugreek seed extract (Fenfuro) in 154 patients suffering from type-2 diabetes mellitus were randomized in two groups. One group of patients received Fenfuro and the other group received Placebo. The subjects were assed clinically and biochemically at pre-defined intervals of 4 weeks during 12 weeks study. Fenfuro effectively caused significant change in blood glucose levels, decrease in HbA1c levels, fasting plasma glucose levels, PP plasma glucose levels and increase in C-peptide levels as compared to Placebo group. Fenfuro-treated group also showed reduction in concomitant anti-diabetic therapy. This fenugreek preparation was also found to be safe in patients with type-2 diabetes as depicted by the safety parameters.

KEYWORDS: furostenolic saponins, (Fenfuro).

INTRODUCTION

Diabetes is a metabolic disease which is shown to cause high blood sugar levels over a prolonged period. Diabetes can be caused due to one of the two reasons *i.e.* either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin which has been already produced by pancreas. According to recent estimates, approximately 552 million people (9.9%) in the age of 20–79 years are prone to have diabetes by 2030.[1] One of the two forms of diabetes *i.e.* Type-2 diabetes, results from an imbalance between insulin sensitivity and insulin secretion .[2] It has been demonstrated that the earliest detectable abnormality in type-2 diabetes is an impairment of the body's ability to respond to insulin. Impaired insulin action is observed in several tissues such as skeletal muscle, adipose tissue and the liver. It leads to increased insulin secretion from the pancreas to overcome impaired insulin action. In individuals at high risk of developing diabetes, the function of beta cells eventually declines and leads to the development of impaired glucose tolerance and eventually overt diabetes mellitus. The most frequently documented risk factors in type-2 diabetes are body mass index (BMI), lipids, smoking, physical inactivity, low education, dietary patterns, family history, and specific genes.[3, 4, 5] Type-2 diabetes also results from genetic predisposition and from lifestyle factors, especially those from western lifestyle, characterized by high calorie intake and lack of exercise.[6, 7] Urban rural differences in the prevalence of diabetes have been consistently reported from India.[8] The prevalence of diabetes is at highest in the urban (12.4%) areas, followed by the midland (8.1%), highland (5.8%) and coastal division (2.5%).[9]

Fenfuro, a group of furostanolic saponins derived from fenugreek seeds (*Trigonella foenum graecum*) by innovative process, is reported to be a major contributor in the treatment of type-2 diabetes mellitus. It helps to cure the state of hyperglycemia in context of insulin resistance and relative lack of insulin. Various studies have been reported about the property of lowering blood glucose and cholesterol levels by the components of fenugreek seed extract *i.e.* saponins and flavonoids.[10] Fenfuro lowers blood glucose by acting as a dual insulin sensitizer. The high fibre furostanolic saponins increase the number of insulin receptor sites and as a result, the cells become more sensitive to insulin and gain the ability to burn glucose**.** These high fibre furostanolic saponins in Fenfuro delay the rate of gastric emptying also and slow down the carbohydrate absorption which results in reduced insulin requirements in the

body.[11] High fibre furostanolic saponins lower cholesterol by increasing the viscosity of digesta. The increase in viscosity inhibits cholesterol absorption from small intestine and re-absorption of bile acid from the terminal ileum. This leads to decrease in VLDL, LDL & triglycerides levels, thereby lowering cholesterol levels in the body.[12, 13]

Keeping in view, clinical significance of fenugreek seed extract in diabetes, present study was planned to evaluate the effect of Fenfuro on fasting & post-prandial blood glucose levels along with its effect on serum C-peptide levels & HbA1c levels.

