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A PKPD INTERACTION BETWEEN ORAL HYPOGLYCEMIC DRUG – GLIMEPIRIDE AND *TRIGONELLA FOENUM-GRAECUM* & HISTOPATHOLOGICAL STUDY

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ABSTRACT

Trigonella foenum-graecum (Fenugreek plant) is a well-known traditionally used medicated herb, possesses different therapeutical activities. Fenugreek leaves have been used as traditional herbal medicines not only for hyperglycemia but also in hyperlipidimia, cellulitis and gastrointestinal disorders. Preliminary animal and human trials suggested the possible antihyperglycemic activity and antihyperlipidemic activity of oral fenugreek leaf extract. *T. foenum-graecum* leaves have also previously been shown to have antihyperglycemic and hypocholesterolemic effects on Type I and Type II Diabetes mellitus patients and experimental induced diabetic animals. However, the research so far on the hypoglycemic effect of fenugreek couldn't establish the optimum dose-level for experimental subjects. Hence, the research studies are required to study the pharmacodynamic and pharmacokinetic properties in order to determine the effect of fenugreek herb on the hyperglycemic patients who are taking the therapy with synthetic drugs. This study was taken up to discover the influence of *Trigonella foenum-graecum on* the pharmacokinetics and pharmacodynamics of Glimepiride in rats. Results have proven the negative (decrease) effect of *Trigonella foenum-graecum on* pharmacokinetics but positive (increase) effect on pharmacodynamics of Glimepiride.

KEYWORDS: *Trigonella foenum-graecum, Glimepiride, hypoglycemic effect.*

1. INTRODUCTION

Herbs are often administered in combination with therapeutic drugs, raising the potential of herb-drug interactions. An extensive review of the literature identified reported herb-drug interactions with clinical significance, many of which are from case reports and limited clinical observations. Cases have been published reporting enhanced anticoagulation and bleeding when patients on long-term warfarin therapy also took *Salvia miltiorrhiza* (danshen). *Allium sativum* (garlic) decreased the area under the plasma concentration-time curve (AUC) and maximum plasma concentration of saquinavir, but not ritonavir and paracetamol (acetaminophen), in volunteers. *A. sativum* increased the clotting time and international normalized ratio of warfarin and caused hypoglycemia when taken with chlorpropamide. A typical example is St. John's wort, widely used for depressive disorders, which is a potent inducer of CYP3A4. It is often evident that diabetic patients often consume herbal preparations along with routinely prescribed antidiabetic agents. The Indian subcontinent has many natural remedies like Ayurveda, Yunani and Siddha. Based on these systems we can able to find new lead molecules upon further research may lead to complete drug. Positive results from clinical trials of these remedies require further investigations along with extensive clinical trials. Most of the plant compounds used as medicine in different diseases is secondary metabolites; they have no role in plant metabolism but has a significant role in defective mechanism of plant. Basic metabolic process of these compounds is almost similar in plants and animals.[1-7]

Fenugreek (Scientific name-*Trigonella foenum graecum*) is the medicinal herb belongs to the family Leguminosae. This is the common part of man's diet. These fenugreek green leaves and dried seeds are used for preparation of different food items at the same time it is used for medicinal use that is the old therapeutic practice of human's history of medical system. This is used to increase the flavor and color of food items, and also modifies the quality of food. Fenugreek's seeds have therapeutic applications like antihypercholestremia, induce lactation, antimicrobial, gastric stimulant, for loss of appetite, antihyperglycemic action, galactagogue, hepatoprotective action and antineoplastic. These medicinal applications on physiological actions including the antihyperglycemic and antihypercholestremic actions of fenugreek leaves and seeds are mainly attributable to

the intrinsic dietary fiber constituents which has been promising the nutraceutical values.[8-15]

Glimepiride acts at ATPase-dependent potassium channels in β cells of the pancreas to stimulate insulin release.14 using euglycemic and hyperglycemic clamp studies it has been shown to improve both first- and second-phase insulin secretion. Glimepiride binds 65-kD proteins on β cells. In healthy volunteers, a linear relationship was shown between serum glimepiride concentrations and insulin release during euglycemia and a nearly linear relationship under hyperglycemic conditions. Maximal glucose-lowering activity and insulin level in T2DM patients is achieved within 2–3 hours of taking glimepiride and can last for 24 hours.[16]

