Comparative evaluation of glipizide and fenugreek (Trigonella foenum-graecum) seeds as monotherapy and combination therapy on glycaemic control and lipid profile in patients with type 2 diabetes mellitus

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ABSTRACT

Background: Diabetes is commonly associated with dyslipidemia, which is one of the major risk factors of coronary heart disease (CHD), the leading cause of mortality in patients with type 2 diabetic. It is thus desirable that an anti-diabetic drug must provide good glycaemic control and in addition cause correction of dyslipidaemia, at the same time being safe. Fenugreek, a traditional drug has been found to have beneficial effect on glycaemic control as well as lipid profile and may be thus useful in such patients. The study was thus planned to further explore the effect of fenugreek seed on glycaemic control and lipid profile by comparing it with a standard anti-diabetic drug glipizide.

Methods: This 12 week, prospective, randomized, open-label, parallel group comparative study was conducted on 60 patients with type 2 diabetes. The patients were randomized to receive either glipizide 5 mg once daily (group A, n=20), fenugreek seed extract 500 mg twice a day (group B, n=20), or a combination of glipizide 2.5 mg and fenugreek seed extract 500 mg once daily (group C, n=20). The primary endpoint were the change in fasting blood glucose (FBG), glycated haemoglobin (HbA1c), and lipid profile from baseline after 12 weeks of treatment.

Results: A statistically significant decline in mean FBG levels (group A -33.97%, p<0.001; versus group B -24.62%, p<0.001; versus group C -29.96%, p<0.001), and in HbA1c levels (group A -12.98%, p<0.0001; group B -9.38%, p<0.0001; and group C -10.62%, p<0.0001) was seen in all three treatment groups. Total cholesterol (TC) reduced non-significantly in group A (-0.98%, p=0.1982), whereas in group B (-5.66%, p<0.001) and group C (-3.87%, p<0.001) it decreased significantly. Non-significant reduction in plasma triglycerides (TG) were seen in group A (-0.74%, p=0.0669), and significant reductions were seen in both group B (-17.23%, p<0.001) and group C (-11.34%, p<0.001). Low density lipoproteins cholesterol (LDL-C) showed non-significant reductions in group A (-0.74%, p=0.5482), and significant reductions in both group B (-4.15%, p<0.001) and group C (-2.68%, p=0.0463). High-density lipoproteins cholesterol (HDL-C) showed non-significant changes in all three groups (group A -0.60%, p=0.1529; group B 0.65%, p=0.2072; and group C 0.76%, p=0.0543). The adverse drug reactions seen were mild in nature and none of the patients was withdrawn from the study because of serious adverse drug reactions.

Conclusions: Monotherapy with fenugreek produced significant improvement in glycaemic control and dyslipidaemia. Glipizide monotherapy was more efficacious in controlling FBG and HbA1c levels than fenugreek monotherapy or in combination with fenugreek; glipizide monotherapy had no effect on lipid profile whereas fenugreek monotherapy was more efficacious in controlling dyslipidaemia than in combination with glipizide. Both drugs as monotherapy or in combination were well-tolerated by the patients.

Keywords: Glipizide, Fenugreek, Type 2 diabetes mellitus, Lipid profile, Glycaemic control
INTRODUCTION

Diabetes mellitus is a chronic disease, affecting nearly 6% of the world population. 

The introduction of new agents for the treatment of T2DM has been primarily aimed at improving glycaemic control. 

Trials have shown that compared to other lipid-lowering agents, fenugreek is associated with a higher incidence of severe hypoglycaemia. 

METHODS

Study design

This 12-week, randomized, open-label, single-group study was conducted in patients with T2DM visiting the outpatient department of the Guru Nanak Dev Hospital, a multispecialty tertiary care hospital attached to government medical college, Amritsar, Punjab, India. 

Study population

A total of 60 patients with mild to moderate T2DM were enrolled in the study. Patients with either males or females aged 30 to 70 years were included in the study. 

Various experimental and clinical studies have reported the beneficial effects of fenugreek (Trigonella foenum-graecum) seeds, a traditional Indian medicine on glycaemic control and lipid profile in patients of T2DM. 

Fenugreek has also been reported to have mild adverse effects (abdominal distension, diarrhoea and dizziness). 

The seeds of fenugreek have the most potent medicinal effects of the plant. 

