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A PKPD INTERACTION BETWEEN *MOMORDICA CHARANTIA*AND ORAL HYPOGLYCEMICDRUG –SITAGLIPTIN IN STZ INDUCED HYPERGLYCEMIC RATS

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ABSTRACT

Rural people are still dependent on indigenous knowledge for health care that are being influenced by culture and socio economic 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 research studies required to be subjected to pharmacodynamic and pharmacokinetic studies in order to determine effect of *Momordica charantia* herb on the hyperglycaemic patients who are taking the therapy with synthetic drugs. This study was to discover the influence of *Momordica charantia on* the pharmacokinetics and pharmacodynamics of sitagliptin and in rats**.**Results have proved the negative (decrease) effect of *Momordica charantia on* pharmacokinetics but positive (increase) effect on pharmacodynamics of Sitagliptin.

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].Sitagliptin prolongs the activity of proteins that increase the release of insulin after blood sugar rises, such as after a meal. Sitagliptin is a selective inhibitor of the enzyme dipeptidyl peptidase-4 (DPP-4), which metabolizes the naturally occurring incretin hormones glucagon-like peptide-1(GLP-1)and glucose-dependent insulinotropic polypeptide (GIP) resultingin enhanced glucose-dependent insulin secretion from the pancreas and decreased hepatic glucose production. Since GLP-1 enhancesinsulin secretion in the presence of raisedbloodglucoselevels,inhibitingDPP-IV activity will increase and prolong the action of GLP-1 by reducing its rate of inactivation in plasma . Sitagliptin reduces hemoglobin A1c (HbA1c), fasting and postprandial glucose by glucose-dependent stimulation of insulin secretion and

Inhibition of glucagon secretion. GLP-1 has other widespread effects including delaying gastric emptying, significantly reducing glucagons levels and possible central effects on the appetite. In clinical trials, Sitagliptin demonstrated an overall incidence of side effects comparable to placebo. The most common side effects in studies were upper respiratory tract infection, stuffy or running nose, sore throat, headache and diarrhea.The incidence of hypoglycemia with Sitagliptin monotherapy was not significantly different than placebo. Pooled data from2 monotherapy and 2 combination trials show that the incidence of hypoglycemia was 1.2% and 0.9% for Sitagliptin100mgandplaceborespectively **[6-9].**

Momordica charantia(M. charantia), commonlyreferred to asbitter gourd, karela and balsampear. Its fruit is also used for the treatment of diabetes and related conditions amongst the indigenouspopulationsof Asia, South America, India and East Africa. Abundant pre-clinical studies have documented in the anti-diabetic and hypoglycaemic effects of *Momordica charantia* through various postulated mechanisms. However, clinical trial data with human subjects are limited and flawed by poor study design and low statistical power. The present review is an attempt to highlight the antidiabetic activity as well as phytochemical and pharmacological reports onM. charantia and callsfor better-designed clinical trialsto further elucidate itspossible therapeutic effects on diabetes.**[10]**

There is scope for the potential herb-interactions between *Momordica charantia* and Sitagliptin. This can causefew 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 takingthe treatment with synthetic drugs.

MATERIALSANDMETHODS

DRUGS AND CHEMICALS

Adult Albino rats weight between 150±20grams (Mahavear enterprises Hyderabad,Telangana.)were used inthis experimental study. These animals were acclimatized to standard laboratory's conditions of suitable temperature (27^{o}C $\pm$ 1^{o}C) 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.

Preparationofcrudeextract:

The fresh fruits of *Momordica charantia* (Bittermelon)were urchased from the local market.The fruits were then washed thoroughly with tapwater and cut into thin slices. The sliced pieces were dried completely under the mildsun and grinded with an electric grinder into coarse powder and used for cold extraction.After extraction they yield was found to be about 35g/1kg bitter melon powder. The authenticity of *M. charantia* was identified by a plant taxonomist from the Department of Botany, University ofSathavahana University.**[11]**

Pre treatment

Albino rats were selected for this study (150±20grams), animals were maintained under the suitable conditions in animal house.[IAEC- 1322/po/s/10/CPCSEA].The rats were 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 Ratsby streptozotocin {60mg/kg}

After 15 days offeedingwith highly fatty food the rats were fasted for a period of 18hrs before the induction of hyperglycemia &single dose administration of the60 mg/kg of Streptozocin (Sigma Aldrich; St. Louis; MO; USA) were injected intra-peritonially (freshly dissolve in the normal saline solution). After STZ administration, the animalswere free accessed withfood (pellet diet) & water. moderate polydipsia and marked polyuria were observed in diabetic hyperglycemic rats. After three days i.e.after 72hrs of injection, fasting blood glucose concentration was 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.The Rats showing the fasting blood glucose level more than 150 mg/dL were considered the hyperglycaemic-rats and selected for the different grouping in the experimental design.

Experimental Study Design - The hyperglycemic rats were divided in to 6 groups 6 animals in each.

IGroup:Diabetic control

II Group:Low dose of *Momordica charantia* (100mg/Kg)

III Group:Highdose of *Momordica charantia* (500mg/Kg)

IV Group:Oralhypoglycemicdrug-100mg/Kg of Sitagliptin.