In a 14-week clinical study, peak concentrations 2 hours after administration of 1, 4, and 8 mg doses of glimepiride were associated with decreases in median fasting plasma glucose (FPG) of 43, 70.5, and 74 mg/dL, respectively. The extra pancreatic effects of glimepiride are similar to those of other sulfonylureas. Although peripheral tissue response to insulin is potentiated like other SUs, the clinical relevance of this is not yet clear. In in vitro studies, glimepiride was found to be two times as potent as glibenclamide in stimulating lipogenesis and glycogenesis.[17-25]

There is scope for the potential herb-interactions between *Trigonella foenum graecum* and Glimepiride. This can cause few adverse reactions as a result, it precipitates potentially life-threatening 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

DRUGS AND CHEMICALS

Adult male Wistar-rats weight between 150±20grams (Mahaveer enterprises Hyderabad, Telangana.) were used in this Experimental study. These animals were acclimatized to standard laboratory's conditions of suitable temperature ($27^oC \pm 1^oC$) and maintained on 12:12 hours light: dark cycle in animal's house. They were maintained in elevated rat's wire cages and provided with regular rat's chow (Standard pellets contains diet), distilled water *ad-libitum* for 14 days. These experimental protocols were conducted according with IAEC/ CPCSEA.

EXTRACTION OF *T. FOENUM-GRAECUM* LEAVES

Collection of Plant material

T. foenum graecum leaves were collected from the vegetable market of Hyderabad (Telangana). The healthy leaves were washed by using distilled water and the surface water drops were removed by using air drying. The fresh leaves are dried in hot-air oven at 40°C for 48 h and powered and are ready for the extraction process.

Procedure for Aqueous extraction

50 g of dried leaf powder of *T. foenum-graecum* is subjected to maceration with the 100 ml sterile distilled H_2O in the blender for 10 minutes. Then the resultant macerate was filtered through the double layered muslin cloth and centrifuged at 4000 rpm for 30 minutes. The supernatant was filtered through the Whatmann filter paper No.1 and heat sterilized at 120°C per 30 minutes. The extract preparation was stored aseptically in the brown colored bottle at 4°C until future use.

Pretreatment

Albino rats were selected for this study (180-250gm), These animals are supplied by the NIN, Hyderabad, Telangana, animals are maintained under the suitable conditions in animal house. [IAEC number]. The rats are kept in the animal cages and high fatty food and water are supplied in the form of carbohydrates: proteins: fat in 42:18:40. for 14days.

Induction of Hyperglycemia in Rats by streptozotocin {60mg/kg}

After 15 days of feeding with highly fatty food the rats were fasted for a period of 18hrs before the induction of hyperglycemia & single dose administration of the 60 mg/kg of Streptozocin (SigmaAldrich; St. Louis; MO; USA) were injected intra-peritoneally (freshly dissolve in the normal saline solution). After STZ administration, the animals are free accessed with food (pellet diet) & water. moderate polydipsia and marked polyuria are observed in diabetic hyperglycemic rats. After three days i.e. after 72hrs of injection, fasting blood glucose concentration were determined by following glucose levels by using commercial glucose estimation kits with UV-Visible Spectrophotometer at 505nm based on the oxidase/peroxidase GOD/POD method. If any rats showing the fasting blood glucose level more than 150 mg/dL were considered the hyperglycemic-rats and selected for the different grouping in the experimental design.

EXPERIMENTAL DESIGN: STUDY DESIGN OF GLIMEPIRIDE - The hyperglycemic rats are divided into 6 groups, 6 animals in each. The hyperglycemic rats are divided into 6 groups with 6 animals in each.

