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Prevention of Pioglitazone Induced Weight Gain by Co Administration of Piperine

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Authors' contributions

This work was carried out in collaboration between all authors. Authors BMB and VLC designed the study and involved in experimental part. Authors BMB and RR wrote the protocol, and wrote the first draft of the manuscript. Author RNA supported and supervised the literature searches, analyses of the study and experimental process. All authors read and approved the final manuscript.

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ABSTRACT

Aim: Diabetes is the most common and one of the leading causes of mortality among non communicable diseases. Pilogitazone is the potent PPARr agonist used for the treatment of diabetes. The drug is associated with a substantial weight gain. The aim of this present study is to try to reduce the drug associated weight gain by co-administration with Piperine.
Methods: Alloxan induced diabetic model was taken as experimental method. After induction of diabetes (except in Group I), animals were classified into five groups, Group I and II were not given with any treatment and they served as normal control and diabetic control groups respectively. Group III, IV and V were given with Pioglitazone (2 mg/Kg PO), Piperine (2 mg/Kg PO) and co-administration of both at 2 mg/Kg PO respectively for 4 weeks. After completion of 4 weeks, the

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blood samples of the animals were estimated for the glucose levels to analyze the diabetic action and the lipid profile along with observation of body weight, food intake and water intake to analyze weight gain.
Results: There was a good control over the blood sugar levels in all the treated groups (≈ 120 mg/dL) except in diabetic control group (330.0±9.661 mg/dL). Along with a control over diabetes, Piperine and Pioglitazone treated animals resulted in reduced lipid profiles and not much increase in weight gain (1.243±0.137%) when compared to monotherapy of Pioglitazone (8.818±0.846%).
Conclusion: Co administration of Piperine in diabetic treatment with Pioglitazone may be a beneficial attempt to reduce weight gain.

Keywords: Diabetes; pioglitazone; piperine and weight gain.

1. INTRODUCTION

Type 2 diabetes is an important metabolic disorder. Its incidence in countries like India and China is on rise [1]. Even after the availability of lot of hypoglycemic agents, still there is a search for appropriate therapy for diabetes.

Pioglitazone is a PPARγ (Peroxisome Proliferator Activator γ Receptor agonist) and is used in type 2 diabetes treatment [2]. Pioglitazone is a new member of glitazones family. They target peroxisome proliferator activated receptors- γ of adipose tissue and liver and enhance the insulin sensitivity in muscle and liver and thus reduces glucose levels. It is associated with a weight gain which through the generation of metabolically active adipocytes [3] and also by stimulating the lipid metabolism [4]. PPARγ agonists are the new and hot solutions for the neurodegenerative disorders also [5]. Pioglitazone was reported to prevent age related dysfunction of vascular tissue by the up regulation of telomerase [6]. It is expected to cross the blood brain barrier and is presently identified for its beneficial effects in memory enhancement [7], in autism and alzheimer's along with improved sensitivity for insulin [8] and reduces depressive symptoms [9]. Weight gain in diabetic patients is the major drawback of Pioglitazone as this obesity further accelerates diabetes and even the cardiovascular diseases [10]. Instead of investigating the new agents it is beneficial and economic to combine the existing agents for therapy. In this scenario the present research was aimed to prevent the drug induced weight gain of Pioglitazone by co-administration of natural spice Piperine.

2. MATERIALS AND METHODS

2.1 Materials

Pioglitazone was a kind gift sample from Dr. Reddy's laboratories, Bachupally, Hyderabad. Piperine, Alloxan monohydrate and Carboxy methyl cellulose were from SD Fine chemicals, Mumbai. All the other chemicals and reagents used were of analytical grade and were from the local sources.

2.2 Animal Experiments

Male albino mice weighing 30-40g (age group of 10-14 weeks) were used for the study. The animals were maintained at 12 H light and dark cycles at a temperature of 25±2ºC. The study protocol was approved by the Institutional Animal Ethics Committee of Swami Ramananda Tirtha Institute of Pharmaceutical Sciences (SRTIPS/FM/1468/PO/a/11/CPCSEA/108/2013) and conducted according to the CPCSEA guidelines on the use and care of experimental animals. The mice were divided into V groups (n=6). After 2 weeks of acclimatization, the mice were subjected to 12 H fasting. All the mice except in Group I (Control) were administered with Alloxan monohydrate at a single dose of 120 mg/Kg [11] by intra peritoneal route to induce diabetes. The mice were observed for 2 weeks with regular feed and dextrose. With the determination of blood glucose levels the mice were considered to be diabetic, if the blood glucose levels are more than 120 mg/dL. Group I and II were not given with any treatment and they served as normal control and diabetic control groups respectively. Group III, IV and V were given with Pioglitazone (2 mg/Kg PO), Piperine (2 mg/Kg PO) and co-administration of both at 2 mg/Kg PO respectively for 4 weeks.

