IJMPR 2020, 4(6), 119-126

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Research Article

SJIF Impact Factor: 5.273

A PHARMACOKINETIC & PHARMACODYNAMIC INTERACTION BETWEEN CAPSICUM FRUIT'S EXTRACT AND ORAL HYPOGLYCEMIC DRUG – PIOGLITAZONE IN HYPERGLYCEMIC RATS

Shravan Kumar Dholi*[1], Syeda Tanveer Fathima[2], Ramakrishna Raparla[3]

[1]Associate Professor, Department of Pharmacology, Vaageswari Institute of Pharmaceutical Sciences, Beside LMD Police Station, Ramakrishna Colony, Karimnagar, Telangana-505481, India.
[2]Post Graduate Student, Department of Pharmaceutics, Vaageswari Institute of Pharmaceutical Sciences, Beside LMD Police Station, Ramakrishna Colony, Karimnagar,Telangana.-505481, India.
[3]Professor & Head, Department of Pharmaceutics, Vaageswari Institute of Pharmaceutical Sciences, Beside LMD Police Station, Ramakrishna Colony, Karimnagar,Telangana.-505481, India.

Received on: 04/11/2020
Revised on: 24/11/2020
Accepted on: 14/12/2020

***Corresponding Author**
Dr. Shravan Kumar Dholi
Associate Professor,
Department of Pharmacology,
Vaageswari Institute of Pharmaceutical Sciences,
Beside LMD Police Station,
Ramakrishna Colony,
Karimnagar, Telangana-505481, India.

ABSTRACT

Traditional medication obtained from the medicated herbal plants are used by about maximum percentage of world population for different chronic disease condition. Diabetes (Hyperglycemia- high blood sugar level) is a very important metabolic disorder in different developed, developing countries including India. It providing to a very serious complications on health of human beings, especially in the rural and subrural areas. Capsicum is an annual herb that anti hyperglycemic activity. Other pharmacological properties such as anti inflammatory, antioxidant, anti microbial, antiviral, hypotensive, and hypercholesterolemia are also exhibited. However, the research so far on the hypoglycaemic effect of Capsicum could't establish the optimum dose-level for experimental subjects. Hence, the research studies required to be subjected to pharmacodynamic and pharmacokinetic studies in order to determine effect of Capsicum herb on the hyperglucemic patients who are taking the therapy with synthetic drugs. This research work was to identify the influence of Capsicum on the pharmacokinetic and pharmacodynamic of Pioglitazone in rats**.** Results have proves the negative (decrease) effect of Capsicum on pharmacokinetics but positive (increase) effect on pharmacodynamics of Pioglitazone.

KEYWORDS: Capsicum, Pioglitazone, Oral hypoglycemic drugs.

1. INTRODUCTION

Diabetic Mellitus (Hyperglycemia) is an endocrine disease and not a single disease which is a group of chronic metabolic or heterogeneous affliction due to the irregular secretions of insulin and action of insulin or both. Absence or reduced insulin in turn leads to abnormal high blood sugar level and glucose intolerance.[1-5]

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, 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.Several reports indicated that diabetes mellitus increased the mucosal susceptibility to ulcerogenic stimuli and predisposition to gastric ulceration. 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.[6]

Capsicum is an annual herb that anti hyperglycemic activity. Other pharmacological properties such as anti inflammatory, antioxidant, anti microbial, antiviral, hypotensive, and hypercholesterolemia are also exhibited.[7]

There is scope for the potential herb-interactions between Capsicum and Pioglitazone. This can cause few adverse reactions as a result, it precipitates potentially life-threatening 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.

2. MATERIALS AND METHODS

Drugs and Chemicals

Adult male wistar-rats weight between 150±20grams (Mahavear 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 – Balaji life sciences, Hyderabad, Telangana.), distilled water ad-libitum for 14 days. These experimental protocols were in conducted according with IAEC/ CPCSEA.

Extraction of Capsicum fruits

Collection of Plant material

Purified capsicum fruits were obtained from local area, from Karimnagar, India.

Preparation of plant extract

500gm of Capsicum fruits were obtained and washed. The collected fruits were dried at room temperatur, pulverized by a mechanical grinder, sieved through 60 mesh and was soxhalates with 70% methanol for 48 hours, concentrated to dryness in vacuum and weighed.[8]

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 suppled 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 & singledose administration of the 60 mg/kg of Streptozocin (SigmaAldrich; St. Louis; MO; USA) were injected intra-peritonially (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 consider the hyperglycaemic-rats and selected for the different grouping in the experimental design.

