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ORIGINAL ARTICLE

Efficacy and Safety of Herbal Formulation Rich in Standardized Fenugreek Seed Extract as Add-on Supplementation in Patients with Type 2 Diabetes Mellitus on Sulfonylurea Therapy: A 12-week, Randomized, Double-blind, Placebo-controlled, Multi-center Study

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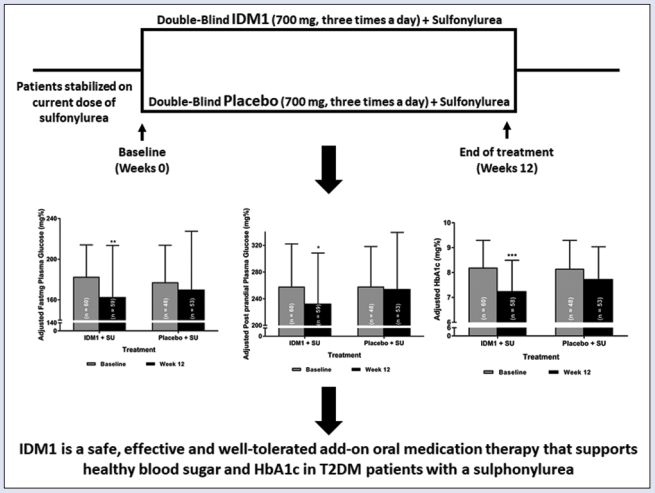
ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a chronic, complex, and progressive illness that often needs combination therapy for better glycemic control. IDM1, an herbal formulation which is rich in standardized fenugreek seed extract. **Aim:** The aim of this study is to evaluate the efficacy and safety of add-on therapy of IDM1 in T2DM patients inadequately controlled on sulfonylurea monotherapy. **Materials and Methods:** In this 12-week, randomized, double-blind, placebo-controlled, multi-centric study, T2DM patients which inadequate glycemic control with background stable dose medication of sulfonylurea was screened (n = 120). The patients were randomized 1:1 to add-on therapy of IDM1 and placebo, 700 mg three times daily for 12 weeks. **Results:** A total of 119 patients were randomized and included in the efficacy analysis (IDM1, n = 60; placebo, n = 59). At week 12, adjusted fasting plasma glucose (FPG) (20 mg%), postprandial plasma glucose (PPPG) (26 mg%), and glycated hemoglobin (HbA1c) (0.9 mg%) was reduced significantly (P < 0.05) from baseline as compared to placebo group (FPG: 7 mg%; PPPG: 4 mg% and HbA1c: 0.4 mg%). These beneficial effects were seen as early as 1 month after consumption of IDM1 and continued until at least 15 days after withdrawal of IDM1. Hypoglycemic events were mostly mild, and none required emergency treatment. There were no major changes in body weight, hematology, and biochemistry at week 12 as compared to baseline. Overall AEs rates were similar in both groups. **Conclusions:** IDM1 is a safe, effective, and well-tolerated add-on oral medication therapy that supports healthy blood sugar levels and glycosylated hemoglobin levels in T2DM patients inadequately controlled with a sulfonylurea.

Key words: Add-on therapy, glycemic control, glycated hemoglobin, standardized fenugreek seed extract, sulfonylureas, type 2 diabetes

SUMMARY

- IDM1, an herbal formulation which is rich in standardized fenugreek seed extract
- In this 12-week, randomized, double-blind, placebo-controlled, multi-centric study, T2DM patients which inadequate glycemic control with a stable dose of sulfonylurea was received add-on therapy of IDM1 (700 mg, three times daily) for 12 weeks
- At week 12, add-on therapy of IDM1 showed significant (P < 0.05) reduction in adjusted FPG (20 mg%), PPPG (26 mg%), and HbA1c (0.9 mg%) from baseline as compared to placebo group
- Thus, IDM1 is a safe, effective, and well-tolerated add-on oral medication therapy that supports healthy blood sugar levels and glycosylated hemoglobin levels in T2DM patients inadequately controlled with a sulfonylurea.



Abbreviation used: AEs: Adverse events; ALP: Alkaline phosphatase; ALT: Alanine transaminase; AST: Aspartate transaminase; BMI: Body mass index; BUN: Blood urea nitrogen; FPG: Fasting plasma glucose; GGT: Gamma glutamyl transferase; HbA1c: Glycated hemoglobin; HDL: High-density lipoproteins; LDH: Lactate dehydrogenase; LDL: Low-density lipoproteins.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex, chronic, and fast-growing multi-system illness which characterized by insulin resistance and pancreatic β-cell dysfunction.[1,2] These leads to consequence such as hyperglycemia, obesity, acute, and chronic diabetic complications including nephropathy, non-traumatic lower-limb amputations, retinopathy, and cardiomyopathy.[3,4] The worldwide prevalence of T2DM has increased three times in the past 30 years, and it is estimated to affect more than 350 million people by 2025.[5] The mortality related to T2DM has estimated to increase twice from 2005 to 2030.[6] It has been reported that in developed countries two-third patients with T2DM unable to control their glucose levels effectively, whereas in developing countries like India this proportion is even at a higher level.[7,8] T2DM is associated with increased health-care cost and economic burden. The total cost of diabetes management in the United States is $322 million[9] whereas, in India, it is USD 353.55 per patient.[10]

