Anti-diabetic effect of Biological activities of 2-(4-[(2-hydroxy benzyl) amino]-phenyl amino-methyl)-phenol derivatives on Alloxan induced rats

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ABSTRACT

The word diabetes describes a category of metabolic disorders characterised and defined by hyperglycemia in the absence of therapy. Type 1 & 2 diabetes mellitus are two main types. It is now widely accepted that failure or loss of pancreatic (beta) cells is the underlying common feature of all types of diabetes. In this study, male Wistar albino rats of approximate weighing 180-250 g were used. Compound 2-(4-[(2-hydroxy benzyl) amino]-phenyl amino-methyl)-phenol derivatives were used to assess the anti-diabetic activity. Derivatives such as hydroxyl amino, acetyl keto, and hydro benzophenone groups are derivatives and are further studied for the screening of anti-diabetic activity. Diabetes was produced by intraperitoneal administration of Alloxan in male Wistar albino rats. Rats were divided into 12 groups of six in each group. The outcomes of the study reveal compound C - 60 mg/kg shows significance in decreasing the blood sugar level when compared to control. A significant effect on blood sugar levels was shown by glibenclamide 20 mg/kg. The study concludes that Biological activities of 2-(4-[(2-hydroxy benzyl) amino]-phenyl amino-methyl)-phenol derivatives of compound C - 60 mg/kg has high blood sugar-lowering activity.

INTRODUCTION

The word diabetes describes a category of metabolic disorders characterised and defined by hyperglycemia in the absence of therapy. Type 1&2 diabetes mellitus are two main types. Historically the difference between the two groups is based on age at first, degree of depletion of (beta) -cell action, degree of resistance to insulin, and the presence of diabetes-related autoantibodies & survival insulin therapy requirements (Leslie et al., 2016).

Diabetes can have hallmark symptoms such as thirst, polyuria, blurring of vision, and weight loss. Often there are genital infections of yeast. The most extreme health sign was ketoacidosis, a non-ketotic hyperosmolar state leads to starvation, coma, and death in the absence of appropriate care. Hyperglycemia is sufficient to induce pathological and functional changes that can occur well before a diagnosis, resulting in complications being present at diagnosis (Zimmet et al., 2001).

Diagnostic tests for diabetes mellitus usually are required, fasting plasma glucose, two-hour post-
load glucose in plasma following a 75 grams’ oral glucose tolerance test, HbA1c & blood glucose at random in the presence of diabetes symptoms & signs. Persons with fasting glucose in plasma values of up to 7.0 millimoles per litre (126 milligrams per deciliter), two-hour post-load glucose in plasma up to 11.1 millimoles per litre (200 milligrams per deciliter), HbA1c up to 6.5 per cent (48 millimoles per mole) or random blood glucose up to 11.1 millimoles per litre (200 milligrams per deciliter) are considered to have diabetes in the presence of signs and symptoms (Güemes et al., 2016).

The prevalence of diabetes globally is projected at 9.3 per cent in 2019 (463 million persons). It is projected to increase to 10.2% by 2030 (578 million) & 2045, 10.9 per cent (700 million). In urban areas, the prevalence is larger (10.8%) than in rural areas (7.2%), And in countries with high incomes (10.4%) than in countries with low incomes (4.0%). One in two people living with diabetes (50.1 per cent) is unaware of having diabetes. In 2019, The worldwide incidence of impaired glucose tolerance was estimated at 7.5 per cent (374 million) and was projected to reach 8.0 per cent (454 million) by 2030 and 8.6 per cent (548 million) by 2045 (Saeedi et al., 2019).

It is now widely accepted that failure or loss of pancreatic β (beta) cells is the underlying feature common to all types of diabetes. Several factors may lead to a decrease in function or damage to β (beta)-cells; these cells are not replaced because the human pancreas is unable to regenerate β (beta)-cells after 30 years of age. Such pathways include hereditary predisposition and defects, cycles of epigenetics, tolerance to insulin, autoimmunity, related infections, inflammation & environmental factors. Differentiating β (beta)-cell malfunction & β (beta)-cell mass decreased may have significant consequences for therapeutic strategies to control or improve glucose tolerance. Comprehension β (beta)-cell status will help identify diabetes subtypes and guide care (Skyler et al., 2017).