It is mainly the defatted fraction, which has hypoglycaemic effects and lipid lowering actions, especially on elevated cholesterol and TG levels in the blood. 

All these factors, i.e., beneficial effect on both blood glucose levels and lipid profile, safety, easy availability and the low cost of fenugreek make it an attractive alternative to be investigated further as an anti-diabetic agent, especially in the Indian context. 

Thus, we planned this study to further explore the anti-diabetic effect and effect on lipid profile of fenugreek seed extract in Indian population and to compare its effects with glipizide, a known anti-diabetic drug while observing the side effects of both agents. 

Although a number of clinical studies have demonstrated the beneficial effects of lipid-lowering agents, literature search showed no published clinical trials that have assessed the protective effect of lipid-lowering agents on CHD exclusively in patients with diabetes. 

Hence, it is necessary to explore the potential of fenugreek as a lipid-lowering agent in the management of T2DM. 

Current available therapeutic options for T2DM such as sulfonylurea, metformin, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, meglitinides, thiazolidinedione’s, etc., have little or no effect on lipid profile, have various adverse effects and are far from satisfactory as far as long-term complications are concerned. Therefore search for agents that are effective, have less adverse effects on long-term use and prevent or control the complications are highly desirable. 

Varying experimental and clinical studies have reported the beneficial effects of fenugreek (Trigonella foenum-graecum) seeds, a traditional Indian medicine on glycaemic control and lipid profile in patients of T2DM.
from all the patients and they were advised regarding diet control and physical activity.

The patients were randomly divided into one of three subgroups i.e. group A, group B and group C comprising of 20 patients each. Group A received glipizide 5 mg once daily 30 minutes before breakfast, group B received fenugreek seed extract 500 mg twice a day half an hour prior to breakfast and dinner, group C received glipizide 2.5 mg once daily before breakfast and fenugreek seed extract 500 mg once daily 30 minutes prior to dinner. The fenugreek seed extract used was a hydroalcoholic extract of fenugreek seeds available commercially in the form of capsules of 500 mg each.

**Laboratory procedures**

After taking initial base line at 0 week, fasting blood glucose (FBG) levels were repeated at intervals of 2, 4, 8 and 12 weeks. HbA1C levels and lipid profile (TC, LDL-C, HDL-C, and TG) were estimated at 0 week and 12 week of the study period. The patient’s hospital visit was scheduled so that the blood samples were drawn in the morning after 12 hours overnight fast. Fasting blood glucose was analysed using GOD/POD method. For HbA1c and lipid profile, blood was allowed to clot at room temperature and serum was analysed by centrifugation at 2000 rpm for 10 minutes at 37 °C. HbA1C level was determined by Ion Exchange Resin Method.

**Statistical analysis**

The data were tabulated as mean±standard deviation. Results were analysed using the Chi-square test, student t-test and ANOVA (one-way), using Graphpad Instat 3 software. A p-value <0.05 was considered statistically significant.

**RESULTS**

A total of 60 patients (29 male and 31 females) completed this study. No patient dropped out from the study. The mean age of the patients was 56.45±10.3 years. The demographic and baseline laboratory characteristics of the patients were comparable between the treatment groups (Table 1).

| Baseline characteristics | Glipizide n=20 | Fenugreek n=20 | Glipizide+fenugreek n=20 |
|--------------------------|----------------|----------------|--------------------------|
| Age (years)              | 56.75±10.67    | 52.95±11.23    | 59.65±7.99               |
| Sex (M:F)                | 10:10          | 10:10          | 9:11                     |
| Family H/o diabetes      | n=7 (35 %)     | n=4 (20 %)     | n=6 (30%)                |
| Mean body weight (Kg)    | 68.9±7.45      | 71.45±11.87    | 70.9±12.12               |
| FBG (mg/dl)              | 172.2±18.96    | 164.9±18.72    | 173.55±16.94             |
| HbA1c (%)                | 8.365±1.16     | 7.932±0.9      | 7.788±0.99               |
| TC (mg/dl)               | 197.45±31.92   | 185.3±24.18    | 181.85±21.65             |
| Triglycerides (mg/dl)    | 199.96±31.71   | 182.91±29.21   | 181.65±32.58             |
| LDL-C (mg/dl)            | 112.8±26.21    | 105.41±20.23   | 102.79±19.48             |
| HDL-C (mg/dl)            | 43.7±5.59      | 43.31±4.46     | 42.74±4.20               |

All values expressed in mean±SD, except sex and family history of diabetes; SD, standard deviation.