The clinical objective of the T2DM treatment is to achieve metabolic control and to reduce the risk of long-term complications.[11,12] The effectiveness of the treatment largely depends on some extent of patient's habits, living style, exercise, medication such as tablets and insulin. Inadequate metabolic control leads to develop the complications, which was associated with many functional limitations and health-related quality of life (QoL).[13,14] It has been well established that failure to maintain the targeted level of glycated hemoglobin (HbA1c) resulted in progressive T2DM. According to the recommendation of the American Diabetes Association (ADA) as well as the European Association for the Study of Diabetes (EASD), lifestyle modifications along with metformin as a first-line treatment for T2DM.[15] Metformin is the first-line treatment choice due to its glucose-lowering potential, lower side effect, and relatively cost-effective.[9] However, patients with higher baseline HbA1c were unable to achieve their glycemic goals using metformin monotherapy despite administration of its maximum tolerated doses.[16,17] In addition, metformin also has approximately 20% failure rate over a period of 5 years.[18] Thus, such patients need additional anti-diabetic medication with different mechanisms of action to control deteriorated glycemic condition. In the view of this, the strategy of step-wise approach for combination therapy has been suggested by the ADA and EASD.[15]

Sulfonylureas and dipeptidyl-peptidase-4 (DPP-4) inhibitors are a second-line treatment for the T2DM that prescribed worldwide.[19,20] Sulfonylureas (SU, such as gliclazide) can direct stimulation of pancreatic β-cells that increases insulin secretion and monitor blood glucose level.[21] However, SU has their downsides such as the risk of hypoglycemia, weight gain, and development of secondary failure.[22] Moreover, SU has limited ability to provide sustained glycemic control over the long term for patients with T2D. Therefore, the American Association of Clinical Endocrinologists clinical guidance now recommended DPP-4 inhibitors (such as sitagliptin), Thiazolidinediones (TZDs) (such as pioglitazone and rosiglitazone), and insulin over sulfonylureas.[23] However, clinical evidence showed the increase in the risk of myocardial events and nephrotoxicity along with the use of this agents.[24] Furthermore, these conventional agents also associated with high-economic burden such as ≤21k for the addition of sulfonylurea to the patients uncontrolled on metformin.[25]

Despite significant development in the pharmaceutical drug industry, management of T2DM using treatment regimen with fewer side effects at lower costs is a major medical problem. In addition, these treatment regimens often more complex and may result in undesirable outcomes including body weight gain, edema, bone loss, β-cell dysfunction, and cardiovascular failure in the long term.[22] Hence, alternative treatment strategies are required. A good number of natural products are popular but have not been scientifically scrutinized for their potential anti-hyperglycemic effects.[26-32] Due to safety, many International guidelines advocated the use of potential options as an add-on therapy for the treatment of T2DM.[9,15,33,34] Thus, medicines from the herbal origin can be a good option for this add-on therapy with relatively safe with fewer undesirable side effects when compared with conventional drugs.

It has been documented that conventional treatment such as DPP-4 or SU acts by a specific mechanism to treat T2DM which is insufficient in current settings.[35] Hence, there is a need for treatment strategy with a combination of various potential ingredients that act on multiple metabolic pathways to exhibits its synergistic effect.[36] Moreover, there is an array of the medicinal plants has been reported to possess a potent diabetic activity that plays a vital role in human health care.[37-41] Although, conventional medicine showed more potency to treat T2DM than herbal medicine, their combination or add-on therapy with the conventional medicine will improve better therapeutic outcomes with fewer side effects.

Trigonella foenum-graecum L. (fenugreek) is a popular plant in the family *Fabaceae* used widely for the treatment of diabetes in Asian countries such as India and China. Fenugreek seeds is abundant source of carbohydrate (mucilaginous fiber and galactomannan), proteins, alkaloids (trigonelline and choline), flavonoids, free amino acids (4-hydroxyisoleucine, arginine, lysine, histidine), saponins (diosgenin, similagenin, savsalpogenin, and yuccagenin), glycosides, vitamins (A, B2, B6, B12, D), β-carotene, calcium, iron, minerals, mucilage, proteids, fixed oil, and volatile oils.[42-48] The presence of 4-hydroxyisoleucine shown to exhibit insulinotropic potential *in vitro*.[49-51] The antidiabetic effect of fenugreek seeds in animal models and diabetic humans has been demonstrated via decreasing blood glucose and improving glucose tolerance.[52,53]

Gymnema sylvestre Schult (family: *Apocynaceae*), *Salacia reticulata* Wight (*Hypocrataceae*), *Camellia sinensis* Linn. (*Theaceae*), *Emblica officinalis* Gaertn.(*Euphorbiaceae*), *Tribulus terrestris (Zygophyllaceae)* and *Linum usitatissimum* (*Linaceae)* are some tropical plants abundantly present in India. Numerous clinical evidence reported antidiabetic potential of these plants in T2DM patients.[54-64] *Piper nigrum* (Marica) have been reported for its potential antidiabetic and antioxidant activity.[65] The previous researcher reported that *Piper nigrum* has the potential to increase the bioavailability of oral hypoglycemic agent such as metformin.[66] This combination is useful to reduce the dose and adverse effect of the conventional antihyperglycemic agent.

Although many studies have been conducted to evaluate the effect of hundreds of herbal supplements, either alone or in combination for the treatment of T2DM, the efficacy outcome remains sluggish in recent years. Furthermore, to the best of our knowledge, no study has been carried out to evaluate the effects of these herbal supplements in alone or in combination as an add-on therapy with conventional treatment. Hence, the present study was undertaken with an aimed to evaluate the efficacy and safety of add-on therapy of herbal formulation which is rich in standardized fenugreek seed extract (IDM1) in a randomized, double-blind, placebo-controlled, multi-centric study in T2DM patients on sulfonylurea.

