Original Article

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EFFECT OF ETHANOLIC EXTRACT OF PIPER CUBEBA LINN. FRUITS ON ACTIVITY OF PIOGLITAZONE

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Abstract

Herb-drug interaction about Oral antidiabetic drugs is a challenging concept, since the consumption of food and other herbal drugs is not documented in diabetic patients profile. Present work was designed with an objective to investigate any possible effect of herbal drug Piper cubeba Linn. fruits on Pioglitazone-Oral antidiabetic drug. Albino male wistar Rats were made diabetic using Alloxan monohydrate 180 mg/ kg and divided into 4 groups of 6 animals each.Group II, Group-III and Group-IV were administered with Ethanolic extract of Piper cubeba Linn. fruits, EtPCLF (400 mg/kg), Pioglitazone and EtPCLF +Pioglitazone 10mg/kg respectively. All the 4 groups were tested with intraperitoneal glucose tolerance test (IPGTT) by administering glucose (2.5%) intraperitoneally and decrease in blood glucose concentration was determined in each group using glucometer. EtPCLF enhanced the activity of Pioglitazone and significantly lowered Blood glucose concentration in EtPCLF + Pioglitazone treated group when compared to Pioglitazone alone treated group. Hence EtPCLF enhances the activity of Pioglitazone.

Key words: Herb-Drug Interaction, Piper cubeba, Pioglitazone, IPGTT, Glucometer.

Introduction

Diabetes mellitus is a common metabolic disorder characterized by hyperglycaemia, glycosuria, polyurea and polydipsia induced by insulin deficiency and insulin resistance. Recent estimates indicate that there were 171 million people in world with Diabetes in year 2000 and this may be projected to increase to 366 millions by 2030. Diabetes mellitus is treated by using Oral hypoglycemic agents such as Sulphonyl Ureas. Biguanides, Meglitinides and Alpha glucosidase inhibitors[1]. Traditional medicines like herbal drugs in primary form or their extracts have been used by many diabetic patients as they are assumed to be non –toxic in nature[2] but pharmacologically active constituents such as alkaloids, flavanoids , anthraquinones etc found in the herbs or their extract can take part in herb-drug interactions[3] .

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Herb-drug interaction about antidiabetic drugs is a challenging concept, since the consumption of food and other herbal drug is not documented on patients profile. Thus the main objective of the present study is to find out any possible Herb-drug interaction occurs between the Ethanolic extract of Piper cubeba Linn.fruits (EtPCLF) and Pioglitazone – a thiazoli--dinedione derivative.

Materials and Methods

Apparatus

Soxhlet Apparatus, Glucometer.

Drugs

Alloxan monohydrate obtained from Research Lab Fine Chemical Industries. Mumbai. Pioglitazone Hcl obtained from Dr.Reddy's Laboratories Pvt.Ltd

Plant material

Piper cubeba Linn. fruits was purchased from local market. Plant material was identified and authenticated by Botanist, Department of Botany, MVS Degree College, Mahbubnagar.

Preparation of extract

The shade dried coarsely powdered fruits of Piper cubeba Linn (400 gms) was extracted with ethanol as solvent by Continuous hot extraction process using Soxhlet apparatus. Extraction was continued till the completion of extraction and the extract was concentrated under reduced pressure. Ethanolic extract was stored in an airtight container in a refrigerator below 10 ° c.

Animals used

Healthy Albino male wistar Rats weighing between 180-220 gms were used for the present study. Animals were kept in cages and fed with standard commercial diet and water *ad libitum*. The experiment protocol was approved by Institutional ethics committee of Smt. Sarojini Ramulamma College of Pharmacy, Mahbubnagar.

Experimental design

Albino male wistar Rats were randomly divided into 4 groups with 6 animals in each group and 180 mg/kg Alloxan monohydrate was administered intraperito-neally to induce diabetes in Rats ,after 48 hours blood was withdrawn from the cut tail tip of Rats and Blood glucose level was measured using Glucometer. Animals showing more than 200 mg/dl were called Diabetic and were selected for the study. Group -I was administered with Glucose 2.5 % i.p, Group - II was administered with EtPCLF 400mg/kg given for 7 days, Group-III was administered with Pioglitazone 10 mg/kg, Group-IV was administered with EtPCLF 400 mg/kg for seven days followed by Pioglitazone on the day of test .An intraperitoneal glucose tolerance test (IPGTT) was carried out in overnight fasted diabetic animals to determine glucose tolerance [4].