V Group:Combinationof5mg/Kg of Sitagliptin+500mg/Kg of *Momordica charantia*

VI Group:Combination of 10mg/Kg of Sitagliptin + 500mg/Kg of *Momordica charantia* **[12].**

Pharmacokinetics study in hyperglycemic rat model:

Singledose Study

These pharmacokinetic studies were carried out in hyperglycaemic rats (weight b/n180gramsand 250grams). These animals were housed in animal's wire cages withfree accessto diet and water *ad-libitum.* The overnight fasting rats were divided in to 6 different groups (n=6) and the followed the treatment mention in the study design.Blood samples were collected at pre determined 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 anaesthesia. The blood samples were subjectd to centrifugation at 3000rpm per 10minutes and plasma was stored at - 20^{0C} for analysis and estimation ofkinetic parameters as AUC 0 - ∞, Cmax ka, ke CL/F, Tmax, V/F, AUC 0-t& $t_{1/2}$.

Multiple dose study

The hyperglycemic rats were dividing into 6 different treatment groups same as mention in study design and daily treatment is carried for 21 days.

Samples of blood were collected from different rat's groups on0^{th},7^{th}, 14^{th}, 21^{st} day immediately after drug treatment. Samplesof blood are collected in to microcentrifugal tubes containing Na^+citrate from retro-orbital puncture under anaesthesia. These blood sampleswere subjected to centrifuged at 3000rpm per 10 minuts and plasma was stores at -20^0 C for analysis and estimationofkinetic parameters as AUC 0 - ∞, V/F, ka, Cmax ,CL/F, Tmax,ke, AUC 0-t & $t_{1/2}$.

Pharmacodynamics study in the hyperglycaemic rats

Singledose 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 thinterval of 0, 1, 2,4, 8, 12and 24 hours by UV spectrophotometer.

Multiple dose study

In this study, daily treatment was given to all groupsof animalsfor 3 weeksas per experimental design. Pharmacodynamic parameter like urea, cholesterol and glucose levels are estimated the time interval of 0, 7, 14and 21 day by UV spectrophotometer.

Statistical Application

ANOVA followed by Dunnet test was performed for comparison between different groups of animals. *P* value fewer than 5% (P<0.05) was consider the statistically significant. All clinical data were 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 *Graph pad prism-9.0*..

Histopathological Study

After estimation of last bloodglucose 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.

RESULTS:

Table No.1Blood glucose levels mg/dL (0th,1st,2nd,4th,8th,12thand24thHour)after oral administration of *Momordica charantia,* Sitagliptin and combination of Sitagliptin and *Momordica charantia* in diabetic rats (n=6).

TREATMENT/ HOURS	BLOOD GLUCOSE LEVELS (mg/dL)					
	DIABETIC CONTROL	MC (DOSE)		SITAGLIPTIN (DOSE)	SITAGLIPTIN+MC(DOSE)	
	Vehicle	100mg/kg	500mg/kg	10mg/kg	5mg/kg +500mg/kg	10mg/kg +500mg/kg
0thHour	450.3±0.76	453.06± 1.0	451.9± 0.80	450± 0.75	450.11± 0.48	452.29± 1.29
1stHour	465.8±1.37	446.9±1.04	431.3± 0.60	403.18± 0.82**	421.51±0.62	386.66± 1.78
2ndHour	462.6±0.80	431.4±0.53	395.4±1.05	281.19± 0.72	356.64± 0.93**	248.91±0.40**
4thHour	432.6±0.87	402.6±1.7	360.5± 1.34	292.82± 0.63	381.12± 0.77	254.44± 1.54
8thHour	422.5±.1.10	412.2± 0.77	391.4± 0.94	321.44±0.85	363.4± 2.00	272.62± 0.86**
12thHour	421.33±1.10	421.1± 1.03	402.3±0.20	367.41±0.37	390.19± 2.16	301.71± 1.91
24thHour	413.9±0.76	443.91± 0	425.24± 0.86	385.43±0.50	418.18±1.75	244.17± 0.65

Table No.2 Blood cholesterol levels mg/dL (0th,1st ,2nd,4th,8th, 12th and 24thHour) after oral administration of *Momordica charantia,* Sitagliptin and combination of Sitagliptin and *Momordica charantia* in diabetic rats (n=6).

TREATMENT/ HOURS	BLOOD CHOLESTEROL LEVELS (mg/dL)					
	DIABETIC CONTROL	MC(DOSE)		SITAGLIPTIN (DOSE)	SITAGLIPTIN+MC(DOSE)	
	Vehicle	100mg/kg	500mg/kg	10mg/kg	5mg/kg +500mg/kg	10mg/kg +500mg/kg
0thHour	201.3±0.87	207.3±1,32	204.9±1.42	207.17± 1.50	198.61± 1.62	193.05± 0.94
1stHour	203.6±0.40	206.4±1.60	197.35±0.95	192.18± 1.39	184.16± 1.34	183.61± 1.34
2ndHour	204.3±0.56	198.1±1.72	184.3±1.51	170.18± 1.40	176.16± 1.25	154.40± 1.38
4thHour	207.19±0.87	188.8±1.20	172.4±1.37	172.91± 1.54	180.28± 1.64	161.18± 1.97
8thHour	201.3±1.07	196.6±1.26	187.9±1.64	180± 1.45	184.61± 2.04	176.05± 1.55
12thHour	203.3±1.85	201.4±0.84	197.3±1.73	184.18 ±1.06	190.16± 1.48	183.61± 1.21
24thHour	204.3±0.90	204.2±1,25	200.3±1,24	192.18± 1.43	192.16± 1.32	188.18± 1.42

Values are given as mean±Standard deviation.
*****Statistica lsignificance p<0.001(compared with the control group***
****Statistical significance p <0.05(compared with the control group)***
MC-Momordica charantia n - number of animals used

Table No.3 Blood urea levels mg/dL (0th,1st,2nd,4th,8th, 12thand 24thHour)after oral administration of *Momordica charantia,*Sitagliptin and combination of Sitagliptin and *Momordica charantia* in diabetic rats (n=6).