Group I: Diabetic Control Group (0.5% Sodium Carboxy Methyl Cellulose Suspension *Per Oral*)
Group II: *T. Foenum-Graecum* (100 Mg/Kg, *Per Oral*)
Group III: *T. Foenum-Graecum* (500 Mg/Kg. *Per Oral*)
Group IV: Combination of Glimepiride (1mg/Kg. *Per Oral*) + *T. Foenum-Graecum* (500 Mg/Kg *Per Oral*).
Group V: Combination of Glimepiride (2Mg/Kg. *Per Oral*) + *T. Foenum-Graecum* (500 Mg/Kg *Per Oral*).
Group VI: Glimepiride (2Mg/Kg. *Per Oral*)[26-29]

Pharmacokinetics study in hyperglycemic rat model
Single dose Study
These pharmacokinetic studies are carried out in hyperglycemic rats (weight b/n 180grams and 250grams). These animals were housed in animal wire cages with free access to diet and water *ad-libitum*. The overnight fasting rats were divided in to 6 different groups (n=6) and the follow the treatment was mentioned in the study design. Blood samples were collected at predetermined intervals of 0hr,1hr,2hr,4hr,8hr,12hr and 24hr in the hinto microcentrifugal tubes containing Na^+ citrate from retro-orbital puncture under di ethyl ether anesthesia. The blood samples are subject to centrifugation at 3000rpm per 10minutes and plasma was stored at -20^{0C} for analysis by using HPLC and estimation of kinetic parameters as AUC 0-∞, Cmax Ka, Ke CL/F, Tmax, V/F, AUC 0-t and $t_{1/2}$.

Multiple dose study
The hyperglycemic rats are divided into 6 different treatment groups same as mentioned in study design and daily treatment is carried out for 21 days. Samples of blood are collected from different rat groups on 0^{th},7^{th},14^{th},21^{st} day immediately after drug treatment. Samples of blood are collected into microcentrifugal tubes containing Na^+ citrate from retro-orbital puncture under anesthesia. These blood samples were subjected to centrifuged at 3000rpm per 10 minutes and plasma was stores at -20^0 C for analysis by using HPLC and estimation of pharmacokinetic parameters as AUC 0 - ∞, V/F, Ka, Cmax, CL/F, Tmax, Ke, AUC 0-t & $t_{1/2}$.

Pharmacodynamics study in the hyperglycemic rats
Single dose study
In this study, treatment was given to all groups of animals as per experimental design. Pharmacodynamic parameters like urea, glucose and cholesterol levels were estimated at the interval of 0, 1, 2,4, 8, 12 and 24 hours by UV spectrophotometer.

Multiple dose study
In this study, daily treatment was given to all groups of animals for 3 weeks as per experimental design. Pharmacodynamic parameters like urea, cholesterol and glucose levels are estimated the time interval of 0, 7, 14 and 21 days by UV spectrophotometer.

Statistical Application
ANOVA followed by Dunnet test is performed for comparison between different groups of animals. *P* value fewer than 5% (P <0.05) was consider the statistically significant. All clinical data are expressed in the form of Mean ± SD.

Pharmacokinetics data was calculated by using *pk* solver software and statistical analysis and graphical representations were done by *INSTANT graph pad* software.

Histopathological Study
After estimation of last blood glucose level, the animals were sacrificed and histopathological studies to estimate the inflammation and necrosis related changes in pancreas. The pancreatic tissues were stained using H&E stains and observed under resolution100_X.

3. RESULTS

Table 1: Single dose study glucose values (mg/dL) expressed in Mean±SD.

TIME (hr)	100mg *Trigonella foenum-graecum*	500mg *Trigonella foenum graecum*	2mg Glimepiride	500mg *Trigonella foenum-graecum*+1mg Glimepiride	500mg *Trigonella foenum-graecum*+2mg Glimepiride	Diabetic control
0	413.04±10.8	394.8±6.6	413.9±6.81	419.8±2.3	424.3±8.2	403.4±11.1
1	403.4±1.21	362.9±9.2	368.3±10.2	398.2±13.8	345.4±8.4	463.6±9.44
2	348.3±12.4	387.3±8.5	312.3±3.1	366.2±10.5	358.1±10.8	464.2±9.33
4	333.5±11.5	364±4.9	351.9±4.6	381.33±8.6	363.8±8.8	426.5±7.0
8	296.8±4.5	275.1±8.7	313.3±4.8	262.5±10.4	255.2±7.4	441.4±8.5
12	311.9±8.5	293.8±5.5	310.3±9.4	266.9±9.4	255.4±12.8	414.9±9.2
24	325.5±9.6	303.9±3.4	353.8±12.2	278.8±11.4	278.6±8.5	416.8±11.5

Table 2: Single dose study cholesterol values (mg/dL) expressed in Mean±SD.

