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Effect of *Gymnema sylvestre* (Gurmar) in Patients Diagnosed with Type 2 Diabetes mellitus in Kathmandu Valley

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ABSTRACT

Introduction:
Diabetes mellitus is a growing public health concern in the Southeast Asia region (SEAR) , where more than 87.6 million people are living with diabetes. *Gymnema sylvestre* (Gurmar) , a medicinal herb, is commonly used as herbal medicine to treat diabetes.

Objectives:
The present study was aimed to examine the effect of *Gymnema sylvestre* (*G. sylvestre*) among patients diagnosed with Type 2 Diabetes mellitus (T2DM) in Nepal.

Materials and Methods: The present study was an open-label uncontrolled clinical trial. Eligible participants were patients aged 30 to 60 years and diagnosed with T2DM. A total of 43 eligible participants were supplemented with 6 gm of *G. sylvestre*, daily for 4 weeks during the study period. Anthropometric and biochemical variables were evaluated by comparing data at baseline and at 4 weeks after starting treatment using chi-square and student's *t*- test.

Results:
There was a decrease in the fasting and post-prandial glucose levels of the participants by 19.3% and 16.7%, after treatment with *G. sylvestre*, respectively. There were no significant changes observed in other clinical variables before and after treatment with *G sylvestre*.

Conclusion:
This study suggests that the use of *G sylvestre* leaf has a potential hypoglycemic action in patients with T2DM. However, further studies are needed to confirm the beneficial effect of *G sylvestre* in T2DM.

Key Words: *Gymnema sylvestre , Type 2 Diabetes mellitus , Nepal*

INTRODUCTION

Diabetes mellitus is a growing public health concern in the Southeast Asia region (SEAR), where more than 87.6 million people are living with diabetes[1]. South Asians are known to have an increased predisposition for Type 2 Diabetes

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mellitus (T2DM) [2]. According to studies conducted in urban and rural population, diabetes prevalence in Nepal varies from 2.4 to 25.9%[3-14]. There were 674,120 cases of diabetes in Nepal in 2011 and it has the highest prevalence of T2DM among Bangladesh, India and Pakistan in SEAR[15,16].

In the Ayurvedic system, *G. sylvestre* is referred to as *Meshasringa* and has indications for use in glucose balance[17]. The leaves of this plant are used to treat diabetes, hypercholesterolemia, and obesity[18-25]. Its constituents include resins, gymnemic acids, saponins, stigmasterol, quercitol, gurmarin and the amino acid derivatives betaine, choline and trimethylamine[26,27]. Gymnemic acid is the active compound in *G. Sylvestre*[28,29]. Both animal and human studies showed that *G. sylvestre* improves glycemic control[30-42]. In one study, in vitro measurements using isolated human islets of Langerhans demonstrated direct stimulatory effects of *G. Sylvestre* extract on insulin secretion from human ß-cells, consistent with an in vivo mode of action through enhancing insulin secretion[31]. Findings of two studies conducted using rat model showed that number of insulin-secreting beta cells in the pancreas were doubled[32] and blood sugar levels returned to almost normal levels when treated with *G. sylvestre* extracts[33], whereas one of the study showed that its extracts inhibited epinephrine-induced hyperglycemia[34]. Other studies added to the evidence of anti-diabetic property of *G. sylvestre* by increasing the activity of enzymes responsible for glucose uptake and utilization[35], and inhibiting peripheral utilization of glucose by somatotrophin and corticotrophin[36]. Several other animal studies have also confirmed the hypoglycemic effect of *G. sylvestre*[37-40].

Three clinical trials suggested that *G. sylvestre* may be effective for improving glycemic control in T2DM patients[31,41,42]. In a cohort study with T2DM patients, oral administration of *G. sylvestre* extract (1 g/day for 60 days) induced significant increases in circulating insulin and C-peptide, which were associated with significant reductions in fasting and post-prandial blood glucose in diabetic patients[31]. In another trial, 22 patients with T2DM were given either 400 mg of a *G. sylvestre* extract daily in addition to their usual oral hypoglycemic medications for 18 to 20 months. Significant decreases in fasting blood glucose (FBG) and glycosylated haemoglobin A1c (HbA1c) levels were noted in this group[41]. The other trial reported that 3 months of treatment with 800 mg daily of a similar extract reduced FBG levels by 11% and HbA1c levels by 0.6% in a mixed population of 65 patients with type 1 and type 2 diabetes[42]. No adverse effects were reported in either trial.