TREATMENT/ HOURS	BLOOD UREA LEVELS (mg/dL)					
	DIABETIC CONTROL	MC(DOSE)		SITAGLIPTIN (DOSE)	SITAGLIPTIN+MC(DOSE)	
	Vehicle	100mg/kg	500mg/kg	10mg/kg	5mg/kg +500mg/kg	10mg/kg +500mg/kg
0thHour	73.89±1.75	73.22±1.03	72.98±1.25	72.72±0.76	73.58±1.34	72.81±1.41
1stHour	75.42±1.04	72.79±1.58	71.88±0.85	72.16±1.44	72.6±1.33	70.18±1.04
2ndHour	78.11±0.70	71.92±1.46	69.92±1.24	63.19± 1.09	67.16±0.94	61.16±1.06
4thHour	79.83±1.45	69.17±0.68	67.48±1.02	66.12±1.31	68.18±1.06	62.16±1.63
8thHour	79.91±1.19	67.18±0.64	68.21±1.10	68.14±1.11	69.82±2.09	63.29±1.89
12thHour	80.55±1.25	70.18±0.94	69.81±1.94	68.28±0.79	70.55±1.10	68.14±2.14
24thHour	81.81±1.11	71.82±1.477	71.18±1.96	70.19±2.27	72.61±1.65	71.15±2.15

Table No.4 Blood glucose levels mg/dL (21st day) after oral administration of *Momordica charantia,* Sitagliptin and combination of Sitagliptin and *Momordica charantia* in diabetic rats (n=6).

TREATMENT/ HOUR	BLOOD GLUCOSE LEVELS (mg/dL)					
	DIABETIC CONTROL	MC (DOSE)		SITAGLIPTIN (DOSE)	SITAGLIPTIN+MC(DOSE)	
	Vehicle	100mg/kg	500mg/kg	10mg/kg	5mg/kg +500mg/kg	10mg/kg +500mg/kg
1	465.8±1.37	422.91±.40	380±1.04	301.28±2.76	364.51±1.43	300.66±0.24
2	462.6±0.80	411.3±1.38	361.4±2.28	192.29±2.57	310.64±1.77	178.92±0.52
4	432.6±0.87	373.5±1.60	338.5±3.61	213.62±2.86	315.22±1.99	198.44±0.87
8	422.5±1.10	391.2±1.01	351.4±1.44	252.44±0.51	341.00±2.50	232.62±0.84
12	421.33±1.10	402.1±1.15	383.3±2.88	301.41±0.86	368.19±0.95	286.71±1.86
24	413.9±0.76	409.91±1.72	392.24±1.96	333.6±2.92	377.18±1.01	303.29±1.18

Table No.5 Blood cholesterol levels mg/dL (21st day) after oral administration of *Momordicacharantia,*Sitagliptin and combination of Sitagliptin and *Momordica charantia* in diabetic rats (n=6).

TREATMENT/ HOUR	BLOOD CHOLESTEROLLEVELS(mg/dL)					
	DIABETIC CONTROL	MC(DOSE)		SITAGLIPTIN (DOSE)	SITAGLIPTIN+MM(DOSE)	
	Vehicle	100mg/kg	500mg/kg	10mg/kg	5mg/kg +500mg/kg	10mg/kg +500mg/kg
1	198.4±1.71	197.3±1.07	162.54±0.97	169.34±0.96	142.61±0.73	198.4±1.71
2	189.1±1.42	184.3±0.52	148.18±0.82	160.65±1.04	127.5±0.92	189.1±1.42
4	179.4±1.63	172.4±0.87	150.91±0.74	170.18±0.74	132.62±1.17	179.4±1.63
8	182.6±1.43	187.9±1.49	168.±1.63	175.61±1.09	138.05±0.86	182.6±1.43
12	201.4±1.79	197.3±1.39	172.18±1.49	181.66±1.10	141.81±0.98	201.4±1.79
24	2.4.2±1.98	200.3±1.42	180.00±1.41	186.16±0.86	168.18±1.21	204.2±1.98

TableNo.6: Blood urea levels mg/dL(21st day) after oral administration of *Momordica charantia,* Sitagliptin and combination of Sitagliptin and *Momordica charantia* in diabetic rats (n=6).