**Fasting blood glucose**

A statistically significant decline in mean FBG levels was observed in group A by 33.97% (-58.5±9.5 mg/dl, p<0.001); in group B by 24.62% (-40.6±7.27 mg/dl, p<0.001); and in group C by 29.96% (-52±9.02 mg/dl, p<0.001), after 12 weeks of treatment (Table 2 and Figure1).

Intergroup analysis of FBG levels showed statistically significant difference between the treatment groups (p=0.0443) and post-hoc test revealed statistically significant difference only between group A and B (<0.05). Glipizide monotherapy was thus most efficacious in controlling FBG levels, followed by combination group, and then by fenugreek monotherapy. ADAs goal of FBGs 130 mg/dl was achieved in additional 17 (85%), 13
(65%) and 16 (80%) patients in group A, B and C, respectively, when compared to the baseline values (Table 3).

![Figure 1: Percentage decrease in fasting blood glucose levels over the study period.](image)

**Table 2: FBG and HbA1c levels expressed in mean±SD at baseline and after 12 weeks.**

|                | Group A |                | Group B |                | Group C |                |
|----------------|---------|----------------|---------|----------------|---------|----------------|
|                | Baseline | After 12 weeks | Mean difference | Baseline | After 12 weeks | Mean difference |
| FBG (mg/dl)    | 172±18.96 | 113.7±12.99 | 58.5±7.47 | 164.9±18.72 | 124.3±14.93 | 40.6±7.2 7* |
| HbA1c (%)      | 8.365±1.16 | 7.28±1.06 | 1.086±0.33* | 7.932±0.9 | 7.188±0.80 | 0.74±0.31* |

*p<0.001

**Table 3: Range of FBG and HbA1c levels at baseline, and goals achieved after 12 weeks, as per ADA guidelines.**

|                | FBG | HbA1c |
|----------------|-----|-------|
| 90-130 mg/dl   | Baseline | After 12 week | Baseline | After 12 week | Baseline | After 12 week |
| ≥ 131 mg/dl    | Baseline | After 12 week | Baseline | After 12 week | Baseline | After 12 week |
| ≤ 6.9%         | Group A (n) | 1 | 18 | 9 | 11 | 18 | 9 |
| ≥ 7.0%         | Group B (n) | 0 | 13 | 7 | 2 | 6 | 18 | 14 |
|                | Group C (n) | 0 | 16 | 4 | 4 | 10 | 16 | 10 |

**Total cholesterol**

On completion of 12 weeks study period, group A showed non-significant reductions in TC by 0.98% (p=0.1982) (Table 4). However, group B and group C showed statistically significant decrease in TC by 5.66% (p<0.001) and 3.87% (p<0.001), respectively. Intergroup analysis showed significant difference in TC levels between group A and B, and group A and C at 12 weeks (p<0.05). The difference between group B and group C was non-significant, although fenugreek alone decreased TC levels slightly more than the combination group. As per ICMR guidelines, the desired goals of TC<180 mg/dl was achieved in additional -1 (-5%), 3 (15%) and 1 (5%) patients in group A, B and C, respectively (Table 5).

**Triglycerides**

Statistically non-significant reduction in TG was seen in group A (-0.74%, p=0.0669), whereas group B (-17.23%, p<0.001) and group C (-11.34%, p<0.001) showed significant decrease in TG levels (Table 4). Intergroup analysis of TG levels showed significant difference between group A versus group B, and group A versus group C at 12 weeks (p<0.001); and the difference between group B and group C was non-significant.
significant group LDL Low to patients achieved guidelines, fall (p>0.05), with fenugreek monotherapy showing greater fall in TG levels than the combination group. As per ADA guidelines, the desired goal of TGs<150 mg/dl was achieved in additional 0 (0%), 8 (40%) and 6 (30%) patients in group A, B and C, respectively, in comparison to the baseline values as shown in (Table 5).