In clinical trials for diabetes treatment, a significant number of extracts from crude plants were evaluated. Apart from these, several chemically synthesised compounds with declining side effects have also checked for diabetes (Izzo and Ernst, 2001). Many novel synthetic compounds for biological activities have been seen previously. The anti-diabetic activity of the aryl-oxy-propanolamines based on chalcone was tested (Satyanarayana et al., 2004). The current research was conducted to show the antihyperglycemic activity of 2-(4-[(2-hydroxy benzyl) amino]-phenyl amino-methyl) phenol derivatives.

**MATERIALS AND METHODS**

**Animals**

In this study, male Wistar albino rats of approximate weighing 180-250 g were used. They were kept under (24-27°C room temperature and 60-65 per cent humidity) conditions with a light & dark period for 12 hours. Ad libitum, food was available in the form of dried pellets & water as per CPCSEA guidelines. The experimental study got approval from the institutional animal ethical committee (Reg.No 04/NMC/2017).

**Drugs**

Compound 2-(4-[(2-hydroxy benzyl) amino]-phenyl amino-methyl)-phenol derivatives were used to assess the anti-diabetic activity. The compound derivatives were synthesised and procured from the Chemistry department, Sri Venkateswara University, Tirupati, Andhra Pradesh, India. Derivatives such as hydroxyl amino, acetyl keto, and hydro benzophenone groups are derivatives and are further studied for the screening of anti-diabetic activity.

1. (Compound A): 2-(4-[(2-Dihydroxybenzylimine) amino]-phenyl amino-methyl)-phenol
2. (Compound B): 2-(4- [(2-hydroxyacetyl benzyl) ketoamino]-phenyl amino-methyl)-phenol
3. (Compound C): 2-(4- [(2-hydroxyacetyl benzyl) ketoamino]-phenyl amino-methyl)- hydrobenzophenon

**Induction of Diabetes mellitus**

Diabetes was induced by intraperitoneal administration of Alloxan in male Wistar albino rats (single dose of 150 mg/kg bw), dissolved in water. After 72 hr rats with hyperglycemia (fasting blood glucose P250 mg/dl) were selected and used for the study.

**Grouping of animals (each group six rats)**

1. Group 1: Control (Normal saline-treated rats)
2. Group 2: Diabetic control (Alloxan induced treated rats)
3. Group 3: Alloxan + Compound A - 20 mg /kg b.w p.o
4. Group 4: Alloxan + Compound B - 20 mg /kg b.w p.o
5. Group 5: Alloxan + Compound C - 20 mg /kg b.w p.o
6. Group 6: Alloxan + Compound A - 30 mg /kg b.w p.o
7. Group 7: Alloxan + Compound B - 30 mg /kg b.w p.o
8. Group 8: Alloxan + Compound C - 30 mg /kg b.w p.o
9. Group 9: Alloxan + Compound A - 60 mg /kg b.w p.o
10. Group 10: Alloxan + Compound B - 60 mg /kg b.w p.o
11. Group 11: Alloxan + Compound C - 60 mg /kg b.w p.o
12. Group 12: Alloxan + Glibenclamide 20 mg /kg, b.w p.o

Blood samples (0.1 ml) were obtained from the tail vein for blood glucose assessment at 0, 1, 2, 3, 4, 5, & 6 h after administration of compounds, and Dextrostix (glucose oxidase method) with the Simple One Touch Accuchec Glucometer was used to calculate blood glucose levels. The findings were compared to those of the 12th group (20 mg Glibenclamide/kg) of rats.

RESULTS AND DISCUSSION

Table 1 shows the Anti-diabetic effect of Biological activities of 2-(4-[[2-hydroxy benzyl] amino]-phenyl amino-methyl)-phenol derivatives of 20 mg on Alloxan induced rats, Alloxan Vs. A, B, C are significance. & A, B, C - 20 Vs. Glibenclamide is significant. Compared with the 0 hr blood sugar levels compounds A, B, C and Glibenclamide significant reduction in blood sugar levels. Compound A, B & C – 45.4%, 39.1%, 47.9% maximum blood sugar lowering effect at 6 hr and Glibenclamide 30 % at 5hr.

Table 2 shows the Anti-diabetic effect of Biological activities of 2-(4-[[2-hydroxy benzyl]amino]-phenyl amino-methyl)-phenol derivatives of 30 mg on Alloxan induced rats, Alloxan Vs. A, B, C are significance. & A, B, C - 30 Vs. Glibenclamide is significant. Compared with the 0 hr blood sugar levels compounds A, B, C and Glibenclamide significant reduction in blood sugar levels. Compound A, B & C – 43.1%, 40.1% and 45.6% maximum blood sugar lowering effect at 6 hr and Glibenclamide 29.8 % at 5hr.