Study Design- Pioglitazone -The hyperglycemic rats are divided in to 6 groups 6 animals in each.

Group I: Diabetic Control Group (0.5% Sodium.Cmc Suspension P.O)

Group II: Capsicum Fruit's Extract (100 mg/Kg,P.O)

Group III: Capsicum Fruit's Extract (500 mg/Kg.P.O)

Group IV: Combination Of Pioglitazone (7.5mg/Kg.P.O) + Capsicum Fruit's Extract (500mg/Kg).

GroupV: Combination Of Pioglitazone (10mg/Kg.P.O) + Capsicum Fruit's Extract (500 mg/Kg).

Group VI: Pioglitazone (10 mg/Kg.P.O).[9]

Pharmacokinetics study in hyperglycemic rat model

Single dose Study

These pharmacokinetic studies are carried out in hyperglycaemic rats (weight b/n 180grams and 250grams). These animals were housed in animal's wire cages with free access to diet and water ad-libitum. The overnight fasting rats were dividing in to 6 different groups (n=6) and the follow the treatment was mention 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 pucture under di ethyl ether anaesthesia. The blood samples are subject to centrifugation at 3000rpm per 10minutes and plasma was stored at -20^{0C} for analysis and estimation of kinetic parameters as AUC 0 - ∞, Cmax ka, ke CL/F, Tmax, V/F, AUC 0-t & $t_{1/2}$.

Multiple dose study

The hyperglycemic rats are dividing into 6 different treatment groups same as mention in study design and daily treatment is carried for 21 days. Samples of blood are collected from different rat's groups on 0^{th},7^{th},14^{th},21^{st} day immediatly after drug treatment. Samples of blood are collected in to microcentrifugal tubes containing Na^+citrate from retro-orbital puncture under anaesthesia. These blood samples were subjected to centrifuged at 3000rpm per 10 minuts and plasma was stores at -20^0 C for analysis and estimation of kinetic parameters as AUC 0 - ∞, V/F, ka, Cmax, CL/F, Tmax,ke, AUC 0-t & $t_{1/2}$.

Pharmacodynamics study in the hyperglycaemic 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 th interval of 0, 1, 2,4, 8, 12 and 24 hours by UV spectrophotometer.

Multiple dose study

In this study, daily treatment given to all groups of animals for 3 weeks as per experimental design. Pharmacodynamic parameter like urea, cholesterol and glucose levels are estimated the time interval of 0, 7, 14 and 21 day by UV spectrophotometer.[10]

Statistical Application

ANOVA followed by Dunnet test is performed for comparision 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 solversoftware 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 histopathologicalstudies to estimate the inflammation and necrosis related changes in pancreas. The pancreatic tissues were stained using H&E stains and observed under resolution100_X.[11]

3. RESULTS

Table 1: Blood glucose levels mg/dL (0^{th},1^{st} ,2^{nd},4^{th},8^{th}, 12^{th} and 24^{th} Hour) after oral administration of Capsicum Extract, Pioglitazone and combination of Pioglitazone and Capsicum Extract in diabetic rats (n=6).

Treatment/ Hours	BLOOD GLUCOSE LEVELS (mg/dL)					
	Diabetic Control	C E (DOSE)		PIOGLITAZONE (DOSE)	PIOGLITAZONE + C E (DOSE)	
	vehicle	100mg/kg	500mg/kg	10mg/kg	7.5mg/kg +500mg/kg	10mg/kg +500mg/kg
0^{th} Hour BLOOD GLUCOSE LEVELS	400.6±13.2	413.04±10.2	391.9±8.4	383.19±4.86	385.11±1.51	375.59±5.78
1^{st} Hour BLOOD GLUCOSE LEVELS	461.8±8.63	418.4±2.62**	361.4±5.3**	361.18±4.16**	343.51±8.3**	343.61±8.01**
2^{nd} Hour BLOOD GLUCOSE LEVELS	464.6±8.15	349.1±12.6**	322.4±7.1**	323.18±4.21**	312.62±4.11**	301.91±12.63**
4^{th} Hour BLOOD GLUCOSE LEVELS	434.1±9.8	333.6±13.8**	312.6±6.1**	312.81±7.13**	304.11±9.36**	282.44±5.51**
8^{th} Hour BLOOD GLUCOSE LEVELS	423.4±6.2	291.1±5.1**	273.4±9.2**	273.44±3.81**	273.94±8.17**	271.64±4.91**
12^{th} Hour BLOOD GLUCOSE LEVELS	422.33±1.5	313.1±2.83**	281.3±8.2**	263.41±4.1**	248.19±2.82**	243.71±4.02**
24^{th} Hour BLOOD GLUCOSE LEVELS	413.9±11.5	324.91±8.2**	316.14±3.9**	275.31±11.22**	253.18±1.91**	246.19±2.24**