Oral hypoglycemic therapy for T2DM has shown some adverse effects though these drugs are easy to use[43,44]. Recently more research interest is centered globally in quest for safer herbal medicines to treat T2DM. In regard to the efficacy of herbal medicines for T2DM, some scientific investigations have resulted herbal medicines to be effective and relatively non-toxic.

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In this context, a study was planned to evaluate the clinical efficacy of *G. sylvestre* in patients with T2DM. However, earlier beneficial evidence of *G. sylvestre* in patients with T2DM is probably insufficient to support the widespread use of *G. sylvestre* for diabetes management in Nepal. If the use of *G. sylvestre* can significantly improve glycemic control in T2DM patients, the clinical implications would be substantial. To our knowledge, no research has been done to investigate the effect of *G. sylvestre* on T2DM patients in Nepal. So, the aim of the study was to conduct an open label, uncontrolled trial to evaluate the efficacy of *G. sylvestre* among patients with T2DM in Nepalese population.

MATERIALS AND METHODS

Study design

This clinical trial was an open-label uncontrolled design to determine the effect of *G. sylvestre* and to justify for a large-scale multicenter clinical trial for T2DM patients in the future. After screening at first visit, baseline tests (FPG, PPG, lipid profile, renal function tests and liver enzymes) of the enrolled participants were performed. Later, patients who fulfilled the inclusion criteria were informed about their final inclusion in the trial and notified the follow-up date and treatment regimens. Eligible patients received a 1 month supply of *G. sylvestre* powder. Patients were instructed to take 3 gm of medicine twice a day before meal at the same time daily without altering their usual dietary and exercise habit. Each participant was given phone numbers of the investigator and advised to call in case of any concerns or queries. The investigator called each participant every week during the study to ensure any compliance and adverse events.

Study area and duration

Candidates were invited by means of advertisement i.e. pamphlets, banners in the study area i.e. Kirtipur, Kathmandu. Participants those willing to participate in the research were given both verbal and written information about the study. The study participants were recruited and at National Ayurveda Research and Training Center (NARTC) and screened. Eligible subjects were further invited and informed the purpose and risks of the study and their written informed consents were obtained. The recruited subjects were given the treatment for one month.

Study participants

The study subjects aged 30 to 60 years were those that visited NARTC for management of diabetes.

Inclusion and exclusion criteria

We included patients who fulfilled the following criteria: men or women aged 30 to 60 years, diagnosed with T2DM. It was characterized by patients having FPG ≥ 120 mg/dL where fasting is defined as no caloric intake for at least 8 h, or 2-h PPG ≥ 150 mg/dL during an oral glucose tolerance test (OGTT) , or in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose (RBG) ≥ 150 mg/dL and willing to give written informed consent.

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Patients were excluded for the following criteria: patients taking insulin; pregnant or nursing women; participants with diabetes related complications, i.e. retinopathy, neuropathy and nephropathy; hepatic, cardiac diseases, severe immune deficiency, hypothyroidism, recent participation in other clinical trials; hospitalizations for hypoglycemic episodes; recent major surgical procedure or any history of malignancy.

MATERIALS

Initially, available samples of *G. sylvestre* leaves were procured from local markets. The five samples were further selected from organoleptic observation and sent to NARTC for testing physical parameters (moisture content and ash content) and microbial parameters viz. aerobic bacteria, gram negative bacteria, *Eschirechia coli*, enterobacteria (*Klebsiella* sps) , *Salmonella* sps. The samples detected with higher level of physical parameters or any microbial parameters were excluded. The final sample selection was based on free state of microbial contamination and was processed for the manufacture of powder form of leaves of *G. Sylvestre* . *G. sylvestre* leaves (50 kg) were carefully washed with sterile water and dried under the sunlight with a transparent sterile cover and stored in the well closed cellophane bags. The dried *G. sylvestre* powder (25 kg) was packed in a sterile container (200 gm each) and labeled with an expiration date. The whole preparation was executed under the instructions and supervision of specialists.