MATERIALS AND METHODS

Study design and protocol

This was a 12-week, randomized, double-blind, placebo-controlled, multi-centric study where the efficacy and safety of herbal formulation which is rich in standardized fenugreek seed extract (IDM1), 700 mg, three times daily was evaluated as add-on therapy in patients with T2DM

inadequately controlled with a sulfonylurea (CTRI Registration Number: CTRI/2018/04/013230).

The study comprised a screening and enrolment period (visits [−1]), where a total of 119 individuals were randomly assigned to the core treatment period at a 1:1 ratio to receive placebo (microcrystalline cellulose, IP grade) and IDM1, 700 mg, three times daily orally before food for 3 months. A stable dose of sulfonylurea was to be continued throughout the run-in period and double-blind treatment phase, unless adjustment was clinically required. Study visits occurred at randomization (visit 0) and every week of double-blind treatment (visit 1 to visit 3). At visit V3, study drug was discontinued, and the patient was followed up after 15 days (visit V4). This marked the end of study including follow-up for the individual patient [Figure 1].

Group assignment of patients was blinded for both the principal investigator and other investigators performing outcome analyses by the use of a coding system, where the codes were kept by the independent allocator and revealed only after completing treatment periods and analyses.

Compliance with ethics

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki (Version: Scotland, Edinburgh, 2000, previous version: Somerset, South Africa 1996) as well as consistent with good clinical practice guidelines as defined by the International Conference on Harmonization. Informed consent was obtained from all patients who were included in the study.

Inclusion and exclusion

Inclusion criteria

(i) Type II (noninsulin dependent) diabetic patients age group of 25–70 years both inclusive (either sex), (ii) fasting plasma glucose (FPG) between 140 mg/dl (7.8 mmol/L) and 250 mg/dl (13.8 mmoI/L) both inclusive, (iii) FPG between 140 mg/dl and 250 mg/dl both inclusive that does not vary more than 30 mg/dl during 15 days run in period, (iv) HbA1c 7.0%–12.0% both inclusive, (v) Body Mass Index (BMI) 22–35 both inclusive, (vi) Stabilized at same dose of medication (sulphonylurea) for a minimum period of 6 weeks, (vii) No history of nephropathy/ketonuria, (viii) No history of HIV, (ix) Pregnancy test negative, (x) No participation in any other trial during the past 30 days, (xi) No history of allergy to the ingredients or plant products or derivatives.

Exclusion criteria

(i) Patients above 71 years, (ii) Patients treated with a drug within the past 30 days that has not received regulatory approval at the time of study entry, (iii) Participation in a clinical study during the past 30 days, (iv) FPG more than or equivalent to 251 mg/dl, (v) liver function test (LFT) (aspartate transaminase [AST], and alanine transaminase [ALT]) ≥2.5 times the upper limit of normal values, (vi) Requiring a dose of insulin for surgery or other indication, (vii) History of HIV, (viii) Creatinine ≥1.5 mg/dl, (ix) Pregnant or intend to become pregnant during the study or not actively practicing birth control measures or breastfeeding, (x) Retinopathy and/or nephropathy with persistent macroalbuminuria, (xi) Patients classified as Class III or Class IV Heart disease, (xii) Abnormal laboratory values revealed on the analysis on base line visit (visit 0), (xiii) Patients with clinical signs and symptoms of drug or alcohol abuse, and (xiv) Patients undergoing therapy for a malignancy other than basal cell or squamous cell skin cancer.

Randomization

Randomization generated based on random number tables before the study. To maintain blinding after randomization, HbA1c and FPG values were masked to study centers unless these values met prespecified glycemic rescue criteria. After completion of the core treatment period, the database was locked, and the study was unblinded for regulatory filing; patients, investigators, and local sponsor personnel remained blinded throughout the extension period.

After randomization, the assignment of patients and their investigational product to the treatments were carried out according to previously reported method.[67]

Study supplementation

After dispensing IDM1 or matching placebo supplementations, baseline characteristics of subjects were recorded. Both IDM1 and placebo were enclosed in bottles-containing capsules that were identical in appearance and individually coded. The IDM1 [Supplementary file 1] and placebo (microcrystalline cellulose, IP grade) capsules were supplied by Indus Biotech Private Limited, Pune. Both IDM1 and placebo were analyzed and complied with quality requirements related to microbial content and heavy metals.

Study outcomes

The primary efficacy outcome was the control of FPG or reduction or FPG levels attributed to the IDM1 therapy. The primary variable on an individual level was the time course of FPG levels, measured as a reduction in FPG values compared over the baseline values during the treatment with IDM1.

The secondary efficacy outcomes were reduction in postprandial plasma glucose (PPPG) levels, HbA1c and lipid profiles (i.e., triglycerides,

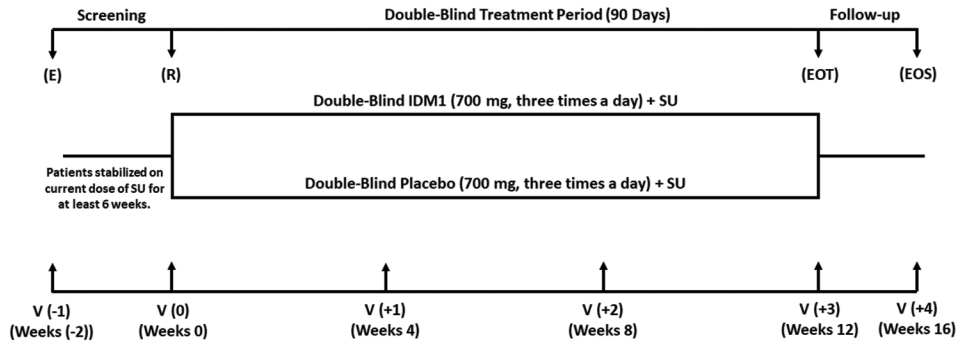

Figure 1: Study design. E: Enrolment; EOT: End of treatment; EOS: End of Study; R: Randomization; SU: Sulphonylurea; V: Visit

high-density lipoproteins-Cholesterol (HDL-C), Low-density lipoproteins-Cholesterol (LDL-C), total cholesterol, and HDL: LDL ratio) from baseline to week 12.