Table 3 shows the Anti-diabetic effect of Biological activities of 2-(4-[[2-hydroxy benzyl] amino]-phenyl amino-methyl)-phenol derivatives of 60 mg on Alloxan induced rats, Alloxan Vs. A, B, C are significance. & A, B, C - 60 Vs. Glibenclamide is significant. Compared with the 0 hr blood sugar levels compounds A, B, C and Glibenclamide significant reduction in blood sugar levels. Compound A, B & C – 45.4%, 39.1%, 47.9% maximum blood sugar lowering effect at 6 hr and Glibenclamide 30 % at 5hr.

Table 1, 2 and 3 relived anti-diabetic effect of Biological activities of 2-(4-[[2-hydroxy benzyl] amino]-phenyl amino-methyl)-phenol derivatives. Comparatively, compound C – 60 mg/kg has a higher decreeing activity of sugar and significance with the Alloxan group.

The current research is conducted to assess the anti-diabetic effect of 2-(4-[[2-hydroxy benzyl]amino]-phenyl amino-methyl)-phenol derivatives on the biological function of Alloxan-induced rats. The outcomes of the study reveal compound A, B, and C lowered blood sugar levels significantly as compared to control and Alloxan, Glibenclamide. However, Compound C 60 mg/kg showed significance action highly in decreasing the blood sugar level when to compare to Alloxan. Glibenclamide 20 mg/kg had a significant effect on levels of blood sugar.

The blood sugar levels of Alloxan induced diabetic rats were significantly higher than those of normal untreated rats. In Alloxan induced rats, compounds A, B & C did not develop any hypoglycemic activity.

At a dosage of 20 mg/kg, compound A, B & C had a 38.4 per cent, 35.2 per cent and 44.0 per cent maximum blood sugar control effect in rats caused by Alloxan after 6 hours of therapy. Treatment of Alloxan rats with Glibenclamide at a dosage of 20 mg/kg demonstrated a peak decrease in blood sugar of 30.3 per cent after 5 hours.

After 6 hours of treatment, compound A, B & C produced 43.1 per cent, 40.1 per cent, and 45.6 per cent maximum blood sugar lowering effect in Alloxan induced rats at a dose of 30 mg/kg. Treatment of Alloxan rats with Glibenclamide at a dosage of 20 mg/kg showed a maximum decrease in blood sugar of 29.8 per cent after 5 hours.

At a dose of 60 mg/kg, compound A, B & C produced 45.4 per cent, 39.1 per cent & 47.9 per cent at 6 hours of treatment, respectively, the maximum blood sugar lowering effect in rats induced by Alloxan. Treatment of Alloxan rats with Glibenclamide at a dosage of 20 mg/kg demonstrated a maximum decrease in blood sugar of 29.8 per cent after 5 hours.
Table 1: Anti-diabetic effect of Biological activities of 2-(4-[(2-hydroxy benzyl) amino]-phenyl amino-methyl)-phenol derivatives 20 mg/kg b.w on Alloxan induced rats