TREATMENT/ DAYS	BLOOD UREA LEVELS (mg/dL)					
	DIABETIC CONTROL	MC (DOSE)		SITAGLIPTIN (DOSE)	SITAGLIPTIN+MC(DOSE)	
	Vehicle	100mg/kg	500mg/kg	10mg/kg	5mg/kg +500mg/kg	10mg/kg +500mg/kg
1	70.68±1.37	69.78±1.02	66.16±1.15	69.19±1.47	66.18±1.59	70.68±1.37
2	70.02±2.02	68.12±1.69	58.83±1.87	63.61±1.31	52.7±1.49	70.02±2.02
4	69.48±1.07	63.48±1.85	60.11±2.23	62.59±2.45	56.06±0.90	69.48±1.07
8	67.91±1.34	65.21±0.96	63.14±1.76	64.12±1.78	59.22±1.46	67.91±1.34
12	68.81±0.74	67.81±1.09	65.28±1.08	66.65±1.09	62.74±1.34	68.81±0.74
24	69.27±1.25	68.28±1.19	67.19±1.62	66.51±0.66	64.25±0.62	69.27±1.25

**** *Statistical significance p<0.01(compared with the control group)***

TableNo.7 Mean plasma Sitagliptin concentrations (µg/ml) (Single dose study).

TREATMENT/ DAYS	PLASMA CONCENTRATIONS (ng/ml)			
	DIABETIC CONTROL	SITAGLIPTIN (DOSE)	SITAGLIPTIN+MM(DOSE)	
	Vehicle	100mg/kg	5mg/kg+500mg/kg	10mg/kg +500mg/kg
1stHour	0	37.65±0.44	17..78±0.31	35.19±0.52
2ndHour	0	61.35±0.12	42.11±0.28	72.03.03±0.39
4thHour	0	58.68±0.52	40.21±0.26	68..65±0.032
8thHour	0	30.71±0.31	18.10±1.29	40.68±0.81
12thHour	0	21.11±0.82	16.23±0.29	38.14±0.52
24thHour	0	3.11±0.21	1.89±0.13	4.1±0.21

TableNo.8 Mean plasma Sitagliptin concentrations (ng/ml) (Multiple dose study).

TREATMENT/DAYS	PLASMACONCENTRATIONS(ng/ml)			
	DIABETIC CONTROL	SITAGLIPTIN(DOSE)	SITAGLIPTIN+MC(DOSE)	
	Vehicle	10mg/kg	5mg/kg+500mg/kg	10mg/kg+500mg/kg
0thDay	0	40.45±0.64	18.73±1.02	38.86±1.22
7thDay	0	62.25±0.64	44.89±0.74	80.52±0.92
14thDay	0	60.02±1.12	42.13±0.04	79.27±0.22
21stDay	0	31.04±0.24	18.99±0.21	47.45±0.34

TableNo.9 Effect of *Momordica charantia* on Pharmacokinetic parameters of Single dose administration of Sitagliptin in diabetic rats (n=6).

Pharmacokinetic parameter	Units for Pharmacokinetic parameters	10mg/kg of SITAGLIPTIN	SITAGLIPTIN+*Momordicacharantia*(DOSE)	
			5mg/kg+500mg/kg	10mg/kg+ 500mg/kg
ka	h^{-1}	1.642±0.19	1.013±0.33	1.319±0.44
ke	h^{-1}	0.145±0.08	0.142±0.28	0.141±1.22
t1/2	h	4.78±0.63	4.85±0.55	4.89±0.63
Tmax	(mg/kg)/(µg/ml)	2.00±0.22	2.00±0.43	2.00±0.22
Cmax	µg/ml	61.35±0.03	42.11±0.65	72.03±0.03
V/F	(mg/kg)/(µg/ml)	0.11 ±0.16	0.08±0.83	0.08 ±0.16
CL/F	(mg/kg)/(µg/ml)/h	0.02±0.39	0.01±0.52	0.01±0.39
AUC0-t	µg/ml*h	616.34±0.26	415.15±0.84	841.08±0.26
AUC0-∞	µg/ml*h	638.04±0.44	428.39±0.18	870.57±0.44
MRT	h	7.93±0.21	8.04±0.11	8.64±0.01

TableNo.10 Effect of *Momordica charantia* on Pharmacokinetic parameters of Multiple dose administration of Sitagliptin in diabetic rats (n=6)

Pharmacokinetic parameter	Units for Pharmacokinetic parameters	10mg/kg of SITAGLIPTIN	SITAGLIPTIN+*Momordicacharantia* (DOSE)	
			5mg/kg+500mg/kg	10mg/kg+500mg/kg
ka	h^{-1}	1.714±0.22	1.018±0.46	1.328±0.51
ke	h^{-1}	0.144±0.06	0.139±0.02	0.137±0.02
t1/2	h	4.80±0.72	4.98±0.55	5.05±0.46
Tmax	(mg/kg)/(µg/ml)	2.00±0.53	2.00±0.43	2.00±0.33
Cmax	µg/ml	62.25±0.74	44.89±0.11	80.52±0.43
V/F	(mg/kg)/(µg/ml)	0.105±0.45	0.079±0.83	0.074±0.28
CL/F	(mg/kg)/(µg/ml)/h	0.015±0.38	0.011±0.52	0.010±0.042
AUC0-t	µg/ml*h	637.06±0.26	434.79±0.84	943.41±0.14
AUC0-∞	µg/ml*h	659.88±0.48	450.39±0.18	981.02±0.23
MRT	h	7.97±0.86	8.13±0.12	8.73±0.11