MATERIALS AND METHODS

Participants

Both male & female participants with age of 25-60 years were recruited for the study. Patients with type-2 diabetes mellitus for <5 years were preferred for the evaluation. Patients were required to be on oral anti-diabetic treatment with no change in the treatment from last one month. those patients were selected who had HbA1c >7.5% & reported to have fasting plasma glucose not exceeding 180 mg/dL. Patient reported with diabetes other than type-2 diabetes mellitus were not included in the study. Those patients were excluded who had evidence of renal disease (Serum creatinine > 1.5mg/ml) and liver disease (AST/ALT >3 times of normal) along with any history of hemoglobinopathy that may affect the determination of glycosylated haemoglobin and a history of intolerance or hypersensitivity to sulfonylurea or metformin or fenugreek seed extract. Pregnant, lactating mothers and women intending pregnancy were not preferred. Participation of patient in any other clinical trial with in the last 30 days was rejected for the study.

Study design

This was a multicentric, randomized, placebo-controlled and double-blinded, Add on clinical trial. This trial involved the estimation of the effect of fenugreek seed extract in patients suffering from type-2 diabetes. The fixed dosage of Fenfuro was administered orally in 154 patients. As the study was double-blinded, codes of the groups were opened only after statistical analysis of the two groups. One group of patients received Fenfuro and the other group received Placebo. Dose of each patient was packed in a sealed aluminium pouch containing 60 capsules equivalent to dose for one month. Patients were randomized as per computer generated randomization code. Each packet was labeled with patient enrolment number and were handed over to the patients on his/her visit. This has been shown in Figure 1.