2.3 Measurement of Food and Water Intake

On 16th day the food and water intake were measured by finding the difference in the weight of food and volume of water during 24H duration.

2.4 Measurement of Body Weight

On weekly basis, the mice were recorded for their differences in weights by using analytical balance.

2.5 Blood Collection and Bioassays

All the blood samples were collected from the overnight fasted mice. Blood samples for the estimation of blood sugar levels were obtained from tail vein by puncturing with sterile needle and were estimated by using one touch glucometer. Blood samples for lipid profiles were obtained on the last day of treatment by retro orbital puncture from the vein behind the eye sockets. The collected blood was estimated for serum cholesterol (SC), high density lipoprotein (HDL) and low density lipoprotein (LDL) by using commercially available kits (Accucare Lab care Diagnostics Pvt limited, India).

2.6 Statistical Analysis

The obtained data was statistically treated by ANOVA (Dunnet's multiple comparison) by using Graph Pad Prism Ver. 6.03.

3. RESULTS

In the present research the results of blood glucose levels (Fig. 1) were treated with ANOVA for significance. The overall interaction of within groups and weeks was found to be significant ($F(12, 75) = 51.68$ at $p<0.0001$). In both the Pioglitazone and Piperine groups the glucose levels were less than the diabetic control group. The animals given with the combination of both have shown still controlled levels of blood glucose.

In this present investigation, from the results of food and water intake (Fig. 2), there is an increase in both the intake in diabetic mice (14.97±0.28 and 10.38±0.74) when compared to normal control mice (6.91±0.24 and 6.20±0.19). With the treatments both the food and water intake were decreased and were almost near to the values of control group.

From the study of body weight changes it was observed that, there was a 0.35±0.12% of weight gain in control group and 3.06±0.17% weight loss in diabetic control group. The interesting and significant ($F(8, 50) = 28.3$ at $p<0.0001$) observation was found in Pioglitazone group where there was almost an average of 8.81±0.84% weight gain in mice. With treatment of Piperine alone there was a weight gain up to 0.78±0.10%. There was a control over the weight gain induced by Pioglitazone with co administration of Piperine and was found in mice as a weight gain of 1.24±0.13%.

The observation of lipid levels (Fig. 3) shows that with Pioglitazone monotherapy, without much change in HDL, cholesterol and LDL levels were increased to 133.33±5.77 mg/dL and 73.5±5.03 mg/dL. The mice co-administered with Piperine, there was a significant ($F(8, 50) = 23.4$ at $p<0.0001$) control over the levels of serum cholesterol and LDL but not up to the levels in control group mice.

4. DISCUSSION

Of the estimated global deaths, the maximum are due to non communicable diseases and among them diabetes is responsible for considerable deaths [12]. Even after the establishment of well known statistics, suitable therapy for diabetes is still questionable. In the present investigation the results of blood glucose levels significantly indicated that, the control over diabetes in all the treated groups. Being PPARγ agonist Pioglitazone increases the utilization of glucose and thus reduced levels in blood [13]. Piperine is a pungent nitrogenous substance and natural antioxidant proven in literature for decreased endoplasmic reticulum stress and increased insulin signaling [14]. Thus even in the Piperine treated group there was also a considerable decrease in the blood glucose levels. There was an increase in body weight in monotherapy with Pioglitazone. This may be due to the effect of it on adipocytes. It also stimulates the genes responsible for increased utilization of glucose in adipose tissue and thus promotes the rapid differentiation of adipocytes and converts the large type hypertropic adipocytes to small type adipocytes to increase insulin activity through PPARγ activation. Thus it is also responsible for increased levels of adipocytokines and as a result, there will be gain in body weight [15]. It also causes fluid retention and thus increased body weight [10]. Only 6-11% of patients will be having the problem of edema/ fluid retention [16]. All these may be the reasons for the increased body weight in mice treated with Pioglitazone. With the induction of diabetes, both the hunger and thirst of animals are going to increase. The decreased intake in the treated groups in comparison to diabetic control group is an

indicative of controlled diabetes. Increase in body weight and lipid levels with Pioglitazone therapy in diabetes is the major problem. Hyperlipidemia and hypercholestremia are the two major problems in diabetic patients and are going to invite the vascular complications. Obesity in LDL oxidation is an important mechanism for the consequences of atherosclerosis and other vascular problems. Natural principles have earlier been shown to be better antioxidants by binding to the LDL and preventing it from oxidation [17]. Obesity induces the oxidative stress by increasing the mitochondrial reactive oxygen species which in turn may cause the insulin resistance [18]. Piperine was reported to inhibit oxidation of human low density lipoprotein in vitro [19]. It regulates the levels of adiponectin and other signaling molecules which play important role in lipogenesis and fatty acid oxidation. It also decreases the expression of lipogenic target genes [20]. Piperidine alkaloids are proved to activate the lipid transfer proteins and fat burning proteins and thus reduce the fat accumulation in body [21]. Pharmacological inhibition of acyl CoA diacylglycerol acyltransferase has emerged as a potential therapy for the treatment of obesity. Piperine is considered potential acyl CoA diacylglycerol acyltransferase inhibitor [22]. These may be the reasons for the control over body weight gain in mice co administered with Piperine.