| Time | Group | 0hr Mean ± SD | 1hr Mean ± SD | 2hr Mean ± SD | 3hr Mean ± SD | 4hr Mean ± SD | 5hr Mean ± SD | 6hr Mean ± SD |
|------|-------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
|      | Normal| 108 ±         | 110 ±         | 106 ±         | 105 ±         | 110 ±         | 106 ±         | 108 ±         | Alloxan vs. A, B, C - 20 mg/kg p.o |
|      | Alloxan| 271 ±         | 264 ±         | 253 ±         | 253 ±         | 241 ±         | 243 ±         | 248 ±         | 5.02 mg/kg b.w p.o *** |
|      | A - 20 mg/kg p.o| 20.4| 259 ±         | 138 ±         | 2.4 ±         | 3.2 ±         | 2.48 ±        | 11.41 ±       | 20 mg/kg b.w p.o *** |
|      | B - 20 mg/kg p.o| 284 ±         | 263 ±         | 241 ±         | 204 ±         | 187 ±         | 191 ±         | 175 ±         | 4.46 mg/kg b.w p.o *** |
|      | C - 20 mg/kg p.o| 3.1| 3.33 ±        | 2.45#         | 4.55#         | 4.2#         | 2.64#         | 2.93#         | 105 ±         | 4.38 mg/kg b.w p.o *** |
|      | Glibenclamide 20 mg/kg p.o| 271 ± | 242 ±        | 238 ±         | 212 ±         | 199 ±         | 189 ±         | 207 ±         | 110 ±         | 7.41 mg/kg b.w p.o *** |
|      | C - 30 mg/kg p.o| 273 ± | 254 ±        | 222 ±         | 186 ±         | 158 ±         | 181 ±         | 153 ±         | 3.18 mg/kg b.w p.o *** |
|      | B - 30 mg/kg p.o| 253 ± | 249 ±        | 221 ±         | 220 ±         | 201 ±         | 181 ±         | 164 ±         | 2.14 mg/kg b.w p.o *** |
|      | A - 30 mg/kg p.o| 20.8| 21.4 ±       | 3.71#         | 2.32#         | 3.44#         | 2.58#         | 2.73#         | 2.14 mg/kg b.w p.o *** |
|      | Normal| 108 ±         | 110 ±         | 106 ±         | 104 ±         | 106 ±         | 107 ±         | 110 ±         | 4.68 mg/kg b.w p.o *** |
|      | Alloxan| 271 ±         | 263 ±         | 252 ±         | 255 ±         | 242 ±         | 243 ±         | 253 ±         | 1.55 mg/kg b.w p.o *** |
|      | A - 30 mg/kg p.o| 290 ± | 251 ±        | 237 ±         | 215 ±         | 202 ±         | 171 ±         | 165 ±         | 0.82 mg/kg b.w p.o *** |
|      | B - 30 mg/kg p.o| 265 ± | 255 ±        | 212 ±         | 184 ±         | 174 ±         | 164 ±         | 158 ±         | 0.89 mg/kg b.w p.o *** |
|      | C - 30 mg/kg p.o| 285 ± | 249 ±        | 246 ±         | 192 ±         | 187 ±         | 171 ±         | 155 ±         | 1.26 mg/kg b.w p.o *** |
|      | Glibenclamide 20 mg/kg p.o| 272 ± | 243 ±        | 237 ±         | 212 ±         | 200 ±         | 191 ±         | 207 ±         | 2.59 mg/kg b.w p.o *** |

ANOVA, followed by the multiple comparison test of Tukey, at < 0.05*, < 0.01**, < 0.001*** level of significance.

*Percentage (%) of the blood sugar-lowering effect in the respective group, compared with the 0 hr blood sugar level.

Table 2: Anti-diabetic effect of Biological activities of 2-(4-[(2-hydroxy benzyl) amino]-phenyl amino-methyl)-phenol derivatives 30 mg/kg b.w on Alloxan induced rats

| Time | Group | 0hr Mean ± SD | 1hr Mean ± SD | 2hr Mean ± SD | 3hr Mean ± SD | 4hr Mean ± SD | 5hr Mean ± SD | 6hr Mean ± SD |
|------|-------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
|      | Normal| 107 ±         | 109 ±         | 106 ±         | 104 ±         | 106 ±         | 107 ±         | 110 ±         | Alloxan vs. A, B, C - 20 mg/kg p.o |
|      | Alloxan| 271 ±         | 263 ±         | 252 ±         | 255 ±         | 242 ±         | 243 ±         | 253 ±         | 4.46 mg/kg b.w p.o *** |
|      | A - 30 mg/kg p.o| 290 ± | 251 ±        | 237 ±         | 215 ±         | 202 ±         | 171 ±         | 165 ±         | 0.91 mg/kg b.w p.o *** |
|      | B - 30 mg/kg p.o| 265 ± | 255 ±        | 212 ±         | 184 ±         | 174 ±         | 164 ±         | 158 ±         | 0.89 mg/kg b.w p.o *** |
|      | C - 30 mg/kg p.o| 285 ± | 249 ±        | 246 ±         | 192 ±         | 187 ±         | 171 ±         | 155 ±         | 1.26 mg/kg b.w p.o *** |
|      | Glibenclamide 20 mg/kg p.o| 272 ± | 243 ±        | 237 ±         | 212 ±         | 200 ±         | 191 ±         | 207 ±         | 2.59 mg/kg b.w p.o *** |

ANOVA, followed by the multiple comparison test of Tukey, at < 0.05*, < 0.01**, < 0.001*** level of significance.

*Percentage (%) of the blood sugar-lowering effect in the respective group, compared with the 0 hr blood sugar level.
Sirasanagandla et al. revealed significant anti-diabetic activity of oral administration to streptozotocin (STZ) induced rats of 2-[(2-hydroxy benzyl) amino]-phenyl amino-methyl)-phenol at 30 mg/kg dose after diabetes mellitus induced by STZ. Thirty-day care of STZ rats with HBPMP 30 mg/kg resulted in a substantial reduction in their fasting blood sugar (FBS) amounts (Sirasanagandla et al., 2013).