Safety assessments included any adverse events (AEs), clinical laboratory parameters, body weight, vital signs (systolic and diastolic blood pressure and heart rate), physical examination, electrocardiogram (ECG) parameters, episodes of hypoglycemia, and number of AEs and serious AEs during the study.

The reported AEs or changes in other safety parameters were evaluated by each investigator at the site to determine whether the events showed a causal relationship with the study drug. Hypoglycemia was defined as a measured plasma glucose level <70 mg/dl and was classified as symptomatic or asymptomatic according to the existence of any symptoms or signs associated with hypoglycemia. Severe hypoglycemia was defined as a hypoglycemic event that required the assistance of another person or hospitalization.

Biochemical and anthropometric analyses

Body weight, height, and date of birth were recorded at baseline. ECG was recorded on Visit 0 and Visit 3.

Blood samples collected at every visit were used for fasting and PPPG levels estimation. Blood samples collected on Visit 0 and Visit 3 were analysed for FPG, HbA1c, PPPG, LFT (ALT, AST, gamma glutamyl transferase [GGT], lactate dehydrogenase, alkaline phosphatase [ALP], total protein, total bilirubin), lipid profile (total cholesterol, HDL-C, LDL-C, HDL: LDL ratio, triglycerides), kidney function test (creatinine, blood urea nitrogen [BUN]), haematology (total leukocyte count, differential leukocyte count, hemoglobin, red blood cell count, platelet count), urine analysis (glucose, albumin, and ketone) by dipstick method.

Urine samples were tested at each visit for glucose, albumin, and ketones. At each visit, pregnancy test was done for female patients of childbearing age.

Statistical analyses

Sample size determination was based on revealing the superiority of IDM1 to placebo at week 12. An estimated 50 randomized patients per treatment group were required to achieve ≥90% power, assuming a between-group difference of 0.5% and a common standard deviation (SD) of 1.0%, and using a two-sample, two-sided *t*-test with a type I error rate of 0.05. The sample size was expanded to 60 patients per group to enhance the safety and tolerability assessment of IDM1 in patients on sulfonylurea.

Results are expressed as means ± SD. Statistical analysis was performed using SAS programs (SAS Release 8.2, SAS Institute Inc., NC, USA). Students *t*-test was used for comparing means of continuous variables at baseline and visit 3 across the groups. Paired "*t*" test was used for comparing the difference between means of continuous parameters within the same group. Chi-square test was used for analysis of the incidence of hypoglycemia across two groups. The glucose levels at each follow-up visits were compared with the start of the diagnosis using Mann-Whitney U test. The difference was considered statistically significant if the *P* value was below 0.05.

RESULTS

Patient disposition, patient demographics, and baseline characteristics

A total of 120 patients were screened of which 119 participants have met the inclusion criteria for this study and received study medication. There was one patient who was dropped before receiving any study medication due to inclusion violation. Of the 119 patients, 50.43% (n = 60/119) of the patient was randomly allocated to the add-on treatment of IDM1 along with SU and remaining 49.57% (n = 59/119) of the patient received the placebo along with SU. Among them, 63.33% (n = 38/60) of patients in the IDM1 group and 67.80% (40/59) of patients in the placebo group completed 12 weeks of treatment [Figure 2].

The most common reason for discontinuation was lack of compliance (40.9% [9/22] in the IDM1 group and 21.05% [4/19] in the placebo). There were three patients in the IDM1 group and two patients in the placebo group who discontinued due to AEs [Figure 2].

The demographic and baseline characteristics of the randomized patients were similar between the treatment groups [Table 1]. At entry to the study, mean age was 51.48 years and 51.42 years in IDM1 and placebo, respectively. The baseline characteristics for IDM1 versus placebo were HbA1c (8.56 mg% vs. 8.50 mg%), BMI (26.08 kg/m^2 vs. 26.36 kg/m^2), and FPG (182.91 mg% vs. 177.42 mg%), respectively [Table 1].

Effects of add-on IDM1 therapy on glucose regulation

The FPG levels did not differ significantly between the IDM1 and placebo at baseline. There was a significant improvement ($P < 0.01$) in FPG at week 12 (162.80 ± 50.72 mg%) in IDM1 add-on therapy group from week 0 (i.e., baseline) (182.68 ± 31.37 mg%), whereas placebo treatment did not show any significant change in the FPG at week 12 (177.20 ± 36.54 mg%) as compared to week 0 (170.05 ± 57.45 mg%). The mean FPG values decreased by approximately 20 mg % from