**Low density lipoproteins cholesterol**

LDL-C levels decreased non-significantly in group A (-0.74%, p=0.5482), and showed statistically significant decrease in group B (-4.15%, p<0.001), and group C (-2.68%, p=0.0463) (Table 4). Non-significant difference was observed on intergroup analysis of LDL-C between group A, B, & C at 12 weeks (p>0.05), although fenugreek group showed maximum decrease in LDL-C levels, followed by the combination group and then by glipizide group. The ADA guidelines target of LDL-C<100 mg/dl were achieved in 0 (0%), 1 (5%) and -1 (-5%) patients in group A, B and C, respectively over and above the corresponding baseline values (Table 5).

| Parameters                      | Group A Baseline | Group A After 12 weeks | p-value | Group B Baseline | Group B After 12 weeks | p-value | Group C Baseline | Group C After 12 weeks | p-value |
|--------------------------------|------------------|------------------------|---------|------------------|------------------------|---------|------------------|------------------------|---------|
| Total cholesterol              | 197.45±31.92     | 195.5±32.29            | 0.1982  | 185.3±4.18       | 174.8±22.38            | <0.0001 | 181.85±21.65     | 174.8±22.44            | <0.0001 |
| Triglyceride                   | 199.96±31.71     | 198.47±33.36           | 0.0669  | 182.91±29.21     | 151.4±22.24            | <0.0001 | 181.65±32.58     | 159.2±25.89            | <0.0001 |
| LDL cholesterol                | 112.8±26.21      | 111.97±28.49           | 0.1529  | 105.41±20.23     | 101.03±19.63           | 0.2072  | 102.79±19.48     | 100.03±20.18           | 0.0543  |
| HDL cholesterol                | 43.7±5.59        | 43.44±5.24             | 0.5482  | 43.31±4.46       | 43.59±4.5              | <0.0001 | 42.74±4.2        | 43.06±3.92             | 0.0463  |

**Table 5: Range of lipid levels at baseline and goals achieved after 12 weeks, as per ADA guidelines.**

| Lipid levels | TC <180 (mg/dl)^ | LDL<100 (mg/dl) | TG<150 (mg/dl) | HDL>45 (mg/dl) |
|--------------|------------------|----------------|----------------|----------------|
|              | Baseline | After 12 week | Baseline | After 12 week | Baseline | After 12 week | Baseline | After 12 week |
| Group A (n)  | 7        | 6              | 8      | 8              | 0        | 0              | 6        | 6              |
| Group B (n)  | 10       | 13             | 8      | 9              | 3        | 11             | 6        | 6              |
| Group C (n)  | 9        | 10             | 10     | 9              | 3        | 9              | 3        | 4              |

^The goals were as per ADA guidelines, except for total cholesterol where ICMR guidelines were followed.

**High density lipoproteins cholesterol**

Changes in HDL-C levels were statistically non-significant in all three groups at 12 weeks: group A showed a reduction in its levels by 0.60% (p=0.1529) whereas group B and C showed an increase in HDL-C values by 0.65% (p=0.2072) and 0.76% (p=0.0543) respectively (Table 4 and Figure 2). Intergroup analysis showed non-significant difference in HDL-C levels between group A, B, and C at 12 weeks (p>0.05); although the combination group of fenugreek and glipizide was slightly better in controlling HDL-C levels than fenugreek group. As per ADA guidelines, the desired goal of HDL-C>45 mg/dl was achieved in additional 0 (0%), 0 (0%) and 1 (5%) patients in group A, B and C, respectively (Table 5).
**Table 6: Number and type of adverse drug reactions in the three treatment groups.**

| Adverse drug reactions | Group A | Group B | Group C |
|------------------------|---------|---------|---------|
| Gastrointestinal tract | 15      | 15      | 15      |
| Dyspepsia              | -       | 2       | -       |
| Pain abdomen           | -       | 1       | -       |
| Flatulence/abdominal bloating | - | 5 | 2 |
| Diarrhoea              | -       | 1       | -       |
| Nausea                 | 1       | -       | -       |
| Hypoglycemia           | 1       | -       | -       |
| Headache               | 2       | -       | -       |
| **Total**              | **31**  | **31**  | **31**  |

**Adverse drug reactions**

15 (25%) adverse drug reactions (ADRs) were reported in 60 patients included in the study (Table 6). Maximum 9 (15%) of the ADRs were seen in patients on fenugreek as gastrointestinal adverse effects of dyspepsia, pain abdomen, abdominal bloating and diarrhoea; one patient had both pain abdomen and abdominal bloating. All the ADRs were mild in nature and none of the patient was withdrawn from the study because of serious adverse drug reactions.