Wang N et al. reported a more powerful insulin enhancement effect on type 2 diabetes mellitus in dB / dB mice it was demonstrated by the vanadyl complex of p-hydroxyl aminophenol derivatives, i.e. vanadyl complex effectively lowered the blood sugar levels, increased glucose tolerance and alleviated stress in type 2 diabetes mellitus in dB / dB mice (Wang et al., 2015).

The novel vanadium compound Bis ((5-hydroxy-4-oxo-4Hpyran- 2-yl) methyl benzoatato) oxovanadium (IV) (BBOV) was synthesised by Wei YB et al. BBOV treatment in STZ induced diabetic rats restored blood glucose levels to standard and increased glucose tolerance (Wei and Yang, 2012).

Mahalingam Gayathri et al. examined the anti-diabetic activity of 2-Hydroxy 4-methoxy benzoic acid (HMBA) isolated from the roots of Hemidemus indicus (H. indicus) for its anti-diabetic activity in streptozotocin (STZ)-induced diabetic rats. The levels of plasma insulin, glycosylated haemoglobin, and liver glycogen were also restored during the administration of HMBA (Gayathri and Kannabiran, 2009).

Beelders, T et al., reported that the extracted benzophenone glucosides of Cyclopa genistoides were tested for their alpha-glucosidase inhibitory activity against an enzyme mixture obtained from rat intestinal acetone powder. A strong dose-response was shown by α-glucosidase inhibitory activity of benzophenones, with higher actions at higher levels of concentration recorded (Beelders et al., 2016). Inference benzophenone has anti-diabetic activity.

### Table 3: Anti-diabetic effect of Biological activities of 2-(4-[(2-hydroxy benzyl) amino]-phenyl amino-methyl)-phenol derivatives 60 mg/kg b.w on Alloxan induced rats

| Time Group | 0 hr Mean ± SD | 1 hr Mean ± SD | 2 hr Mean ± SD | 3 hr Mean ± SD | 4 hr Mean ± SD | 5 hr Mean ± SD | 6 hr Mean ± SD |
|------------|----------------|---------------|---------------|---------------|---------------|---------------|---------------|
| Normal     | 107± 6.2%     | 109± 4.37     | 104± 5.55     | 104± 3.75     | 106± 6.34     | 108± 3.25     | 106± 6.00     |
| Alloxan    | 270± 5.33     | 264± 3.33     | 250± 1.64     | 253± 7.57     | 245± 7.74     | 243± 7.48     | 253± 7.86     |
| A – 60 mg/kg | 273± 6.64     | 256± 5.10     | 210± 1.03#    | 181± 0.82#    | 163± 2.93#    | 151± 3.33#    | 149± 2.51#    |
| B – 60 mg/kg | 266± 5.05     | 252± 4.18#    | 218± 1.64#    | 210± 9.11#    | 179± 5.75#    | 160± 2.90#    | 162± 2.58#    |
| C – 60 mg/kg | 265± 1.17     | 237± 3.44     | 183± 2.00#    | 147± 2.42#    | 145± 3.62#    | 143± 2.53#    | 138± 0.89#    |
| Glibenclamide 20 mg/kg | 273± 5.06     | 243± 2.80     | 237± 2.14#    | 212± 4.05#    | 200± 5.60#    | 191± 5.78#    | 206± 4.67#    |
| Glibenclamide 20 mg/kg | 273± 5.06     | 243± 2.80     | 237± 2.14#    | 212± 4.05#    | 200± 5.60#    | 191± 5.78#    | 206± 4.67#    |

ANOVA, followed by the multiple comparison test of Tukey, at 0.05*, 0.01**, 0.001*** level of significance.

*< 0.001 compared with the 0 hr blood sugar level.

Percentage (%) of the blood sugar-lowering effect in the respective group, compared with the 0 hr blood sugar level.

CONCLUSION

The present self-funded study concludes that Biological activities of 2-(4-[(2-hydroxy benzyl) amino]-phenyl amino-methyl)-phenol derivatives in Alloxan induced diabetic rats, compound A, B & C significantly decreed blood sugar levels. However, compound C has highly significant blood sugar-lowering activity at 60 mg dose when compared to the control group. Further extensive pre-clinical research should be done to evaluate the safety and efficacy of compound C use as an anti-diabetic agent.
Conflict of Interest
In this research, the authors note that they have no conflict of interest.

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