TIME (hr)	100mg Trigonella foenum graecum	500mg Trigonella foenum graecum	2mg Glimepiride	500mg Trigonella foenum-graecum+1mg Glimepiride	500mg Trigonella foenum-graecum+ 2mg Glimepiride	Diabetic control
0	205.4±9.3	202.5±12.1	209.9±14.11	208.3±13.2	198.1±15.2	199.3±12.8
1	201.4±9.4	195.2±14.2	200.1±6.4	190.1±8.2	188.2±16.5	194.9±10.4
2	184.6±4.8	181.6±7.8	168.13±.9.5	179.6±.6.5	171.5±4.1	201.6±6.11
4	176.5±7.8	171.6±7.5	153.5±7.6	164.2±7.4	161.1±8.4	204.31±12.6
8	149.4±5.5	148.11±8.2	160.1±12.4	143.6±.9.5	136.6±10.6	201.8±8.11
12	155.11±6.4	153.2±6.5	166.3±18.6	149.8±9.5	144.5±8.51	213.6±8.13
24	178.6±8.2	163.8±2.6	182.5±11.6	169.3±8.6	158.3±11.5	212.3±7.8

Table 3: Single dose study urea values (mg/dL) expressed in Mean±SD.

TIME (hr)	100mg Trigonella foenum graecum	500mg Trigonella foenum graecum	2mg Glimepiride	500mg Trigonella foenum-graecum+1mg Glimepiride	500mg Trigonella foenum-graecum+ 2mg Glimepiride	Diabetic control
0	64.9±5.5	75.36±4.1	75.52±5.9	66.88±6.6	71.78±4.2	63.92±7.5
1	65.72±7.8	66.5±5.1	74.38±5.5	63.02±6.5	62.48±2.6	64.18±2.6
2	63.02±5.2	66.24±7.1	68.18±6.2	59.78±6.32	59.7±8.1	69.34±9.2
4	58.4±6.2	59.24±5.4	56.1±5.2	55.16±6.35	54.08±5.5	65.96±5.6
8	51.76±6.4	49.6±5.8	58.23±7.1	46.36±5.4	44.2±4.4	69.04±4.5
12	55.1±6.6	55.38±7.4	65.26±5.2	49.52±5.4	48.36±7.4	68.12±4.4
24	62.56±5.2	58.4±7.5	64.36±5.1	54.23±5.4	51.35±4.4	68.14±9.0

Table 4: Multiple dose study Glucose values (mg/dL) expressed in Mean±SD.

Time (Day)	100mg Trigonella foenum graecum	500mg Trigonella foenum graecum	2mg Glimepiride	500mg Trigonella foenum-graecum+1mg Glimepiride	500mg Trigonella foenum-graecum+2mg Glimepiride	Diabetic control
0	418.3±2.2	394.6±1.2	418.2±3.1	385.9±3.3	421.9±1.3	411.5±4.5
7	239.3±2.4	232.±3.3	218.6±5.6	202.5±1.14	253.5±6.3	395.2±.4.4
14	181.6±1.5	152.6±3.4	121.6±2.6	114.5±2.4	191.5±2.4	386.5±3.4
21	133.6±2.4	123.5±2.5	102.9±1.6	91.9±1.4	142.4±.3.4	393.9±3.4

Table 5: Multiple dose study Cholesterol values (mg/dL) expressed in Mean±SD.