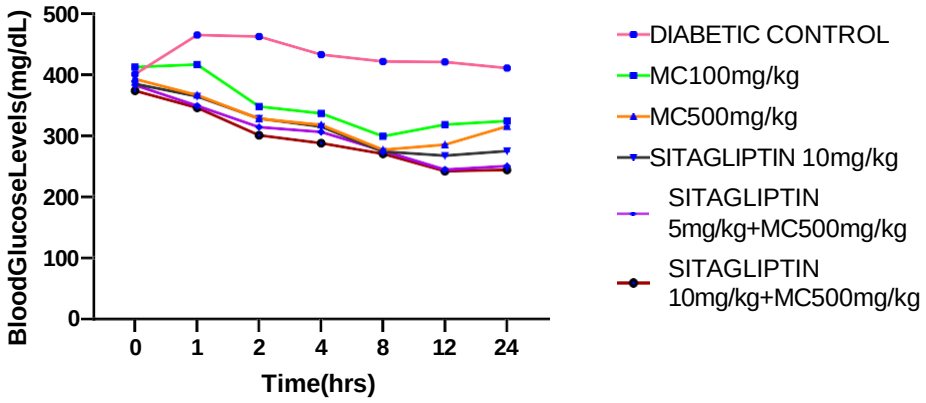
Values are given as mean±Standard deviation.

**** *Statistical significance p<0.01(compared with the controlgroup)***

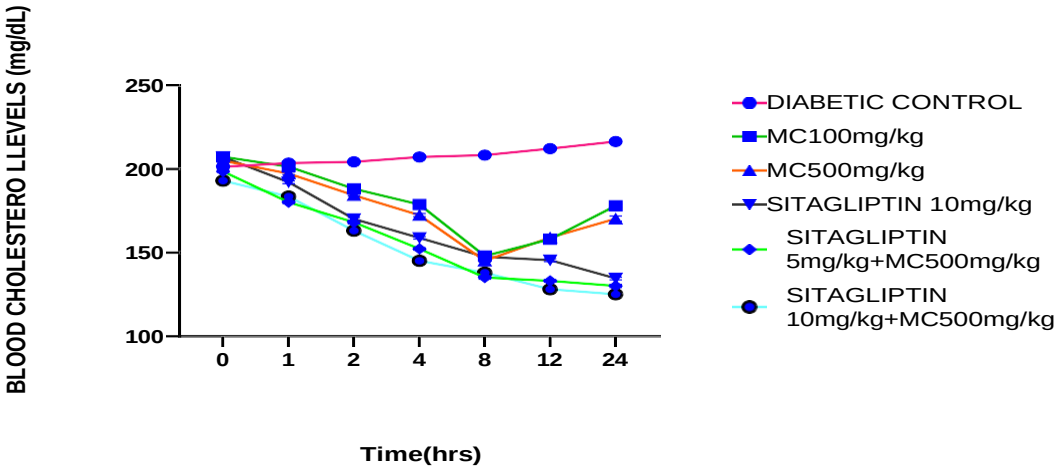
****Statistical significance p<0.05(compared with the control group)***

MC-Momordica charantian - number of animals used.

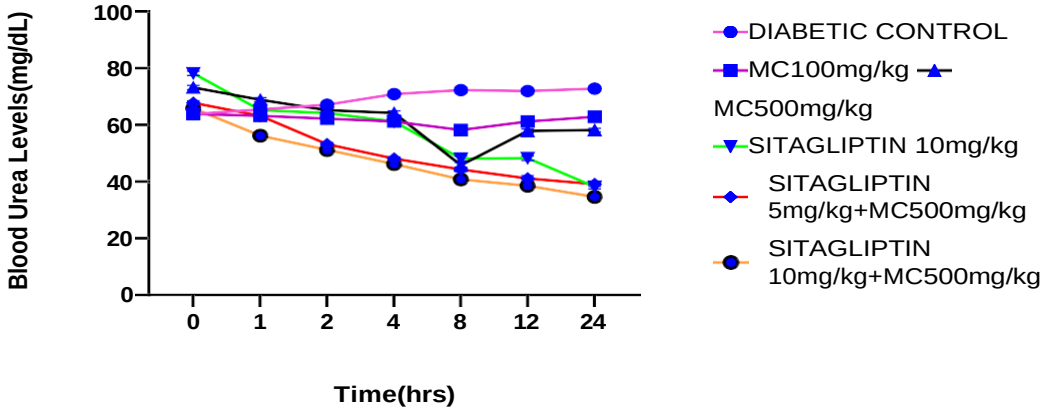
Graph.1: Blood glucose levels mg/dL (0th,1st ,2nd,4th,8th, 12th and 24th Hour) after oraladministration of Momordica charantia, Sitagliptin and combination of Sitagliptin andMomordica charantia in diabetic rats (n=6).