Table 2: Blood cholesterol levels mg/dL (0^{th},1^{st} ,2^{nd},4^{th},8^{th}, 12^{th} and 24^{th} Hour) after oral administration of Capsicum Extract, Pioglitazone and combination of Pioglitazone and Capsicum Extract in diabetic rats (n=6).

Treatment/ Hours	BLOOD CHOLESTEROL LEVELS (mg/dL)					
	Diabetic Control	C E (DOSE)		PIOGLITAZONE (DOSE)	PIOGLITAZONE + C E (DOSE)	
	vehicle	100mg/kg	500mg/kg	10mg/kg	7.5mg/kg +500mg/kg	10mg/kg +500mg/kg
0^{th} Hour BLOOD CHOLESTEROL LEVELS	203.1±10.8	206.3±8.1	204.9±9.1	205.17±8.35	194.61±13.88	193.05±10.23

1st Hour BLOOD CHOLESTEROL LEVELS	201.6±14.3	201.4±3.6	194.3±11.4	192.18±3.12	183.16±2.51*	184.21±14.55**
2nd Hour BLOOD CHOLESTEROL LEVELS	203.3±10.3	187.1±4.2**	183.3±8.1**	173.18±9.12**	163.16±2.12**	162.18±6.81**
4th Hour BLOOD CHOLESTEROL LEVELS	202.11±11.4	175.8±2.7**	171.4±2.8**	153.91±3.68**	151.28±7.11**	142.18±4.13**
8th Hour BLOOD CHOLESTEROL LEVELS	202.35±4.51	144.02±2.6**	143.19±2.5**	143.51±4.2**	133.19±5.17**	136.16±4.16**
12th Hour BLOOD CHOLESTEROL LEVELS	213.18±4.21	154.02±4.2**	155.1±3.4**	146.5±9.02**	133.18±4.52**	124.08±10.12**
24th Hour BLOOD CHOLESTEROL LEVELS	213.4±2.3	174.01±7.2**	173.32±3.4**	135.51±9.31**	132.15±5.02**	124.19±9.08**

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

Treatment/Hours	**BLOOD UREA LEVELS (mg/dL)**					
	DIABETIC CONTROL	**C E (DOSE)**		**PIOGLITAZONE (DOSE)**	**PIOGLITAZONE + C E (DOSE)**	
	vehicle	100mg/kg	500mg/kg	10mg/kg	7.5mg/kg +500mg/kg	10mg/kg +500mg/kg
0th Hour BLOOD UREA LEVELS	62.88±3.4	62.91±4.2	72.19±4.1	73.22±3.28	61.81±3.22	64.85±2.31
1st Hour BLOOD UREA LEVELS	63.42±4.1	62.13±6.1	69.28±2.6	65.15±3.18	63.12±5.11	57.13±5.21
2nd Hour BLOOD UREA LEVELS	69.12±8.2	61.25±4.11*	66.13±8.2	62.15±2.24	54.15±2.13*	50.12±5.24**
4th Hour BLOOD UREA LEVELS	70.83±3.2	60.13±2.3	63.15±4.9	60.11±6.12*	49.13±7.84**	47.15±5.64**
8th Hour BLOOD UREA LEVELS	71.23±5.2	59.14±8.1**	44.85±6.3**	49.13±5.92**	45.21±1.72**	41.83±3.94**
12th Hour BLOOD UREA LEVELS	71.93±5.81	60.14±5.1**	56.84±6.1**	48.23±3.14**	42.15±6.12**	37.52±2.92**
24th Hour BLOOD UREA LEVELS	71.16±6.4	62.82±6.8	59.11±8.9	33.19±3.19	34.16±3.29	36.61±5.61

Table 4: Blood glucose levels mg/dL (0^{th},7^{th}, 14^{th} and 21^{st} day) after oral administration of Capsicum Extract Pioglitazone and combination of Pioglitazone and Capsicum Extract in diabetic rats (n=6).