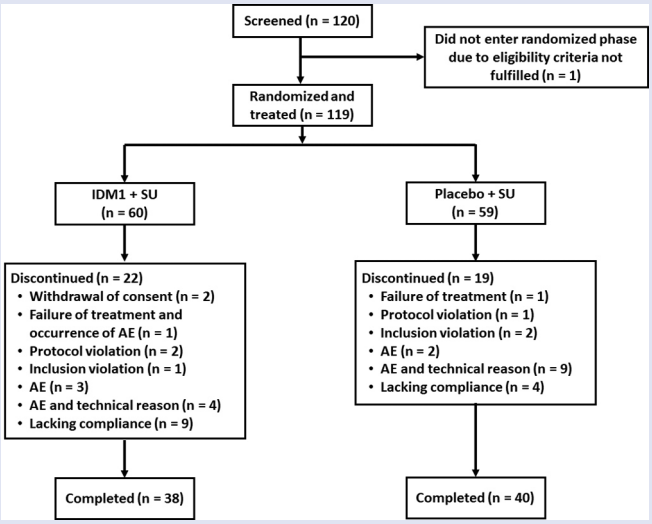

Figure 2: Patient disposition. AE: Adverse event; SU: Sulphonylurea

Table 1: Patient demographics and clinical characteristics

Characteristic	IDM1 + SU (*n*=60)	Placebo + SU (*n*=59)
Age (year)	51.48 (9.30)	51.42 (9.61)
Height (cm)	157.01 (10.84)	154.51 (8.70)
Weight (kg)	64.68 (12.36)	62.95 (8.97)
BMI (kg/m^2)	26.08 (3.49)	26.36 (3.28)
Male (*n*)	29 (48.33)	24 (40.67)
Female (*n*)	31 (51.66)	35 (59.32)
HbA1c (mg %)	8.56 (1.19)	8.50 (1.20)
PPPG (mg %)	258.2 (64.01)	258.278 (60.04)
FPG (mg %)	182.91 (31.42)	177.42 (36.6)

Values are presented as the mean (SD). BMI: Body mass index; FPG: Fasting plasma glucose; HbA1c: Glycated hemoglobin; PPPG: Postprandial glucose; SU: Sulphonylurea; SD: Standard deviation

baselines in the IDM1 group while a decrease in the placebo group was only 7 mg% [Figure 3a].

At baseline, PPPG level in IDM1 group did not differ significantly as compared to placebo control group. The addition of IDM1 to sulfonylurea significantly ($P < 0.05$) reduced PPPG from baseline (258.15 ± 64.01 mg%) to week 12 (232.46 ± 76.04 mg%) as compared with placebo added to sulfonylurea (from 258.23 ± 60.03 mg% to 254.49 ± 84.93 mg%). The mean PPPG values decreased by approx. 26 mg% from baselines in the IDM1 group while a decrease in the placebo group was only 4 mg% [Figure 3b].

Add-on treatment with IDM1 showed a significant reduction ($P < 0.05$ and $P < 0.001$) in FPG starting at week 8 and week 16 (i.e., at follow-up period) as compared to baseline. Moreover, there was a significant reduction ($P < 0.05$) in PPPG starting at week 4 and week 8 as when compared with baseline. However, the placebo-treated group did not show any significant reduction in FPG and PPPG over a period of week 4, 8, 12, and 16 as compared to baseline.

Subgroup analysis was conducted at week 12 for patients who experience no change in sulfonylurea dose over the study period. This showed a significant reduction ($P < 0.01$) in FPG and PPPG at week 12 as compared with baseline. However, in subgroup analysis, placebo-treated patients did not show any significant reduction in FPG and PPPG levels at week 12 as compared to baseline [Table 2].

Effects of add-on IDM1 therapy on secondary efficacy endpoints

There was no statistically significant difference in HbA1c in IDM1 group as compared to placebo at baseline. At week 12, HbA1c level in IDM1 add-on group was significantly ($P < 0.001$) reduced from baseline (from 8.20 ± 1.10 mg% to 7.25 ± 1.24 mg%), whereas placebo group did not show any significant reduction in HbA1c from baseline (8.15 ± 1.14 mg%) to week 12 (7.74 ± 1.30 mg%). The mean HbA1c values decreased by approx. 0.9 mg% over 12 weeks in the IDM1 group while a decrease in the placebo group was only 0.4 mg% [Figure 4].

Subgroup analysis showed a significant reduction ($P < 0.001$) in HbA1c level at week 12 as compared to baseline. However, in subgroup analysis, placebo-treated patients did not show any significant reduction in HbA1c level at week 12 as compared to baseline [Figure 4].

At the baseline, evaluations of all selected T2DM patients revealed no statistically significant differences for lipid profile (total cholesterol, HDL-C, LDL-C, and triglycerides) between groups assigned to treatment with IDM1 and placebo. The addition of IDM1 to the SU treatment significantly increases total cholesterol and LDL-C from baseline to week 12 [Table 3]. However, in IDM1 add-on treatment group, there was no significant change in HDL-C, triglycerides, and HDL: LDL ratio in week 12 from baseline. However, these statistical differences were within the normal limits. Furthermore, the placebo-treated group also did not show any significant differences in lipid profile at week 12 as compared to baseline [Table 3].

