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Effect of *Gymnema sylvestre* on the pharmacokinetics and pharmacodynamics of 0.5mg & 0.6mg Glibenclamide in diabetic rats

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Abstract

Traditional medicines derived from medicinal plants are used by about 60 per cent world population. Diabetes is an important human ailment officiating many from various walk of life in different countries including India. It providing to a major health problem, especially in the rural and subrural areas. *Gymnema sylvestre* R.Br. (Asclepiadaceae) is a herb distributed throughout the world. The leaves of the plant are widely used for the treatment of diabetes and as diuretic in India proprietary medicine. *Gymnema sylvestre* an Ayurvedic herb came to be known as "destroyer of sugar" because, in ancient times, Ayurvedic physicians observed that chewing a few leaves of G. sylvestre suppressed the taste of sugar. It is used totally all over India for controlling blood sugar. This study was to determine effect of *Gymnema sylvestre* on the pharmacokinetics and pharmacodynamics of Glibenclamide in streptozotocin induced diabetic rats**.** Results have indicated the negative effect of *Gymnema Sylvestre* on pharmacokinetics but positive effect on pharmacodynamics of Glibenclamide.

Keywords: *Gymnema sylvestre*, Pharmacokinetics, pharmacodynamics, Diabetes. Glibenclamide

1. Introduction

Many medicinal herbal and pharmaceutical drugs are therapeutic at one dose and toxic at another dose. Interactions between herbal and pharmaceutical drugs can increase or decrease the pharmacological or toxicological effects of either component, herbal drugs are traditionally used to decrease glucose concentrations in diabetic patients [1] could theoretically precipitate hypoglycaemia if taken in combination with conventional drugs.

Experimental studies have shown that herb-drug interactions have both a pharmacokinetic and pharmacodynamic basis, most of that are attributed to the induction or inhibition of hepatic and intestinal microsomal enzymes (primarily cytochrome P_{450}) drug transporters [2].

Glibenclamide interferes with glucose transport modulation by ATP-sensitive potassium channels in peripheral tissues [3] and NO-mediated vasorelaxation induced by a high glucose level [4]. Glibenclamide interferes with mitochondrial bioenergetics in nonpancreatic cells by inducing the changes in the membrane ion permeability [5]. Noninsulin dependent glucose transport via GLUT1 protein appears to be one of the possible additional mechanisms of the drug antidiabetic action. It has been reported that glibenclamide significantly increases the total content and the plasma membrane level of GLUT1 in L6 myotubes. The chronic application of sulfonylurea to cultured cardiomyocytes was found to produce an approximate doubling of the basal glucose uptake rates by an insulin-independent pathway most probably involving the increased protein expression of GLUT1 [6] *Gymnema sylvestre* is used in different systems of medicine as a remedy for the treatment of diabetes, rheumatism, and cough [7]. The major phytoconstituents of *Gymnema sylvestre* are gymnemic acids, gudmarin and saponins. Gymnemic acid ($C_{43}H_{68}O_{14}$) is a pentacyclic triterpenoid and is the main active phytoconstituents of *Gymnema sylvestre*, exhibiting potent anti-diabetic activity [8]. Gymnemic acid show different physiological activities as lower blood glucose and levels of insulin in the diabetic subjects and inhibit intestinal glucose absorption [9]. Recent times have witnessed increased incidence of diabetes across the globe, along with increased popularity of herbal products in the international market [10].

Rural people are still dependent on indigenous knowledge for health care that are being influenced by culture and socioeconomic aspects, providing a cheaper and accessible alternative to the high cost pharmaceutical remedies. In spite of the overwhelming influence and our dependence on modern medicine and tremendous advances in synthetic drugs, many

people still rely on herbs the reason is that, if the herbs are used properly they don't have any side effects. Hence, the study needs to be subjected to pharmacological studies in order to discover their effect on the patients who are taking the treatment with synthetic drugs.

