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An Open Label Study on the Supplementation of *Gymnema sylvestre* in Type 2 Diabetics

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ABSTRACT. Diabetes mellitus is a complex metabolic disorder characterized by chronic hyperglycemia, and associated with long-term damage and dysfunction of various organs. Management of diabetes is therefore vital and involves maintaining euglycemia as much as possible by reducing blood glucose and by increasing insulin sensitivity and peripheral glucose uptake. Ayurveda has promoted the management of diabetes by regulating carbohydrate metabolism using several medicinal herbs, one of which is *Gymnema sylvestre* (GS). GS has been used in parts of India as a hypoglycemic agent and the results have been encouraging. Accordingly, we planned a quasi-experimental study to investigate the efficacy of the herb among type 2 diabetics. Patients enrolled from free-living population were purposively assigned to experimental or control groups, based on their willingness to participate in the study. The experimental group was supplemented with 500 mg of the herb per day for a period of 3 months, and the efficacy of the herb was assessed through a battery of clinical and biochemical tests. Supplementation of the diet with GS reduced polyphagia, fatigue, blood glucose (fasting and post-prandial), and glycated hemoglobin and there was a favorable shift in lipid profiles and in other clinico-biochemical tests. These findings suggest a beneficial effect of GS in the management of diabetes mellitus.

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KEYWORDS. *Gymnema sylvestre*, alternate therapy, NIDDM, management of diabetes

INTRODUCTION

Diabetes mellitus is a complex metabolic disorder that involves numerous biochemical abnormalities, a heterogeneous clinical picture, and a polygenic hereditary component. The term describes a group of metabolic disorders that are characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both, and reciprocal changes in glucagon. Chronic hyperglycemia in diabetes is associated with long-term damage and dysfunction of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. These consequences, and the high prevalence of the disease, indicate the urgency in developing effective management strategies that can reduce the risk of developing or retarding the progression of complications. Exercise, diet, and weight control are essential as is improving glucose homeostasis. However, lifestyle management measures may be insufficient and patient compliance difficult, rendering conventional drug therapies (i.e., oral hypoglycemics and insulin injections) necessary for many patients. However, because of high cost, incomplete effectiveness, side effects, and other issues, new medicinal herbs with antihyperglycemic activities are increasingly sought as a cheaper and safer alternative approach (Dey, Attele, & Yuan, 2002).

A number of medicinal herbs and functional foods, such as *tulsi* (Rai, Iyer, & Mani, 1997), spirulina (Mani, Desai, & Iyer, 2000; Parikh, Mani, & Iyer, 2001), flaxseed (Pan et al., 2007), and cereal pulse mix with spices and condiments (Mani et al., 1994; Mani, Iyer, Mani, & Desikachar, 1997), have been found to help diabetics. Supplementation of the diet with these foods has brought about substantial reductions in blood glucose levels as well as in lipid profiles, both of which are extremely beneficial in managing type 2 diabetes. One herb that has been used in traditional Ayurvedic therapy for treating diabetes mellitus (Shastri, 1994) is *Gymnema sylvestre* (GS) (*gurmar* or *meshashringi*), a woody creeper belonging to the *Asclepiadaceae* family, and widely known as “sugar destroyer.” Its active components include two resins (one of which is soluble in alcohol), gymnemic acids (I–VII, IX) (Murakami et al., 1996), peptide gumarin, anti-sweet saponins (Wencai et al., 2001), stigmasterol, quercitol, and the amino acid derivatives betaine, choline, and trimethylamine (Kharamov, Spaspov, & Samokhina, 2008). Exploratory studies have shown GS to be a hypoglycemic agent (Shanmughasundaram et al., 1990a; Shanmughasundaram et al., 1990b). Different parts of the plant have also been found to work as astringent, stomachic, diuretic, stimulant, laxative, and tonic (Warrier, Nambiar, & Ramankutty, 1995). One study was carried out in 22 type 2 diabetic patients by administering 400 mg of extract from GS leaves (GS4) daily for 18–20 months as a supplement to oral hypoglycemic drugs. After supplementation with GS, a significant reduction was observed in blood glucose, glycosylated hemoglobin, and glycosylated plasma proteins, strongly indicating the beneficial effects of GS4. Further, five of the 22 diabetics were able to discontinue their conventional anti-diabetic drugs and maintain their blood glucose homeostasis with GS4 alone (Bhaskaran et al., 1990).