Treatment/Days	BLOOD GLUCOSE LEVELS (mg/dL)					
	DIABETIC CONTROL	C E (DOSE)		PIOGLITAZONE (DOSE)	PIOGLITAZONE + C E (DOSE)	
	vehicle	100mg/kg	500mg/kg	10mg/kg	7.5mg/kg +500mg/kg	10mg/kg +500mg/kg
0^{th} day BLOOD GLUCOSE LEVELS	411.3±2.8	413.9±2.8	391.1±2.6	401.29±2.92	382.10±6.13	370.13±4.41
7^{th} day BLOOD GLUCOSE LEVELS	391.9±5.3	233.8±2.9**	236.9±3.1**	219.02±4.51**	215.19±3.09**	195.63±4.31**
14^{th} day BLOOD GLUCOSE LEVELS	384.4±5.3	182.1±6.8**	153.3±5.1**	155.91±3.06**	123.01±5.51**	124.63±5.82**
21^{st} day BLOOD GLUCOSE LEVELS	391.1±4.4	131.9±2.9**	125.6±2.9**	116.04±2.51**	119.03±3.62**	118.06±6.55**

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)**
C E- Capsicum Extract n - number of animals used.

Table 5: Blood cholesterol levels mg/Dl (0^{th},7^{th}, 14^{th} and 21^{st} day) after oral administration of Capsicum Extract Pioglitazone and combination of Pioglitazone and Capsicum Extract in diabetic rats (n=6).

Treatment/Days	BLOOD CHOLESTEROL LEVELS (mg/dL)					
	Diabetic Control	C E (DOSE)		PIOGLITAZONE (DOSE)	PIOGLITAZONE + C E (DOSE)	
	vehicle	100mg/kg	500mg/kg	10mg/kg	7.5mg/kg +500mg/kg	10mg/kg +500mg/kg
0^{th} day BLOOD CHOLESTEROL LEVELS	192.6±4.13	184.1±6.53	184.1±11.01	183.16±6.53	174.16±4.01	176.93±5.13
7^{th} day BLOOD CHOLESTEROL LEVELS	195.8±5.4	107.1±8.21**	104.6±6.51**	114.16±7.41**	93.16±6.63**	92.14±8.01**
14^{th} day BLOOD CHOLESTEROL LEVELS	192.1±6.1	88.4±8.14**	86.13±6.51**	85.63±3.42**	73.13±4.03**	78.15±5.31**
21^{st} day BLOOD CHOLESTEROL LEVELS	184.4±3.9	75.8±9.12**	69.04±10.23**	69.03±4.81**	60.74±4.51**	58.43±6.44**

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

Treatment/Days	BLOOD UREA LEVELS (mg/dL)					
	DIABETIC CONTROL	C E (DOSE)		PIOGLITAZONE (DOSE)	PIOGLITAZONE + C E (DOSE)	
	vehicle	100mg/kg	500mg/kg	10mg/kg	7.5mg/kg +500mg/kg	10mg/kg +500mg/kg
0^{th} day BLOOD UREA LEVELS	68.13±1.24	65.24±6.53	68.14±3.73	64.24±6.52	69.83±8.14	58.04±6.13
7^{th} day BLOOD UREA LEVELS	75.14±7.13	45.16±2.71**	40.14±5.81**	34.14±4.53**	32.61±9.03**	24.33±5.39**
14^{th} day BLOOD UREA LEVELS	78.61±5.01	35.14±6.91**	34.81±3.62**	28.81±5.64**	24.83±5.92**	21.87±1.06**
21^{st} day BLOOD UREA LEVELS	80.27±3.16	32.26±8.34**	28.46±1.35**	21.95±6.06**	17.36±2.54**	16.42±6.22**

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)**
C E- Capsicum Extract
n - number of animals used.