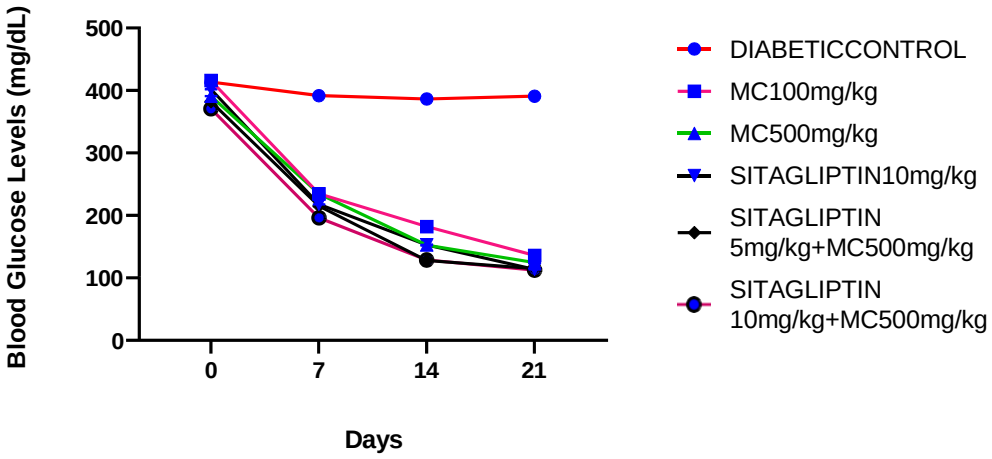
Graph.2Blood cholesterol level smg/dL(0th,1st,2nd,4th,8th,12thand24thHour) after oral administration of Momordica charantia,Sitagliptin and Combination of Sitagliptin and Momordica charantia in diabetic rats(n=6)



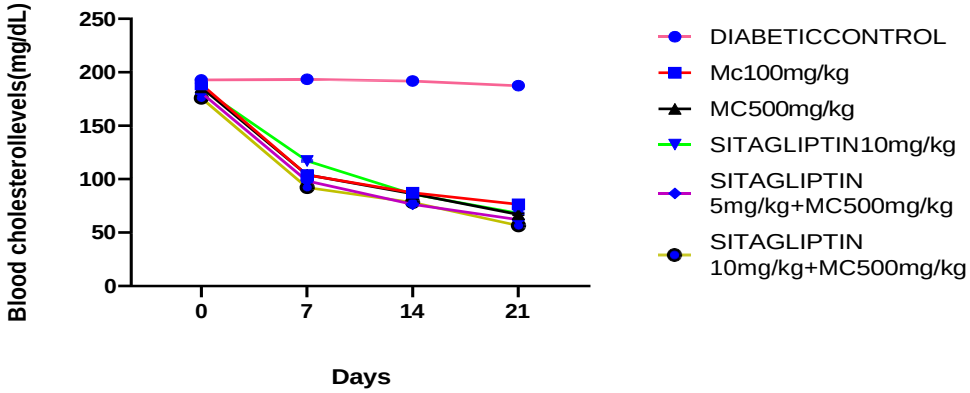
Graph.3 Blood urea levels mg/dL(0th,1st,2nd,4th,8th,12thand24thHour) after oral administration of Momordica charantia,Sitagliptin and Combination of Sitagliptin and Momordica charantia in diabetic rats(n=6).



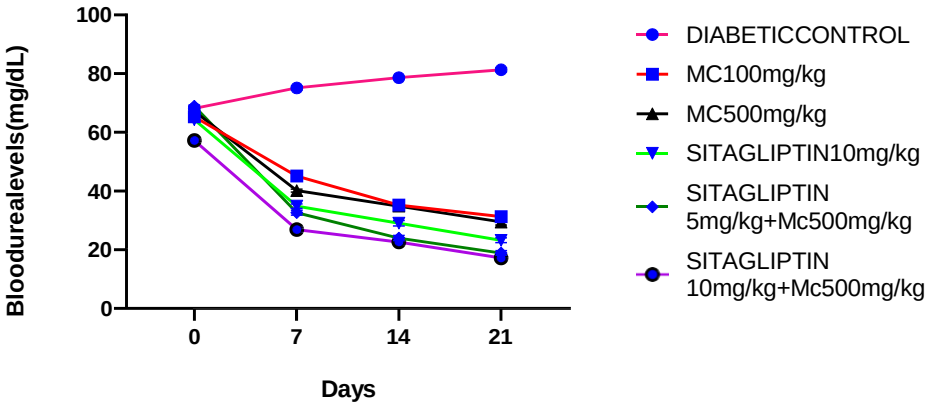
Graph.4 Blood glucose levels mg/dL(0th,7th, 14thand21stday) after oral administration of Momordica charantia,Sitagliptin and Combination of Sitagliptin and Momordica charantia in diabetic rats(n=6).