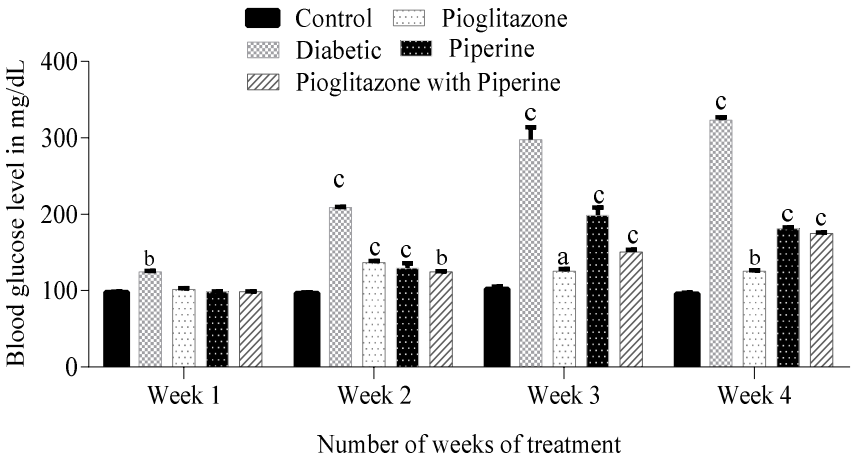

Fig. 1. Blood glucose levels in various groups of animals (a indicates the significance at *P*>0.05, b at *P*<0.05 and c at *P*<0.01)

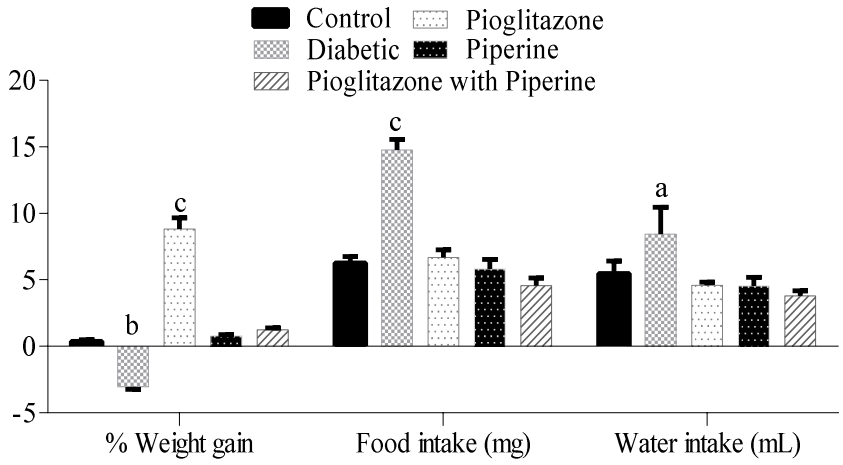

Fig. 2. % weight gain, food and water intake during the study (a indicates the significance at *P*>0.05, b at *P*<0.05 and c at *P*<0.01)

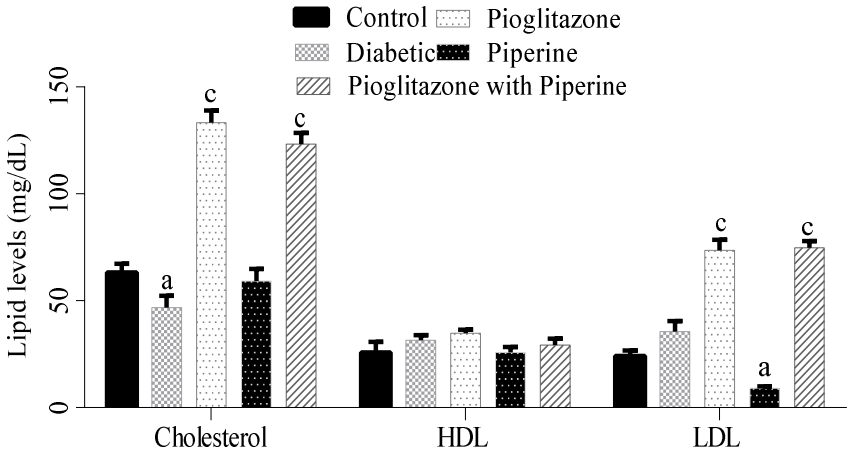

Fig. 3. Serum lipid levels after the study period of 4 weeks (a indicates the significance at *P*>0.05, b at *P*<0.05 and c at *P*<0.01)

5. CONCLUSION

Apart from the antidiabetic activity Pioglitazone was proved in literature for its beneficial effects. The adverse effect of weight gain and further complications can be prevented with co-administration of antioxidants like Piperine.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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