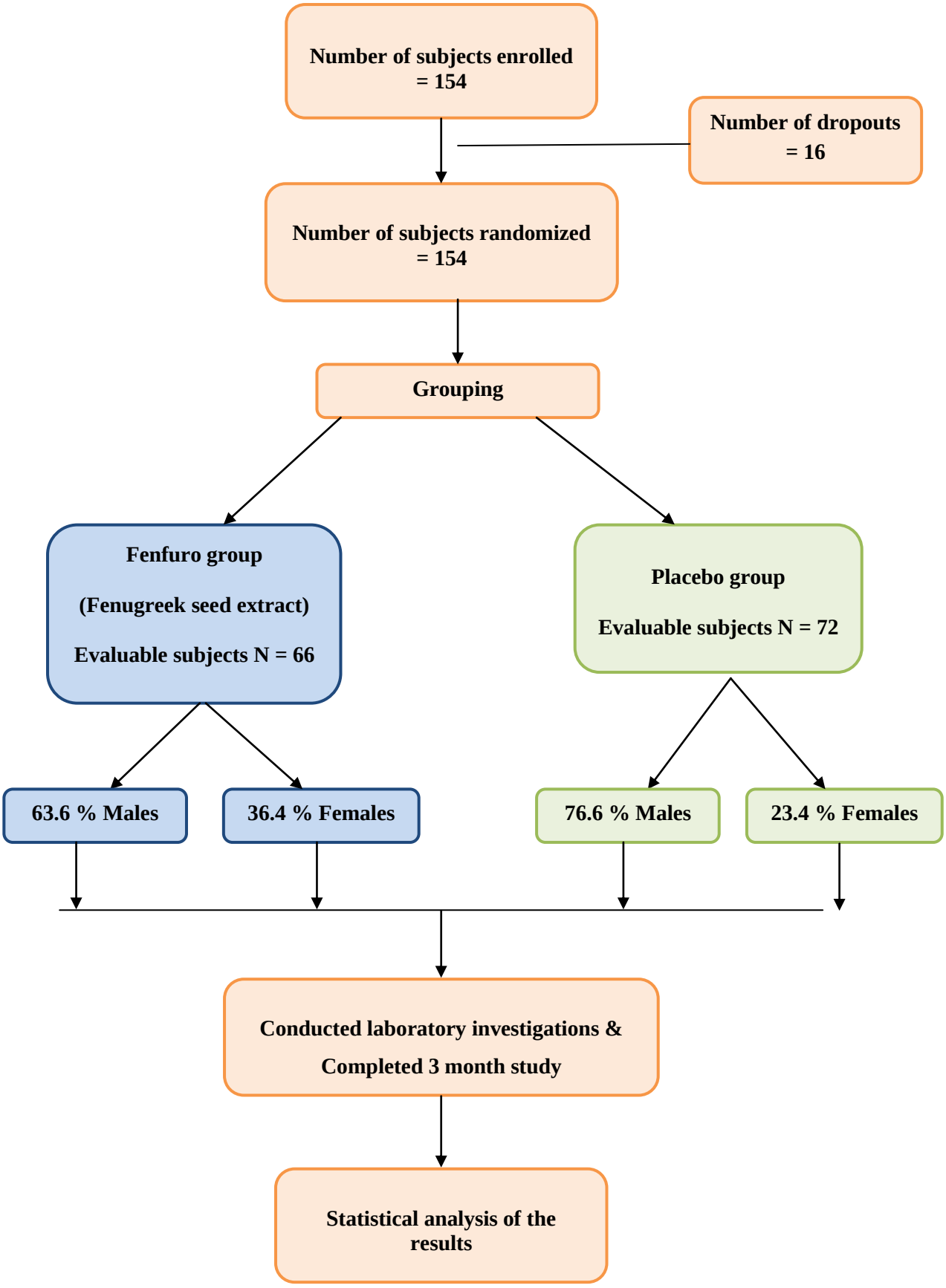

Figure 1: Flow chart of study design

Demographic data

There was no significant difference in mean body weight of Fenfuro group as compared to Placebo group. Age of the study population was between 49-52 years. The average age of Fenfuro group was 51.06 years and that of Placebo group was 49.76 years. In Fenfuro group, 63.6% of the patients were males and 36.4% of the patients were females. In Placebo group, 76.6% of the population consisted of male subjects and 23.4% of the population were females. In Fenfuro group, mean systolic and diastolic blood pressure were 123.4 mmHg and 82.51 mmHg, respectively, while in Placebo group, mean systolic and diastolic blood pressure were 127.18 mmHg and 84.9 mmHg, respectively. There was no significant difference in mean pulse of both the groups.

Efficacy assessment criteria

After a minimum run-in period of four weeks patients were randomly assigned to 12 weeks of treatment with Fenfuro & placebo. The study was double-blind. Participants were reviewed every four weeks and blood samples were obtained after fasting overnight. The following laboratory investigations were performed on each visit of patient.

- HbA1c
- Liver function tests (AST, ALT, ALP and bilirubin)
- Renal function tests (urea and creatinine)
- Haematogram
- FBG
- PPBG
- Serum C-peptide
- Serum bilirubin

Safety analysis

Safety was evaluated by measuring urea, creatinine, ALP, AST, ALT, Bilirubin, Hb and TLC levels in all patients who had taken at least one dose of medication. All adverse effects that were observed during the clinical trial were recorded. Physical examinations and clinical laboratory determinations were performed upon screening, randomization, and study termination.

Statistical analysis

Data was described as mean ± SD. The baseline characteristics were compared with outcome on completion of the dosing period as well as with Placebo group. Appropriate parametric and non parametric tests were used for analysis of the data.

RESULTS

Efficacy Analysis

i. Effect on fasting plasma sugar levels

A significant decrease in fasting blood sugar levels was observed in Fenugreek seed extract treated group (Fenfuro) as compared to Placebo treated group on completion of the treatment as shown in Figure 2. Fenfuro treated group showed average 22% decrease in fasting plasma sugar levels as compared to the baseline where as Placebo treated group showed only 7.6% decrease in fasting blood sugar levels as compared to respective baseline.

A significant decrease in fasting sugar levels was observed after 4 weeks, 8 weeks and 12 weeks of initiation of Fenfuro treatment as compared to its respective baseline. In Placebo group, no significant change in fasting blood sugar levels was observed after 4 weeks and 8 weeks as compared to its baseline. In Placebo treated group, a significant decrease in fasting sugar level was observed as compared to its respective baseline after the time period of 12 weeks.

In Fenfuro treated group, 69.7% of the patients showed decrease in fasting blood sugar levels after 4 weeks, whereas in Placebo treated group 55.6% of the patients showed decrease in fasting sugar levels as compared to its respective baseline.