Table 2: Subgroup analysis for patients showing no change in dose of sulfonylurea

Characteristic[#]	IDM1 + SU		Placebo + SU	
	Week 0 (*n*=44)	Week 12 (*n*=32)	Week 0 (*n*=38)	Week 12 (*n*=33)
FPG (mg %)	176.55±30.2	146.21±47.99**	172.48±40.59	155.78±56.19
PPPG (mg %)	248.17±64.66	205.34±66.06**	241.67±61.09	225.00±73.36
HbA1c (mg %)	8.19±1.15	6.88±1.13***	8.08±1.18	7.40±1.20

Values are presented as the mean±SD. Data was analysed by paired *t*-test; **$P<0.01$ and ***$P<0.001$ as compared with baseline; [#]Adjusted values. FPG: Fasting plasma glucose; HbA1c: Glycated hemoglobin; PPPG: Postprandial glucose; SU: Sulphonylurea; SD: Standard deviation

Effects of add-on IDM1 therapy on safety and tolerability outcomes

Over the 12-week treatment period, the overall incidence of AEs was similar across treatment groups and summarized in Table 4. The incidence of AEs leading to study discontinuation was low and similar to IDM1 ($n = 3$) compared with placebo ($n = 2$). During the study period, overall incidences of drug-related AEs were higher with IDM1 compared with placebo (41.66% vs. 32.20%). The severe AEs were experienced by 1 (1.66%) patient in the IDM1 group and 1 (1.69%) patient in the placebo group. In IDM1 group, one AEs was hypertriglyceridemia which considered unrelated to study medication. The incidence of hypoglycemia related to study medication was experienced by 10 (16.66%) patients in IDM1 group and 3 (5.08%) patients in the placebo group. However, none of the hypoglycemia events were classified as severe, and none of them led to the discontinuation from the study.

The changes in body weight, BMI, hematology, creatinine, BUN, ALT, AST, ALP, albumin, GGT, and total bilirubin were not significantly different between the IDM1 and placebo groups at baseline [Supplementary files 2 and 3]. The glycemic improvement was achieved by IDM1 add-on therapy without any major change of hematology and

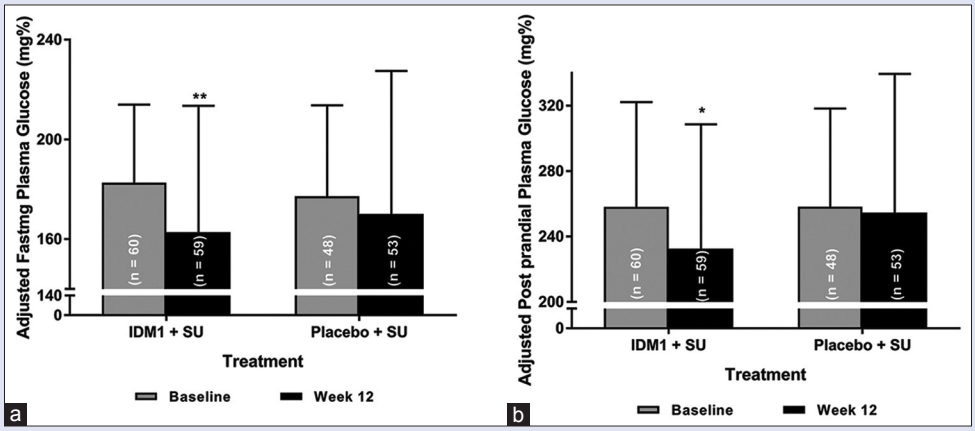

Figure 3: Adjusted fasting plasma glucose level (a) and post prandial plasma glucose level (b) at baseline and week 12. Values are shown as the mean (standard deviation). Data were analyzed by paired *t*-test, *$P < 0.05$ and **$P < 0.01$ as compared with baseline. SU: Sulphonylurea

biochemistry at week 12 as compared to baseline. Similarly, no significant changes in the body weight, BMI, hematology, and biochemistry in the placebo group at week 12 when compared with baseline.

Treatment compliance

A total of 20 patients were found to have overall compliance <75% of which 12 belonged to IDM1 and 7 belonged to the placebo group. Overall 25% of patients from the IDM1 group and 13.46% of patients from placebo group had inadequate compliance. Only two of these patients were withdrawn due to lack of compliance. All others were withdrawn due to various other reasons. None of these patients was withdrawn due to an AE.

DISCUSSION

T2DM is the most prevalent disease worldwide, and due to increased insulin resistance, it is a major cause of morbidity and mortality.[68] In a dynamic therapeutic landscape of anti-diabetic medications, patient-related factors (lifestyle and glycemic monitoring) have evolved as a decisive facet responsible for optimal glycemic balance, in T2DM patients.[69] In the present study, the add-on treatment with an herbal formulation which is rich in standardized fenugreek seed extract (IDM1), 700 mg for 12 weeks in T2DM patients significantly reduced FPG, PPPG and HbA1c levels as compared to placebo treatment. Subgroup analysis in the patients who experience no change in sulfonylurea dose over the study period also showed a significant reduction in FPG, PPPG and HbA1c levels. These beneficial effects were seen as early as 1 month after consumption of IDM1 and continued until at least 15 days after withdrawal of IDM1. Thus, add-on therapy with IDM1 to sulfonylurea therapy was well tolerated without any alterations in body weight, BMI, and serious AEs.

