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A PHARMACOKINETIC & PHARMACODYNAMIC INTERACTION BETWEEN *MOMORDICA DIOICA* FRUIT'S EXTRACT AND ORAL HYPOGLYCEMIC DRUG – METFORMIN IN HYPERGLYCEMIC RATS

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Abstract:
Traditional medication obtained from the medicated herbal plants are used by about maximum percentage of world population for different chronic disease condition. Diabetes (Hyperglycaemia- 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. Momordica dioica 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 Momordica dioica 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 Momordica dioica on the hyperglycemic patients who are taking the therapy with synthetic drugs. This research work was to identify the influence of Momordica dioica on the pharmacokinetic and pharmacodynamic of Metformin in rats. Results have proves the negative (decrease) effect of Momordica dioica on pharmacokinetics but positive (increase) effect on pharmacodynamics of Metformin.

Key words: Momordica dioica, Metformin, Oral hypoglycemic drugs.

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1. INTRODUCTION:

Diabetic Mellitus (Hyperglycemiea) is an endocrine disease and not a single disease which is a group of chronic metabolic or heterogeneous afflictions with the irregular secretion of hormone-insulin and action of insulin or both. Absence or reduced insulin in turn leads to abnormal high blood sugar level and glucose intolerance. [1-3]**.** Honey has been shown to interfere with bioavailability of carbamazepine and diltiazem in rabbits [4]. Allicin present in garlic is reported inhibit CYPA34 and also p-glycoprotein mediated efflux of HIV protease inhibitors [5] Clove on the other hand is known to reduces the hepatic cytochromes [6]. Piperine isolated from pepper is reported to enhance the bioavailability of spartine, curcumin, barbiturate, oxyphenbutazone, zoxazolamine, propranolol and theophylline in experimental animals [7]. *Cassia auriculata* increases the antihyperglycemic activity of pioglitazone in diabetic rats [8]. Pharmacokinetics of tacrolimus are affected by Grape fruit juice [9]**.** 18α-glycyrrhizin increases the bioavailability of glibenclamide in diabetic rat [10]. On the basis of pharmacokinetics and pharmacodynamics drug-herb interactions are clinically significant. [11].

Metformin HCL tablet should be given in divided doses with meal. Metformin HCl tablet should be started at a lower dose, with gradually increasing dose escalation, both to reduce the side effects related to Gastrointestinal tract and to permit the identification of the minimum dose needed for adequate blood glucose control in diabetic patients.

2.MATERIALS ANS METHODS:

Collection of plant material

Fruits will be collected from local area

Processing of plant material

The fruits of *M. dioica* will be washed in running water and cut into small bits to facilitate drying and grind by according to standard procedure. The powered sample were wrapped in paper and packed in polythene bag to avoid moisture and contamination.

Solvent extraction

The extraction of *Momordica dioica* was carried out by soxhlation method (Harborne 1844) dried powder was subjected to soxhlet extraction unit and ethanol used as solvent. soxhlation process was allowed to carry out for 12 cycle with the maintenance of 78^0c for ethanolic solvent respectively the solvent extract was concentrate in water bath at temperature 400c using beaker and preserved in air tight bottles at 50C for further experimentation the extract were diluted and then used for the test.[26]

Pretreatment

Albino rats were selected for this study (180-250gm), these animals are supplied by the NIN, Hyderabad, Telangana, and 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 animal are free accessed with food (pellet diet) & water. Moderate polydipsia and marked polyuria are observed in diabetic hyperglycemic rat. After three days i.e. after 72hrs of injection, fasting blood glucose concentration were determined by following glucose level 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 levels more than 150 mg/dL were consider the hyperglycaemic-rats and selected for the different grouping in the experimental designs.

STUDY DESIGN:

THE HYPERGLYCEMIC RATS ARE DIVIDED IN TO 6 GROUPS 6 ANIMALS IN EACH.

Group I: Diabetic - Control group (0.5% Sodium Carboxymethyl Cellulose (cmc) Suspension
Group II: *Momordica dioica* (100 mg/kg)
Group III: *Momordica dioica (*500 mg/kg)
Group IV: Combination of Metformin (100 mg/kg) + *Momordica dioica* (500 mg/kg).
Group V: Combination of Metformin (50 mg/kg) + *Momordica dioica* (500 mg/kg).
Group VI: Metformin (100 mg/kg)

Pharmacokinetics study in hyperglycemic rat model:

Single dose-Study (Acute study):

These pharmacokinetic studies are carried out in hyperglycaemia 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 & $t_{1/2}$.

Chronic Study (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}, 7th, 14th, 21st 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 (acute treatment)
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.