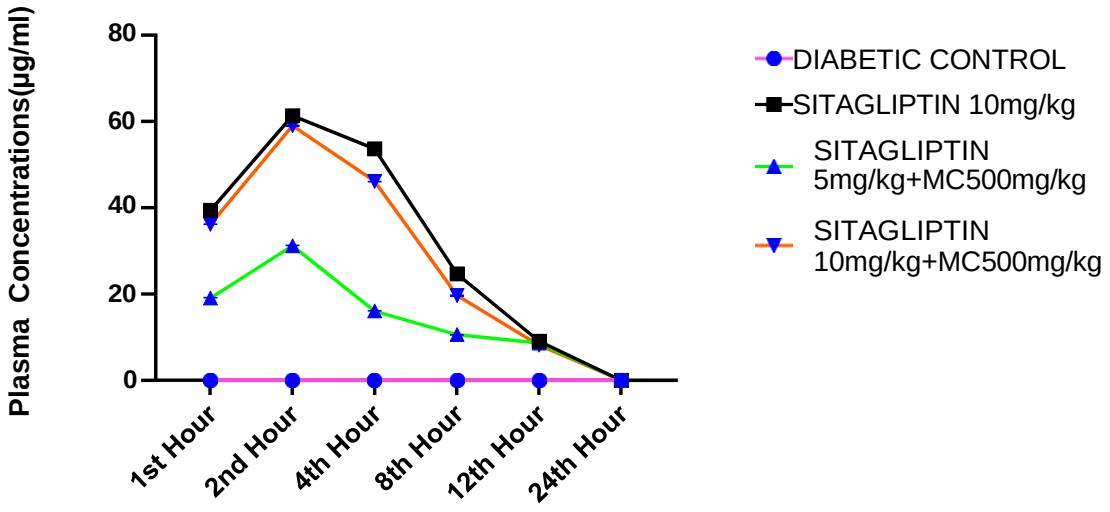
Graph.5 Blood cholesterol levels mg/dL (0th,7th, 14th and 21st day)after oral administration of Momordicacharantia, Sitagliptinand combinationofSitagliptin and Momordic acharantia in diabetic rats(n=6).



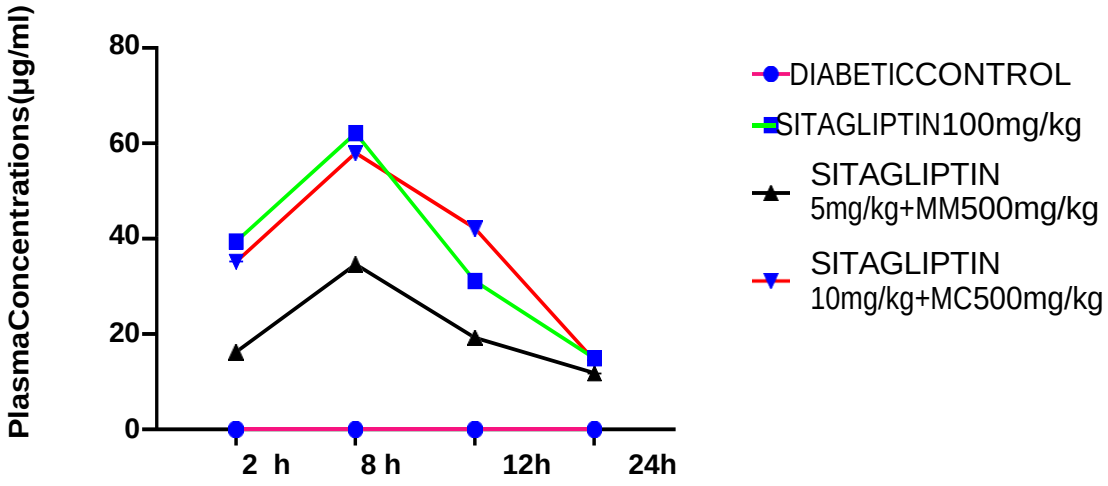
Graph.6Bloodurealevelsmg/dL(0th,7th,14thand21stday) afteroraladministrationofMomordicacharantia,Sitagliptinand combinationofSitagliptinandMomordicacharantiaindiabeticrats(n=6).



Graph.7 Mean plasma Sitagliptin concentrations(µg/ml) (Single dosestudy)



Graph.8 Mean plasma Sitagliptin concentrations(µg/ml) (Multiple dose study)



DISCUSSION:

Pharmacodynamic study:

The combination of high dose of Sitagliptin (10 mg/kg) with 500mg/kg *Momordica charantia* showed maximum hypoglycemic action, decrease in serum cholesterol and urea levels. The effect produced by combination of Sitagliptin (5 mg/kg) with *Momordica charantia* was greater than the hypoglycaemic action produced by *Momordica charantia* (500 mg/kg) alone and Sitagliptin (10 mg/kg).

Pharmacokinetic study:

The Single dose study shows that, 32.83% increase in AUC(0 - ∞) in 500mg/kg of *Momordica charantia* and 5mg/kg of Sitagliptin. 36.46% increase AUC (0 - ∞) in 500mg/kg of *Momordica charantia* and 10mg/kg of Sitagliptin when compare with 10mg/kg Sitagliptin alone. C max was decreased by 31.36% in 500mg/kg of *Momordica charatia* and 5mg/kg of Sitagliptin, 17.4% increased in 500mg/kg of *Momordica charantia* and 10mg/kg of Sitagliptininsingledose study.Significantly increase in clearance 2.24% in 500mg/kg of *Momordica charantia* and 5mg/kg of Sitagliptin 5.61% in 500mg/kg of *Momordica charantia* and 10mg/kg of Sitagliptin compared to 10mg/kg Sitagliptin

