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Research Article

A Pharmacokinetic Interactions Between Metformin And *Capsicum Annuum* & Histopathological Study

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ABSTRACT

Over the past three decades, formulation technology has significantly advanced, particularly in drug delivery systems. Innovations include novel dosage forms and new uses for existing drugs, offering benefits like improved patient compliance, sustained drug concentration, reduced dosing frequency, targeted delivery, and minimized side effects. Transdermal drug delivery systems (TDDS) are key developments, allowing controlled, continuous medication administration through the skin, bypassing gastrointestinal degradation and hepatic first-pass metabolism, and enhancing bioavailability and patient compliance. The FDA approves roughly one transdermal product every 2.2 years, with the first patch approved four decades ago. This research examines the skin's role as a barrier, clinical trials, patents, commercialization, and the benefits and limitations of TDDS. Various TDDS methods are reviewed, highlighting their advantages, disadvantages, and potential applications. Recent advancements demonstrate TDDS's effectiveness and potential across diverse sectors, emphasizing their transformative impact on drug delivery and therapeutic practices.

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 [1-2]. 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

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clinical trials of these remedies require further investigations along with extensive clinical trials. Most of the plant compounds use 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[3-5]. Metformin is an oral antidiabetic drug in the biguanide class. It is the first-line drug of choice for the treatment of type 2 diabetes, in particular, in overweight and obese people and those with normal kidney function. Metformin works by suppressing glucose production by the liver. Metformin is the only anti-diabetic drug that has been conclusively shown to prevent the cardiovascular complications of diabetes. It helps reduce LDL cholesterol and triglyceride levels, and is not associated with weight gain. There is scope for the potential herb-interactions between Capsicum annuum and Metformin. 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.

MATERIALS AND METHODS

PLANT MATERIALS

Preparation, authentication and evaluation of Capsicum annuum Linn.

The dried fruits of Capsicum annuum Linn were procured from local market. The fruits were coarsely powdered and extracted in a Soxhlet extractor using ethanol. The extract was dried on a rotary evaporator to get a thick reddish brown oleoresin containing capsaicinoids. The oleoresin was analysed to quantitate the capsaicin content.

A stock solution of standard capsaicin (1mg/ml) was prepared and it was diluted to prepare a working standard of 100µg/ml. The calibration curve for capscaicin was prepared in the range of 20-100µg/ml. The linearity response for capsaicin was assessed in the range of 0.2 µg/spot to 1ug/spot in terms of slope, intercept and correlation coefficient values. HPTLC was performed on precoated silica gel G plates in the solvent system Toluene: Ethylacetate (7:3) and was scanned at 280nm. A 1:50 dilution of the oleoresin was carried out and 10µl of the oleoresin was co chromatographed with standard capsaicin to determine the content of capsaicin in the oleoresin sample.[6]

DRUGS AND CHEMICALS

Adult male wistar-rats weight between 150±20grams were used in this Experimental study. These animals were acclimatized to standard laboratory's conditions of suitable temperature (27oC + 1oC) 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 in conducted according with IAEC/ CPCSEA.

Bio analysis of Metformin in rat plasma

Chromatographic condition

A Shimadzu LC-6AT with SPD-10A detector was used for HPLC analysis. The reagents used for preparation of mobile phase were of HPLC grade. High performance liquid chromatographic method was developed using phenomenex C 18 ODS (5 µ) 250 x 4.60 mm column, mobile phase selected for this method contains acetonitrile, aqueous sodium di hydrogen phosphate buffer (40:60) pH adjusted to 6 with o-phosphoric acid which was filtered through 0.2 µ membrane filter. Flow rate employed was 1.0ml/ min. Detection of eluent was carried out at 234 nm and separation was carried out at ambient temperature

Extraction procedure:

Preparation of standard stock solution:

2 ug/ml solution of Metformin was prepared by dissolving in methanol-water 1:1 ratio.

Preparation of plasma stock solution:

Plasma stock solution was prepared by diluting 50 ul of the above standard stock solution with 950 ul of Plasma.