Time (day)	100mg Trigonella foenum graecum	500mg Trigonella foenum graecum	2mg Glimepiride	500mg Trigonella foenum-graecum+ 1mg Glimepiride	500mg Trigonella foenum-graecum+ 2mg Glimepiride	Diabetic control
0	189.5±9.5	183.8±12.2	185.6±6.3	192.9±8.4	186.8±9.2	191.9±11.5
7	106.5±9.6	103.5±8.4	104.4±8.1	95.8±6.6	114.6±8.6	195.1±10.6
14	85.8±9.23	85.6±7.8	76.6±8.24	73.29±5.8	93.11±10.8	185.33±9.5
21	74.8±10.4	71.1±9.2	68.3±8.4	54.22±7.8	73.4±6.4	190.3±7.8

Table 6: Multiple dose study Urea values (mg/dL) expressed in Mean±SD.

Time (Day)	100mg Trigonella foenum graecum	500mg Trigonella foenum graecum	2mg Glimepiride	500mg Trigonella foenum-graecum+1mg Glimepiride	500mg Trigonella foenum-graecum+2mg Glimepiride	Diabetic control
1	69.13±8.3	68.6±6.54	79.35±4.32	75.45±4.35	72.44±3.91	73.6±4.83
7	43.26±2.42	39.13±4.01	38.34±4.31	36.22±4.21	51.26±6.81	75.66±9.21
14	31.3±8.51	33.06±6.03	28.32±5.45	25.15±9.14	38.46±8.24	78.26±7.33
21	33.49±9.23	31.13±8.54	25.36±10.08	21.76±9.94	35.18±8.64	71.09±6.25

Table 7: Pharmacokinetic parameters after single oral administration of 2mg Glimepiride, 500mg Trigonella foenum-graecum+ 1mg Glimepiride, 500mg Trigonella foenum-graecum+ 2mg Glimepiride in diabetic rats.

Parameter	Unit	2mg Glimepiride	500mg Trigonella foenum-graecum+ 1mg Glimepiride	500mg Trigonella foenum-graecum+ 2mg Glimepiride
Ka	1/h	0.91±0.04	0.51±0.11	0.56±0.31
Ke	1/h	0.24±0.01	0.23±0.01	0.26±0.05
t1/2	h	3.35±0.25	3.18±0.32	2.93±1.34
V/F	(mg/kg)/(µg/mL)	23.28±0.82	29.33±3.14	35.94±16.26
CL/F	(mg/kg)/(µg/mL)/h	4.71±0.25	6.51±0.33	8.56±0.61
T_{max}	h	2.06±0.09	2.39±0.19	2.66±0.46
C_{max}	µg/mL	1.46±0.02	0.96±0.08	0.68±0.08
AUC_{0-t}	µg/h*mL	9.61±0.29	6.89±0.39	4.96±0.48
$AUC_{0-\infty}$	µg/ h*mL	10.65±0.49	7.44±0.36	5.65±0.33

Table 8: Mean plasma Glimepiride concentrations (µg/mL) (Single dose study).

Time (hours)	Diabetic Control	2mg/kg of GLIMEPIRIDE	GLIMEPIRIDE + T. foenum-graecum (DOSE)	
			1mg/kg+500mg/kg	2mg/kg+ 500mg/kg
1	0	25.18±0.081	12.99±0.045	27.22±0.018
2	0	45.79±0.066	18.25±0.042	26.81±0.044
4	0	16.19±0.018	11.62±0.043	23.82±0.042
8	0	11.64±0.015	9.04±0.055	10.68±0.029
12	0	8.19±0.095	7.83±0.036	9.41±0.062
24	0	0	0	0

Table 9: Mean plasma Glimepiride Concentrations (µg/mL) (Multiple dose study).

TREATMENT DAYS	DIABETIC CONTROL	2mg/kg of GLIMEPIRIDE	GLIMEPIRIDE + T. foenum-graecum (DOSE)	
			1mg/kg+500mg/kg	2mg/kg+ 500mg/kg
0	0	25.82±0.063	19.03±0.041	22.91±0.022
7	0	48.19±0.044	29.03±0.022	33.92±0.071
14	0	21.09±0.081	14.82±0.052	18.91±0.058
21	0	15.19±0.033	8.92±0.019	14.04±0.029

Table 10: Effect of T. foenum-graecum on Pharmacokinetic parameters of Single dose administration of Glimepiride in diabetic rats (n=6).