Outcome measures

Trained laboratory technicians and doctors performed the standard biochemical and anthropometric measurements at hospital building of NARTC.

Primary outcomes

The primary outcome measure was the difference in the change in FPG and PPG between groups.

Secondary outcomes

Secondary outcomes monitored were blood urea, serum creatinine, total bilirubin, direct bilirubin, hepatic transaminases i.e. alanine aminotransferase (ALT) and aspartate aminotransferase (AST) , alkaline phosphatase, total cholesterol , high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol and triglycerides.

Physical examination

Blood pressure, weight, height, waist and hip circumference were measured by trained medical persons. Weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively. Body Mass Index (BMI) was calculated as body weight in kilograms divided by the square of height in meters. Waist circumference (WC) was measured at the midpoint between the lower costal margin and iliac crest to the nearest 0.1 cm. Hip circumference was measured around the point with the maximum circumference over the buttocks to the nearest 0.1 cm. Waist-Hip Ratio

(WHR) was the ratio of the circumference of the waist to that of the hip in centimeters.

Blood specimen collection and analysis

To assess RBG for screening, experienced lab technicians withdrew 3 ml of blood specimen of the participants. After screening, the eligible participants were further contacted for second visit and 5 ml of fasting blood specimens were collected after an eight hour overnight fast. The blood samples were sent to the diagnostic pathology laboratory of NARTC for analysis.

Data analysis

Clinical characteristics for categorical variables were expressed as frequencies and that for continuous variables were shown as mean (Standard error mean) . Welch's *t*-test was used for the comparison of variables between male and female groups. Mean changes from baseline values after treatment were determined using one sample *t*-test. *P* value < 0.05 was considered to indicate statistical significance. Analysis was conducted by use of Statistical Package for the Social Sciences (SPSS) .

Ethical consideration

The study was conducted according to the common guidelines for clinical trial (Ethical Guidelines for Health Research in Nepal). The study was approved by the ethical committee of NARTC.

RESULTS

The total number of the participants screened for the study was 132, out of which 76 patients were found to be diabetic. After exclusion of those with age ≥ 60 yrs (n = 3) , insulin dependent diabetic patients (n = 2) , liver disease (n = 1) and controlled diabetic patients (n = 19) , 51 patients were eligible for our study. But, only 40 patients (36 uncontrolled T2DM and 4 newly diagnosed T2DM) participated and completed the trial. The reasons of withdrawals were: 1 participant went out of the valley and 10 patients did not well responded on further contact.

Of the total study participants, 70 % were men and 30% were women. The mean age of study participants was 50.40 ± 6.70 years. Among the 40 patients, all patients had the abdominal obesity based on waist-hip ratio (waist-hip ratio ≥ 0.90 for male and ≥ 0.85 for female) , 13 were overweight (BMI: ≥ 25.0 to < 30.0 kg/m^2) and 11 were obese (BMI: ≥ 30 kg/m^2) . The numbers of patients with other clinical biomarkers that were marginally high were 14 with systolic blood pressure (SBP) ≥ 130 or diastolic blood pressure (DBP) ≥ 85 mmHg, 13 with AST ≥ 40 IU/L, 14 with ALT ≥ 35 IU/L, 12 with total cholesterol ≥ 200 mg/dL and 13 with triglyceride ≥ 160 mg/dL. Other lifestyle characteristics of the participants included: 12 patients were current cigarette smokers, 15 patients were current alcohol users and 16 patients were found to be physically active (Data not shown) .

The baseline characteristics of the study participants, stratified by sex (men and women) are shown in Table 1. There were no significant differences in other variables except for body height, blood urea and serum creatinine between

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men and women (Table 1) . Men had significantly higher body height, blood urea and serum creatinine than women (Table 1) .

Table 2 showed that there is no strong negative correlation between BMI and FPG; and BMI and PPG. Similarly, no strong positive correlation was seen between WHR and FPG; and WHR and PPG (Table 2) .

