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Research Article
Antidiabetic Activity of 1-(4-Chlorobenzylidene)-5-(2-oxoindolin-3-ylidene) Thiocarbohydrazone in Chick Model

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Abstract

Background and Objective: The rat and mouse models were generally used to screen the new compounds for the antidiabetic activity. There is a high need to discover the alternative animal models to reduce the cost of experimentation. This study, implemented the existed chick model for the screening of new compound for antidiabetic activity. The present study was aimed to evaluate the antidiabetic activity of selected indole derivative 1-(4-Chlorobenzylidene)-5-(2-oxoindolin-3-ylidene) thiocarbohydrazone using chick diabetes model. **Methodology:** Diabetes was induced in chicks by administration of alloxan monohydrate on the 14th day of incubation at a dose of 0.9 mg/egg, which was confirmed with birth of chicks with elevated blood glucose levels when compared with those of chicks without any alloxan treatment. One way ANOVA was used to analyze the data. **Results:** After administration of test compound, it was found that the significant reduction in the glucose levels with a doses of 10 and 30 mg kg^{-1} doses. **Conclusion:** Selected indole derivative 1-(4-Chlorobenzylidene)-5-(2-oxoindolin-3-ylidene) thiocarbohydrazone showed significant antidiabetic activity.

Key words: Chick, diabetes model, 1-(4-Chlorobenzylidene)-5-(2-oxoindolin-3-ylidene) thiocarbohydrazone, indole, isatins

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Diabetes mellitus (DM) is a common metabolic disorder characterized by hyperglycemia that develops as a consequence of defects in insulin synthesis or secretion and or insulin resistance. Type 2 diabetes encompasses individuals who have insulin resistance (IR) and usually relative (rather than absolute) insulin deficiency. The chronic diabetes may leads to both microvascular and macrovascular complications. Chronicity of hyperglycemia is associated with long-term damage and failure of various organ systems mainly affecting the eyes, nerves, kidneys, and the heart (standards of medical care in diabetes care-2016)[1].

Isatin and its analogs are versatile substrates, and are used in organic synthesis and they are used in evaluating new product that possesses different biological activities. Literature survey revealed that isatin (1H-indole-2,3-dione) possesses diverse chemotherapeutic activities, such as anticancer[2] anti-HIV[3], anti-bacterial[4], anti-inflammatory[5] and anti-convulsant[6]. Among these properties, cytotoxic and anti-proliferative activities of this moiety have been found to be interesting. It has been reported in the literature that compounds bearing 1,3,4-oxadiazole ring possess significant biological properties such as anticancer[7] activities. In view of the biological importance of these isatin or indole derivatives, it was selected 1-(4-Chlorobenzylidene)-5-(2-oxoindolin-3-ylidene) thiocarbohydrazone for possible evaluation for the antidiabetic activity using chick diabetic model. Implementation of this chick model not only reduces the cost of experiment but also helps in enlightening to the scientists about alternative models.

MATERIALS AND METHODS

This experiment was carried out in the laboratories of the Institution in February, 2017. The method used in the experiment was adopted from Reddy *et al.*[8].

Test compound: 1-(4-Chlorobenzylidene)-5-(2-oxoindolin-3-ylidene) thiocarbo-hydrazone was selected for the evaluation of antidiabetic activity and its synthesis, characterization, antioxidant and antimicrobial activity of this compound was reported[9]. The compound is solubilized in dimethyl sulfoxide (DMSO) and is insoluble in water (Fig. 1).

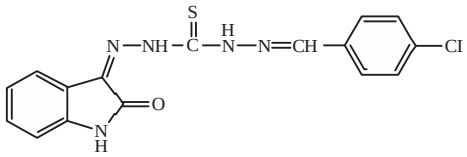

Fig. 1: 1-(4-Chlorobenzylidene)-5-(2-oxoindolin-3-ylidene) thiocarbohydrazone

Preparation of test suspension: As the compound is insoluble in water, suspension of test compound was prepared using standard methods and gum tragacanth used as suspending agent. A test concentration of 10 and 30 mg mL^{-1} were prepared and used for the study.

Chemicals: Alloxan monohydrate (Sigma, St Louis, U.S.A), glibenclamide (Gift sample, Dr. Redyy's, Hyderabad), methanol (E-Merck, Mumbai, India), sod CMC (Central drug house, New Delhi).

Evaluation of anti-diabetic activity in chick model:

Induction of diabetes in Chicks: Fertile eggs of (30/60 g) country chicken were obtained and incubated for 14 days (99°F,87% humidity) in a suitable incubator. On the 14th day of incubation, small holes were made on the shells using driller and then the toxic drug alloxan at a dose of 0.9 mg/egg was injected into the each egg under sterile conditions. A control group of 6 eggs were maintained. After alloxan/vehicle injection, holes were closed using plaster or tape, then eggs were incubated for another 7 days. On the 21st day chicks come out from eggs. After few days, glucose levels were estimated by taking the blood from tip of finger using chem strip method[8,10]. Blood glucose levels were found as greater than 300 mg dL^{-1} were considered as hyperglycemic when compared with the normal levels (230.8±13.9). This indicated the successful induction of diabetes in chicks.

Study design: All the fasting (for 12 h) diabetic chicks were divided into four groups with each group with six chicks (n=6).