On completion of study therapy period, in Fenfuro treated group, 83.3% of the patients showed decrease in fasting sugar levels, whereas in Placebo treated group, 62.5% of the patients showed decrease in fasting sugar levels as compared to its respective baseline.

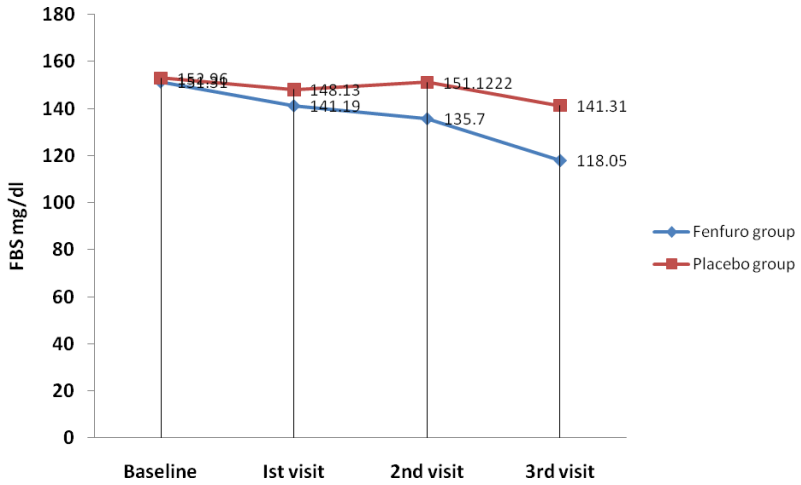

Figure 2: Patient population showing decrease in fasting plasma glucose levels (mg/dL)

ii. Effect on post-prandial (PP) plasma glucose levels

A significant decrease in PP blood glucose levels was observed in Fenfuro treated group as compared to Placebo treated group on completion of the treatment as shown in Figure 3. Fenfuro treated group showed 30.72% of decrease in PP sugar levels as compared to baseline, where as Placebo treated group showed only 17.39% of decrease in PP blood sugar levels as compared to respective baseline.

A highly significant decrease in PP sugar levels was observed after 4 weeks, 8 weeks and 12 weeks (P=0.000) of Fenfuro treatment as compared to its respective baseline. In Placebo group, a significant change in PP blood sugar levels was observed after 4 weeks (p=0.027), 8 weeks (p=0.012) and 12 weeks (p=0.000) of the dosing as compared to its baseline.

After 4 weeks of the enrolment, in Fenfuro treated group, 75.8% of the patients showed decrease in PP blood sugar levels, whereas in Placebo treated group, 59.7% of the patients showed decrease in PP blood sugar levels as compared to its respective baseline. On completion of study therapy period, in Fenfuro treated group, 89.4 % of the patients showed decrease in PP sugar levels, whereas in Placebo treated group, 72.2 % of the patients showed decrease in PP sugar levels as compared to its respective baseline.

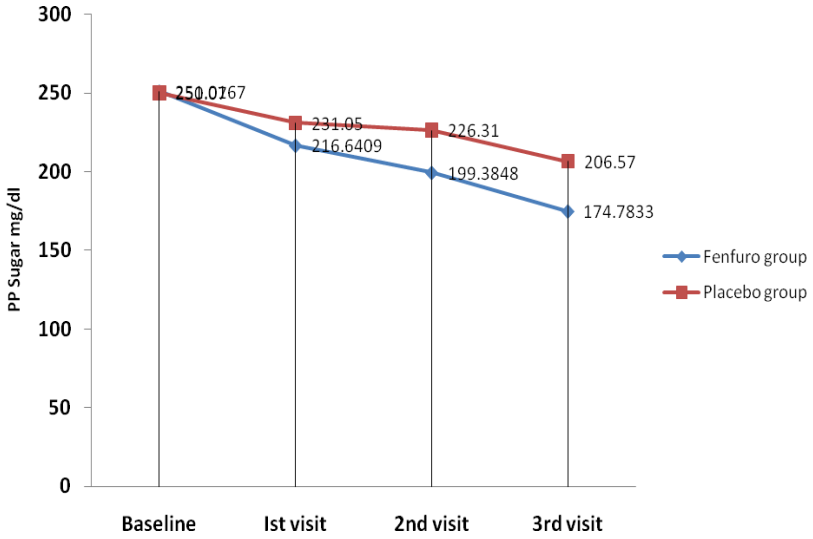

Figure 3: Patient population showing decrease in PP plasma sugar levels (mg/dL)