Extraction of Metformin from plasma:

To the plasma stock solution equal volume of acetonitrile was added for deproteinization and vortex for 10 mins followed by centrifugation at 10000nm for 10 mins. The supernatant was collected was filter and subjected to analysis at 234 nm by HPLC. A 20 microlitre sample was injected in HPLC for estimation of Metformin.

Retention Time of Metformin:

Retention time observed was at 3.8 min at flow rate of 1.0ml/min and variation in retention time was not significant at different injections.

Pretreatment:

Albino rats of either sex (150 to 180 g) were acclimatized in an air-conditioned room at20-220C for 2 weeks. They were housed in elevated wire cages and were provided with high fat diet (carbohydrates: proteins: fat in 42:18:40 ratios) and water ad libitum for a period of 15 days

Experimental Induction of Diabetes in Rats:

Hyperglycaemia was induced in overnight fasted adult wistar rats weighing 150-180g by a single intraperitoneal injection of freshly prepared Alloxan monohydrate in normal saline (150 mg/kg body weight) in a volume 1ml/kg body weight. Hyperglycaemia was confirmed by the elevated glucose level in plasma, determined at 48 h after injection. The Rats found hyperglycaemic were screened for the Antihyperglycaemic study[8].

Study design:

The diabetic rats are divided in to five groups 6 animals in each.

Group I:

Control group (0.5% Na.CMC suspension p.o)

Group II:

Capsicum annuum extract(50 mg/kg,p.o)

Group III:

Capsicum annuum extract (100 mg/kg.p.o)

Group IV:

Combination of Metformin (100 mg/kg.p.o) + Capsicum annuum extract (100 mg/kg).

GroupV:

Combination of Metformin (50 mg/kg.p.o) + Capsicum annuum extract (100 mg/kg).

Group VI:

Metformin (100 mg/kg.p.o)

Pharmacokinetic study:

Single dose study

The studies were carried out in diabetic albino rats (weighing about 180-230g).they were housed in elevated wire cages with free access to food and water ad libitum. The overnight fasted rats were divided in to six different groups (n=6);and the treat was given as mentioned above. Post- dosing the blood samples were collected at predetermined intervals of 1,2,4,8,12 and 24 hinto micro-centrifugal tubes containing sodium citrate from retro-orbital sinus under,mild ether anesthesia. The blood was subjected to centrifugation at 3000 rpm for 10 min and plasma was stored at -200C until analysis.

Multiple dose study:

The diabetic rats were divided into 6 different treatment groups same as mentioned above and the treatment was carried for 21 days(3 weeks).blood samples were collected from different groups on 0,7,14,21st day immediately after treatment. Blood samples were collected in to micro-centrifugal tubes containing sodium citrate from retro-orbital sinus under,mild ether anesthesia. The blood was subjected to centrifugation at 3000

rpm for 10 min and plasma was stored at -200 C until analysis.

Pharmacodynamic study in diabetic rats

Single dose study:

Determination of different biochemical parameters in Diabetic rats

Adults albino rats weighing 180-250g with fasting serum glucose >150 mg/dl are considered as diabetic. The treatment was given as mentioned above. Different biochemical parameters like serum glucose, cholesterol, urea concentrations are measured at different time intervals of 0, 1, 2, 4, 8, 12 and 24h by using semi auto analyzer. These values are considered as acute study values.

Multiple dose study:

The diabetic rats were divided into 6 different treatment groups same as mentioned above and the treatment was carried for 21 days(3 weeks).Different biochemical parameters like glucose, cholesterol, urea concentrations of the overnight fasted rats were determined on 1,7,14,21 st day using semi auto analyzer.[9-13]

Statistical analysis:

- All data are expressed as mean+Sd. For comparison amongst different groups, One-way analysis of variance (ANOVA) followed by Dunnet test was performed. P value less than 5% (P <0.05) was considered to be statistically significant.
- Pharmacokineticdata was calculated by using pk solver software and statistical analysis was done by INSTANT graph pad software.[14]