2. Materials and Methods

2.1 Drugs and Chemicals: Albino rats of either sex weighing between 180 and 250 g obtained from National institute of Nutrition India. These animals were maintained proper conditions in animal house of Vaageswari College of pharmacy {IAEC number VCP/2012/10/6/16}. Streptozotocin (Neocare Naturals Pvt. Ltd, Hyderabad, India).*Gymnema sylvestre* collected from Mahadevepur forests India and Plant is authenticated by Dr. E. Narasimha Murthy, Department of Botany, Satavahana University, Karimnagar, Andhra Pradesh. {Specimen Accession Number ENM-100127}.

2.2 Extraction procedure of *Gymnema sylvestre:* 500gm of leaves of *Gymnema sylvestre* were taken, a small amount of dust present as dust was removed by shifting through a sieve of mesh number 30.initial identification was done by chewing few leaves for a minute. the mouth rinsed clean with water few grains of sugar were placed in mouth and disappearance of sugars sweetness was felt.1gm powdered material was shaken vigorously with water and examined for more than 30 minutes for froth test confirmed presence of saponin glycosides that is gymnemicacid.500gm of powdered dry leaf powder was packed soxhlet thimble and extracted continuously with 80% of ethanol until the material was completely exhausted. The final product was dark green amorphous powder after evaporation of solvent [11].

2.3 Pretreatment: Albino rats of both gender weight between 180 and 250 g obtained from National institute of Nutrition, Hyderabad, India. These animals were maintained under standard conditions in animal house of Vaageswari College of pharmacy [IAEC number VCP/2012/10/6/16]. Each were kept in elevated wire cages and were provided with high fat food (carbohydrates: proteins: fat in 42:18:40 ratios) and water *ad libitum* for a period of 14 days [12].

2.4 Induction of Diabetes in Rats by using 60mg/kg of streptozocin [13]:

After 2 weeks of feeding with high fat food the rats were fasted for a period of 18 hours before induction of diabetes, and were injected intra-peritonially with a single dose of Streptozocin 60 mg/kg (Sigma–Aldrich, St. Louis, MO, USA), freshly dissolved in normal saline solution. After the administration, the rats had free access to food (normal pellet diet) and water *ad libitum*. Diabetes in rats was identified by moderate polydipsia and marked polyuria. After 3 days i.e. 72hrs of injection, the fasting blood glucose levels were determined by following glucose oxidase/peroxidase GOD/POD method using a commercial glucose estimation kit with UV-Visible Spectrophotometer at 505nm. The rats showing fasting blood glucose more than 150 mg/dL were considered diabetic rats and selected for the grouping in experimentation.

2.5 Study Design: The hyperglycemic rats are divided in to 6 groups 6 animals in each.

Group I: Diabetic Control group (0.5% Na.CMC suspension *p.o*)
Group II: *Gymnema sylvestre* (100 mg/kg, *p.o*)
Group III: *Gymnema sylvestre* (500 mg/kg. *p.o*)
Group IV: Glibenclamide (0.6 mg/kg. *p.o*)
Group V: Combination of Glibenclamide (0.5mg/kg. *p.o*) + *Gymnema sylvestre* (500 mg/kg).
Group VI: Combination of Glibenclamide (0.6 mg/kg. *p.o*) + *Gymnema sylvestre* (500 mg/kg). [14]

2.6 Pharmacokinetic study in diabetic rats:

Single dose study (acute study): The studies were carried out in diabetic rats (weight between 180g and 250g).They were housed in elevated wire cages with free access to food and water *ad libitum.* The overnight fasted rats were divided in to six different groups (n=6) and the treatment was given as mentioned in study design. Post- dosing the blood samples were collected at predetermined intervals of 0,1,2,4,8,12 and 24hr in hinto micro-centrifugal tubes containing sodium citrate from retro-orbital sinus under mild ether anaesthesia. The blood samples were subjected to centrifugation at 3000 rpm for 10 min and plasma was stored at -20^0C for analysis and determination of pharmacokinetic parameters as ka, ke, t1/2, V/F, CL/F, T_{max}, C_{max}, AUC 0-t, AUC 0 - ∞ .

