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STUDIES ON THE EFFECT OF *GYMNEMA SYLVESTRE* ON DIABETICS

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Abstract: *Gymnema sylvestre* (T. Sirukurincha) is used in indigeneous medicine for control of glycosuria. In this work the hypoglycaemic effect of *G. sylvestre* was studied in 16 normal subjects and in 43 mild diabetics. Normal subjects and diabetics were between 43 and 68 years of age. All the subjects were administered with *G. Sylvestre* leaf powder (10 g/day) for 7 days. Oral glucose tolerance test was performed on all subjects before the administration of *G. sylvestre* leaf powder. Normal subjects had the zero and 2 hour blood glucose levels of 80.8 (± 11.9) mg dl^{-1} and 72.6 (± 14.4) mg dl^{-1}respectively, while 43 mild diabetics had 152.7 (± 28.5) mg dl^{-1} and 240.0 (± 22.5) mg dl^{-1}. From 7th day, 36 mild diabetics were treated with tolbutamide for one week as prescribed by their doctors, while the remaining 7 diabetics continued the intake of *G. Sylvestre* leaf powder for another two weeks. Fasting blood glucose levels of normals, 36 diabetics on *G. Sylvestre* and on tolbutamide, and 7 diabetics who continued with *G. sylvestre* leaf powder, were measured on zero, and 7th days; on zero, 7th and 14th days and on zero, 11th and 21st days respectively. Fasting blood glucose levels on the 7th day for normals and mild diabetics were 71.6 (± 12.9) mg dl^{-1} and 136.3 (± 20.3) mg dl^{-1} respectively. The mean fasting blood glucose levels of both normals and diabetics had significantly decreased 7 days after the administration of *G. Sylvestre* leaf powder. Fasting blood glucose levels of the 36 diabetics on tolbutamide for 7 days (on 14th day of commencement of the experiment) was 131.1 (± 15.1) mg dl^{-1}. Mean fasting blood glucose levels of 36 diabetics on 7th day (136.3 ± 20.3 mg dl^{-1}) and 14th day (131.1 ± 15.1 mg dl^{-1}) showed no significant difference. Fasting blood glucose levels of 7 diabetics who took *G. Sylvestre* leaf powder for 3 weeks showed improved glucose tolerance on the 21st day, (101.2 ± 31.9 mg dl^{-1}). This indicates that *G. Sylvestre* leaf powder has probably had a hypoglycaemic effect comparable to tolbutamide. Serum triacylglycerol, free fatty acids and cholesterol levels of the normals were unaffected by the intake of *G. sylvestre* leaf powder for one week, whereas that of diabetics had significantly decreased. Serum ascorbic acid and iron levels of normals and diabetics were elevated significantly due to the intake of *G. sylvestre* leaf powder. Intake of *G. Sylvestre* had not affected the excretion of creatine in normals whereas in diabetics it had decreased the excretion of creatine. SGOT and SGPT levels of normals and diabetics, before and after the administration of *G. sylvestre*, were not significantly different.

Introduction

Diabetes mellitus is a chronic condition which affects the metabolism of carbohydrate, protein, fat, electrolyte and water. Consequences of this disease are frequently associated with irreversible functional and structural changes in cells, particularly those of vascular system, and manifests as arterial degeneration including coronary and cerebral artery diseases and obliterative arterial disease in legs.[1] These changes will lead to complications in untreated cases.

Blood glucose levels of 50% of the diabetic patients can be controlled adequately by diet alone, while 30% need hypoglycaemic drugs and the rest need insulin treatment.[2] Sulphonylureas and tolbutamide are used as oral hypoglycaemic drugs in Western Medicine. *Gymnema sylvestre* is recommended in Ayurvedic Medicine for the control of glycosuria and is also prescribed as a diuretic. *G. sylvestre* is a climber and this plant is known as 'Sirukurincha' in Tamil and 'Sinnuga' in Sinhala. It has been reported to have a curative effect on diabetes mellitus.[3] When chewed, the leaves of *G. sylvestre* abolish the sensation of sugar for a few hours and hence the name 'Sarkarai kolli' in Tamil, meaning destroyer of sweetness.

Mahaskar and Caius[3] have suggested that *G. sylvestre* can act not only as a hypoglycaemic agent but also as a probable cure of diabetes. Shanmugasundram *et al.*[4] had studied the effect of *G. sylvestre* on eight normal individuals and 4 diabetic patients, and reported the hypoglycaemic effect of *G. sylvestre*.