Pharmacokinetic parameter	Units for Pharmacokinetic parameters	2mg/kg of GLIMEPIRIDE	GLIMEPIRIDE + T. foenum-graecum (DOSE)	
			1mg/kg+500mg/kg	2mg/kg+500mg/kg
Ka	h-1	1.568±0.22	1.189±0.29	1.218±0.66
Ke	h-1	0.1218±0.05	0.1293±0.06	0.1282±0.04
t1/2	h	5.91±0.45	5.19±0.69	5.25±0.51
V/F	(mg/kg)/(µg/mL)	1.09±0.018	1.15±0.22	1.24±0.065**
CL/F	(mg/kg)/(µg/mL)/h	0.90±0.004	0.92±0.31	0.96±0.004
T_{max}	h	3.62 ±0.51	3.89±0.43	3.94 ±0.32*
C_{max}	µg/mL	49.05±0.043	19.53±0.086**	26.36±0.081**
AUC_{0-t}	µg/h*mL	79.31±0.18	69.18±0.93**	73.27±0.16*
$AUC_{0-\infty}$	µg/ h*mL	89.03±0.087	71.08±0.42**	81.28±0.19

*Values are given as mean± Standard deviation. * *Statistical significance p < 0.01 (compared with the control group)*Statistical significance p < 0.05 (compared with the control group) T F G- T. foenum-graecum; n - number of animals used.*

Table 11: Effect of T. foenum-graecum on Pharmacokinetic parameters of Multiple dose administration of Glimepiride in diabetic rats (n=6).

Pharmacokinetic parameter	Units for Pharmacokinetic parameters	2mg/kg of GLIMEPIRIDE	GLIMEPIRIDE + T. foenum-graecum (DOSE)	
			1mg/kg+500mg/kg	2mg/kg+500mg/kg
Ka	h-1	6.618±0.85	5.891±0.77	6.190±0.44
Ke	h-1	0.2810±0.04	0.2901±0.06	0.3008±0.02
t1/2	h	5.89±0.32	5.09±0.24	5.74±0.56
V/F	(mg/kg)/(µg/mL)	2.89±0.043	2.35±0.048**	2.56±0.034**
CL/F	(mg/kg)/(µg/mL)/h	1.90±0.004	1.99±0.005**	2.06±0.007**
T_{max}	h	1.85 ±0.34	1.89±0.26	2.10 ±0.91
C_{max}	µg/mL	44.18±0.042	29.08±0.054**	38.41±0.048**
AUC_{0-t}	µg/ h*mL	150.65±10.268	130.93±8.92**	142.19±9.05
$AUC_{0-\infty}$	µg/ h*mL	189.78±11.936	159.08±11.278**	168.28±10.45*

Values are given as mean± Standard deviation. *Statistical significance p < 0.01 (compared with the control group)*Statistical significance p < 0.05 (compared with the control group); T F G- T. foenum-graecum; n - number of animals used.*

Table 12: Volume of islet cells in pancreas in different Groups after multiple dose study of Glimepiride (n=6).

Group	Pancreatic Beta islets Volume (mm3/mm3) / Volume of pancreas (mm3/mm3
Control	0.091 ± 0.003
T. foenum-graecum (100 mg/kg, p.o.)	0.199 ± 0.044**
T. foenum-graecum (500 mg/kg, p.o.)	0.251 ± 0.009**
Glimepiride (2 mg/kg, p.o.)	0.174 ± 0.003**
Glimepiride (1mg/kg, p.o.) + T F G (500 mg/kg, p.o.)	0.248 ± 0.009**
Glimepiride (2mg/kg, p.o.) + T F G (500 mg/kg, p.o.)	0.289± 0.019**

Values are given as mean± Standard deviation. *Statistical significance p < 0.01 (compared with the control group)*

Statistical significance p < 0.05 (compared with the control group) TF G-T.foenum-graecum n - number of animals used.