Table 7: Effect of Capsicum Extract 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 + Capsicum Extract (DOSE)	
			7.5mg/kg+500mg/kg	10mg/kg+500mg/kg
ka	**h^{-1}**	1.431±0.19	1.238±0.18	1.193±0.43
ke	**h^{-1}**	0.1216±0.02	0.1292±0.05	0.1281±0.03
t1/2	**h**	5.90±0.44	5.18±0.68	5.24±0.52
V/F	**(mg/kg)/(µg/ml)**	1.08±0.016	1.14±0.21	1.23±0.045**
CL/F	**(mg/kg)/(µg/ml)/h**	0.91±0.003	0.91±0.32	0.95±0.003
Tmax	**h**	3.61 ±0.52	3.88±0.42	3.93 ±0.31*
Cmax	**µg/ml**	48.04±0.042	19.52±0.085**	25.36±0.082**
AUC 0-t	**µg/ml*h**	79.33±0.17	69.17±0.91**	73.26±0.14*
AUC 0 - ∞	**µg/ml*h**	89.02±0.086	71.04±0.41**	81.26±0.15

Table 8: Effect of Capsicum Extract 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 + Capsicum Extract (DOSE)	
			7.5mg/kg+500mg/kg	10mg/kg+500mg/kg
ka	**h^{-1}**	6.614±0.83	5.894±0.75	6.194±0.42
ke	**h^{-1}**	0.2814±0.03	0.2903±0.04	0.3005±0.01
t1/2	**h**	5.85±0.31	5.06±0.23	5.73±0.52
V/F	**(mg/kg)/(µg/ml)**	2.84±0.041	2.33±0.045**	2.53±0.031**
CL/F	**(mg/kg)/(µg/ml)/h**	1.91±0.003	1.98±0.004**	2.07±0.003**
Tmax	**h**	1.84 ±0.33	1.85±0.25	2.13 ±0.92
Cmax	**µg/ml**	44.16±0.041	29.05±0.051**	38.42±0.041**
AUC 0-t	**µg/ml*h**	150.44±11.261	130.91±8.72**	143.19±9.25
AUC 0 - ∞	**µg/ml*h**	188.78±11.136	158.08±10.178**	165.18±11.41*

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)
C E- Capsicum Extract n - number of animals used.

4. DISCUSSION

Pharmacodynamic study

The combination of high dose of Pioglitazone (10 mg/kg) with 500mg/kg Capsicum fruits showed maximum hypoglycemic action, decrease in serum cholesterol and urea levels. The effect produced by combination of Pioglitazone (7.5 mg/kg) with Capsicum fruits was greater than the hypoglycaemic action produced by Capsicum fruits (500 mg/kg) alone and Pioglitazone (10 mg/kg) alone.

Pharmacokinetic study

The Single dose study shows that, 24.51% decrease in AUC (0 - ∞) in 500mg/kg of Capsicum fruits and 7.5mg/kg of Pioglitazone. 9.04% decrease AUC (0 - ∞) in 500mg/kg of Capsicum fruits and 10mg/kg of Pioglitazone.

C max was decreased by 71.62% in 500mg/kg of Capsicum fruits and 7.5mg/kg of Pioglitazone, 53.19% in 500mg/kg of Capsicum fruits and 10mg/kg of Pioglitazone in single dose study.

Significant decrease in absorption rate constant Ka by about 26.91% in Lower dose of 500mg/kg of Capsicum fruits and 7.5mg/kg of Pioglitazone, 19.04% in 500mg/kg of Capsicum fruits and 10mg/kg of Pioglitazone. Significantly increase in clearance 4.83% in 500mg/kg of Capsicum fruits and 7.5mg/kg of Pioglitazone. 9.65% in 500mg/kg of Capsicum fruits and 10mg/kg of Pioglitazone compared to 10mg/kg Pioglitazone.

The multiple dose study shows that, 19.04% decrease in AUC (0 - ∞) in 500mg/kg of Capsicum fruits and 7.5mg/kg of Pioglitazone. 8.94% decrease AUC (0 - ∞) in 500mg/kg of Capsicum fruits and 10mg/kg of Pioglitazone.

C max was decreased by 41.05% in 500mg/kg of Capsicum fruits and 7.5mg/kg of Pioglitazone, 23.64% in 500mg/kg of Trigonella foenum-graecum and 10mg/kg of Pioglitazone in multiple dose study.

