Shravan Kumar Dholi et al. / International Journal of Pharmacy & Therapeutics, 6(4), 2015, 205-212.
e- ISSN 0976-0342
Print ISSN 2229-7456

International Journal of Pharmacy & Therapeutics

Journal homepage: www.ijptjournal.com

IJPT

EFFECT OF *GYMNEMA SYLVESTRE* ON THE PHARMACOKINETICS AND PHARMACODYNAMICS OF 7.5mg & 10mg PIOGLITAZONE IN DIABETIC RATS

Shravan Kumar Dholi*[1], Ramakrishna Raparla[2], Kannappan[3]

[1] Research Scholar, Depatment of Pharmacology, JNTUK, Kakinada, Andhra Pradesh -533003, India.
[2]Depatment of Pharmaceutics, Vaageswari Institute of Pharmaceutical Sciences, Beside LMD Police Station, Ramakrishna Colony, Karimnagar, Andhra Pradesh.-505481, India.
[3]Department of Pharmacy, Annamali University, Annamali Nagar, Tamilnadu-608002. India.

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, Ayurvedia 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 Pioglitazone in streptozotocin induced diabetic rats**.** Results have indicated the negative effect of *Gymnema sylvestre* on pharmacokinetics but positive effect on pharmacodynamics of Pioglitazone.

Key Words:- *Gymnema sylvestre*, Pharmacokinetics, Pharmacodynamics, Diabetes, Pioglitazone.

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 (Bailey CJ *et al*., 1989) could theoretically precipitate hypoglycaemia if taken in combination with conventional drugs.

Corresponding Author

Shravan Kumar Dholi
Email:- shravanjntuk@rediffmail.com

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 P450) drug transporters (Izzo A *et al.*, 2005).

Pioglitazone is an oral drug for the treatment of type 2 diabetes mellitus and it belongs to the class of thiazolidinedione derivative (TZDS). TZDS has been approved for type 2 diabetes mellitus, particularly for overweight patients who are in adequately controlled by diet and exercise alone for whom metformin is inappropriate because of contraindications or intolerance (Tack CJJ *et al*., 2006) whereas, pioglitazone is as a potent and highly selective

agonist for the peroxisome proliferator–activated receptor-(PPAR-). Activation of these receptors promotes the production of gene products involved in lipid and glucose metabolism. It also improves insulin response to target cells with increasing the pancreatic secretion of insulin (Thomsen RW *et al.,* 2006). Several reports indicated that diabetes mellitus increased the mucosal susceptibility to ulcerogenic stimuli and predisposition to gastric ulceration (Aditi C *et al*., 2009). However, incidences of gastric ulcer in diabetes may be infrequent, gastric bleeding is often fatal in diabetes.Severe acute gastric inflammation or ulcer disease can occur with high prevalence and with complications such as bleeding in patients with diabetes mellitus with little or no dyspeptic symptoms (Boehme MW *et al.,* 2007).

Gymnema sylvestre is used in different systems of medicine as a remedy for the treatment of diabetes, rheumatism, and cough (Patel K *et al*., 2012). 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 (Shivani *et al.,* 2011). Gymnemic acid show different physiological activities as lower blood glucose and levels of insulin in the diabetic subjects and inhibit intestinal glucose absorption (Ankit *et al*., 2010).Recent times have witnessed increased incidence of diabetes across the globe, along with increased popularity of herbal products in the international market (John B Classen *et al*., 2012).

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 need to be subjected to pharmacological studies in order to discover their effect on the patients who are taking the treatment with synthetic drugs.

MATERIALS AND METHODS

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}.

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 (Farzana C *et al.,* 2010).

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 (Reed *et al.,* 2000).

Induction of Diabetes in Rats by using 60mg/kg of streptozocin

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.

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)
Group II: *Gymnema sylvestre* (100 mg/kg)
Group III: *Gymnema sylvestre* (500 mg/kg)
Group IV: Pioglitazone (10 mg/kg)
GroupV: Combination of Pioglitazone (7.5mg/kg) + *Gymnema sylvestre* (500 mg/kg).
Group VI: Combination of Pioglitazone (10 mg/kg) + *Gymnema sylvestre* (500 mg/kg). (Talari et al., 2010).

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^{0}C for analysis and determination of pharmacokinetic parameters as ka, ke, t1/2, V/F, CL/F, Tmax, Cmax, 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, Tmax, Cmax, AUC 0-t, AUC 0 - ∞ .

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 (Shavi *et al*., 2010).

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.

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 (Navetabhishekam *et al.,* 2009).