Multiple dose study (chronic study): The diabetic rats were divided into 6 different treatment groups same as mentioned in study design and Daily treatment was carried for 21 days(3 weeks).Blood samples were collected from different groups on 0,7,14,21st day immediately after treatment. Blood samples were collected in to micro-centrifugal tubes containing sodium citrate from retro-orbital sinus under, mild ether anaesthesia. The blood samples were subjected to centrifugation at 3000 rpm for 10 min and plasma was stored at -20^0 C for analysis and determination of pharmacokinetic parameters as absorption rate constant, elimination rate constant, t1/2, V/F, CL/F, T_{max}, C_{max}, AUC 0-t, AUC 0 - ∞ .

2.7 Pharmacodynamic study in diabetic rats

Single dose study (acute study): Adults albino rats weighing 180-250g with fasting serum glucose >150 mg/dl are considered as diabetic. The treatment was given as mentioned in study design. Different biochemical parameters as serum glucose, cholesterol, urea concentrations are measured at different time intervals of 0, 1, 2, 4, 8, 12 and 24hr by using semi

auto analyzer. These values are considered as acute study values.

Multiple dose study (chronic study): The diabetic rats were divided into 6 different treatment groups same as mentioned in study design and Daily treatment was carried for 21 days (3 weeks).Different biochemical parameters as glucose, cholesterol, urea concentrations of the overnight fasted rats were determined on 0,7,14,21st day using semi auto analyzer.[15]

2.8 Statistical analysis: All data are expressed as Mean±Sd. For comparison amongst different groups, One-way analysis of variance (ANOVA) followed by Dunnet test was performed. P value fewer than 5% (P <0.05) was considered to be statistically significant. Pharmacokinetic data was calculated by using pk solver software and statistical analysis was done by INSTANT graph pad software.

2.9 Histopathological studies: After the last blood glucose estimation, the rats were sacrificed and pancreas were excised and subjected to histopathological studies to determine the inflammatory and necrotic changes. The tissues were stained using H&E stain and observed under 100 × magnifications. [16].

3. Results

Table 1: Blood glucose levels mg/dL (0th, 1st, 2nd, 4th, 8th, 12th and 24th Hour) after oral administration of *Gymnema sylvestre*, Glibenclamide and combination of Glibenclamide and *Gymnema sylvestre* in diabetic rats (n=6).

Treatment/Hours	Blood Glucose levels (mg/dL)					
	Diabetic Control	G S (Dose)		Glibenclamide (Dose)	Glibenclamide + G S (Dose)	
	vehicle	100mg/kg	500mg/kg	0.6mg/kg	0.5mg/kg + 500mg/kg	0.6mg/kg+ 500mg/kg
0th Hour Blood Glucose levels	402.4±14.2	413.04±10.9*	393.8±6.6*	410.5±4.16*	401.18±6.18*	398.14±6.15*
1st Hour Blood Glucose levels	463.5±9.48	408.4±1.26*	363.8±9.3*	375.5±6.15*	371.16±11.2*	362.18±8.15*
2nd Hour Blood Glucose levels	464.8±9.32	349.2±12.3*	367.8±8.5*	362.13±1.26*	358.19±9.01*	351.16±9.16*
4th Hour Blood Glucose levels	429.8±7.91	337.6±13.5*	365.4±4.9*	355.12±2.41*	351.16±8.15*	348.91±4.14*
8th Hour Blood Glucose levels	420.8±8.5	298.68±4.5*	273.1±8.7*	261.24±4.8*	253.18±9.05*	241.16±6.15*
12th Hour Blood Glucose levels	414.8±6.2	314.8±8.5*	294.8±5.6*	259.18±1.26*	249.16±8.91*	238.81±15.62*
24th Hour Blood Glucose levels	415.8±13.5	323.6±9.6*	301.8±3.4*	262.11±3.29*	255.16±10.15*	239.18±10.24*

Values are given as mean± Standard deviation; *Statistical significance p < 0.05 (compared with the control group) G S - *Gymnema sylvetsre* ; n - Number of animals used.