Balasubramaniam et al.[5] have studied the effect of *G. sylvestre* on 7 mild diabetic patients. In this experiment the leaf powder (10 g) was administered orally once per day for 21 days and this led to a significant improvement in glucose tolerance. In addition 50% of the patients showed an increase in their body weight. Normal SGPT level indicated the non-toxic effect of the leaf powder.

The hypoglycaemic effect of *G. sylvestre* on 16 normals and 43 mild diabetics was studied. Comparison was made with the hypoglycaemic effects of tolbutamide and *G. sylvestre* leaf powder on mild diabetic patients. In addition investigations made on the changes in serum triacylglycerol, free fatty acids, cholesterol, ascorbic acid, iron, serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) levels in both normals and diabetics are included. Effects on urinary excretion of creatine, and changes in body weight, before and after the administration of *G. sylvestre* leaf powder in normal and diabetic people are also included.

Methods and Materials

Selection of subjects

Mild diabetic patients (43) and 16 normals were selected in the age group of 43 to 68 years. Glucose tolerence test was performed with the diabetic patients. The patients, those who have had tolerence curves similar to that of mild diabetics[6] were selected for this research.

Preparation of *G. sylvestre* leaf powder

G. sylvestre leaves were collected and dried in a room at 40^0C. Dried leaves were powdered and packed in 10 g packets.

Administration of *G. sylvestre* leaf powder and hypoglycaemic drug

The 43 diabetic patients (Group I) and the 16 normal subjects (Group II) were administered with *G. sylvestre* leaf powder (10 g/day) for 7 days. The diabetic patients were divided into two groups (group IA & IB). The diabetic patients in group IA (7 patients) were administered with *G. sylvestre* leaf powder for further 14 days. The diabetic patients in group IB (36 patients) were treated with tolbutamide for 7 days.

Glucose tolerance test

Glucose tolerance test[6] was done on zero day, which was before the administration of *G. sylvestre* leaf powder. Modified glucose tolerance test was done on 11th and 21st day for group IA diabetic patients and on 7th and 14th day for group IB diabetic patients. For group II (normal) subjects, modified oral glucose tolerance test was done on 7th day. In the modified oral glucose tolerance test blood glucose level was estimated in zero and 2 hour blood samples.

Analysis of serum and urine sample

Triacylglycerol,[7] free fatty acids,[6] cholesterol,[8] ascorbic acid,[9] iron,[6] SGOT[10] and SGPT[10] levels in serum and urinary excretion of creatine[6] were estimated on zero and 7th day in group I and group II subjects. Body weight of the group I and group II subjects was measured on zero and 7th days.

Statistical Analysis

Standard error (S.E.) of the difference between two means is calculated by the following formula.

$$S.E. = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{SD_1^2}{n_1} + \frac{SD_2^2}{n_2}}}$$

$\bar{X}_1$ - mean of 1st group.
$\bar{X}_2$ - mean of 2nd group.
SD_1 - standard deviation of the 1st group.
SD_2 - standard deviation of the 2nd group.
n_1 - number of subjects in the 1st group.
n_2 - number of subjects in the 2nd group.

The results (S.E.) are taken either as critical ratio (C.R.) or normal deviate (N.D.).

Results and Discussion

Mean fasting blood glucose levels of patients (group IA and IB subjects) before the oral administration of *G. sylvestre* leaf powder were well above 120 mg dl^{-1} and blood glucose level at 2 hours had not returned to their fasting levels (Table 1). Mean blood glucose level of the normal individuals (group II subjects) was 80.8 mg dl^{-1} and at 2 hours the level had returned to normal level (Table 1).

Glucose tolerance of group IA and IB diabetic patients had improved significantly on the 7th day after the administration of *G. sylvestre* leaf powder. It was observed that in group IB patients blood glucose level at 2 hours had returned almost to the fasting glucose level after one week administration of *G. sylvestre* leaf powder (Table 1). Mean fasting blood glucose level of normals (group II) on 7th day was lower than that of the zero day and the differences was statistically significant (C.R. = 2.1).