However, there have been few comprehensive and detailed human studies on supplementation of GS. This prompted us to design a study to analyze the efficacy of GS

supplementation in controlling hyperglycemia and dyslipidemia among type 2 diabetics when GS is given along with conventional anti-diabetic drugs.

METHODS AND MATERIALS

Study Group

A total of 58 type 2 diabetics from the free-living population in Vadodara, India were enrolled into the study. They were counseled about the benefits of GS and about the requirement of the study so that their diet, physical activity pattern, and drug usage during the study period should remain unaltered.

Experimental Design and GS Supplementation

Enrollees were purposively assigned to one of the two groups: a control group (N = 19) and an experimental group (N = 39). The selection criterion for group assignment in this study, which has a quasi-experimental design, was based on the willingness of the subject to participate in the study. Information regarding general habits, dietary intake, physical activity pattern, clinical, and medical history of each subject was collected using a pre-tested, semi-structured questionnaire. The questionnaire was also used to elicit information on, and qualitatively assess the commonly occurring symptoms in diabetic patients (appetite, polyphagia, polyuria, fatigue, bowel–bladder status, etc.) before and after the intervention. Each member of the experimental group was given 250 mg of GS in the form of capsules containing extracts of the leaves to be consumed twice a day before meals for a period of 3 months. Their anthropometric, biophysical, and biochemical parameters were assessed thrice—at the beginning of the study (baseline), after 2 months (60 days), and after 3 months (90 days). The control group received no supplementation or placebo and their anthropometric, biochemical, and biophysical parameters were assessed twice—at baseline and 3 months after enrolment (Figure 1). Approval from the departmental medical ethics committee was obtained before conducting this clinical trial.

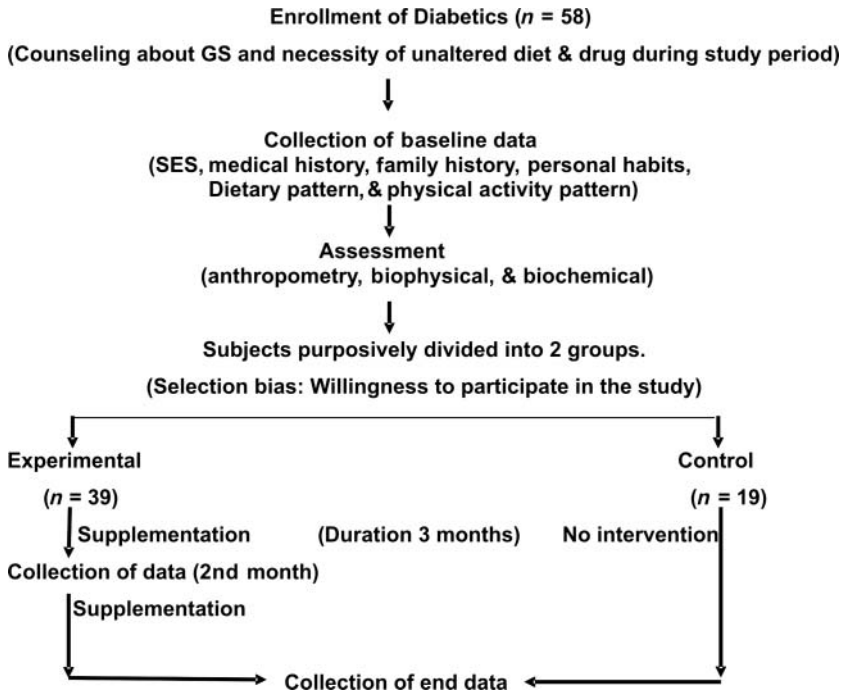
Anthropometric and Biophysical Assessment