Table 2*:* Blood cholesterol levels mg/dL (0th, 1st, 2nd, 4th, 8th, 12th and 24th Hour) after oral administration of *Gymnema sylvestre*, Glibenclamide and combination of Glibenclamide and *Gymnema sylvestre* in diabetic rats (n=6).

Treatment/Hours	Blood Cholesterol Levels (mg/dL)					
	Diabetic Control	G S (Dose)		Glibenclamide (Dose)	Glibenclamide + G S (Dose)	
	vehicle	100mg/kg	500mg/kg	0.6mg/kg	0.5mg/kg +500mg/kg	0.6mg/kg+ 500mg/kg
0th Hour Blood Cholesterol levels	196.4±12.4	205.3±9.3*	203.15±12.1*	209.15±11.26*	197.19±11.36*	196.1±11.23*
1st Hour Blood Cholesterol levels	194.61±10.14	200.5±9.4*	195.14±14.2*	193.63±4.18*	189.11±6.28*	187.8±10.16*
2nd Hour Blood Cholesterol levels	201.14±6.41	184.6±4.8*	181.41±7.8*	178.16±.3.19*	175.51±.5.68*	173.16±5.29*
4th Hour Blood Cholesterol levels	204.41±12.6	175.8±7.8*	170.61±7.5*	161.14±1.28*	156.61±5.81*	153.19±6.15*
8th Hour Blood Cholesterol levels	203.8±8.31	148.9±5.5*	145.14±8.2*	141.18±10.61*	136.28±8.16*	133.28±11.28*
12th Hour Blood Cholesterol levels	210.9±8.13	154.14±6.4*	151.22±6.5*	139.19±9.05*	131.28±8.73*	129.18±6.71*
24th Hour Blood Cholesterol levels	212.6±7.8	178.09±8.2*	169.81±2.6*	145.25±10.24*	136.18±6.26*	134.18±10.91*

Values are given as mean± Standard deviation.; *Statistical significance p < 0.05 (compared with the control group) G S - *Gymnema sylvetsre;* n - Number of animals used**.**

Table 3: Blood urea levels mg/dL (0th, 1st, 2nd, 4th, 8th, 12th and 24th Hour) after oral administration of *Gymnema sylvestre,* Glibenclamide and combination of Glibenclamide and *Gymnema sylvestre* in diabetic rats (n=6).

Treatment/Hours	Blood urea levels (mg/dL)					
	Diabetic control	G S (Dose)		glibenclamide (dose)	glibenclamide + G S (dose)	
	vehicle	100mg/kg	500mg/kg	0.6mg/kg	0.5mg/kg + 500mg/kg	0.6mg/kg+ 500mg/kg
0th Hour Blood Urea levels	63.72±7.35	64.18±5.5*	74.13±4.1*	75.19±3.16*	67.88±6.16*	65.83±5.93*
1st Hour Blood Urea levels	63.18±2.46	64.72±7.18*	67.5±5.31*	66.28±4.19*	61.02±6.25*	59.18±6.91*
2nd Hour Blood Urea levels	66.34±9.12	62.02±5.12*	65.24±7.31*	63.26±5.84*	58.78±6.52*	56.68±6.34*
4th Hour Blood Urea levels	66.96±5.16	59.41±6.12*	57.24±5.14*	53.18±6.53*	51.16±6.35*	49.08±6.36*
8th Hour Blood Urea levels	68.04±4.35	50.76±6.14*	48.6±5.18*	46.36±6.94*	44.36±5.18*	41.29±6.18*
12th Hour Blood Urea levels	69.12±4.46	54±6.16*	52.38±7.34*	50.14±4.61*	47.52±5.44*	45.63±6.85*
24th Hour Blood Urea levels	68.24±9.08	61.56±5.12*	59.4±7.55*	53.19±6.84*	50.24±5.44*	48.84±6.95*

Values are given as mean± Standard deviation.; *Statistical significance $p < 0.05$ (compared with the control group); G S - *Gymnema sylvetsre;* n - Number of animals used.

Table 4: Blood glucose levels mg/dL (0th, 7th, 14th and 21st day) after oral administration of *Gymnema sylvestre,* Glibenclamide and combination of Glibenclamide and *Gymnema sylvestre* in diabetic rats (n=6).