Histopathological studies

- After the last blood glucose estimation, the rats were sacrificed and pancreas were excised and subjected to histopathological studies to determine the inflammatory and necrotic changes. The tissues were stained using H&E stain and observed under 100 × magnifications. The volume of islet cells in pancreas was determined using eyepiece reticule following point count method using the formula.[15]

$$\text{Volume of islets (mm3)/Volume of tissue (mm3)} = \frac{\text{Number of points on the islets}}{\text{Total number of points in the reticule}} \times 100$$

RESULTS

Table1: Blood Glucose levels at 0th,1st,2nd,4th,8th, 12th and 24thHour after oral administration of Capsicum annuum, Metformin and combination of Metformin + Capsicum annuum in diabetic rats (n=6)

TIME (Hours)	TREATMENT (Single dose study)					
	Diabetic Control	Capsicum annuum (Dose in mg/kg)		Metformin (Dose in mg/kg)	Metformin + Capsicum annuum (Dose in mg/kg)	
	Vehicle	100	50	100	100 + 100	50 + 100
	BLOOD GLUCOSE LEVEL (mg/dl)					
0	402.1±10.4	412.03±9.8	391.8±5.9	411.3±3.15	403.15±6.15	397.13±5.16
1	461.4±7.43	407.2±1.19**	362.7±8.3**	374.5±4.15**	372.14±11.3**	362.15±5.15**
2	463.8±5.15	343.1±11.2**	363.3±6.5**	362.11±1.25**	354.14±9.01**	352.14±6.14**
4	425.5±6.92	334.4±11.2**	364.2±3.1**	353.11±2.41**	352.14±6.14**	344.61±3.15**
8	423.1±7.3	298.51±2.3**	272.3±7.3**	262.21±3.4**	253.13±8.03**	242.15±5.12**
12	413.7±5.4	314.8±7.1**	294.4±6.2**	257.77±1.23**	248.19±6.13**	237.71±5.64**
24	414.8±9.3	329.4±4.2**	301.9±4.5**	262.51±4.13**	254.12±11.14**	237.14±9.13**

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)

n - number of animals used.

Table 2: Blood Cholesterol levels at 0th,1st,2nd,4th,8th, 12th and 24thHour after oral administration of Capsicum annuum, Metformin and combination of Metformin + Capsicum annuum in diabetic rats (n=6)

TIME (Hours)	TREATMENT (Single dose study)					
	Diabetic Control	Capsicum annuum (Dose in mg/kg)		Metformin (Dose in mg/kg)	Metformin + Capsicum annuum (Dose in mg/kg)	
	Vehicle	100	50	100	100 + 100	50 + 100
	BLOOD GLUCOSE LEVEL (mg/dl)					
0	199.3±11.4	205.4±8.4	203.13±10.3	209.13±8.22	196.16±9.21	196.2±10.33
1	201.1±11.2	201.4±8.4	195.11±13.4	193.53±4.21	186.16±6.15	185.5±9.14
2	203.14±6.31	184.3±3.3**	182.32±5.11**	175.13±.1.13**	175.33±.4.53**	174.14±4.35**
4	204.32±10.2	175.4±6.4**	171.42±6.5**	163.13±1.54**	154.21±4.75**	154.21±5.23**
8	203.9±4.15	147.1±6.6**	143.13±5.4**	140.14±10.54**	136.21±7.14**	131.12±10.15**
12	208.5±8.12	154.12±5.1**	151.42±7.1**	132.12±7.03**	131.16±6.52**	129.14±5.64**
24	212.2±6.4	174.04±7.5**	169.61±1.1**	145.24±10.16**	136.13±5.24**	135.16±10.24**

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)

n - number of animals used.

Table 3: Blood Urea levels at 0th,1st,2nd,4th,8th, 12th and 24thHour after oral administration of Capsicum annuum, Metformin and combination of Metformin + Capsicum annuum in diabetic rats (n=6)

