Antidiabetic effect of 2-(4-[(2-hydroxyacetyl benzyl) ketoamino]-phenyl amino-methyl)- hydrobenzophenon on Alloxan induced rats

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ABSTRACT
Diabetes Mellitus is known as a syndrome, a collection of disorders with high blood glucose level & glucose intolerance as its feature, either because of insulin deficiency or insulin impairment or both. Diabetes Mellitus, based on insulin, is broadly classified into two types. Type one indicates the distraction of pancreatic β - cells that leads to diabetes mellitus, in which insulin is necessary to prevent ketoacidosis, coma, death. Type two diabetes is characterized by disorders of insulin resistance & secretion. Male Wistar albino rats with an average weight of 180-250 g were used in this study. With a 12 hours’ light and dark period, they were kept under normal conditions (room temperature 24-27°C and humidity 60-65 %). The free access of drinking water & pellet diet to male Wistar albino rats was allowed, as per the CPCSEA guidelines. Anti-diabetic activity of Compound 2-(4-[(2-hydroxyacetyl benzyl) ketoamino]-phenyl amino-methyl)- hydrobenzophenon, male Wistar albino rats were divided into four different groups. 1ml of blood samples were collected directly into anticoagulant bottles from the tail vein & later plasma was collected after centrifugation. Blood sugar levels were determined by spectrophotometer. There was a significant decrease in blood sugar levels in Alloxan + Glibenclamide and Alloxan + Compound groups on compared to control. The present self-funded study concludes that antidiabetic activity of 2-(4-[(2-hydroxyacetyl benzyl) ketoamino]-phenyl amino-methyl)- hydrobenzophenon in Alloxan induced diabetic rats significantly shows decreed blood sugar levels when compared to the control group.

INTRODUCTION
Diabetes Mellitus, a disease as old as mankind, is a collection of disorders with high blood glucose level and glucose intolerance as its feature, either because of insulin deficiency or insulin impairment, or both. Diabetes Mellitus classified into two types. A few other types are less predominant and are categorized as hereditary, endocrine, exocrine pancreatic, and diabetes mellitus caused by medications. (Care, 2020)

In India, it is estimated that presently 77 million individuals are affected by this deadly disease,
which is likely to go up to 134 million by the year 2045 (Kannan, 2020). Diabetes Mellitus of all types can lead to complications in the body and increase premature death. Kidney malfunction, gangrene lead to limb amputation, loss of vision, and nerve injury are possible risks. Adults with diabetes mellitus may have a two to three times higher chance of strokes and heart attacks. Poorly controlled diabetes mellitus in pregnancy raises the risk of fetal death and other complications. In millions of cases around the world, these symptoms are seen. Diabetic retinopathy, which happens due to damage to the eye’s blood vessels, can be attributed to about 3 percent of global blindness. Kidney disease is also among the leading causes of diabetes mellitus. Nerve damage and reduced blood flow to the limbs may lead to foot ulcers, limb amputation may result from related infections and complications in diabetes mellitus. (Faselis et al., 2020)

Type 1 diabetes mellitus cannot be prevented at present. Appropriate approaches are available to prevent type 2 diabetes mellitus. These include policies and practices around whole communities and particular contexts (school, home, workplace) that lead to good health for all, irrespective of whether they have Diabetes, such as daily exercise, balanced diet, smoke cessation, blood pressure & lipid control. Early detection is the starting point for living well with diabetes mellitus; the longer a person lives with undiagnosed and untreated diabetes mellitus, the worse will be their health. In primary health care facilities, convenient access to blood sugar testing should be available. For complications, patients will require regular specialist examination or care. (Care, 2019)

Insulin and several oral antidiabetic agents, such as sulfonylureas, meglitinides, biguanides, thiazolidinediones, glucosidase inhibitors, DPP-4 & SGLT2 inhibitors, and other oral antidiabetic agents are currently available for the treatment of Diabetes mellitus and have some severe side effects (Shrestha et al., 2017). Therefore, there is a growing interest in natural and novel synthetic anti-diabetic remedies due to their efficacy, minimum clinical adverse effects. Herbal medicines or their extracts are commonly prescribed even though their biologically active compounds are unclear (Samad et al., 2009)

To collect knowledge about different pathological disorders, animal models are commonly used. Several animal models of Diabetes mellitus have been developed so far. It is important for an animal model of Diabetes mellitus to be able to mirror the pathogenesis of diabetes mellitus. The most widely used compounds for the induction of type 1 diabetes mellitus are alloxan and streptozotocin chemical substances. (Radenković et al., 2016)

In preclinical and clinical studies to cure diabetes mellitus, plant extracts and drugs have been evaluated. Apart from these, several chemically synthesized compounds with reducing adverse effects have also been tested for diabetes mellitus. Many novel synthetic biological activity compounds have been seen previously. Vanadyl complex of p-hydroxyl aminophenol derivatives, vanadium compound Bis ((5-hydroxy-4-oxo-4Hpyran-2-yl) methyl benzoatato) oxovanadium (IV) and 2-Hydroxy 4-methoxy benzoic acid (HMBA) isolated from the roots of Hemidemus indicus were tested for anti diabetic activity. (Wei and Yang, 2012)

We have reported earlier that the of 2-((2-hydroxyacetetyl benzyl) ketoamino]-phenyl amino-methyl)-hydrobenzophenon has acute anti-diabetic activity. The present research was done to demonstrate the effect of 2-(4-((2-hydroxyacetetyl benzyl) ketoamino]-phenyl amino-methyl)-hydrobenzophenon on long term anti-diabetic activity.