Table 1 Baseline characteristics and differences between genders (n = 40)

Variables	Men (n = 28)*	Women (n = 12)*	*P* – value**
Age (years)	51.0 (3.1)	49.0 (2.5)	0.63
Body weight (kg)	63.0 (3.9)	60.3 (5.3)	0.71
Body height (m^2)	2.7 (0.07)	2.3 (0.04)	0.001
Body mass index (kg/m^2)	23.6 (1.2)	26.3 (2.0)	0.32
Waist circumference (cm)	89.9 (2.8)	84.3 (5.3)	0.42
Hip circumference (cm)	91.9 (1.7)	93.3 (3.3)	0.72
Waist-hip ratio	1.0 (0.02)	0.9 (0.02)	0.06
Systolic blood pressure (mm Hg)	135.1 (8.0)	123.3 (3.3)	0.21
Diastolic blood pressure (mm Hg)	84.9 (4.1)	76.7 (3.3)	0.16
FBG (mg/dL)	170.4 (21.7)	151.0 (16.5)	0.50
PPG (mg/dL)	281.6 (28.2)	223.3 (47.2)	0.36
Blood urea (mg/dL)	31.7 (3.0)	21.0 (1.2)	0.01
Serum creatinine (mg/dL)	1.0 (0.1)	0.8 (0)	0.03
Bilirubin Total (mg/dL)	0.8 (0.03)	0.7 (0.06)	0.28
Bilirubin Direct (mg/dL)	0.3 (0.03)	0.2 (0.03)	0.62
AST (IU/L)	62.0 (23.7)	34.3 (9.21)	0.31
ALT (IU/L)	64.9 (23.7)	35.7 (12.3)	0.31
Alakaline Phosphatase (IU/L)	102.0 (11.9)	97.7 (24.4)	0.88
Total cholesterol (mg/dL)	162.9 (20.2)	167.3 (13.5)	0.86
HDL cholesterol (mg/dL)	39.1 (2.0)	39.0 (1.7)	0.96
LDL cholesterol (mg/dL)	87.6 (17.9)	92.7 (21.1)	0.86
VLDL cholesterol (mg/dL)	36.4 (11.5)	33.1 (5.2)	0.80
Triglycerides (mg/dL)	181.3 (57.6)	165.3 (26.2)	0.81

*Variables are expressed as mean (standard error mean) **Analyzed by *t*-test.

Table 2 Correlation matrix of BMI, WHR, FPG and PPG in the study participants

	FPG	PPG	BMI
BMI	-0.41	-0.30	1.00
WHR	0.16	0.31	0.18

The anthropometric parameters of the study participants before (baseline) and after treatment (30 days) are summarized in Table 3. At the end of the study period, no significant changes in body weight, BMI, waist and hip circumferences, or WHR were observed in the participants when compared with baseline parameters (Table 3).

Table 3 Anthropometric parameters of study participants before and after treatment of *G. sylvestre*

Study participants (n = 40)			
Parameter	**Before treatment (Baseline) ***	**After treatment (30 days) ***	***P* – value****
Body weight (kg)	62.0 (3.03)	61.0 (3.2)	0.07
BMI (kg/m^2)	24.4 (1.1)	23.9 (1.1)	0.07
Waist circumference (cm)	88.2 (2.5)	87.8 (2.56)	0.10
Waist-hip ratio	0.96 (0.02)	0.95 (0.02)	0.06

*Variables are expressed as mean (standard error mean) **Analyzed by *t*-test

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There was no significant difference in SBP and DBP values between baseline and after 30 days (data not shown) .

The nearly significant decrease after treatment in FPG levels of the subjects accounted for a 19.3% (31.8 mg/dL) mean change when compared with the baseline values (Table 4) . Similarly, there was a 16.7% (35.8 mg/dL) decrease in the PPG levels of the study participants after treatment but not statistically significant (Table 4) .

There was no significant change in other clinical biomarkers after treatment with powdered *G. sylvestre*: blood urea, serum creatinine, total bilirubin, direct bilirubin, AST and ALT, alkaline phosphatase, total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol and triglycerides (Table 4).