Height was measured without shoes to the nearest 0.5 cm and weight was measured on a pre-standardized weighing scale. Body mass index (BMI) and basal metabolic rate (BMR) were calculated using standard formulas. Body composition (fat percentage) was measured using a body fat monitor. Waist circumference (WC) and hip circumference (HC) were measured to the nearest centimeter with a dressmaker's tape. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using a sphygmomanometer.

Assay Methods

Venous blood samples and urine samples of the subjects were collected after an overnight fast (12 hr) and 2 hr after meal consumption. The venous blood sample was collected in vacutainers with appropriate preservatives. Serum was used for the estimation of fasting and post-prandial blood glucose (FBS and PP₂BS), liver function

FIGURE 1. Experimental design.



tests (SGOT and SGPT), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) using standard diagnostic kits. Glycated hemoglobin (HbA_{1c}) was assessed by automated high-performance liquid chromatography (HPLC) and fasting serum insulin was assayed on an automated immulite system by chemiluminescence. Estimated insulin resistance and β cell function (G/I, HOMA IR and I/G, HOMA B) were calculated by standard formulas. Apolipoproteins A and B (Apo A and Apo B) were assessed by antigen-antibody reaction using rate nephelometry, and high-sensitivity C-reactive protein (CRP) was estimated by chemiluminescence. To assess kidney function, microalbuminuria (MAU) was analyzed by immuno rate nephelometry. Urine was also tested for albumin, acetone, and sugar excretion.

Statistical Analysis

Results are expressed as Mean \pm SD. Student's Paired *t*-test was used to identify significant differences between pre- and post-intervention values for each group. Microsoft Excel and SPSS 11.5 were used to analyze the data and all tests were considered significant at the $p < .05$ level (95% Confidence Interval (CI)).

RESULTS

The general characteristics of the subjects enrolled are given in Table 1. The average age and duration of the disease in both the control and the experimental group were

TABLE 1. General Characteristics of Subjects

Variables	Control Group N = 19 (M = 11; F = 8)	Experimental Group N = 39 (M = 18; F = 21)
Age (years)	56 ± 9.5	56 ± 7.6
Duration of disease (years)	8.1 ± 7.3	8.6 ± 7.4
Tobacco consumers	2 (11%)	6 (15%)
Smokers	0 (0%)	6 (15%)
Alcohol consumers	0 (0%)	5 (13%)
Physically active diabetics	15 (79%)	28 (72%)

comparable. Substance abuse (tobacco, smoking, and alcohol consumption) was found to be prevalent in both the groups, but was higher in the experimental group. A majority of subjects were physically active in both the groups and the level of activity remained unaltered during the intervention.

The medical and clinical data (Table 2) revealed that the majority of subjects used oral hypoglycemic agents (OHA) to control hyperglycemia. After supplementation, two subjects (10.3%) from the experimental group were able to discontinue their conventional OHA therapy (with their clinicians' consent). On the other hand, 37% of the control subjects showed an increase in drug consumption (OHA, antihypertensives, and statins). From the post-intervention data collected, it appeared that the experimental group did not show any change in clinical profiles, but the prevalence of secondary complications was found to be higher in the control group.

Supplementation with GS reduced the prevalence of fatigue by 56.4% and also lowered polyphagia and suppressed excessive hunger in 21% of diabetics.