Treatment/Days	Blood Glucose levels (mg/dL)					
	Diabetic control	G S (Dose)		Glibenclamide (Dose)	Glibenclamide + G S (Dose)	
	vehicle	100mg/kg	500mg/kg	0.6mg/kg	0.5mg/kg +500mg/kg	0.6mg/kg+ 500mg/kg
0ty day Blood Glucose levels	410.15±4.15	419.33±2.2*	395.16±1.2*	403.46±6.81*	385.91±6.03*	375.18±6.80*
7th day Blood Glucose levels	394.12±.4.4	238.31±2.4*	231.1±3.3*	216.68±8.91*	210.93±5.83*	200.28±8.52*
14th day Blood Glucose levels	385.35±3.14	180.36±1.5*	151.36±3.4*	145.91±9.06*	135.90±6.72*	129.05±9.06*
21st day Blood Glucose levels	391.49±3.4	131.16±2.4*	122.51±2.5*	116.58±4.81*	110.94±5.84*	101.38±8.05*

Values are given as mean± Standard deviation.; *Statistical significance $p < 0.05$ (compared with the control group); G S - *Gymnema sylvetsre;* n - Number of animals used.

Table 5: Blood cholesterol levels mg/dL (0th, 7th, 14th and 21st day) after oral administration of *Gymnema sylvestre,* Glibenclamide and combination of Glibenclamide and *Gymnema sylvestre* in diabetic rats (n=6).

Treatment/Days	Blood Cholesterol levels (mg/dL)					
	Diabetic control	G S (Dose)		Glibenclamide (dose)	Glibenclamide + G S (Dose)	
	vehicle	100mg/kg	500mg/kg	0.6mg/kg	0.5mg/kg +500mg/kg	0.6mg/kg+ 500mg/kg
0ty day Blood Cholesterol levels	193.19±11.5	188.51±9.5*	182.18±12.2*	178.94±5.95*	171.52±6.81*	169.08±8.16*
7th day Blood Cholesterol levels	194.91±10.6	105.15±9.6*	102.35±8.4*	100.64±6.81*	94.38±6.6*	91.18±5.71*
14th day Blood Cholesterol levels	186.33±9.55	86.38±9.23*	84.46±7.8*	78.06±6.11*	70.25±6.81*	65.70±9.05*
21st day Blood Cholesterol levels	191.3±7.88	73.18±10.4*	70.41±9.2*	66.41±9.03*	58.81±6.79*	56.91±5.84*

Values are given as mean± Standard deviation; *Statistical significance $p < 0.05$ (compared with the control group); G S - *Gymnema sylvetsre;* n - Number of animals used.

Table 6: Blood urea levels mg/dL (0^{th}, 7^{th}, 14^{th} and 21^{st} day) after oral administration of *Gymnema sylvestre*, Glibenclamide and combination of Glibenclamide and *Gymnema sylvestre* in diabetic rats (n=6).

Treatment/ Days	Blood Urea Levels (mg/dL)					
	Diabetic Control	G S (Dose)		Glibenclamide (Dose)	Glibenclamide+ G S (Dose)	
	vehicle	100mg/kg	500mg/kg	0.6mg/kg	0.5mg/kg +500mg/kg	0.6mg/kg+ 500mg/kg
0^{th} day Blood Urea levels	71.26±4.83	68.13±8.34*	69.46±6.54*	66.89±8.95*	61.04±6.95*	58.36±5.33*
7^{th} day Blood Urea levels	77.86±9.21	42.36±2.42*	38.53±4.01*	35.68±5.60*	32.85±5.83*	30.38±5.04*
14^{th} day Blood Urea Levels	79.66±7.33	33.4±8.51*	32.08±6.03*	29.06±4.95*	26.40±8.06*	21.01±9.68*
21^{st} day Blood Urea Levels	70.39±6.25	32.69±9.23*	30.43±8.54*	26.15±6.09*	21.39±6.01*	19.05±3.06*

Values are given as mean± Standard deviation.; *Statistical significance $p < 0.05$ (compared with the control group); G S - *Gymnema sylvetsre;* n - Number of animals used.