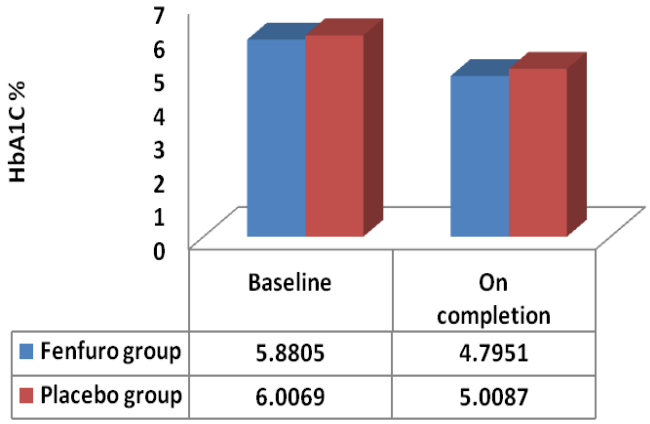

Figure 4: Effect of HbA1c levels (%)

iii. Effect on HbA1c level

HbA1c level was also reduced in subjects in both Fenfuro group and Placebo treated groups. The decrease in HbA1c levels was significant in both the groups as compared to respective baseline values. In Fenfuro treated group, the decrease was 18.36%, whereas in Placebo treated group, the decrease was 16.63% of the respective baseline values.

iv. Effect on fasting C-peptide levels

A significant increase in fasting C-peptide levels were observed as compared to respective baseline value between the two groups as shown in Table 1.

Table 1: Effect on fasting C-peptide levels

Groups	Variables	Mean	Std. Deviation	Paired t-value	Paired p-value	Independent test t-value	Independent test p-value
Fenfuro Group	C-Peptide Baseline	2.6026	1.68410	4.423	.000**	1.140	0.260ns
	C- Peptide Final	4.1091	2.07685				
Placebo Group	C-Peptide Baseline	3.2836	2.28910	4.283	.001**	0.871	0.389ns
	C- Peptide Final	4.7900	3.09035				

v. Post prandial (PP) C-peptide levels

A significant increase in PP C-peptide levels were observed as compared to respective baseline value, whereas no comparative change in PP C-peptide levels was observed between the two groups.

Table 2: Effect on PP c-peptide levels

Groups	Variables	Mean	Std. Deviation	Paired t-value	Paired p-value	Independent test t-value	Independent test p-value
Fenfuro group	C-Peptide Baseline	2.56	2.107	7.210	.000**	.438	.663ns
	C- Peptide Final	5.40	2.779				
Placebo Group	C-Peptide Baseline	2.33	1.636	5.427	.001**	1.285	.205ns
	C- Peptide Final	4.47	2.528				

vi. Decrease in anti-diabetic drug therapy

In Fenfuro treated group, the dosage of prescribed anti-diabetic therapy was reduced in 48.8% of the patients, where as in Placebo treated group, the dosage of prescribed anti-diabetic therapy was reduced in 18.05% of the patients.

Safety Analysis

On the completion of study therapy period, no significant change was seen in any of the safety parameters including urea levels, creatinine levels, serum bilirubin levels, AST activity, ALT activity, ALP activity hemoglobin levels and Total Leukocyte Count (TLC) as compared to respective baseline values in both the groups.