Mean fasting blood glucose level of group IA subjects had decreased to 104.3 ± 35.1 mg dl^{-1} on the 11th day and to 101.2 ± 31.9 mg dl^{-1} on the 21st day. These decreases in blood glucose levels from the zero day value were statistically significant (C.R. = 2.5 and 2.8). However, there was no significant decrease in mean fasting blood glucose levels of 11th and 21st day. As opposed to group IA, group IB patients were treated with tolbutamide from 8th day. Their mean fasting glucose level on 14th day was 133.1 ± 15.6 mg dl^{-1} and values differ significantly (C.R. = 4.6) from that of zero day value. However, difference in mean fasting blood glucose level of 7th and 14th days of group IB patients was statistically not significant. Decrease in mean fasting blood glucose level of group IA patients from 7th to 11th day was 37.1 mg dl^{-1}, whereas decrease in mean fasting blood glucose level of group IB subjects from 7th to 14th day was only 3.2 mg dl^{-1}. These results show that *G. sylvestre* leaf powder probably had an effect comparable to the oral hypoglycaemic drug tolbutamide. Nevertheless the difference between 7th and 11th day values of group IA subjects

seems to be 10 times higher than that of the difference between 7th and 14th day values of group IB subjects. This increased hypoglycaemic effect of *G. sylvestre* compared with tolbutamide may either be due to the difference in the mode of action of *G. sylvestre* from that of tolbutamide or the concentration of active principle which acts as hypoglycaemic drug. A test with increased dose of *G. sylvestre* leaf powder may confirm these suppositions.

Table 1 : Fasting and post prandial blood glucose levels in diabetic patients and normal subjects before and after treatment.

	Blood Glucose (mg dl^{-1})		
	Diabetic Patients		Normal Subjects
	Group IA*	Group IB**	Group II***
Zero day Oh	151.7 ± 34.7	157.8 ± 28.5	80.8 ± 11.9
2h	215.7 ± 84.2	244.8 ± 78.6	72.6 ± 12.9
7th day Oh	141.4 ± 10.8	136.3 ± 20.3	71.6 ± 12.9
2h	ND	144.7 ± 22.5	68.8 ± 11.8
11th day Oh	104.3 ± 35.1	ND	ND
2h	121.3 ± 46.6	ND	ND
14th day Oh	ND	133.1 ± 15.6	ND
2h	ND	135.5 ± 24.4	ND
21st day Oh	101.2 ± 31.9	ND	ND
2h	141.5 ± 52.5	ND	ND

Group IA* - Diabetics who were treated with **G. sylvestre** for 3 weeks.

Group IB** - Diabetics who were treated with **G. sylvestre** for one week followed by tolbutamide for one week.

Group II*** - Normal subjects.

ND - Not determined.

Shanmugasundram *et al.*[4] have reported that mean fasting blood glucose level of four diabetics had decreased from 117.0 to 85 mg dl^{-1} and that of eight normal subjects had decreased from 79.8 mg dl^{-1} to 64.5 mg dl^{-1} after the intake of *G. sylvestre* leaf powder.

Fasting serum triacylglycerol, free fatty acids and cholesterol levels of group I patients and group II subjects were measured on zero and 7th day fasting blood samples (Table 2). Difference in mean serum triacylglycerol levels between zero and 7th day of group I patients was statistically significant (C.R. = 2.78). Similarly difference in serum free fatty acids levels between zero and 7th day of group I patients was statistically significant (C.R. = 3.48). However, there was no statistically significant difference in both serum triacylglycerol levels and free fatty acids levels in normal subjects (group II) before and after the intake of *G. sylvestre* leaf powder. Difference in serum cholesterol levels of group I patients between zero day and 7th day was 39.9 mg dl^{-1} and that of group II subjects was 16.8 mg dl^{-1}. Difference in mean serum cholesterol levels of group I patients was significantly decreased (C.R. = 4.57). Significant decrease in triacylglycerol, free fatty acids and cholesterol levels in diabetics (group I patients) indicate that *G. sylvestre* has a definite role in controlling carbohydrate metabolism, which has influenced lipid metabolism and decreased the mobilization of fat into blood. Blood cholesterol level of diabetic animals are mainly affected due to the uncontrolled synthesis and reduced catabolism of cholesterol.[11]

These changes in cholesterol metabolism are due to the deficiency in insulin, which controls cholesterol metabolism. Observations made in this work indicate that *G. sylvestre* had acted like insulin in promoting cholesterol catabolism. This could be further confirmed by measuring the catabolic products of cholesterol, such as coprostanol in feces.

Table 2 : Serum triacylglycerol, free fatty acids and cholesterol levels in diabetic patients and normal subjects before and after the administration of *G. sylvestre*.