RESULTS

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

Treatment/Hours	Blood Glucose Levels (mg/dL)					
	Diabetic Control	G S (Dose)		Pioglitazone (Dose)	Pioglitazone + G S (Dose)	
	vehicle	100mg/kg	500mg/kg	10mg/kg	7.5mg/kg +500mg/kg	10mg/kg +500mg/kg
0th Hour Blood Glucose Levels	402.4±11.2	413.02±10.8*	391.8±6.4*	384.11±5.90*	380.98±3.48*	374.81±6.91*
1st Hour Blood Glucose Levels	463.5±9.44	409.4±1.21*	363.9±9.2*	355.18±9.71*	351.34±9.16*	343.83±9.03*
2nd Hour Blood Glucose Levels	464.4±9.33	348.2±12.4*	327.6±8.5*	312.14±3.13*	309.72±6.09*	299.91±11.31*

4th Hour Blood Glucose Levels	429.5±7.9	337.5±13.5*	315±4.9*	310.23±6.18*	301.91±7.02*	281.65±6.72*
8th Hour Blood Glucose Levels	440.4±8.5	298.8±4.5*	274.1±8.7*	270.18±8.16*	265.14±6.11*	260.41±5.83*
12th Hour Blood Glucose Levels	414.8±9.2	314.9±8.5*	294.8±5.5*	261.99±9.4*	241.71±1.28*	238.04±9.81*
24th Hour Blood Glucose Levels	415.8±11.5	323.5±9.6*	301.9±3.4*	276.11±10.06*	249.08±2.61*	241.66±1.26*

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

Treatment/Days	Blood Glucose Levels (mg/dL)					
	Diabetic Control	G S (Dose)		Pioglitazone (Dose)	Pioglitazone + G S (Dose)	
	vehicle	100mg/kg	500mg/kg	10mg/kg	7.5mg/kg +500mg/kg	10mg/kg +500mg/kg
0ty day Blood Glucose Levels	410.5±4.5	419.3±2.2*	395.6±1.2*	400.16±4.51*	384.33±8.16*	375.91±3.48*
7th day Blood Glucose Levels	394.2±.4.4	238.3±2.4*	231.±3.3*	214.99±8.19*	200.13±5.22*	196.05±3.49*
14th day Blood Glucose Levels	385.5±3.4	180.6±1.5*	151.6±3.4*	145.81±6.05*	131.02±6.15*	121.88±6.81*
21st day Blood Glucose Levels	391.9±3.4	131.6±2.4*	122.5±2.5*	119.04±5.18*	118.36±8.19*	110.06±9.05*

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

Treatment/Hours	Blood Cholesterol Levels (mg/dL)					
	Diabetic Control	G S (Dose)		Pioglitazone (Dose)	Pioglitazone + G S (Dose)	
	vehicle	100mg/kg	500mg/kg	10mg/kg	7.5mg/kg +500mg/kg	10mg/kg +500mg/kg
0th Hour Blood Cholesterol Levels	199.4±12.8	205.2±9.3*	203.5±12.1*	200.81±10.13*	196.38±10.91*	191.08±10.41*
1st Hour Blood Cholesterol Levels	194.6±10.4	200.4±9.4*	195.1±14.2*	191.03±4.19*	183.06±6.13*	180.15±10.63*
2nd Hour Blood Cholesterol Levels	201.4±6.11	184.5±4.8*	181.4±7.8*	169.32±8.04*	166.04±5.96*	160.31±3.81*
4th Hour Blood Cholesterol Levels	204.11±12.6	175.5±7.8*	170.6±7.5*	158.06±6.13*	152.04±3.42*	143.05±5.06*
8th Hour Blood Cholesterol Levels	203.21±8.24	148.33±5.5*	145.33±8.4*	141.82±11.8*	133.08±9.84*	130.66±9.31*
12th Hour Blood Cholesterol Levels	210.6±8.13	154.11±6.4*	151.2±6.5*	138.3±10.13*	130.80±6.91*	126.81±9.15*
24th Hour Blood Cholesterol Levels	212.5±7.8	178.9±8.2*	169.8±2.6*	131.45±10.94*	128.16±8.04*	121.05±8.01*