Table 7: Mean plasma Glibenclamide concentrations (µg/ml) (Single dose study)

Hours	Diabetic Control	0.6mg/kg of Glibenclamide	Glibenclamide + *Gymnema sylvestre* (Dose)	
			0.5mg/kg+500mg/kg	0.6mg/kg+ 500mg/kg
1^{st} Hour	0	2.85±0.02	2.61±0.08	2.76±0.04
2^{nd} Hour	0	5.62±0.05	4.91±0.01	5.08±0.09
4^{th} Hour	0	5.12±0.04	4.52±0.03	4.96±0.08
8^{th} Hour	0	4.14±0.04	3.66±0.05	4.05±0.01
12^{th} Hour	0	3.17±0.03	2.91±0.08	3.11±0.05
24^{th} Hour	0	2.04±0.04	1.81±0.06	1.99±0.08

Table 8: Mean plasma Glibenclamide concentrations (µg/ml) (Multiple dose study).

Treatment/ Days	Diabetic Control	0.6mg/kg of Glibenclamide	Glibenclamide + *Gymnema sylvestre* (Dose)	
			0.5mg/kg+500mg/kg	0.6mg/kg+ 500mg/kg
0^{th} Day	0	2.63±0.05	2.51±0.06	2.58±0.05
7^{th} Day	0	6.15±0.09	4.83±0.04	5.53±0.05
14^{th} Day	0	5.03±0.03	4.43±0.06	4.64±0.05
21^{st} Day	0	4.53±0.06	3.66±0.04	3.85±0.03

Table 9: Effect of *Gymnema sylvestre* on Pharmacokinetic parameters of Single dose administration Glibenclamide in diabetic rats (n=6)

Pharmacokinetic parameter	Units for Pharmacokinetic parameter	0.6mg Glibenclamide	Glibenclamide + *Gymnema sylvestre* (Dose)	
			0.5mg/kg+500mg/kg	0.6mg/kg+500mg/kg
ka	h^{-1}	0.7767±0.097	0.6503±0.019	0.7132±0.088
ke	h^{-1}	0.8977±0.151	0.9038±0.118	0.9105±0.363
t1/2	h	10.03±0.05	10.01±0.04	10.02±0.09
V/F	(mg/kg)/(µg/ml)	1.54±0.01	1.61±0.04	1.69±0.08
CL/F	(mg/kg)/(µg/ml)/h	0.07±0.03	0.08±0.06	0.09±0.01
T_{max}	h	2.04±0.09	2.09±0.08	2.16±0.05
C_{max}	µg/ml	5.63±0.05	4.81±0.06	5.43±0.09
AUC 0-t	µg/ml*h	83.49±0.84	70.01±0.41	79.05±0.33
AUC 0 - ∞	µg/ml*h	100.64±0.48	82.06±0.51	94.11±0.81

Values are given as mean± Standard deviation.; *Statistical significance $p < 0.05$ (compared with the control group); G S - *Gymnema sylvetsre;*n - Number of animals used.

Table 10: Effect of *Gymnema sylvestre* on Pharmacokinetic parameters of multiple dose administration Glibenclamide in diabetic rats (n=6).

Pharmacokinetic parameter	Units for Pharmacokinetic parameter	0.6mg Glibenclamide	Glibenclamide + *Gymnema sylvestre* (DOSE)	
			0.5mg/kg+500mg/kg	0.6mg/kg+500mg/kg
ka	h^{-1}	0.054±0.061	0.041±0.016	0.049±0.035
ke	h^{-1}	0.042±0.05	0.035±0.06	0.046±0.08
t1/2	h	10±0.02	10.01±0.04	10.02±0.09
V/F	(mg/kg)/(µg/ml)	1.55±0.02	1.41±0.01	1.61±0.06
CL/F	(mg/kg)/(µg/ml)/h	0.07±0.00	0.08±0.05	0.09±0.08
T_{max}	h	2.04±0.09	2.02±0.05	2.19±0.08
C_{max}	µg/ml	5.99±0.05	4.83±0.02	5.18±0.06
AUC 0-t	µg/ml*h	92.41±0.84	62.03±0.18	71.11±0.09
AUC 0 - ∞	µg/ml*h	101.64±0.48	83.91±0.58	92.76±0.83

Values are given as mean± Standard deviation; *Statistical significance $p < 0.05$ (compared with the control group); G S - *Gymnema sylvetsre;* n - Number of animals used.