- **Group I:** Chicks served as control and treated with (1 mL kg^{-1}, p.o) of 0.5% sod CMC.
- **Group II:** Served as diabetic/disease control and received 0.5% sod CMC (1 mL kg^{-1}, p.o)
- **Group III:** Diabetic chicks treated with MEHB at a dose of 10 mg kg^{-1}, (p.o)
- **Group IV:** Diabetic chicks treated with MEHB at a dose of 30 mg kg^{-1}, (p.o)
- **Group V:** Diabetic chicks treated with standard, glibenclamide (2.5 mg kg^{-1}, p.o)[11]

Table 1: Mean±SD of blood glucose levels (mg dL^{-1}) after administration of test compound in chick model

Group/time	0 h	1 h	3 h	5 h
Normal control	225.8±18.6	225.2±17.4	229.1±20.8	231.5±21.5
Diabetic control	450.7±27.1	451.4±27.8	453.7±30.5	455.6±29.4
Test compound (10 mg kg^{-1})	453.7±32.1	418.7±32.8** (7.8%)	382.6±27.9** (15.7%)	319.0±17.5** (29.6%)
Test compound (30 mg kg^{-1})	456.0±35.7	401.3±29.9** (12.1%)	354.7±29.5** (22.4%)	280.5±25.7** (38.6%)
Glibenclamide (2.5 mg kg^{-1})	469.5±28.6	325.1±20.9** (30.75)	241.5±15.7** (48.56)	201.4±16.0** (57.10)

All the values of Mean±SD, n = 6, **p<0.01 vs diabetic control, In brackets % reduction of glucose levels were mentioned

Blood samples were collected at 0, 1, 3 h of after test drug administration and analyzed for blood glucose levels using strip method.

Statistical analysis: All the experimental values were expressed as Mean±SD (N = 6). One-way analysis of variance (ANOVA) and Dunnett's test were used to compare means from the control group and each of the test groups and the statistical significance was judged at the 0.05 probability level.

RESULTS AND DISCUSSION

The physical data of the 1-(4-Chlorobenzylidene)-5-(2-oxoindolin-3-ylidene) thiocarbohydrazone was found as 357 as molecular weight, 138-140^{0}C as melting point, $C_{16}H_{12}ClN_5OS$ as molecular formula and 54% percentage of yield.

The test compound showed the moderate antidiabetic activity and was found to be as dose dependent manner. The results were showed in Table 1. Administration of test compound a doses of 10 and 30 mg kg^{-1} to diabetes chicks produced a significant reduction in the blood glucose levels in a dose dependant manner ($p<0.01$). The significant glucose levels were reduced ($p<0.01$) after 1 h of administration of test compound. The maximum reduction of blood glucose levels were observed at 5th h i.e., 29.6 and 38.6% with doses of 10 and 30 mg kg^{-1}, respectively (Table 1).

Diabetes mellitus is a chronic disorder caused by partial or complete insulin deficiency, which produces inadequate glucose control and leads to acute and chronic complications. Alteration in the serum lipid profile is known to occur in diabetes and this is likely to increase the risk of coronary heart disease[12]. Glucose control is essential, but this provides only minimal benefit with respect to CHD prevention. An ideal treatment for diabetes would be a drug that not only controls the glycemic levels but also prevents the development of arteriosclerosis and other complications of diabetes[13].

Diabetes mellitus is considered as one of the 5 leading causes of death in the world[14]. Alloxan (2, 4, 5, 6,-Tetraoxypyrimidine, 2, 4, 5, 6-Pyrimidinetetrone) is an oxygenated pyrimidine derivative[15]. Alloxan is toxic glucose analogue, when administered to rats and many other species like chicks, which selectively destroys insulin-producing beta cells in the pancreas resulting in insulin-dependent diabetes mellitus (alloxan diabetes) with characteristics similar to type 1 diabetes in humans[15]. It was also previously used this chick model for the evaluation of antidiabetic activity of methanolic extract of *Hiptage bengalensis* leaves[16].

The present study results indicated the dose dependant antidiabetic activity of test compound in chick model. Some studies to investigate whether diabetes model can be made by treatment of STZ in chick embryos and this model can be used to predict the effect of drug[10]. Administration of alloxan (0.6 mg/30 g egg) into the egg sac at 14th days of incubation resulted in the development of chicks with diabetic condition and the blood glucose levels were found greater than 300 mg dL^{-1}. This indicated the successful induction of diabetes in chicks. Administration of test compounds at doses of 10 and 30 mg kg^{-1} to these diabetic chicks reduced the fasting blood glucose levels ($p<0.01$) to near normal range (Table 1). This model was successfully used for the screening of compound for the antidiabetic activity and further research and focus has to be needed on this model.

CONCLUSION

It is concluded that the chick model was successfully used for the screening of 1-(4-Chlorobenzylidene)-5-(2-oxoindolin-3-ylidene) thiocarbohydrazone for the antidiabetic activity and the compound was found with moderate activity. Further research is required to purify the compound and to screen the compound for the antidiabetic activity in a systematic method in various animal models.

SIGNIFICANCE STATEMENTS

The study discovers the alternative animal models for the screening of the synthetic and natural compounds for the antidiabetic activity. This study supports the chick model as an alternative screening model for the evaluation of antidiabetic activity. This study will help the researchers to uncover the critical areas of alternative animal models that many

researchers were not able to explore. Thus a new model on chicks may be arrived at.

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