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

Treatment/Days	Blood Cholesterol Levels (mg/dL)					
	Diabetic Control	G S (Dose)		Pioglitazone (Dose)	Pioglitazone + G S (Dose)	
	vehicle	100mg/kg	500mg/kg	10mg/kg	7.5mg/kg +500mg/kg	10mg/kg +500mg/kg
0^{ty} day Blood Cholesterol Levels	193.9±11.5	188.5±9.5*	182.8±12.2*	178.24±9.04*	175.61±9.04*	170.66±8.18*
7^{th} Day blood Cholesterol Levels	194.1±10.6	105.5±9.6*	102.5±8.4 *	99.61±8.06*	95.84±8.16*	91.34±9.83*
14^{th} day Blood Cholesterol Levels	186.33±9.5	86.8±9.23*	84.6±7.8 *	80.72±1.95 *	78.06±6.28*	75.81±8.36*
21^{st} day Blood Cholesterol Levels	191.3±7.8	73.8±10.4*	70.1±9.2 *	67.11±5.16 *	61.07±1.66*	59.03±8.19*

*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 urea levels mg/dL (0^{th},1^{st} ,2^{nd},4^{th},8^{th}, 12^{th} and 24^{th} Hour) after oral administration of *Gymnema sylvestre*, Pioglitazone and combination of Pioglitazone and *Gymnema sylvestre* in diabetic rats (n=6)

Treatment/Hours	Blood Urea Levels (mg/dL)					
	Diabetic Control	G S (Dose)		Pioglitazone (Dose)	Pioglitazone + G S (Dose)	
	vehicle	100mg/kg	500mg/kg	10mg/kg	7.5mg/kg +500mg/kg	10mg/kg +500mg/kg
0^{th} Hour Blood Urea Levels	63.72±7.5	64.8±5.5*	74.36±4.1*	71.32±6.18*	68.15±4.58*	66.08±1.38*
1^{st} Hour Blood Urea Levels	63.18±2.6	64.72±7.8*	67.5±5.1*	63.14±4.52*	60.11±4.19*	58.11±6.05*
2^{nd} Hour Blood Urea Levels	66.34±9.2	62.02±5.2*	65.24±7.1*	60.81±3.63*	55.81±5.93*	51.81±7.63*
4^{th} Hour Blood Urea Levels	66.96±5.6	59.4±6.2*	57.24±5.4*	54.81±8.94*	50.16±8.04*	48.26±6.19*
8^{th} Hour Blood Urea Levels	68.04±4.5	50.76±6.4*	48.6±5.8*	46.14±9.13*	43.06±3.68*	40.11±3.48*
12^{th} Hour Blood Urea Levels	69.33±4.21	53.1±6.11*	53.28±5.4*	51.99±6.14*	41.98±8.06*	38.54±6.18*
24^{th} Hour Blood Urea Levels	68.24±9.0	61.56±5.2*	59.4±7.5*	50.12±6.08*	40.96±6.33*	36.91±8.04*

*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*, Pioglitazone and combination of Pioglitazone and *Gymnema sylvestre* in diabetic rats (n=6)

Treatment/Days	Blood Urea Levels (mg/dL)					
	Diabetic Control	G S (Dose)		Pioglitazone (Dose)	Pioglitazone + G S (Dose)	
	vehicle	100mg/kg	500mg/kg	10mg/kg	7.5mg/kg +500mg/kg	10mg/kg +500mg/kg
0^{th} day Blood Urea Levels	71.6±4.83	68.13±8.3*	69.6±6.54*	65.06±8.18*	61.22±9.06*	59.96±5.04*
7^{th} day Blood Urea Levels	77.66±9.21	42.26±2.42*	38.13±4.01*	33.81±6.08*	31.63±8.11*	29.81±6.93*
14^{th} day Blood Urea Levels	79.26±7.33	33±8.51*	32.06±6.03*	29.11±4.18*	23.19±6.85*	20.11±3.59*

21st day Blood Urea Levels	70.09±6.25	32.49±9.23*	30.13±8.54*	25.81±11.26*	19.66±1.62*	17.99±8.64*

*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. Effect of *Gymnema sylvestre* on Pharmacokinetic parameters of Single dose administration of Pioglitazone in diabetic rats (n=6)

Pharmacokinetic parameter	Units for Pharmacokinetic parameters	10mg/kg of Pioglitazone	Pioglitazone + *Gymnema sylvestre* (Dose)	
			7.5mg/kg+500mg/kg	10mg/kg+500mg/kg
ka	h^{-1}	1.462±0.18	1.136±0.34*	1.219±0.51
ke	h^{-1}	0.1199±0.04	0.1183±0.09*	0.1281±0.01
t1/2	h	5.78±0.63	5.03±0.55*	5.11±0.48
V/F	(mg/kg)/(µg/ml)	1.05±0.014	1.14±6.19*	1.28±0.081
CL/F	(mg/kg)/(µg/ml)/h	0.91±0.003	0.81±0.25*	0.98±0.006
Tmax	h	3.16 ±0.64	3.73±0.55*	3.88 ±0.14
Cmax	µg/ml	5.7±0.19	4.81±0.03*	5.1±0.14
AUC 0-t	µg/ml*h	78.92±6.126	65.18±0.83*	71.33±5.181
AUC 0 - ∞	µg/ml*h	86.60±7.039	69.05±0.28*	79.18±6.103