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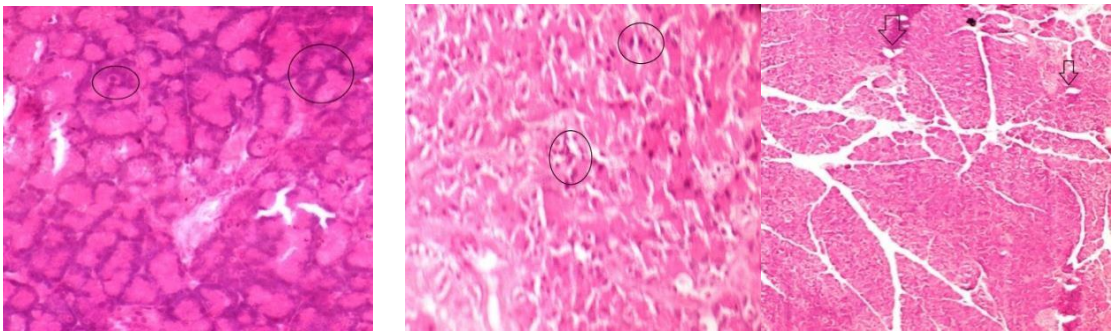
The multiple dose study shows that, 31% decrease in AUC(0 - ∞) in 500mg/kg of *Momordica charantia* and 5mg/kg of Sitagliptin. 48% increase AUC(0 - ∞) in 500mg/kg of *Momordica charantia* and 10mg/kg of Sitagliptin. C max was decreased to 27% in 500mg/kg of *Momordica charantia* and 5mg/kg of Sitagliptin,C max was increased 29.34% in 500mg/kg of *Momordica charantia* and 10mg/kg of Sitagliptin in multiple dose study. Significantly decrease in clearance 26% in 500mg/kg of *Momordicacharantia* and 5mg/kg of Sitagliptin. 33% in 500mg/kg of *Momordica charantia* and 10mg/kg of Sitagliptin compared to 10mg/kg Sitagliptin alone.

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

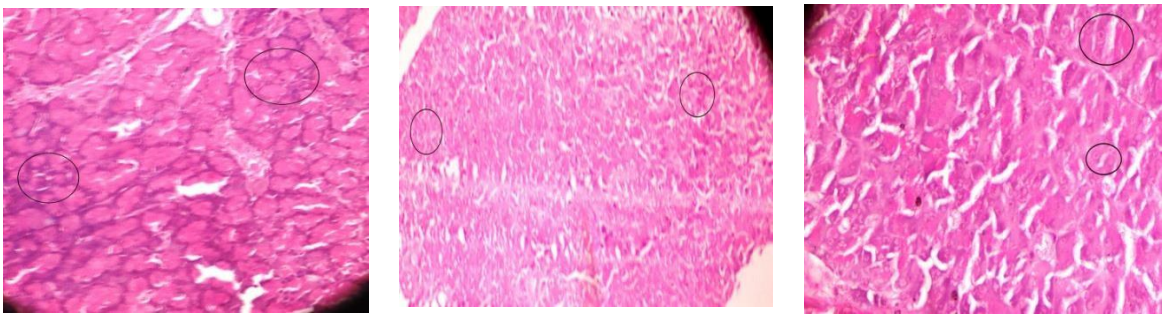
Histological study:

The histological study shows that the combination therapy(Sitagliptin + *Momordica charantia*) involved in the increase the number of islets and recovered the partially damaged β cells in pancreas when compare to the Individual treatment.

Slide 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 Sitagliptin. Figures C,D,E,F shows that β cells are regenerated in pancreatic tissue. Normal ß-cells were observed in low and high doses of Sitagliptin and *Momordica charantia*.(Slides: D&F). In the Sitagliptin group more damaged ß-cells as compared withthe500mgof*Momordicacharantia* +100 mg of Sitagliptin and 500mgof *Momordica charantia* +50mg ofSitagliptin (Figures: B,C&E).



A **B** **C**



D **E** **F**

H&S Staining of Pancreatic islets of Diabetic Control, *Momordica charantia* alone, Sitagliptin alone and combination of *Momordica charantia* & Sitagliptin treated Diabetic Rats. A. diabetic control , B. 100mg of *Momordica charantia* C. 500mg of *Momordica charantia,*D.10 mgof Sitagliptin.E.500mgof*Momordicacharantia*.+5mgofSitagliptin,F. 500mgof*Momordicacharantia*+10mgof Sitagliptin

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 Sitagliptin 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 Sitagliptin produced increment to thevolume of islets in pancreas compared to individual treatment.In this study, *Momordica charantia* was decrease the absorption and increase the clearance of Sitagliptin. Hence care must be taken when the combination is taken by diabeticpatients.

CONCLUSION: The above herb-drug interaction reveals that combination of Sitagliptin(10mg/kg) with500mg/kg of *Momordica charantia* have hypoglycemic action significantly as comparedtothe Sitagliptin(5mg/kg) with *Momordica charantia*(500mg/kg) and Sitagliptin (10 mg/kg) alone in pharmacodynamic studies. Combination of Sitagliptin(10 mg/kg) with 500mg/kg of *Momordica charantia*have increasedAUC,Cmax,absorption rate constant Ka and decreased clearance as compared to the Sitagliptin (5 mg/kg) with *Momordicacharantia* (500 mg/kg) in pharmacokinetic studies

Ethical issue:

All experimental process of animals was approved by the Institutional Animal Ethical Committee of SRR college, of pharmacy.

Conflictof interest

The authors declare that there are no conflicts of interest.

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