4.15.2 Multiple dose study (chronic 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.

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. [27-29]

3.EXPERIMENTAL RESULTS:

TREATMENT/DAYS	BLOOD CHOLESTEROL LEVELS (mg/dL)					
	DIABETIC CONTROL	MD (DOSE)		Metformin (DOSE)	Metformin+ MD (DOSE)	
	vehicle	100mg/kg	500mg/kg	100mg/kg	50mg/kg +500mg/kg	100mg/kg +500mg/kg
0thday BLOOD CHOLESTEROL LEVELS	193.4±10.9	188.5±8.5	181.8±11.4	186.5±4.5	180.8±6.4	175.5±8.4
7th day BLOOD CHOLESTEROL LEVELS	194.5±9.8	105.3±8.6**	102.4±7.6**	105.2±7.2**	93.6±4.4**	91.5±7.8**
14th day BLOOD CHOLESTEROL LEVELS	188.4±8.6	88.5±8.14**	85.4±6.9**	78.4±7.43**	74.1±4.9**	69.4±9.1**
21st day BLOOD CHOLESTEROL LEVELS	192.4±8.4	74.6±9.4**	71.3±8.3**	68.4±7.1**	53.1±6.3**	50.4±5.1**

Blood Cholesterol (mg/dL) levels at 0^{th}, 7^{th}, 14^{th} and 21^{st} day after oral administration of *Momordica dioica* , Metformin, and combination of Metformin + *Momordica dioica* in diabetic

Blood Urea (mg/dL) levels at 0th, 7th, 14th and 21st day after oral administration of *Momordica dioica* , Metformin, and combination of Metformin + *Momordica dioica* in diabetic rats (n=6)

TREATMENT/DAYS	BLOOD UREA LEVELS (mg/dL)					
	DIABETIC CONTROL	MD (DOSE)		Metformin(DOSE)	Metformin+ MD (DOSE)	
	vehicle	100mg/kg	500mg/kg	100mg/kg	50mg/kg +500mg/kg	100mg/kg +500mg/kg
0th day BLOOD UREA LEVELS	71.42±3.24	69.18±7.35	68.43±5.34	79.13±3.14	74.16±3.41	70.18±3.71
7th day BLOOD UREA LEVELS	78.69±8.52	44.27±2.54**	38.15±4.06**	36.29±3.42**	35.52±5.32**	31.25±6.41**
14th day BLOOD UREA LEVELS	79.42±8.25	31.08±8.63**	33.08±5.06**	26.35±4.66**	28.19±9.25**	25.42±8.18**
21st day BLOOD UREA LEVELS	82.22±5.21	33.46±8.14**	30.12±7.35**	25.31±10.49**	25.71±9.13**	21.18±8.65**

Volume of islet cells in pancreas in differen *Momordica dioica* Groups after multiple dose administration of Metformin. (n=6).

GROUP	Volume of islets (mm3/mm3) / Volume of pancreas (mm3/mm3)
Diabetic Control	0.082 ± 0.002
M D (100 mg/kg, *p.o.)*	0.195 ± 0.054**
M D (500 mg/kg, p.o.)	0.244 ± 0.006**
Metformin (100 mg/kg, p.o.)	0.138 ± 0.004*
Metformin (50 mg/kg, p.o.) + *M D* (500 mg/kg, p.o.)	0.246 ± 0.028**
Metformin(100 mg/kg, p.o.) + *M D* (500 mg/kg, p.o.)	0.288 ± 0.035**

4.DISCUSSION:

Diabetes is a chronic metabolic disorder which needs prolonged treatment for maintenance of normal blood glucose levels and to control several complications induced by this disease like retinopathy, nephropathy, peripheral neuropathy, cardiomyopathy and an underlying high oxidant stress. The aim of present study is to determine whether *Momordica dioica* influences the pharmacokinetics and pharmacodynamics of different doses of metformin, in diabetic rats or not. In addition, we also check the safety combination effects in same animal models.

The blood glucose levels reduction was found to be

high with *Momordica dioica* when combined with oral hypoglycemic drugs (Group VI) compared to effect showed by the groups treated with *Momordica dioica* (Group III) and oral hypoglycemic drugs alone (Group IV). A long with reduction in blood glucose levels, blood cholesterol and urea levels were also found to be reduced in the Group VI treated with *Momordica dioica* combine with oral hypoglycemic drugs in comparision to groups treated with individual oral hypoglycemic drugs (Group IV). and *Momordica dioica* alone (Group III).

STUDY DESIGN

Pharmacodynamic study:

The combination of high dose of metformin (100 mg/kg) with 500mg/kg *Momordica dioica* showed maximum hypoglycemic action, decrease in serum cholesterol and urea levels. The effect produced by combination of metformin (50 mg/kg) with *Momordica dioica* was greater than the hypoglycaemic action produced by *Momordica dioica* (500 mg/kg) alone and metformin (100 mg/kg) alone.

Pharmacokinetic study:

The Single dose study shows that, 25.44% decrease in AUC(0 - ∞) in 500mg/kg of *Momordica dioica* and 50mg/kg of metformin. 8.01% decrease AUC (0 - ∞) in 500mg/kg of *Momordica dioica* and 100mg/kg of metformin.

C max was decreased by 73.59% in 500mg/kg of *Momordica dioica* and 50mg/kg of metformin, 51.22% in 500mg/kg of *Momordica dioica* and 100mg/kg of metformin in single dose study.