The anthropometric and biophysical parameters (Table 3) of the experimental group exhibited a shift toward a healthier profile, with marginal reductions in weight, BMI, HC, fat percentage, and significant decreases in WC, SBP, and DBP. The control group,

TABLE 2. Medical History and Clinical Profile of Subjects

Variables	Control Group N = 19 (M = 11; F = 8)		Experimental Group N = 39 (M = 18; F = 21)	
Medications consumed by diabetics				
No medication	0 (0%)		3 (8%)	
OHA	18 (95%)		32 (82%)	
Insulin	2 (11%)		8 (21%)	
Antihypertensives	7 (37%)		17 (44%)	
Statins	4 (21%)		7 (18%)	
Prevalence of secondary complications				
	Pre	Post	Pre	Post
Cardiovascular diseases	2 (11%)	3 (16%)	5 (13%)	5 (13%)
Retinopathy	1 (5%)	2 (11%)	0 (0%)	0 (0%)
Neuropathy	1 (5%)	1 (5%)	0 (0%)	0 (0%)
Nephropathy	0 (0%)	0 (0%)	2 (5.1%)	2 (5.1%)

TABLE 3. Anthropometric and Biophysical Profile of Subjects (Mean \pm SD)

Biophysical Parameters	Control Group		Experimental Group	
	N = 19		N = 39	
	Pre	Post	Pre	Post
Height (cm)	161 \pm 8.4	161 \pm 8.4	157.5 \pm 9.8	157.5 \pm 9.8
Weight (kg)	64.0 \pm 10.9	64.5 \pm 10.5 ^{0.03a}	67.1 \pm 15.0	66.5 \pm 14.8 ^{0.10}
BMI ^c	24.8 \pm 3.8	25.0 \pm 3.7 ^{0.02a}	27.1 \pm 5.7	26.8 \pm 5.5 ^{0.12}
Waist circumference (WC) (cm)	88.9 \pm 9.7	89.3 \pm 9.6 ^{0.23}	90.6 \pm 11.9	89.3 \pm 10.8 ^{0.01a}
Hip circumference (HC) (cm)	96.0 \pm 9.9	95.8 \pm 10.1 ^{0.64}	102.0 \pm 10.9	101.2 \pm 10.7 ^{0.08}
Fat (%)	31.9 \pm 6.2	32.6 \pm 5.5 ^{0.02a}	35.2 \pm 6.9	34.6 \pm 6.4 ^{0.14}
BMR	1329.0 \pm 185	1346.8 \pm 173.4 ^{0.16}	1368.9 \pm 243.5	1368.0 \pm 231.9 ^{0.91}
SBP (mmHg)	136.3 \pm 19.7	140.8 \pm 19.1 ^{0.04a}	139.1 \pm 19.9	132.4 \pm 18.3 ^{0.001b}
DBP (mmHg)	85.7 \pm 12	88.4 \pm 8.7 ^{0.06}	84.1 \pm 11.6	81.6 \pm 8.6 ^{0.04a}

^aSignificantly different from values at baseline at the $p < .05$ level.

^bSignificantly different from values at baseline at the $p < .005$ level.

^cWeight (kgs)/height (m²).

BMR = basal metabolic rate; SBP = systolic blood pressure; DBP = diastolic blood pressure.

on the other hand, showed significant increases in weight, BMI, fat percentage, and SBP.

The biochemical profiles of both the groups are represented in Table 4. A significant reduction was observed in FBS and PP₂BS over 3 months that concurrently reduced HbA_{1c} levels significantly in the experimental group. Insulin values were higher during the second month of supplementation (15.5 \pm 14.5), but by the end of the study were similar to baseline levels. After supplementation, a significantly lower glucose/insulin ratio (G/I) indicated a decrease in insulin resistance, and an increased insulin/glucose ratio (I/G) indicated an improvement in insulin secretion. A decrease in insulin resistance after supplementation was also indicated by homeostatic assessment of insulin resistance (we found a decrease in HOMA IR) and by increased β cell function (we found an increase in HOMA B values). Liver enzyme levels decreased, indicating healthier liver function and an absence of hepatotoxicity post-supplementation. A decrease in CRP levels was observed in the supplemented group. A significant decrease in Apo B and TG levels, and a modest reduction in TC, LDL-C, and the L/H ratio were found, along with a marginal rise in Apo A, indicating an improvement in the lipid profile of the subjects post-supplementation. There was a significant improvement in kidney function, as indicated by lower MAU levels (47%).