	Group I*		Group II**	
	0 Day	7th Day	0 Day	7th Day
Triacylglycerol (m mol l^{-1})	1.63 ±0.44	1.36 ±0.4	1.4 ±0.4	1.4 ±0.4
Free fatty acids (μ mol l^{-1})	1.12 ±0.4	0.8 ±0.4	0.7 ±0.2	0.67 ±0.11
Cholesterol (mg dl^{-1})	284.2 ±3.3	244.3 ±4.0	216.7 ±2.3	199.9 ±6.6

Group I* - Diabetic patients.
Group II** - Normal subjects.

Serum ascorbic acid and iron levels of group I patients and group II subjects were estimated before and after the administration of *G. sylvestre* leaf powder (Table 3). Increase in serum ascorbic acid level in group I (2.00 mg dl^{-1}) and group II (2.36 mg

dl^{-1}) were statistically significant (group I C.R. = 8.35; group II C.R. = 4.68). Elevation in serum iron levels of group I (38.0 $\mu g\ dl^{-1}$) and group II (57.1 $\mu g\ dl^{-1}$) were statistically significant (group I C.R. = 4.32; group II C.R. = 2.44). These significant increases in ascorbic acid and iron could probably be due to their high content in dark green leaves, the *G. sylvestre*. Analysis of the leaf powder for ascorbic acid and iron contents may confirm these assumptions.

Table 3 : Serum ascorbic acid and iron levels before and after the administration of *G. sylvestre*.

	Group I*		Group II**	
	0 Day	7th Day	0 Day	7th Day
Ascorbic acid ($mg\ dl^{-1}$)	0.84 ±0.4	2.84 ±1.4	0.84 ±0.44	3.2 ±2.0
Iron ($\mu g\ dl^{-1}$)	168.8 ±32.9	205.8 ±39.9	135.2 ±63.6	192.3 ±68.5

Groupings as in Table 2.

To determine the toxic effect of G. sylvestre, SGOT and SGPT levels in group I and II subjects were measured before and after the administration of *G. sylvestre* leaf powder (Table 4). Difference in SGOT and SGPT values between zero and 7th day of group I patients and group II subjects was statistically not significant (SGOT for group I C.R. = 0.33; group II C.R. = 0.74 and SGPT for group I C.R. = 1.1; group II C.R. = 0.51). These SGOT and SGPT values probably indicate the non-toxicity of the leaf.

Table 4 : SGOT and SGPT levels before and after the administration of *G. sylvestre*.

	Group I*		Group II**	
	0 Day	7th Day	0 Day	7th Day
SGOT ($IU\ l^{-1}$)	7.01 ±2.8	7.60 ±1.6	14.25 ±3.6	13.40 ±2.4
SGPT ($IU\ l^{-1}$)	7.60 ±2.1	8.20 ±2.5	12.33 ±5.22	13.33 ±5.9

Groupings as in Table 2.

Urinary excretion of creatine levels of group I patients and group II subjects were also measured on zero and 7th day (Table 5). The intake of *G. sylvestre* has not

affected the excretion of creatine in normal subjects; whereas in diabetics (group I) creatine excretion had been significantly decreased (C.R. = 4.86). This observation indicates the anabolic effects of *G. sylvestre* on protein metabolism, which is comparable to that of insulin.

Mean body weight of both diabetics and normals were not changed significantly after the intake of *G. sylvestre* leaf powder (Table 5).

Table 5 : Urinary excretion of creatine and body weight before and after the administration of *G. sylvestre*.

	Group I*		Group II**	
	0 Day	7th Day	0 Day	7th Day
Creatine (mg/day)	87.8 ±15.3	69.0 ±17.5	49.2 ±8.7	47.5 ±3.8
Body Weight (Kg)	59.7 ±9.3	60.4 ±9.4	59.8 ±9.9	59.0 ±10.8

Groupings as in Table 2.

The results indicate that *G. sylvestre* has a definite hypoglycaemic effect on both diabetic and normal subjects. This effect on both groups is comparable to that of the oral hypoglycaemic drug tolbutamide. Continued intake of *G. sylvestre* appears to influence carbohydrate, lipid and protein metabolisms by increasing insulin secretion or by increasing insulin receptors in peripheral tissues. In addition intake of *G. sylvestre* leaf powder provides useful nutrients like ascorbic acid and iron. The non-toxic nature is an additional advantage of using G. sylvestre as a drug but this needs confirmation. Further research should be carried out to determine the mode of action of *G. sylvestre* and to isolate the active principle. Even though the *Gymnema sylvestre* does not show toxicity on the diabetics for short period (7 days), the long term toxic effect should be studied.

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