Significant decrease in absorption rate constant Ka by about 6.93% in Lower dose of 500mg/kg of Capsicum fruits and 7.5mg/kg of Pioglitazone, 3.48% in 500mg/kg of Capsicum fruits and 10mg/kg of Pioglitazone. Significantly increase in clearance 29.61% in 500mg/kg of Capsicum fruits and 7.5mg/kg of Pioglitazone. 8.17% in 500mg/kg of Capsicum fruits and 10mg/kg of Pioglitazone compared to 10mg/kg Pioglitazone.

The exact reason behind the reduction in pharmacokinetic parameters was unknown but, it was understood that the combination of Capsicum fruits extract with Glibenclamide in fact reduces exposure of the synergic drugs without reducing the pharmacodynamic activity. The proposed combination allows a safe therapy with less adverse effects.

Histological study

The histological study shows that the combination therapy (pioglitazone + Capsicum fruits) involved in the increase the number of islets and recovered the partially damaged B cells in pancreas when compare to the Individual treatment.

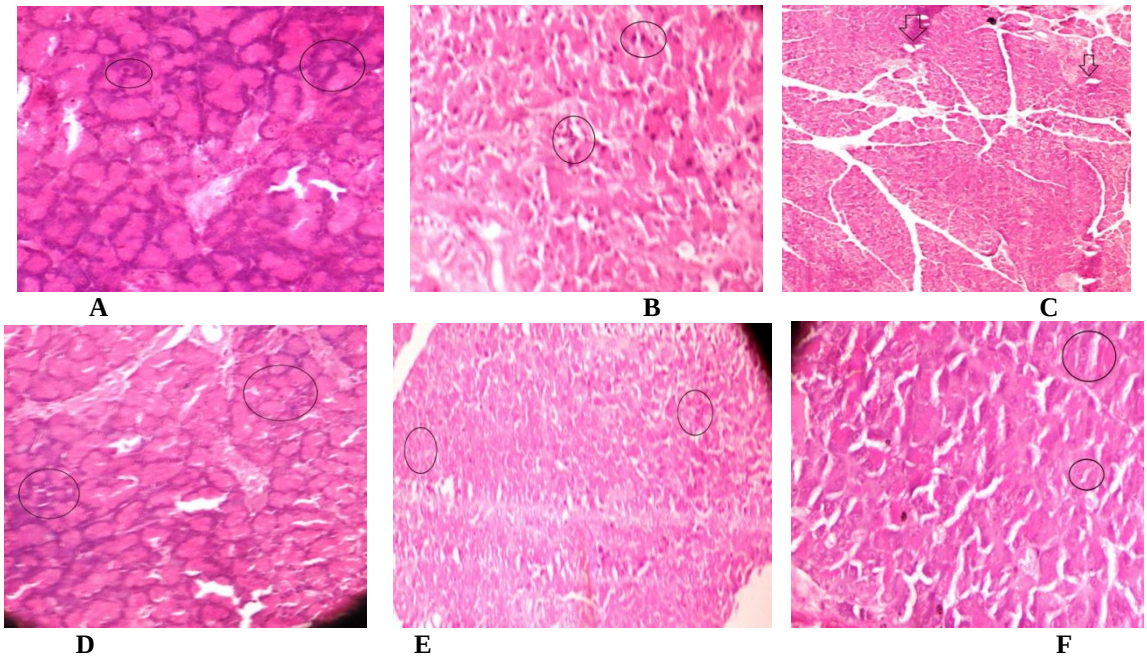

Figure 1: H&S Staining of Pancreatic islets of Diabetic Control, Capsicum fruits Extract alone, Pioglitazone alone and combination of Capsicum fruits Extract & Pioglitazone treated Diabetic Rats. A. diabetic control , B. 100mg of Capsicum fruits Extract C. 500mg of Capsicum fruits Extract D.10mg of Pioglitazone.E.500mg of Capsicum fruits Extract +7.5mg of Pioglitazone, F. 500mg of Capsicum fruits Extract +10mg of Pioglitazone.

Figure A shows that pancreatic cells were damaged due to development of diabetes from STZ. Figure B shows that few pancreatic cells were damaged due to pioglitazone. Figures C,D,E, F shows that B cells are regenerated in pancreatic tissue.