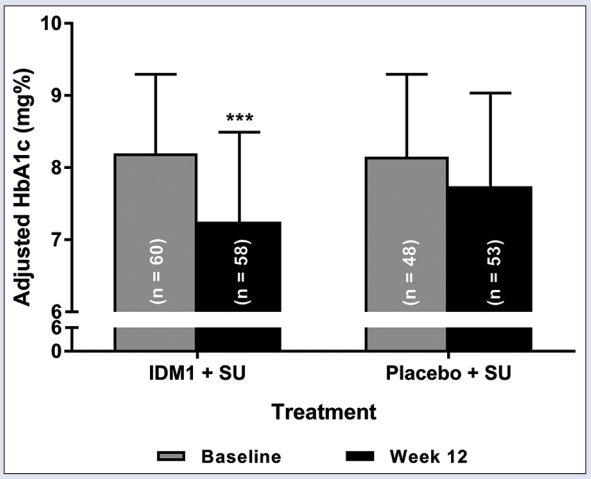

Figure 4: Adjusted HbA1c level at baseline and week 12. Values are shown as the mean (standard deviation). Data were analyzed by paired *t*-test, ***$P < 0.001$ as compared with baseline. HbA1c: Glycated hemoglobin; SU: Sulphonylurea

It has been well reported that increased FPG levels are associated with major micro and macrovascular complications.[70-72] Furthermore, fluctuation in FPG and PPPG affects HbA1c which is considered as a measure for prevention of diabetes and its complications.[73] Thus, amelioration of FPG levels is beneficial for prevention of progression of diabetes and related microvascular disease. The currently available treatment regimen such as oral antidiabetic drugs and insulin are associated with undesirable effects that limit their efficacy.[15] Hence, many T2DM patients need add-on treatment along with present conventional therapy to ameliorates glycemic levels. In the present study, add-on treatment with IDM1 with sulfonylurea showed improved FPG and PPPG levels as compared with placebo over 12 weeks. The onset of glycemic control started after 1 month of IDM1 consumption and continued until at least 15 days after withdrawal of IDM1. The previous researcher showed that administration of fenugreek did not show any significant lowering of blood glucose level.[74] The result of the present investigation is not in agreement with the findings of the previous study, and this might be due to the administration of fibers constituent isolated from fenugreek. Many researchers have shown that the presence of 4-Hydroxyisoleucine and trigonelline moieties from fenugreek seed responsible for its glucose-lowering potential.[75,76] IDM1 is rich in standardized fenugreek seed extract which contains 4-Hydroxyisoleucine and trigonelline that might contribute to its glucose-lowering potential in T2DM patients. In addition, the presence of polyphenols, gymnemic acid, tannins, and saponins from other herbs in IDM1 may improve glycemic control.

In the present study, add-on treatment with IDM1 to sulfonylurea showed an increase in the incidence of hypoglycemia. However, all these episodes were of mild-to-moderate nature, and none required emergency treatment. The previous investigator also reported the similar effect where combination treatment with sulfonylurea associated with risk of hypoglycemia.[77,78] In the present study, this hypoglycemic incidence confirms the enhanced hypoglycemic efficacy of add-on therapy of IDM1 with sulfonylurea as compared to sulfonylurea alone. Thus, clinically, it is important to consider the risk of hypoglycemia when IDM1 used as add-on therapy with a sulfonylurea in practice. In addition, a tight glucose monitoring is also recommended, and reduction in dose of sulfonylurea should be considered if hypoglycemia occurs.

It is well recognized that poor control of diabetes is associated with poorer clinical outcomes and increased risk of complications.[71] The use of HbA1c to monitor glucose levels forms a central part of the management of patients with T2DM. Hence, many professional bodies and national health-care agencies worldwide have laid down recommendations on optimal frequency of monitoring using HbA1c to help maintain glycemic levels within clinically defined limits. HbA1c, with the support of clinical data from UK Prospective Diabetes Study[79] and Diabetes

Table 3: Efficacy variables of lipid profile

Characteristic	IDM1 + SU		Placebo + SU	
	Week 0 (*n*=60)	Week 12 (*n*=48)	Week 0 (*n*=58)	Week 12 (*n*=53)
Total cholesterol[#] (mg %)	194.52±40.30	206.47±36.16***	188.79±36.00	198.01±39.52
LDL cholesterol[$] (mg %)	113.63±41.06	121.98±31.30**	114.76±28.79	122.51±32.40
HDL cholesterol[$] (mg %)	45.63±8.35	47.40±8.99	45.69±8.86	45.53±7.74
Triglyceride (mg %)	213.31±153.21	187.35±125.50	180.86±87.47	162.62±77.96
HDL/LDL ratio	0.49±0.32	0.41±0.15	0.42±0.14	0.40±0.16

Values are presented as the mean±SD. Data was analysed by paired *t*-test; **P<0.01 and ***P<0.001 as compared with baseline; [#]Adjusted values; [$]Estimated values. BMI: Body mass index; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; SU: Sulfonylurea; SD: Standard deviation

Table 4: Summary of adverse events

AEs	IDM1 + SU (*n*=60)	Placebo + SU (*n*=59)
Adverse events by system		
Skin and appendages disorder	0	3
Musculoskeletal system disorders	4	2
Central and peripheral nervous system	10	8
Autonomic nervous system disorders	0	1
Vision disorders	1	1
Hearing and vestibular disorders	0	1
Psychiatric disorders	2	3
Gastrointestinal system disorders	10	13
Liver and Biliary system	9	9
Metabolic and nutritional disorders	42	43
Cardiovascular disorders	7	2
Heart rate and rhythm disorders	2	2
Respiratory system disorders	6	6
Red blood cell disorders	8	2
White cells disorders	8	13
Platelet bleeding and clotting disorders	1	1
Urinary system disorders	4	3
Female reproductive disorders	1	1
Body as a whole-general disorder	30	28
Resistance mechanism disorders	4	0
Total drug-related AEs	25	19
The frequency of severe adverse events		
Hypertriglyceridemia	1	0
Leucocytosis	0	1
Frequency of hypoglycaemia		
Related	10	3
Unrelated	2	2