Blood was withdrawn at the start of experiment, half an hour after drug administration, Glucose (2.5%) was administered to animals by intraperitoneal route and the Blood Glucose Level was estimated at 0 min, 2 hours, and 4 hours after glucose administration.The data obtained was expressed as Mean ± S.D .Results were analysed statistically by one way ANOVA followed by Tukey-Kramer Multiple Comparisons Test.

Table 01: Effect of EtPCLF and Pioglitazone on Blood Glucose Concentration in Alloxan induced Diabetic Rats after IPGTT

Group	Treatment	Blood Glucose Concentration (mg/dl)			
		Before glucose administration	After glucose administration		
			O hrs	2 hrs	4 hrs
I	Glucose (2.5%)	310.94±9.09	471.66±10.37	454.49±10.57	461.34±7.57
II	Extract treated (400 mg/kg)	310.37±12.56	467.13±6.89	465.39±7.1	464.49±14.89
III	Pioglitazone (10 mg/kg) treated	376.17±15.21	442.5±18.66	526.25±7.97	413.66±4.11
IV	Extract + Pioglitazone (10mg/kg)treated	345.55±16.51	425.50±13.63	505.36±11.97*	454.22±10.45**

Values are Mean ± S.D, n=6,
Statistical analysis by One-way ANOVA followed by Tuckey Kramer Multiple comparision test.
*P values < 0.01 when compared to Pioglitazone alone treated group.
** P values < 0.001 when compared to Glucose alone treated group.

Results

In a group treated with EtPCLF + Pioglitazone, a significant lowering (P<0.01) of blood glucose concentration was seen when compared to Pioglitazone alone treated groups at 2 hours as shown in the Table 01. At 4 hours, the group treated with EtPCLF + Pioglitazone has shown a significant lowering (P<0.001) of blood glucose concentration when compared to glucose alone treated group. Thus the EtPCLF and Pioglitazone treated group has shown a decrease in blood glucose levels at 0, 2 and 4 hours but more precisely the glucose tolerance was shown at 2 hours as shown in the Table 01.

Discussion

Pioglitazone is an insulin sensitizer acting primarily on Peroxisome proliferator activated receptor subtype gamma type (PPAR-γ) [5,6] against insulin resistance. Pioglitazone enhances tissue sensitivity to insulin rather than stimulating insulin secretion. Alloxan decreases the insulin sensitivity and decreases the glucose uptake of cells. Blood glucose level of EtPCLF alone treated group when compared to Glucose alone (Control) treated group showed no significant change which clearly indicates that EtPCLF as such doesn't have any antihyperglycemic activity.

The blood glucose concentration of EtPCLF +Pioglitazone treated group when compared to Pioglitazone alone treated group has shown significant reduction in blood glucose level which clearly indicates that the decrease in blood glucose level was due to synergistic effect of EtPCLF on Pioglitazone. As earlier reported the combinative therapy with 4-Hydroxyisoleucine and Pioglitazone proved beneficial than Pioglitazone alone treated group[7] and the risk of administration of Carica papaya extract with oral hypoglycemics which led to Hypoglycemic condition [8] but the present studies has not shown any hypoglycemic condition but shown antihyperglycemic action . Enhanced antihyperglycemic action of EtPCLF treated Pioglitazone group over Pioglitazone alone treated group may be due to metabolic inhibition of Pioglitazone in intestine by the EtPCLF as Pioglitazone is metabolized by CYP3A4 and CYP2C8 [9, 10] and EtPCLF inhibits CYP3A4 enzymes [11] , thus leading to Herb-Drug interaction .

Conclusion

Administration of Ethanolic extract of Piper cubeba Linn. fruits with Pioglitazone led to herb drug interaction and augmented the antihyperglycemic activity of Pioglitazone significantly. Thus it is necessary to adjust the dose of Pioglitazone when it is administered with Piper cubeba fruits to minimize the adverse effects of Pioglitazone.

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