Normal ß-cells were observed in low and high doses of Pioglitazone and Capsicum fruits Extract (Figures: D&F). In the Pioglitazone group more damaged ß-cells as compared with the 500mg of Capsicum fruits Extract +10 mg of Pioglitazone and 500mg of Capsicum fruits Extract +7.5mg of Pioglitazone (Figures: B,C&E).

Histopathological studies revealed that the volume of islet cells in pancreas was significantly more in drug treated animals compared to the Diabetic control. The islet cells were shrunken and lytic cellular changes were observed in Diabetic control, Individual treatment had improved it but combination groups with a higher dose of Pioglitazone showed the return of islets close to original cytoarchitecture. In combination group, islets were big and cells were clear with good vascular pattern. The results of combination group with a high dose of Pioglitazone produced increment to the volume of islets in pancreas compared to individual treatment. In this stu dy, Capsicum fruits Extract was decrease the absorption and increase the clearance of pioglitazone. Hence care must be taken when the combination is taken by diabetic patients.

5. CONCLUSION

The interaction appears to be pharmacokinetic interaction at absorption, elimination. Capsicum extract inhibits the absorption of Pioglitazone that results in a significant decrease in the bioavailability of the later and combination group with a lower dose of Pioglitazone 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 Pioglitazone 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. 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.

7. REFERENCES

1. Morgan M, Deoraj A, Felty Q, Yoo C, Roy D Association between Exposure to Estrogenic Endocrine Disruptors- Polychlorinated Biphenyls, Phthalates, and Bisphenol A and Gynecologic Cancers- Cervical, Ovarian, Uterine Cancers. J Carciong Mutagen, 2016; 7: 275.
2. Lyons RA, Benvenuti L Deposition and Distribution Factors for the Endocrine Disruptor, 4-Nonylphenol, in the Sierra Nevada Mountains, California, USA. J Environ Anal Toxicol, 2016; 6: 388.
3. Messinaa G, AValenzano A, Moscatelli F, Triggiani AI, CapranicaL, et al. Effects of Emotional Stress on Neuroendocrine and Autonomic Functions in Skydiving. J Psychiatry, 2015; 18: 280.
4. Reuveni D, Gertel-Lapter S, Aricha R, Mittleman M, Fuchs S, et al. Erythropoietin Ameliorates Experimental Autoimmune Myasthenia Gravis. J Clin Exp Neuroimmunol, 2016; 1: 108.
5. Zou L, Karim RM, Wang YF The Research Progress of Long Noncoding RNAs in Autoimmune Diseases. J Neurol Neurophysiol, 2016; 7: 359.
6. Al-Majed A, Bakheit AH, Abdel Aziz HA, Alharbi H, Al-Jenoobi FI: Pioglitazone. Profiles Drug Subst Excip Relat Methodol, 2016; 41: 379-438. doi: 10.1016/bs.podrm.2015.11.002. Epub 2016 Feb 2.
7. Shravan Kumar Dholi, Ramakrishna Raparla, Kannappan Nagappan. In vivo Antidiabetic Evaluation of capsicum Extract in Alloxan Induced Rats. Int.J.Nov.Res.Eng & Pharm.Sci., 2014; 1(01): 48-53.
8. Ayesha Noor, Gunasekaran, A.soosai manickam and M.A. Vijayalaxmi. Anti diabetic activity of capsicum and histology of organs in STZ-induced diabetic rats. Current science, 2008; 94: 1070-76.
9. Shravan kumar Dholi, Ramakrishna Raparla, Kannappan. Effect of Gymnema sylvestre on Pharmacokinetics and Pharmacodynamics of oral hypoglycemic drugs – 7.5mg & 10mg Pioglitazone in STZ induced Diabetic rats. International Journal of Pharmacy & Therapeutics, 2015; 6(4): 205-212.
10. Shravan kumar Dholi, Ramakrishna Raparla, Kannappan. Effect of Gymnema sylvestre on Pharmacokinetics and Pharmacodynamics of Metformin in Diabetic rats. JPR:BioMedRx:An International Journal, 2013; 1(7): 657-664.
11. Shravan kumar Dholi, Ramakrishna Raparla, Kannappan. Effect of Gymnema sylvestre on Pharmacokinetics and Pharmacodynamics of 0.5mg and 0.6mg Glibenclamide in Diabetic rats. IJPR, 2015; 5(8): 172-178.