Table 4 Change clinical biomarkers of the study participants before and after treatment

Clinical biomarkers	Before treatment (baseline)*	After treatment (30 day)*	*P* – value**
FPG (mg/dL)	164.6 (12.5)	132.8 (5.0)	0.05
PPG (mg/dL)	214.0 (15.0)	178.2 (11.8)	0.08
Blood Urea (mg/dL)	28.5 (2.6)	25.5 (1.9)	0.25
Serum creatinine (mg/dL)	1.0 (0.1)	0.9 (0.05)	0.55
Bilirubin Total (mg/dL)	0.8 (0.03)	0.8 (0.04)	0.80
Bilirubin Direct (mg/dL)	0.3 (0.02)	0.3 (0.02)	0.34
AST (IU/L)	53.7 (16.9)	48.2 (16.4)	0.18
ALT (IU/L)	56.1 (17.1)	53.0 (17.0)	0.48
Alakaline Phosphatase (IU/L)	100.7 (10.3)	98.7 (8.4)	0.74
Total cholesterol (mg/dL)	164.2 (14.2)	154.4 (11.5)	0.61
HDL cholesterol (mg/dL)	39.1 (1.5)	41.7 (1.4)	0.13
LDL cholesterol (mg/dL)	89.1 (13.4)	85.8 (11.3)	0.85
VLDL cholesterol (mg/dL)	35.4 (8.0)	27.4 (4.1)	0.41
Triglycerides (mg/dL)	176.5 (40.0)	132.7 (20.7)	0.36

*Variables are expressed as mean (standard error mean).

**Analyzed by *t*-test.

DISCUSSION

Several studies have focused on the relationship between anthropometric indices of adiposity and T2DM risk. A study in 721 Mexican-Americans aged 25–64 years, showed that WC was a better risk predictor for T2DM than BMI, independently of age and sex[45]. Corroborating such results, another study in 12,814 African Americans and white participants aged 45–64 years, showed that WC was higher than for BMI in African men and women[46]. Finally, a meta-analysis involving 32 studies showed that the pooled relative risks for the incidence of T2DM were similar for WC, BMI, and WHR[47]. However, in the present study there was weak positive correlation between WHR and T2DM as shown in Table 2. In contrast to previous studies, weak negative correlation was seen between BMI and T2DM (Table 2) . This may suggest WHR is better risk predictor for T2DM than BMI like the previous study[46].

Results from the present study showed the beneficial effects of *G. sylvestre* in Nepalese adults diagnosed with T2DM. A daily dose of 6 gm of powdered *G. sylvestre* decreased FBG (19.3%) and PPG (16.7%) in T2DM patients with

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uncontrolled plasma glucose level after one month of treatment. In the present study, there were no significant changes in body weight, BMI, waist-hip ratio and other clinical variables of the study participants between baseline i.e. before treatment and after treatment with *G. sylvestr*e as shown in Table 3 and 4. It might be possible as the dietary and physical activity advice was not suggested by the investigator team. This suggests that the T2DM patients with uncontrolled blood sugar level can be supplemented with *G. sylvestre* powder to control their hyperglycemia.

G. sylvestre (sugar destroyer)–is a medicinal woody climber found in central and western India. Leaves of *G. sylvestre* (sugar destroyer) are widely used in Ayurvedic medicine to treat diabetes. A non-randomized open label trial with two parallel groups (n = 22) showed significant decrease in FBG (170 mg/dL to 120 mg/dL) and HbA1c (11.9% to 8.4%) from 18 to 20 months use of 400 mg of *G. sylvestre* extract daily with oral hypoglycemic agent in patients with T2DM[41]. However, there were no data available regarding whether other anthropometric and clinical biomarkers changed. In another similar trial with mixed population of type 1 (n= 23) and type 2 diabetes (n = 4) , the use of 400 mg daily of a *G. sylvestre* extract plus insulin therapy was compared with 37 type 1 patients with insulin therapy for 6 to 30 months. The reduction in hypoglycemic episodes and insulin dose by 10 units were observed in the group that was treated with the extract plus insulin therapy[48]. Another uncontrolled clinical trial with mixed population of type 1 and type 2 diabetes (n = 65) have provided supporting evidence for the hypoglycemic effect of *G. sylvestre*. In this study, daily use of 800 mg *G. sylvestre* extract showed decrease in FBG and HbA1c by 11% and 0.6 %, respectively[42]. Similarly in another study, oral administration of *G. sylvestre* extract (1 gm/day, 60 days) induced significant increases in circulating insulin and C-peptide, which were associated with significant reductions in fasting and post-prandial blood glucose in a small cohort of patients with T2DM[31]. In the present study 6 gm/day of dried *G. sylvestre* leaves were administered unlikely extract of *G. sylvestre* in previous studies. The dose in the present study (6 gm of the dried herb was equivalent to 800 mg of the alcoholic extract of *G sylvestre)* was chosen with reference to personal discussions with senior ayurvedic practitioners as well as ayurveda textbook. There were no adverse effects reported in previous studies as well as the present study.