MATERIALS AND METHODS

Animals
Male Wistar albino rats with an average weight of 180-250 g were used in this study. With a 12 hours’ light and dark period, they were holding under normal conditions (room temperature 24-27 degree centigrade and humidity 60-65 percent). The free access of drinking water and pellet diet to male Wistar albino rats was allowed, as per the CPCSEA guidelines. The experimental study got approval from the institutional animal ethical committee (Reg.No 04/NMC/2017).

Induction of Diabetes
In male Wistar albino rats, diabetes was induced by intraperitoneal administration of water-dissolved Alloxan (single dose of 150 mg/kg b.w.). After 72 hours, rats with marked hyperglycemia (P250 mg/dl fasting blood glucose) were selected and included in the study.

Drugs
To evaluate the antidiabetic activity, compound 2-(4-((2-hydroxyacetetyl benzyl) ketoamino]-phenyl amino-methyl)-hydrobenzophenon compounds was used. The compound was synthesized and procured from the Chemistry department, Sri Venkateswara University, Tirupati, Andhra Pradesh, India.

Grouping of animals
For the long-term studies (30 days) anti-diabetic
Table 1: Long term studies (30 days) anti diabetic activity of 2-(4- [(2-hydroxyacetyl benzyl) ketoamino]-phenyl amino-methyl)- hydrobenzophenon - 60 mg on Alloxan induced rats

| Blood sugar levels | 0 day       | 15 day      | 30 day      |
|--------------------|-------------|-------------|-------------|
| Group              | Mean ± SD   | Mean ± SD   | Mean ± SD   |
| I - Control        | 91.7±2.04   | 90.5±1.64   | 90.98±1.35  |
| II - Control + Compound C 60 mg/kg b.w, p.o | 90.07±0.82 | 91.43±4.7 | 91.33±3.88 |
| III - Alloxan      | 281.5±6.6   | 264.33±4.32 | 264.33±4.32 |
| IV - Alloxan + Compound C 60 mg/kg b.w, p.o | 278.5±7.82 | 161.50±6.66 | 126.8±4.11 |
| V - Alloxan + Glibenclamide 20 mg/kg p.o b.w | 287.5±4.32 | 151.83±3.76 | 115.5±4.81 |

ANOVA: followed by the Tukey multiple comparison tests, at 0.05*, 0.01**, 0.001*** level of significance < 0.001 compared with the 0 day blood sugar level.

The present research is conducted to assess the anti-diabetic activity of 2-(4- [(2-hydroxyacetyl benzyl) ketoamino]-phenyl amino-methyl)- hydrobenzophenon on Alloxan induced male Wistar albino rats. The outcome of the study reveals compound 60 mg/kg b.w significantly decreased the blood sugar levels when compared to control and did not develop any hypoglycemic activity.

Three new aminophenol-derivatized nitrilotriacetic acid vanadyl complexes (VOohpada, VOmhpada, VOphpada) were synthesized and demonstrated antidiabetic action by Wang et al. (2015). The anti-diabetic action of bis((5-hydroxy-4-oxo-4H-pyran-2-yl)methyl benzoatato) oxovanadium (IV) in streptozoticin induced diabetic rats was stated by Wei and Yang (2012), Mahalingam Gayathri documented antidiabetic activity in streptozoticin-induced diabetic rats of 2-Hydroxy 4-methoxy benzoic acid isolated from the roots of Hemidemus indicus (H. indicus). (Gayathri and Kannabiran, 2009). Xing-hua Zhang et al. tested 19 β-acetamide ketones in vitro anti-diabetic activity, demonstrated relatively low activity. (Zhang et al., 2011).
Escandón-Rivera et al. reported that due to the high activity of metabolites such as 6-hydroxyethyl-5-hydroxy-2,2-dimethyl-2H-chromene, brickellia cavanillesii has a hypoglycaemic effect. (Escandón-Rivera et al., 2012). Yan-Yan Ma et al. demonstrated antidiabetic activity of compound 5 among 19 phenolic compounds isolated from the flower of E. gardneri in streptozotocin induced diabetic mice (Ma et al., 2015). The antidiabetic properties of N(1)-2,4-dihydroxybenzylidene-N(4)-2-hydroxybenzylidene-S-methylthiosemicarbazidato in streptozotocin induced diabetic rats were reported by Yanardag et al. (2009). Thus stating that hydroxyacetyl, benzyl, aminomethyl, hydroxy benzyl groups have antidiabetic activity in accordance with the present study.

CONCLUSION

The present self-funded study concludes that antidiabetic activity of 2-(4-[(2-hydroxyacetyl benzyl) ketoamino]-phenyl amino-methyl)- hydrobenzophenon in Alloxan induced diabetic rats significantly shows decreased blood sugar levels when compared to the control group. Further extensive pre-clinical research should be done to evaluate this compound’s safety and efficacy as an antidiabetic agent.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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