*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 8. Effect of *Gymnema sylvestre* on Pharmacokinetic parameters of Multiple dose administration of Pioglitazone in diabetic rats (n=6)

Pharmacokinetic parameter	Units for Pharmacokinetic parameters	10mg/kg of Pioglitazone	Pioglitazone + *Gymnema sylvestre* (Dose)	
			7.5mg/kg+500mg/kg	10mg/kg+500mg/kg
ka	h^{-1}	6.258±0.91	5.915±0.82	6.109±0.96
ke	h^{-1}	0.2901±0.08	0.2619±0.05	0.3118±0.03
t1/2	h	5.66±0.48	5.18±0.18	5.61±0.39
V/F	(mg/kg)/(µg/ml)	2.61±0.035	2.42±0.086	2.88±0.044
CL/F	(mg/kg)/(µg/ml)/h	1.93±0.008	1.86±0.006	2.08±0.006
Tmax	h	1.81 ±0.55	1.63±0.11	2.15 ±0.64
Cmax	µg/ml	11.84±0.63	9.17±0.59	10.18±0.22
AUC 0-t	µg/ml*h	153.81±9.316	135.02±9.01	141.81±8.06
AUC 0 - ∞	µg/ml*h	182.93±10.825	151.06±10.305	165.11±9.18

*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 of Pioglitazone (n=6)

Group	Pancreatic Beta islets Volumne (mm3/mm3) / Volume of pancreas (mm3/mm3
Control	0.082 ± 0.004
Gymnema sylvestre (100 mg/kg, *p.o.)*	0.195 ± 0.052*
Gymnema sylvestre (500 mg/kg, p.o.)	0.244 ± 0.007*
Pioglitazone (10 mg/kg, p.o.)	0.164 ± 0.005*
Pioglitazone (7.5 mg/kg, p.o.) + G S (500 mg/kg, p.o.)	0.236 ± 0.011*
Pioglitazone (10 mg/kg, p.o.) + G S (500 mg/kg, p.o.)	0.271± 0.028*

*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*

DISCUSSION

The histopathological studies reveal that Pioglitazone (100 mg/kg) and *Gymnema sylvestre* combination not only increased the volume of islets but also recovered partially destroyed beta cells.

Pharmacodynamic study

The combination of high dose of Pioglitazone (10 mg/kg) with 500mg/kg *Gymnema sylvestre* showed maximum antihyperglycaemic action, antihypercholestremia. The effect produced by combination of Pioglitazone (7.5 mg/kg) with *Gymnema sylvestre* was greater than the hypoglycaemic action produced by *Gymnema sylvestre* (500 mg/kg) alone but was comparably less than Pioglitazone (10 mg/kg).

The pharmacokinetic study shows that, 20.26% decrease in AUC (0 - ∞) in 500mg/kg of *Gymnema sylvestre* and 7.5mg/kg of Pioglitazone. 8.56% decrease AUC (0 - ∞) in 500mg/kg of *Gymnema sylvestre* and 10mg/kg of Pioglitazone. C max was decreased by 15.61% in 500mg/kg of *Gymnema sylvestre* and 7.5mg/kg of Pioglitazone, 10.52% in 500mg/kg of *Gymnema sylvestre* and 10mg/kg of Pioglitazone that was attributed by significant decrease in absorption rate constant Ka by about 22.29% in Lower dose of 500mg/kg of *Gymnema sylvestre* and 7.5mg/kg of Pioglitazone, 16.62% in 500mg/kg of *Gymnema sylvestre* and 10mg/kg of Pioglitazone. Significantly increase in clearance 3.29% in 500mg/kg of *Gymnema sylvestre* and 7.5mg/kg of Pioglitazone. 7.69% in 500mg/kg of *Gymnema sylvestre* and 10mg/kg of Pioglitazone compared to 10mg/kg Pioglitazone.

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.

ACKNOWLEDGEMENT

I take this privilege and pleasure to acknowledge the contributions of many individuals who have been inspirational and supportive throughout my work undertaken and endowed with the precious knowledge to see success in my endeavour.

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