**DISCUSSION**

Our results indicate that fenugreek seed extract 500 mg twice daily have hypoglycaemic and hypolipidaemic effects. As compared to the standard oral hypoglycaemic drug glipizide, which showed almost no effect on lipid profile, fenugreek caused significant improvement in dyslipidemia. Glipizide, on the other hand displayed better effect on glycaemic control than fenugreek. In combination therapy of fenugreek and glipizide, favourable effects were observed on both glycaemic control and lipid profile, which has shown addition of their pharmacological actions on said parameters.

**Glycaemic control**

In the present study, glipizide 5 mg once daily caused significant improvement in glycaemic control, as shown by significant decrease in FBG and HbA1c levels after 12 weeks of treatment. The hypoglycaemic effect of glipizide is well documented. In a similar study, a reduction in FBG levels by 42 mg/dl (25%) and HbA1c levels of 1.8% with glipizide therapy was reported by Testa et al. In another study, reduction in FBG level by 57-74 mg/dl and in HbA1c levels of 1.5-1.82 % after 3-5 month treatment with glipizide have been observed. Our study showed similar decrease in FBG levels, but lesser decrease in HbA1c levels.

Patients on fenugreek monotherapy also showed a statistically significant improvement in glycaemic control, although lesser than glipizide. In a similar double blind study by Gupta et al in 25 patients with T2DM on 500 mg twice daily dose of fenugreek seed extract, a reduction in FBG levels by 19.15% (148.3±44 to 119.9±25) and in HbA1c levels by 8.61% (8.25±1.2 to 7.54±0.9) over a study period of 8 weeks was reported. Our study showed similar decrease in FBG levels by 21.38% at 8 weeks (Figure 1), and in HbA1c levels at 12 weeks. Another study involving 60 patients with type 2 diabetes whose diets were supplemented with 25 g powdered fenugreek seeds per day for 24 weeks, patients with mild type 2 diabetes were benefitted the most and were able to completely withdraw from the use of oral medications and insulin. Also, the hypoglycaemic effect of fenugreek has been shown by studies of Sharma et al, Bordia A et al, Sharma RD et al. These above studies except the one by Gupta et al, have used powdered fenugreek seeds, whereas in our study the hydro-alcoholic extract of fenugreek seeds was used; it could probably be associated with similar effects at lower dose.

The defatted seed that remains after lipid extraction is primarily thought to be responsible for lowering blood glucose levels. The hypoglycaemic effects of fenugreek is attributed to several mechanisms: 4-hydroxyisoleucine, an amino acid extracted from fenugreek seeds increases glucose-induced insulin secretion from pancreatic beta cells; fibre in the seed delays gastric emptying and slows carbohydrate absorption; activates insulin signaling pathways in adipocytes and liver cells, leading to stimulatory effect on cellular glucose uptake; inhibits the activities of alpha-amylase and sucrase, two intestinal enzymes involved in carbohydrate metabolism; increases the number of insulin receptors, and improve peripheral glucose utilization; improves insulin sensitivity and decreases insulin resistance. Certain studies have shown that fenugreek has no effect on fasting or postprandial blood glucose in non-diabetic subjects.

Combination therapy with fenugreek and glipizide also showed significant improvement in glycaemic control. There is no such study in literature that reports a combination of fenugreek and glipizide. Although half the doses of monotherapy of glipizide and fenugreek were used, glycaemic control was better than that of fenugreek alone.