Possible antidiabetic effect of *G. sylvestre* was not clearly defined in previous studies. However, the active constituents of *G. sylvestre* i.e. gymnemic acids and gurmarin are mainly accounted for its anti-diabetic property in animal studies[26,49]. The feeding of powdered leaves of *G. sylvestre* showed a hypoglycemic effect in beryllium nitrate treated rats[33]. Similarly, hypoglycemic effect of methanolic extract of *G. sylvestre* leaves demonstrated that gymnemic acids decreased blood glucose levels as compared to glibenclamide in streptozotocin diabetic mice[38].The FBG was significantly decreased in

diabetic rats treated with *G. sylvestre* and the effects were found to be similar to insulin and glibenclamide treated diabetic rats[38]. In another experimental study, the use of ethanolic *G sylvestre* leaf extract had an antihyperglycemic effect by its antioxidant property in diabetic rats[50]. The possible mode of action of *G. sylvestre* has been postulated through its stimulation in insulin secretion from pancreas and by degrading absorption of glucose in the blood[51]. The gymnemic acids and gurmarin, the active compounds of *G. sylvestre*, fill the receptors present in the taste buds of tongue thereby reducing its activation by the glucose molecule in the food. Gymnemic acids also attach to the receptors of intestine, thus lowering blood glucose levels by inhibiting glucose absorption in the intestine[52,53]. Hypoglycemic effect of gymnemic acids is by incretin-mimetic mechanism which activates secretion and release of insulin. It also promotes regeneration of pancreatic islet cells and increases activities of enzymes responsible for glucose uptake thereby causing inhibition of glucose absorption in the small intestine[53]. Gymnemic acids interact with glyceraldehyde-3-phosphate dehydrogenase in glycolysis pathway resulting in hypoglycemic activity of glycemic acids derivatives[54]. Another possible mechanism of antihyperglycemic property of *G. sylvestre* could be explained in terms of overcoming the insulin resistance by stimulating the insulin to enter into cells via insulin receptors in T2DM[55].

In the study, there were also significant difference in blood urea and serum creatinine levels when compared between men and women. However, we do not have immediate biological explanation for the observed results. The findings may have been due to chance because of small number of the study participants.

This clinical trial is the first in Nepal to attempt the use of *G. sylvestre*, a classical therapeutic medicinal herb, in patients with diabetes. Our aim is the successful implementation of this trial in contributing to further improvements in the use of herbal medicines, such as *G. sylvestre*, through intervention programs that help prevent diabetes in developing countries like Nepal. Herbal medicine could be a viable alternative to achieving a better understanding of diabetes and managing glucose levels in patients with T2DM, thereby reducing complications in the long run. Nonetheless, further randomized placebo controlled trials are required to confirm the efficacy of *G. sylvestre* in patients diagnosed with T2DM.

CONCLUSION

This study was designed to find the efficacy of *G. sylvestre* in patients diagnosed with T2DM, residing in Kathmandu valley. This study suggested that the use of *G. sylvestre* leaf has a potential hypoglycemic action in patients with T2DM. The present study did not show any beneficial effects in obesity. However, further studies are needed to confirm the beneficial effect of *G sylvestre* in T2DM.

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From findings of the study, we could recommend intake of *G. sylvestre* leaf as a supplement for the patients diagnosed with uncontrolled T2DM in context of Nepal.

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