4. DISCUSSION

In pharmacodynamic study, the combination of high dose of glimepiride (2 mg/kg) with 500mg/kg Trigonella foenum-graecum showed maximum hypoglycemic action, decrease in serum cholesterol and urea levels. The effect produced by combination of glimepiride (1mg/kg) with Trigonella foenum-graecum was greater than the hypoglycemic action produced by Trigonella foenum-graecum (500 mg/kg) alone and glimepiride (2mg/kg) alone when compare with the study of Milk thistle (Silybum marianum) does not have inhibitory or inductive effects on CYP1A2, CYP2D6, CYP2E1, CYP3A4, or P-gp, as demonstrated in multiple human studies and gives highly potent herbs involved in the reducing hyperglycemia, hyperlipidemia, hypercholesteremia.[30] In pharmacokinetic studies, pharmacokinetic parameters like the Single dose study shows that, 24.51% decrease in AUC0-∞ in 500mg/kg of Trigonella foenum-graecum and 1mg/kg of glimepiride 9.04% decrease AUC0-∞ in 500mg/kg of Trigonella foenum-graecum and 2mg/kg of glimepiride when compare with the study of comparison study of hypoglycemic activity of Atorvastatin with the Rosiglitazone these gives potent action of oral hypoglycemic drugs in combination.[31] In pharmacokinetic studies Cmax was decreased by 71.62% in 500mg/kg of Trigonella foenum-graecum and 1mg/kg of glimepiride, 53.19% in 500mg/kg of Trigonella foenum-graecum and 2mg/kg of glimepiride in single dose study when compare with the study of itraconazole increases the action of gliclazide in rats indicates Pioglitazone maintain the optimum pharmacokinetic profile.[32]

In pharmacokinetic studies, pharmacokinetic parameters like significant decrease in absorption rate constant Ka by about 26.91% in lower dose of 500mg/kg of Trigonella foenum-graecum and 1mg/kg of glimepiride, 19.04% in 500mg/kg of Trigonella foenum-graecum and 2mg/kg of glimepiride. Significantly increase in clearance 4.83% in 500mg/kg of Trigonella foenum-graecum and 1mg/kg of glimepiride. 9.65% in 500mg/kg of Trigonella foenum-graecum and 2mg/kg of glimepiride compared to 2mg/kg glimepiride when compare with the study of combined effect of eprosertan and Rosiglitazone is more when compared to Rosiglitazone alone give maximal pharmacodynamic actions.[33]

In pharmacokinetic studies, 19.04% decrease in AUC0-∞ in 500mg/kg of Trigonella foenum-graecum and 1mg/kg of glimepiride. 8.94% decrease AUC0-∞ in 500mg/kg of Trigonella foenum-graecum and 2mg/kg of glimepiride concomitant administration of ginger extract (25 or 50 mg/kg) and Rosiglitazone (5 mg/kg) in streptozotocin (STZ)-induced diabetic rats, decreased the non-fasting blood glucose level significantly. When compared with the study of the blood glucose levels should be monitored in patients taking sulfonylureas and ginger together, to avoid the occurrence of hypoglycemia gives the safety of combination.[34]

In pharmacokinetic studies Cmax was decreased by 41.05% in 500mg/kg of Trigonella foenum-graecum and 1mg/kg of glimepiride, 23.64% in 500mg/kg of Trigonella foenum-graecum and 2mg/kg of glimepiride in multiple dose study when compare with the study of Carvedilol will interact with pharmacokinetics and Pharmacodynamic of glipizide in normal and diabetic rats indicates there is no abnormality in the normoglycemic levels.[35]

5. CONCLUSION

The interaction appears to be pharmacokinetic interaction at absorption and elimination. *T. foenum-graecum* inhibits the absorption of glimepiride that results in a significant decrease in the bioavailability of the later and combination group with a lower dose of glimepiride and increment to the volume of islets in pancreas is observed in combination group when compared to individual treatment. Since the interaction was seen in rats it is likely to occur in humans leading to decreased activity of glimepiride that can need dose adjustments. Hence care must be taken when the combination is taken by the diabetic patients. The present study warrants next plan to find out the relevance of the interaction in human beings.

6. REFERENCES

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