In contrast, after 90 days the control group had significantly higher FBS and HbA_{1c} values compared to baseline. A reduction was also observed in fasting insulin levels. These changes in FBS and insulin resulted in a significant increase in HOMA IR levels and an elevated G/I ratio, indicating higher insulin resistance. All lipid indices except TG were marginally lower in the control group in comparison to their baseline data, but MAU levels were higher, indicating that although they were under control, there was deterioration in their metabolic profiles.

TABLE 4. Biochemical Profile of Subjects (Mean \pm SD)

Biophysical Parameters	Control Group		Experimental Group	
	N = 19		N = 39	
	Pre	Post	Pre	Post
FBS (mg/dl)	139.7 \pm 43.2	164.2 \pm 58.5 ^{0.03a}	188.9 \pm 63.7	162.7 \pm 37.8 ^{0.002b}
PP ₂ (mg/dl)	195.8 \pm 54.9	233.1 \pm 97 ^{0.60}	275.3 \pm 103	216.0 \pm 72.3 ^{0.000c}
Insulin (μ IU/ml)	7.92 \pm 5.85	7.92 \pm 5.48 ^{0.36}	12.2 \pm 9.3	12.2 \pm 10.0 ^{0.99}
G/I ^d	31.1 \pm 30.7	34.0 \pm 31.9 ^{0.58}	29.8 \pm 26.0	19.8 \pm 16.4 ^{0.01}
I/G ^e	0.41 \pm 1.29	0.37 \pm 1.27 ^{0.69}	0.06 \pm 0.05	0.1 \pm 0.13 ^{0.15}
HOMA IR ^f	2.96 \pm 2.51	3.11 \pm 2.3 ^{0.01a}	5.68 \pm 4.90	4.81 \pm 4.07 ^{0.36}
HOMA B ^g	2.36 \pm 1.96	2.24 \pm 2.39 ^{0.55}	2.52 \pm 2.16	3.03 \pm 2.90 ^{0.26}
SGOT (U/L)	22.0 \pm 10.1	19.32 \pm 7.4 ^{0.23}	20.3 \pm 10.1	19.0 \pm 6.3 ^{0.29}
SGPT (U/L)	23.3 \pm 14.1	22.5 \pm 11.9 ^{0.63}	25.4 \pm 14.6	22.4 \pm 9.2 ^{0.05}
C-reactive protein (CRP) (mg/L)	3.09 \pm 2.85	1.85 \pm 1.72 ^{0.01}	5.6 \pm 6.29	4.25 \pm 4.24 ^{0.23}
TC (mg/dl)	186.4 \pm 46.2	181.8 \pm 38.2 ^{0.56}	195 \pm 37.1	188.4 \pm 34.6 ^{0.15}
HDL-C (mg/dl)	44.4 \pm 9.2	43.3 \pm 11.4 ^{0.47}	45.4 \pm 13.4	44.9 \pm 10.6 ^{0.58}
LDL-C (mg/dl)	125.3 \pm 39.7	123.4 \pm 36.5 ^{0.79}	130.9 \pm 32.5	126 \pm 29.8 ^{0.17}
LDL-C/HDL-C	2.87 \pm 0.85	3.01 \pm 1.02 ^{0.47}	3.07 \pm 0.95	2.94 \pm 0.94 ^{0.11}
TG (mg/dl)	118.7 \pm 43.5	137.9 \pm 73.6 ^{0.13}	167.3 \pm 100.4	142.7 \pm 62.7 ^{0.049a}
Apo A (mg/dl)	108.8 \pm 17.0	109.3 \pm 34.6 ^{0.95}	110 \pm 22.1	113.1 \pm 19.9 ^{0.26}
Apo B (mg/dl)	102.2 \pm 36.2	100.5 \pm 27.4 ^{0.76}	110.5 \pm 29.4	102.8 \pm 27.3 ^{0.048a}
A/B	1.22 \pm 0.59	1.23 \pm 0.49 ^{0.90}	1.06 \pm 0.49	1.17 \pm 0.37 ^{0.05}
HbA1c	8.0 \pm 1.6	8.5 \pm 2.0 ^{0.04a}	9.6 \pm 1.9	8.6 \pm 1.6 ^{0.000c}
MAU (mg/gm)	26.6 \pm 45.2	28.1 \pm 32.28 ^{0.86}	24.6 \pm 24.6	16.7 \pm 10.0 ^{0.049a}