**Lipid profile**

Studies have shown that glipizide does not show significant effect on lipid profile, and also was not shown in this study. The results of the present study are in consistent with diabetes control and complication trial research group and UK prospective diabetes study group.
In the present study, administration of fenugreek seed extract 500 mg twice daily caused a statistically significant improvement in dyslipidemia, except for HDL-C where it caused non-significant increase. Also, among the lipoproteins, LDL-C is considered to be one of the most important risk factor in causing CHD; however the reduction in LDL-C were much lesser than with TGs and slightly less than TC. Similar study by Gupta et al reported that incorporating 1 gram per day of hydroalcoholic extract of fenugreek seed in patients with T2DM over 8 weeks decreased the levels of TGs by 28.88% (-53.2 mg/dl) from the initial baseline concentrations. However, the levels of TC, LDL-C and HDL-C increased by 8.1% (14 mg/dl), 19.74% (18.3 mg/dl) and 4.19% (1.9 mg/dl), respectively.\textsuperscript{22} Our study showed significant but lesser decrease in TGs and much lesser increase in HDL-C, however TC and LDL-C levels decreased significantly; these could be associated with longer duration of the present study conducted over 12 weeks in comparison to 8 weeks by Gupta et al. In another study, which involved administration of defatted fenugreek seeds powder (50 gm/d and 100 gm/d to different groups) over 20 days, showed that the levels of TC were decreased by 26.07% and 33.1%, TGs by 26.5% and 39.26%, and LDL-C by 30.6% and 38.22% in groups on 50 gm/d and 100 gm/d powder respectively. The levels of HDL-C were decreased by 6.67% and 6%.\textsuperscript{32} Another study shows the effect of fenugreek on 15 non obese, asymptomatic, hyperlipidemic adults administered 100 g defatted fenugreek powder per day for three weeks. Their TG and LDL-C levels were lower than baseline values and slight decreases in HDL levels were also noted.\textsuperscript{33} Lipid profiles were normalized in 60 patients with T2DM whose diets were supplemented with 25 g powdered fenugreek seeds per day for 24 weeks.\textsuperscript{30} Also, the anti-cholesterolemic actions of fenugreek has been shown by studies of Borda et al, Sharma RD et al.\textsuperscript{23,25} These above studies show better effect on lipid profile than the present study, this probably could be associated with much larger doses of fenugreek seed powder administered over shorter duration in these studies. Also, all these studies except the one by Gupta et al have used fenugreek seed powder, whereas in our study the hydroalcoholic extract of fenugreek seeds was used, which could probably be associated with similar effects at lower dose.

A number of mechanisms are responsible for hypolipidaemic effects of fenugreek; inhibit the intestinal absorption of cholesterol, this is attributed to sapogenins which absorb bile acids and increase their excretion in faeces, which leads to an increased conversion of cholesterol into bile acids by the liver, thus decreasing its levels.\textsuperscript{56,55-57} Another mechanism is attributed to fibre in the seed, it absorbs bile salts and might influence the enterohepatic circulation of bile acids and enhances cholesterol metabolism, thus reducing triglyceride levels.\textsuperscript{58} Also, the estrogenic constituent of fenugreek may cause decrease in lipid levels, by indirectly increasing thyroid hormone T4.\textsuperscript{59}

In patients on combination therapy, a statistically significant improvement in lipid profile is seen except that for HDL-C which showed non-significant increase. The improvement was however, lesser than that seen with fenugreek monotherapy. Literature search could not reveal any study involving a combination of fenugreek and glipizide.

**Safety profile**

Glipizide monotherapy was well-tolerated by the patients, and safety profile was similar to earlier studies.\textsuperscript{24,60} Earlier investigators had reported excellent tolerability profile with fenugreek seeds, and was similarly observed in the present study, although in our study more number of patients (40%) on fenugreek monotherapy had ADRs, which were mild in nature and most improved after few days of use.\textsuperscript{25} It has also been observed that ADRs of fenugreek on gastrointestinal system are dose-dependent, as in the combination therapy, only 10% of patients experienced these adverse effects.

Some limitations associated with the study were small sample size; the patients were followed only over 12 weeks, longer follow-up would have revealed better effect on the efficacy and safety of the drugs; and the study was open-label.

**CONCLUSION**

In conclusion, Glipizide and fenugreek seed extract as monotherapy and combination therapy showed significant improvement in glycaemic control in patients with type 2 diabetes at the end of 12 weeks study period; with glipizide showing superior efficacy followed by combination group and then by fenugreek monotherapy. Glipizide monotherapy had no favourable effect on lipid profile; fenugreek as monotherapy and in combination with glipizide produced significant improvement in dyslipidemia, with fenugreek monotherapy showing better response. The drugs were safe and well tolerated. Fenugreek seed extract as monotherapy or add-on therapy can prove to be a useful agent in treatment of mild type 2 diabetes mellitus with or without dyslipidemia, provided its favourable effects are confirmed in multi-centric trials involving larger number of patients over longer duration.

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