Table 9: Volume of islet cells in pancreas in different groups after multiple dose study (n=6)

Group	Volume of islets (mm3/mm3) / Volume of pancreas (mm3/mm3)
Control	0.082 ± 0.004
GS (100 mg/kg, *p.o.)*	0.195 ± 0.052*
GS (500 mg/kg, p.o.)	0.244 ± 0.007*
Glibenclamide (0.6 mg/kg, p.o.)	0.151 ± 0.008*
Glibenclamide (0.5 mg/kg, p.o.) + GS (500 mg/kg, p.o.)	0.256 ± 0.061*
Glibenclamide (0.6 mg/kg p.o.) + GS. (500 mg/kg, p.o.).	0.278±0.011*

Values are given as mean± Standard deviation; *Statistical significance $p < 0.05$ (compared with the control group); G S - *Gymnema sylvetsre;* n - Number of animals used.

3. Discussion

The histopathological studies reveal that the combination of Glibenclamide (0.6 mg/kg) and *Gymnema sylvestre* not only increased the volume of islets and also recovered partially destroyed beta cells.

3.1 Pharmacodynamic study:

The combination of high dose of Glibenclamide (0.6 mg/kg) with 500mg/kg *Gymnema sylvestre* showed maximum hypoglycaemic action, decrease in serum cholesterol, urea levels. The influence produced by combination of Glibenclamide (0.5 mg/kg) with *Gymnema sylvestre* was greater than the hypoglycaemic action produced by *Gymnema sylvestre* (500 mg/kg) alone but less than Glibenclamide (0.6 mg/kg).

3.2 Pharmacokinetic study:

The pharmacokinetic study shows that, 17% decrease in AUC $_{(0 - \infty)}$ in 500mg/kg of *Gymnema sylvestre* and 0.5mg/kg of Glibenclamide. 8.7% decrease AUC $_{(0-\infty)}$ in 500mg/kg of *Gymnema sylvestre* and high dose of Glibenclamide. C max was decreased by 19% in 500mg/kg of *Gymnema sylvestre* and 0.5mg/kg of Glibenclamide. 13% in 500mg/kg of *Gymnema sylvestre* and high dose of Glibenclamide that was attributed by significant decrease in absorption rate constant Ka by about 24% in Lower dose of 500mg/kg of *Gymnema sylvestre* and 0.5mg/kg of Glibenclamide, 9% in 500mg/kg of *Gymnema sylvestre* and high dose of Glibenclamide, increment in clearance 14 % in 500mg/kg of *Gymnema sylvestre* and 0.5mg/kg of Glibenclamide. 29% in 500mg/kg of *Gymnema sylvestre* and high dose of Glibenclamide compared to high dose Glibenclamide group.

4. Conclusion

The interaction of modern medicine with herbs is a developing area with research activities being carried out in different parts of the world. The interaction of herbs with various classes of drugs have been reported and some drugs such as terfenadine and astemizole from the market due to such interactions.

The interaction appears to be pharmacokinetic interaction at absorption, elimination. *Gymnema sylvestre* inhibits

the absorption of Glibenclamide that results in a significant decrease in the bioavailability of the later and combination group with a lower dose of Glibenclamide produced increment to the volume of islets in pancreas compare to individual treatment. Since the interaction was seen in rats it is likely to occur in humans leading to decreased activity of Glibenclamide that can need dose adjustments. Hence care must be taken when the combination is prescribed for clinical benefit in diabetic patients. The present study warrants next plan to find out the relevance of the interaction in human beings.

Conflict of Interest

The Authors declare that they have no competing interests.

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