Table 3: Effect on safety parameters

Parameter		Fenfuro group		Placebo group		t-value	Sig.
		Mean	Standard Deviation	Mean	Standard Deviation		
Urea	**Baseline**	26.16	8.62	25.79	7.15	0.274	.784ns
	Visit 1	26.65	7.84	26.35	8.52	0.212	.833ns
	Visit 2	24.93	6.20	25.76	7.82	0.683	.496ns
	COT	24.45	5.89	25.24	8.05	0.651	.516ns

Creatinine	**Baseline**	.83	0.26	0.80	0.17	0.888	.376ns
	Visit 1	0.81	0.25	0.81	0.16	0.215	.830ns
	Visit 2	0.76	0.18	0.78	0.17	0.518	.605ns
	COT	0.75	0.17	0.79	0.18	1.389	.167ns
S Bilirubin	**Baseline**	0.53	0.29	0.55	0.25	0.439	.661ns
	Visit 1	0.52	0.20	0.53	0.24	0.275	.784ns
	Visit 2	0.50	0.19	0.52	0.27	0.696	.488ns
	COT	0.47	0.18	0.58	0.59	1.383	.169ns
AST	**Baseline**	34.09	21.79	34.59	17.48	0.149	.882ns
	Visit 1	31.58	19.72	31.51	16.79	0.023	.982ns
	Visit 2	28.97	10.37	29.44	10.65	0.262	.794ns
	COT	28.76	15.62	27.03	8.04	0.830	.408ns
ALT	**Baseline**	38.31	20.65	43.41	28.42	1.195	.234ns
	Visit 1	36.16	24.74	39.31	26.65	0.719	.474ns
	Visit 2	34.08	14.68	35.64	18.48	0.547	.585ns
	COT	32.23	13.52	31.96	14.82	0.108	.914ns
ALP	**Baseline**	106.14	48.02	107.35	31.96	0.177	.860ns
	Visit 1	99.50	34.47	104.15	30.22	0.846	.399ns
	Visit 2	98.49	33.10	103.41	36.03	0.833	.406ns
	COT	93.35	30.29	95.04	30.29	0.327	.744ns
HB	**Baseline**	13.76	1.78	13.47	1.53	1.031	.304ns
	COT	14.02	1.69	13.75	1.66	0.956	.341ns
TLC	**Baseline**	2721.77	4139.51	2962.87	4149.82	0.341	.733ns
	COT	2358.19	3562.91	2718.45	3784.73	.574	.567ns

DISCUSSION

In the present study, Fenfuro (Fenugreek seed extract) was found to be effective and safe in type-2 diabetic patients. The treatment with Fenfuro was compared with Placebo group and caused reduction in hyperglycemia state and insulin resistance during 12 weeks of the study. Laboratory investigations accomplished both the primary and secondary objectives of the study with positive outcome.

With respect to the safety parameters of the study, no adverse event or patient death was occurred. As given in Table 3 of safety parameters, no significant change in serum SGOT, SGPT & ALP activities was observed. There was not any significant change in blood urea nitrogen and creatinine levels were observed. These findings in the present study indicate that investigational product (Fenfuro) is safe for liver functions and kidney functions. It was also observed that no significant change in hematological parameters took place in the patients. By keeping these biochemical and hematological results in view, investigational product is found to be safe for human consumption.

In the current study, the safety parameters achieved the desired outcome of the Fenfuro supplement. The primary objectives of the study were attained by performing laboratory investigations with the blood samples withdrawn from the dosed patients after intervals of 4 weeks till the study period of 12 weeks. The primary objective of the trial included the study of hyperglycemia parameters *i.e.* it included the evaluation of the effect of Fenfuro on fasting blood sugar levels, post-prandial blood sugar levels, HbA1c levels and C-peptide levels.