Significant decrease in absorption rate constant Ka by about 24.55% in Lower dose of 500mg/kg of *Momordica dioica* and 50mg/kg of metformin, 18.03% in 500mg/kg of *Momordica dioica* and 100mg/kg of metformin. Significantly increase in clearance 5.33% in 500mg/kg of *Momordica dioica* and 50mg/kg of metformin. 10.63% in 500mg/kg of *Momordica dioica* and 100mg/kg of metformin compared to 100mg/kg metformin.

The multiple dose study shows that, 18.01% decrease in AUC(0 - ∞) in 500mg/kg of *Momordica dioica* and 50mg/kg of metformin. 9.15% decrease AUC(0 - ∞) in 500mg/kg of *Momordica dioica* and 100mg/kg of metformin.

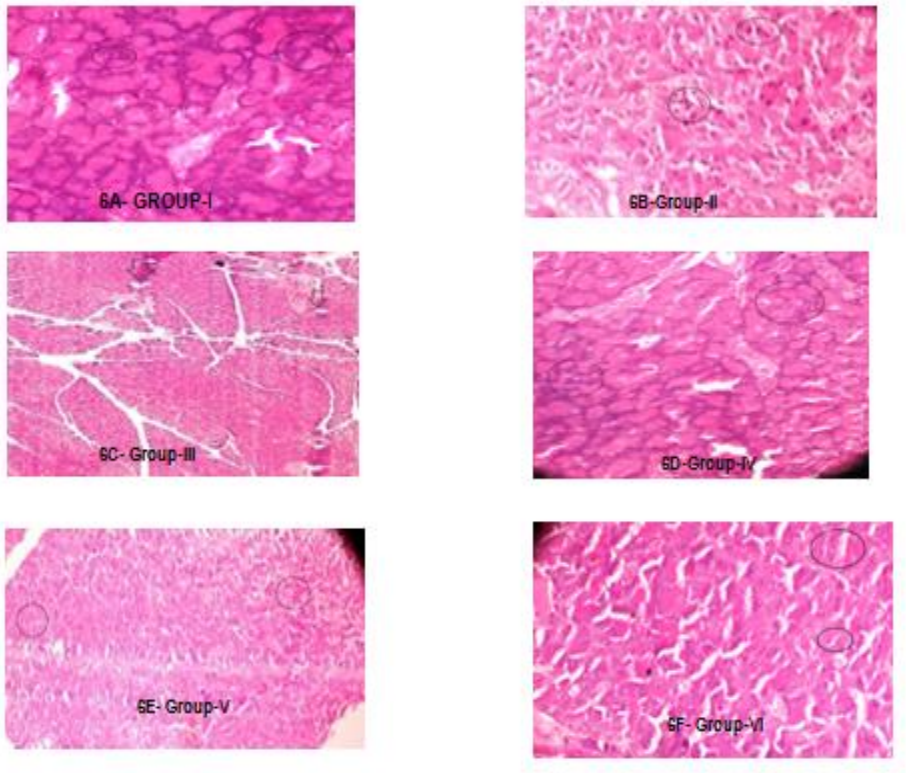
C max was decreased by 39.22% in 500mg/kg of *Momordica dioica* and 50mg/kg of metformin, 24.51% in 500mg/kg of *Momordica dioica* and 100mg/kg of metformin in multiple dose study.

Significant decrease in absorption rate constant Ka by about 8.14% in Lower dose of 500mg/kg of *Momordica dioica* and 50mg/kg of metformin, 4.15% in 500mg/kg of *Momordica dioica* and 100mg/kg of metformin. Significantly increase in clearance 28.58% in 500mg/kg of *Momordica dioica* and 50mg/kg of metformin. 9.51% in 500mg/kg of *Momordica dioica* and 100mg/kg of metformin compared to 100mg/kg metformin.

The exact reason behind the reduction in pharmacokinetic parameters was unknown but, it was understood that the combination of Momordica *dioica* with metformin 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 (metformin + *Momordica dioica*) involved in the increase the number of islets and recovered the partially damaged B cells in pancreas when compare to the Individual treatment.



SLIDE I shows that pancreatic cells were damaged due to development of diabetes from STZ. SLIDE II shows that few pancreatic cells were damaged due to pioglitazone. SLIDES III,IV,V,VI shows that B cells are regenerated in pancreatic tissue.

Normal ß-cells were observed in low and high doses of Metformin and Momordica dioica Extract (Figures: IV&V). In the Metformin group more damaged ß-cells as compared with the 500mg of Momordica dioica Extract +100 mg of Metformin and 500mg of Momordica dioica Extract + 5Omg of Metformin (SLIDES: II,III&V).

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 Metformin 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 Metformin produced increment to the volume of islets in pancreas compared to individual treatment. In this stu dy, Momordica dioica Extract was decrease the absorption and increase the clearance of Metformin. 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. Momordica dioica Extract inhibits the absorption of oral hypoglycemics that results in a significant decrease in the bioavailability of the later and combination group with a lower dose of oral hypoglycemics 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 oral hypoglycemic 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.

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