^aSignificantly different from baseline values at $p < .05$ level.

^bSignificantly different from baseline values at the $p < .005$ level.

^cSignificantly different from baseline values at $p < .000$ level.

^dFBS (mg/dl)/Insulin (μ IU/ml).

^eInsulin (μ IU/ml)/ FBS (mg/dl).

^fInsulin (μ IU/ml) \times FBS (mg/dl)/405.

^g20 \times Insulin (μ IU/ml)/FBS (mg/dl)–63.

DISCUSSION

Hyperglycemia, the clinical expression of diabetes, initiates a cascade of interrelated metabolic imbalances leading to vascular damage, and dysfunction and failure of various organs. Thus, type 2 diabetes is a chronic metabolic disorder that has a significant negative impact not only on the health, quality of life, and life expectancy of the patients but also on the health care system (Dey et al., 2002). Ancient Ayurvedic scriptures suggest that physicians in India have effectively managed diabetes with a balance of therapeutic diets, herbs, and plant food sources (functional food). In the modern era, extensive research has shown the effectiveness of medicinal herbs that have anti-diabetic activity and over the past decade these herbs have become increasingly popular. Plants and their derivatives, like GS, have been found to be beneficial in controlling blood glucose in some earlier exploratory studies (Shanmugasundaram et al., 1990a, 1990b).

In the present study, supplementation with GS was found to ameliorate overt clinical symptoms of diabetes, such as excessive hunger, tiredness, polyuria, and nocturia. Favorable changes were also observed in the anthropometric and biophysical profiles of our subjects. The biochemical parameters in the experimental group showed considerable

improvement, as there was a significant reduction in hyperglycemia and hypertriglyceridemia. These indices indicate a shift toward a better lipid profile along with improved kidney function and a reduction in systemic inflammation.

Supplementation with GS reduced polyphagia, suppressed excessive hunger, and decreased the prevalence of fatigue in diabetics. The mechanism is not established, but GS has been found to profoundly impair perception of the sweet sensation and to dramatically alter the perception of sweetness without altering the perception of other primary tastes (Schroeder & Schroeder, 2005). Thus, GS might be helpful in curbing sweet cravings among diabetics. A study performed on rats showed an inhibition of glucose-stimulated Gastric Inhibitory Peptide (GIP) secretion that has an insulin-releasing effect during glucose influx (Fushiki et al., 1992). These observations suggest that GS consumption may elicit a similar effect in humans that could reduce sudden surges or spikes in insulin levels that cause food cravings, thereby controlling hunger and polyphagia.

Supplementation with GS led to marginal reductions in weight, BMI, WC, HC, and fat percentage. Animal studies have shown a reduction in weight in overweight and obese rats supplemented with GS extracts. This appeared to be due to inhibition of oleic acid absorption and the ability to lower triglycerides without any withdrawal or rebound symptoms (Luo et al., 2006). Thus, there is a possibility of even greater weight reduction if supplementation of GS is continued for a longer period, helping diabetics achieve the desirable goal of weight management.