Fenfuro has been postulated to exert hypoglycemic effect by stimulating glucose-dependent insulin release by beta cells or via inhibition of α-amylase and sucrase activity. As given in Figure 2, Fenfuro caused significant reduction in the fasting blood sugar levels as compared to baseline values. This reduction was also better than the Placebo group which has not shown much reduction in fasting blood sugar levels. In Fenfuro treated group, 69.7% of the patients showed decrease in fasting blood sugar levels after 4 weeks of the dosage of Fenfuro, whereas in Placebo treated group 55.6% of the patients showed decrease in fasting sugar levels as compared to its respective baseline. On the completion of study therapy period, in Fenfuro treated group, 83.3% of the patients showed decrease in fasting sugar levels, whereas in Placebo treated group, 62.5% of the patients showed decrease in fasting sugar levels as compared to its respective baseline values.[14]

As shown by Figure 3, Fenfuro was also found to be effective to cause reduction in one more hyperglycemia parameter *i.e.* post-prandial blood sugar levels, which gave the direct measurement of efficacy of the herbal supplement in type-2 diabetic patients. Fenfuro caused significant reduction in the post prandial (PP) blood sugar levels as compared to Placebo group and baseline value as well. Figure 3 shows that after 4 weeks of the enrolment, in Fenfuro treated group, 75.8% of the patients were found to have decreased levels of PP blood sugar, whereas in Placebo treated group, 59.7% of the patients showed decrease in PP blood sugar levels as compared to its respective baseline. On the completion of study therapy period, in Fenfuro treated group, 89.4 % of the patients showed decrease in PP sugar levels, whereas in Placebo treated group, 72.2 % of the patients showed decrease in PP sugar levels as compared to its respective baseline. Thus, Fenfuro is effective to bring down the levels of PP blood sugar to cure patients from hyperglycemia.[15]

A significant decrease in HbA1C levels as compared to respective baseline values was observed in dosed patients as shown by Figure 4. In Fenfuro treated group, the decrease was

18.36%, whereas in Placebo treated group, the decrease was 16.63% of the respective baseline values. As given in Table 1 and Table 2, a significant increase in fasting C-peptide levels and PP C-peptide levels was observed as compared to respective baseline value between the two groups. C-peptide levels helped to determine how much natural insulin a person has produced as C-peptide is secreted in equimolar amounts to insulin. C-peptide is found to be a better measure of portal insulin secretion than insulin itself.[16] It was observed by clinical parameters that 48.8% of the patients reported reduced dosage of anti diabetic therapy in Fenfuro treated group; where as 18.05% of the patients reported reduced dosage of anti diabetic therapy in Placebo treated group.

Several mechanisms has been reported which depict the anti-diabetic effect of fenugreek seed extract. It has been seen that fenugreek induces a rapid, dose-dependent stimulatory effect on cellular glucose uptake by activating cellular responses that lead to GLUT4 translocation to the cell surface.[17] It acts on the beta cells to release insulin in normal amounts. Fenugreek seed extract is capable of specifically activating insulin receptor and its downstream signalling molecules in adipocytes and liver cells to bring the levels of glucose at normal levels in the body. This is carried out by initially entering some glucose into the β-cells with the help of glucose transporter 2 (GLUT2), which is phosphorylated by the enzyme glucokinase enzyme. This modified glucose is, then, further metabolized to produce adenosine-triphosphate (ATP). The increase in ATP: adenosine-diphosphate (ADP) ratio causes the closure of ATP-gated potassium channels in the cell membrane thereby preventing the passage of potassium ions. Due to this change there is a rise in the internal positive charge of the cell causing its depolarization. The net effect is the activation of voltage-gated calcium channels, which transports calcium ions into the cell. The increase in intracellular calcium concentration triggers the export of the insulin stored granules (by a process known as exocytosis) from β-cells into the nearby blood vessels. The insulin stimulation followed by cascade signaling enhances glucose intake, utilization and storage in various tissues. Thus, fenugreek seed extract helps to stimulate the secretion of insulin, reduce insulin resistance, and decrease blood sugar levels.[18]

CONCLUSION

The overall effect of Fenfuro in reducing symptoms and biochemical parameters suggests that Fenugreek seed extract (Fenfuro) is effective in patients with Type-2 diabetes. This benefit is appeared to be clinically significant. Fenfuro is well tolerated and safe than the other

prescriptional medications. Thus, when Fenfuro was given as "an add on" to concurrent therapy of type-2 diabetes, it comes out to be synergistic and effective in better management of the disease.

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