TIME (Hours)	TREATMENT (Single dose study)					
	Diabetic Control	Capsicum annuum (Dose in mg/kg)		Metformin (Dose in mg/kg)	Metformin + Capsicum annuum (Dose in mg/kg)	
	Vehicle	100	50	100	100 + 100	50 + 100
	BLOOD UREA LEVEL (mg/dl)					
0	195.4±11.4	205.6±8.2	205.15±11.9	208.14±10.24	198.16±10.25	196.4±10.84
1	201.2±11.4	200.5±8.3	195.13±13.5	193.53±3.24	186.14±5.15	185.4±9.14
2	202.13±5.35	183.4±3.4**	180.34±5.6**	179.13±.1.19**	175.33±.4.51**	173.15±4.35**
4	202.34±10.4	173.9±6.4**	171.43±6.4**	164.13±1.54**	155.23±4.74**	154.21±5.25**
8	202.8±6.14	148.2±6.5**	145.11±5.3**	141.12±10.54**	136.23±7.14**	132.12±10.15**
12	208.9±8.19	154.15±5.5**	151.43±7.4**	132.15±7.06**	130.18±6.53**	129.18±5.64**
24	213.4±6.3	178.06±7.5**	169.64±1.9**	145.25±10.19**	136.16±5.23**	135.18±10.25**
0	195.4±11.4	205.6±8.2	205.15±11.9	208.14±10.24	198.16±10.25	196.4±10.84

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)

n - number of animals used.

Table 4: Blood Glucose levels at 0th,7th, 14th and 21st day after oral administration of Capsicum annuum, Metformin and combination of Metformin + Capsicum annuum in diabetic rats (n=6)

TIME (Day)	TREATMENT (Multiple dose study)					
	Diabetic Control	Capsicum annuum (Dose in mg/kg)		Metformin (Dose in mg/kg)	Metformin + Capsicum annuum (Dose in mg/kg)	
	Vehicle	100	50	100	100 + 100	50 + 100
	BLOOD GLUCOSE LEVEL (mg/dl)					
0	409.13±3.66	415.28±1.4	394.12±1.9	403.12±5.65	385.53±7.26	191.22±5.22
7	394.18±5.8	238.23±1.3**	231.14±1.2**	213.64±7.81**	213.12±4.64**	203.19±6.15**
14	385.19±3.16	184.33±1.8**	155.13±2.5**	145.62±8.91**	138.15±5.22**	129.04±8.58**
21	391.32±1.3	133.15±2.5**	122.64±1.6**	118.16±5.93**	113.83±4.11**	103.24±7.05**

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)

n - number of animals used.

Table 5: Blood Cholesterol levels at 0th,7th, 14th and 21st day after oral administration of Capsicum annuum, Metformin and combination of Metformin + Capsicum annuum in diabetic rats (n=6)

TIME (Day)	TREATMENT (Multiple dose study)					
	Diabetic Control	*Capsicum annuum* (Dose in mg/kg)		Metformin (Dose in mg/kg)	Metformin + *Capsicum annuum* (Dose in mg/kg)	
	Vehicle	100	50	100	100 + 100	50 + 100
	BLOOD CHOLESTEROL LEVEL (mg/dl)					
0	193.22±10.4	188.43±5.1	181.14±10.2	178.16±6.12	171.13±7.94	166.05±7.14
7	194.81±9.2	105.16±8.2**	103.15±7.4**	104.53±5.33**	95.25±5.1**	93.12±4.62**
14	186.73±8.33	85.24±8.93*	85.74±8.1**	75.08±7.15**	71.65±4.33**	64.53±8.13**
21	191.4±6.55	72.38±9.6**	71.68±8.4**	65.85±8.02**	59.86±7.61**	54.85±4.93**

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)

n - number of animals used.

Table 6: Blood Urea levels at 0th,7th, 14th and 21st day after oral administration Capsicum annuum, Metformin and combination of Metformin

TIME (Day)	TREATMENT (Multiple dose study)					
	Diabetic Control	Capsicum annuum (Dose in mg/kg)		Metformin (Dose in mg/kg)	Metformin + Capsicum annuum (Dose in mg/kg)	
	BLOOD UREA LEVEL (mg/dl)					
0	69.16±3.44	66.14±7.18	67.29±2.24	63.18±7.54	61.14±2.82	58.19±4.33
7	74.48±8.32	42.18±1.55**	38.41±5.08**	35.64±4.29**	31.48±1.18**	30.28±5.03**
14	79.54±8.66	33.18±6.41**	32.08±7.08**	28.09±3.84**	25.45±7.09**	21.05±8.63**
21	83.04±5.24	32.68±7.25**	32.48±7.53**	26.15±5.33**	20.22±5.06**	19.08±2.04**

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)

n - number of animals used.