AE: Adverse events; SU: Sulfonylurea

Control and Complications Trial,[80] has now become an essential tool of monitoring the glycemic control in T2DM patients. HbA1c reflects mean glycemic levels over the past 6–8 weeks.[81,82] For diabetic patients, this is important as the risk of developing complications is directly proportional to the fluctuations in the levels of HbA1c. This, in turn, is responsible for initiation of a chain reaction leading to decrement of QoL and simultaneous increment of health-care resource utilization, in chronic diabetics. In the United Kingdom, as per the National Institute for Health and Care Excellence, HbA1c testing should be performed at intervals of 2–6 months for unstable diabetes to gauge the magnitude and subsequent measurements made at <3-month intervals as an indicator of the direction of change.[83] In the present study, add-on therapy with IDM1 showed significant amelioration in elevated HbA1c level (approximately 0.9%). The reduction in HbA1c level may attribute to the presence of 4-hydroxyisoleucine (4-HI) moiety in the fenugreek extract of IDM1. The previous investigator also provides the anti-diabetic credential of fenugreek to the presence of 4-HI, both *in vivo*[76,84,85] and *in vitro*.[86]

Guidelines from the ADA as well as EASD suggested that the selection of treatment regimen for the T2DM patient should give importance to a patient-centered approach.[15] Thus, there is an array of treatment regimen commonly used either alone or in combination which includes metformin and sulfonylurea. However, these treatments are associated with a severe AE such as weight gain.[15] Thus, for patients with HbA1c ≥8.5%, the addition of insulin therapy was recommended by the ADA/EASD rather than a noninsulin agent.[15] However, this additional therapy was again associated with weight gain and hypoglycemia.[15] The network meta-analysis reported that many antidiabetic treatment therapies (including insulin, DPP-4 inhibitors, and a TZD) added to metformin or sulfonylurea exerts similar effect ameliorating diabetes mellitus in T2DM.[87] However, besides its efficacy, the absence of any side effect along with tolerability can be considered as a major determinant for selection of add-on treatment for metformin or sulfonylurea. In the present study, the addition of IDM1 to sulfonylurea treatment showed significant improvement in the blood glucose control without any severe AE, and it was well tolerated. As a result, the present study had great compliance.

T2DM patients are associated with the prevalence of obesity, and thus weight management in these patients is urgently needed. Furthermore, the conventional treatments such as insulin or oral glucose-lowering agents such as sulfonylurea can improve glycemic control, but they are associated with the common side effect of weight gain.[88] In the present study, a patient with add-on therapy of IDM1 with sulfonylurea did not show any weight gain when compared with placebo group over 12 weeks. Thus, the beneficial effect of the addition of IDM1 to sulfonylurea therapy was achieved without any detrimental effect on weight or BMI of patients.

Further investigations, in the measurement of lipids, the addition of IDM1 to the SU therapy caused an increase in total cholesterol and LDL cholesterol at week 12. However, a similar trend was reported after treatment with a potential hypoglycemic agent such as a sulfonylurea.[89,90] Further, this modulation in lipid profile might be a secondary effect resulting from improved glycemic control, and it was also inconsistent. In addition, there was no clinically or statistically significant change in mean systolic or diastolic blood pressure of patients in both the groups over 3 months of the treatment period.

It has been reported that T2DM is a multifactorial disease. Hence, there is a need of treatment which shows its potential by acting on the various mechanism.[91] In the present investigation, a combination of standardized extracts of *Trigonella foenum-graecum*, *Gymnema sylvestre*, *S reticulata, Camellia sinensis*, *Emblica officinalis*, *Tribulus terrestris* and *Linum usitatissimum* may exert its antidiabetic potential in T2DM patients via orchestrated multiple mechanisms. *G. sylvestre* and *C. sinensis* improve fasting blood glucose (FBG) and HbA1c levels in T2DM patients.[54,55,92] Whereas, *S. reticulata* improves HbA1c and serum insulin levels.[57-59] Administration of *E. officinalis* in T2DM patient showed a beneficial effect in term of a decrease in postprandial blood glucose level, plasma glucose, HbA1c, total cholesterol, triglycerides, and LDL-C levels.[56,60] *T. terrestris* also showed lipid-lowering potential in T2DM patients.[62,63] These multifaceted mechanisms of action may help to potentiate the anti-diabetic activity of IDM1.

Limitations

The present investigation has several limitations. The study was conducted on patients with relatively small sample size and for short (12-week) duration of treatment. Thus, the study with large sample size and long-term duration may be desirable to determine the long-term impact of IDM1 on glycemic control in T2DM patients along with its possible rare AEs. Second, the present investigation enrolled the patient who was on medication of sulfonylurea with baseline HbA1c of 7.0%–12% (both inclusive); hence, the findings of present investigation may not be generalizable to patients with the beyond the range toward with extreme values HbA1c and patients who are on other antihyperglycemic medication treatment than sulfonylurea.

CONCLUSIONS

Add-on therapy of herbal formulation, rich in standardized fenugreek seed extract (IDM1), with sulfonylurea showed improved glycemic control regarding FPG, PPPG and HbA1c levels compared with placebo over 12 weeks in patients with T2DM. These beneficial effects were seen as early as 1 month after consumption of IDM1; continued until

at least 15 days after withdrawal of IDM1 and without any weight gain. Overall, findings from this study suggested IDM1 as a safe, effective and well-tolerated add-on oral medication therapy that supports healthy blood sugar levels and glycosylated hemoglobin levels in T2DM patients inadequately controlled with a sulfonylurea.

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Conflicts of interest

The authors declare that they have no any conflicts of interest.

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