The group supplemented with GS showed a 14.3% drop in fasting glucose levels and 21.5% in post-prandial glucose levels. These significantly lowered blood glucose levels resulted in a 1% reduction in HbA_{1c}, indicating an average drop of 30 mg/dl in circulating glucose levels. The reduction in hyperglycemia would help in bringing down nonenzymatic glycation, thereby reducing the metabolic risk of development of secondary complications of diabetes (Stratton et al., 2000). Higher levels of fasting insulin were observed in the second month of supplementation; however, they were comparable to baseline levels at the third month. A study examining the effect of GS extracts on insulin secretion by pancreatic β cells confirmed the stimulatory effect of GS on insulin release (Shanmugasundaram et al., 1990a; Liu et al., 2009). Studies on the insulinotropic activity of aqueous extracts of GS on human islets have shown that insulin secretagogue effects in the cells were partially dependent on the presence of extracellular calcium, without compromising β cell viability (Liu et al., 2009). In addition, GS has been found to act by increasing cell permeability, rather than by stimulating exocytosis by regulated pathways (Persaud et al., 1999). Increased membrane permeability could be the mechanism behind the hypoglycemic effects of GS. These favorable changes in blood glucose and insulin levels not only helped in reducing estimated insulin resistance (G/I and HOMA IR) but also in improving β cell function (I/G and HOMA B) in the experimental group.

Research conducted in rats showed significant decreases in fat digestibility and fecal excretion of neutral and acidic sterols after consumption of GS extracts. GS also influenced cecal fermentation of fat into short-chain fatty acids. A reduction was also observed TC and TG levels, and increased blood Lecithin Cholesterol Acyltransferase activity (LCAT) influencing overall lipid metabolism (Shigematsu et al., 2001). As the lowering of blood lipids was also observed among subjects consuming GS in our study, one of the plausible mechanisms of action of GS could be alterations in lipid metabolism as seen in the animal module.

Glucose homeostasis, induced by supplementation with GS also helped improve kidney function by bringing down MAU levels significantly in the present study. The studies carried out among type 2 diabetics have established MAU as an integrated indicator for renal and cardiovascular risk. Decrease in MAU levels lower the risk of nephropathy and cardiovascular anomalies. A reduction in microalbuminuria induced by aggressive multifactorial control is considered to be a marker for evaluating the beneficial efficacy of therapeutic interventions to improve outcomes (Araki et al., 2007).

High-sensitivity CRP is a good indicator of systemic inflammation and a predictor of metabolic aberrations. The reduction in inflammatory markers (CRP) after supplementation with GS may be associated with decreases in systemic inflammation and endothelial dysfunction that should reduce the occurrence of secondary complications of diabetes. In addition, CRP levels were a stronger predictor of cardiovascular events than LDL-C. Multiple studies have demonstrated that CRP levels predict early and late mortality in acute coronary ischemia, and add to the predictive value of cardiac troponin (Ridker, 2003). In the present study, a reduction in CRP levels indicated a reduction in metabolic risk in the GS-supplemented group.

The limitations of this study are that group assignment was based on patient preference and not on randomization. No placebo was given to the control group. The study was not blinded. Thus, the conclusions of our study need to be substantiated by conducting a randomized, controlled trial. In addition, studies should be carried out to explore the effect of the herb after a washout or a withdrawal period to further establish its efficacy.

CONCLUSION

Gymnema sylvestre supplementation is a novel therapy that may be effective in the management of type 2 diabetes because it helps not only in maintaining euglycemia but also in controlling weight and blood pressure, lowering atherogenic lipid indices and inflammatory markers, improving metabolic control, and thereby reducing the risk of development of secondary complications of diabetes. The observations of this quasi-experimental study should be validated by repeating it with a larger group and an improved research design (randomized, placebo controlled).

Declaration of interest: The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

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