Table 7. Mean plasma Metformin concentrations (µg/ml) (Single dose study).

Time(Hr)	LD+M	HD+M	M	DC
1	27.54	12.88	27.92	0
2	26.98	18.38	49.81	0
4	25.05	13.22	18.93	0
8	11.53	8.32	14.83	0
12	6.83	5.02	7.34	0
24	0	0	0	0

Table 8. Various pharmacokinetic parameters after single oral administration of Metformin alone, Metformin+low dose of Capsicum annuum and Metformin + High dose of Capsicum annuum in diabetic rats .

parameter	Unit	M	LD	HD
ka	1/h	0.95±0.03	0.56±0.12*	0.58±0.32
ke	1/h	0.21±0.03	0.23±0.03	0.27±0.09
t1/2	h	3.36±0.27	3.15±0.32	2.95±1.17
V/F	(mg/kg)/(µg/ml)	22.66±0.82	29.33±3.35	37.94±16.18*
CL/F	(mg/kg)/(µg/ml)/h	4.70±0.23	6.48±0.33**	8.85±0.51**
Tmax	h	2.07±0.07	2.69±0.19**	2.74±0.46**
Cmax	µg/ml	1.44±0.04	0.95±0.07**	0.68±0.07**
AUC 0-t	µg/ml*h	9.52±0.29	6.87±0.40**	4.98±0.47**
AUC 0 - ∞	µg/ml*h	10.67±0.50	7.76±0.39**	5.67±0.33**

Table 9. Volume of islet cells in pancreas in different groups under dynamic study.

Group	Volumne of islets (mm3/mm3) / Volume of pancreas (mm3/mm3)
control	0.085 ± 0.004
Capsicum annuum (100 mg/kg, p.o.)	0.193 ± 0.055
metformin (100 mg/kg, p.o.)	0.131 ± 0.009
metformin (50 mg/kg, p.o.) + Capsicum annuum (30 mg/kg, p.o.)	0.147 ± 0.044
metformin (100 mg/kg, p.o.) + Capsicum annuum (30 mg/kg, p.o.)	± 0.039

DISCUSSION:

Pharmacodynamic study:

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

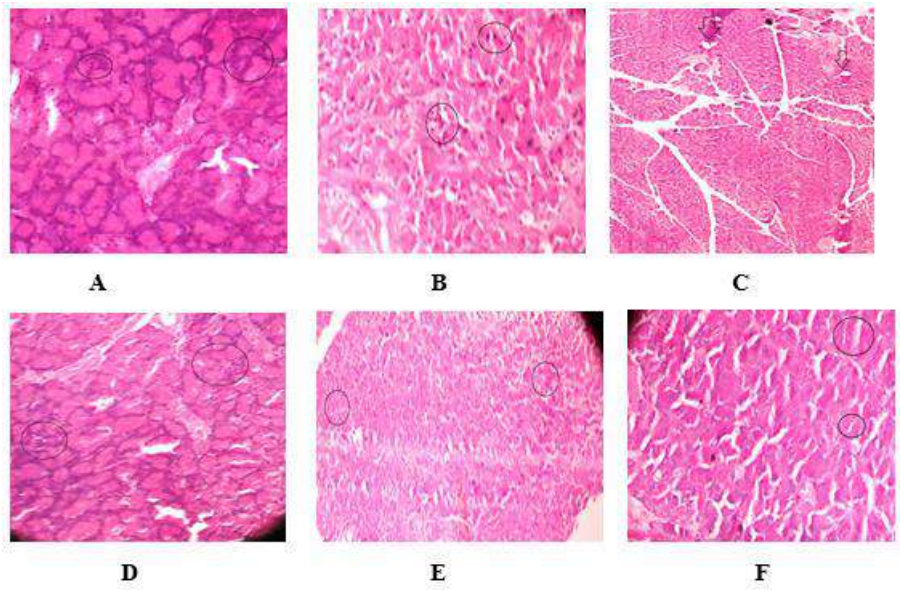
Pharmacokinetic study:

The Single dose study shows that, 96% decrease in AUC(0 - ∞) in 100mg/kg of Capsicum annuum and 50mg/kg of Metformin, 97% decrease AUC (0 - ∞) in 100mg/kg of Capsicum annuum and 50mg/kg of Metformin when compared with the 50mg/kg of Metformin group. C max was decreased by 91% in 100mg/kg of Capsicum annuum and 50mg/kg of Metformin, 99% in 100mg/kg of Capsicum annuum and 50mg/kg of Metformin in single dose study when compared

with the 5mg/kg of Metformin group. Significant decrease in absorption rate constant Ka by about 60% in Lower dose of 100mg/kg of Capsicum annuum and 50mg/kg of Metformin, 81% in 100mg/kg of Capsicum annuum and 50mg/kg of Metformin when compared with the 5mg/kg of Metformin group. Significantly increase in clearance 2% in 100mg/kg of Capsicum annuum and 2.5mg/kg of Metformin. 5.45% in 500mg/kg of Capsicum annuum and 50mg/kg of Metformin compared to 50mg/kg Metformin when compared with the 50mg/kg of Metformin group. The multiple dose study shows that, 96% decrease in AUC(0 - ∞) in 100mg/kg of Capsicum annuum and 50mg/kg of Metformin. 98% decrease AUC(0 - ∞) in 100mg/kg of Capsicum annuum and 50mg/kg of Metformin when compared with the 50mg/kg of Metformin group. C max was decreased by 88% in 500mg/kg of Capsicum annuum and 50mg/kg of Metformin, 96% in 100mg/kg of Capsicum annuum and 50mg/kg of Metformin in multiple dose study when compared with the 50mg/kg of Metformin group. Significant decrease in absorption rate constant Ka by about 58% in Lower dose of 100mg/kg of Capsicum annuum and 50mg/kg of Metformin, 76% in 100mg/kg of Capsicum annuum and 50mg/kg of Metformin when compared with the 50mg/kg of Metformin group. Significantly increase in clearance 4% in 100mg/kg of Capsicum annuum and 50mg/kg of Metformin. 10% in 100mg/kg of Capsicum annuum and 50mg/kg of Metformin compared to 50mg/kg Metformin group. The exact reason behind the reduction in pharmacokinetic parameters was unknown but, it was understood that the combination of Metformin extract 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. The histological study shows that the combination therapy (Metformin + Capsicum annuum) involved in the increase the number of islets and recovered the partially damaged B cells in pancreas when compare to the Individual treatment.

Histological study:

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



H&S Staining of Pancreatic islets of Diabetic Control, Capsicum annuum alone Metformin alone and combination of Capsicum annuum & Metformin treated Diabetic Rats. 6A. diabetic control , 6B. 100mg of Capsicum annuum 6C. 100mg Capsicum annuum, 6D.50mg of Metformin.6E.100mg of Capsicum annuum. +50mg of Metformin, 6F. 100mg of Capsicum annuum +50mg of Metformin.

Slide A shows that pancreatic cells were damaged due to development of diabetes from STZ. Figure 6B shows that few pancreatic cells were damaged due to Metformin. Figures 6C,6D,6E, 6F shows that B cells are regenerated in pancreatic tissue. Normal ß-cells were observed in low and high doses of Metformin and Capsicum annuum. (Slides: 6D&6F). In the Metformin group more damaged ß-cells as compared with the 100mg of Capsicum annuum +50mg of Metformin and 100mg of Capsicum annuum +50mg of Metformin (Figures: 6B,6C&6E). 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 study Capsicum annuum was decrease the absorption and increase the clearance of Metformin. Hence care must be taken when the combination is taken by diabetic patients.

CONCLUTION

The interaction appears to be pharmacokinetic interaction at absorption, elimination. Capsicum annuum inhibits the absorption of Metformin that results in a significant decrease in the bioavailability of the later and combination group with a lower dose of Metformin and increment to the volume of islets in pancreas is observed in combination group when compare to individual treatment. Since the interaction was seen in rats it is likely to occur in humans leading to decreased activity of Metformin 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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