Evaluation of in vivo Antidiabetic Activity of Umbelliferone in Streptozotocin Induced Diabetic Rats

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A B S T R A C T

The first line of treatment in Diabetes mellitus includes the use of oral hypoglycemic agents which are associated with several side effects. Herbal agents are known for their effectiveness due to their fewer side effects and relatively low cost. Umbelliferone, a coumarin has been reported to reduce or decrease blood glucose, elevated plasma insulin, protein profile, and cause hypolipidemic effect. Six groups of rats were used as control, diabetic control, umbelliferone at 20 mg/kg b.wt., umbelliferone at 40 mg/kg b.wt. and combination of glibenclamide and umbelliferone at 20 mg/kg b. wt., was used in the study. Diabetes was induced in male Wistar rats and serum estimation of glucose as well as histological study and Immunohistochemical expression of Insulin in islets was evaluated on 15th, 30th and 45th day of experiment. The control rats showed normal body weight values throughout the experimental period. The diabetic rats showed significant hyperglycaemia with reduced body weight and few insulin positive cells. Whereas, the umbelliferone treated groups showed significant decrease in serum glucose levels as well as increase in the body weight profiles by the end of the experimental period. The umbelliferone treated rats showed improvement in morphology of islets of Langerhans and showed increased insulin positive cells. Thus, our results show that umbelliferone alone (20mg/kg. b. wt. and 40mg/kg. b. wt.) possessed antihyperglycemic properties. The significant improvement in serum glucose levels and histoarchitecture of the islets of Langerhans with increased insulin positive cells in the current study could be attributed to bioactivity of umbelliferone and were statistically comparable with the glibenclamide treated group.

Introduction

Diabetes mellitus (DM) is an annihalatory chronic metabolic disorder that has attained the status of a global pandemic, spreading from affluent industrialized nations to the emerging economies of Asia, Latin America and Africa (Ranjit et al., 2017) which is characterized by increased glucose concentration in the blood leading to altered carbohydrate, protein and fat metabolism. Due to diabetes, patients experience various
vascular complications, such as atherosclerosis, coronary heart disease, retinopathy, nephropathy and neuropathy (Sheetz, 2002). The first line of treatment in DM includes the use of oral hypoglycemic agents. However, they are associated with several side effects and are inadequate to alter the course of diabetic complications (Venkatesh et al., 2010). Insulin therapy is considered to be the only satisfactory approach in DM, though it has several drawbacks like insulin resistance, anorexia, brain atrophy and fatty liver in chronic administration and a sudden burst of hypoglycaemic episodes (Weidmann et al., 1995). Many studies have been carried out to prove the efficacy of herbal extracts in controlling hyperglycemia and in the management of diabetes. In recent years, some of the new bioactive molecules isolated from plants with potential hypoglycemic contents have exhibited antidiabetic activity with more efficacy than oral hypoglycemic agents (Patel et al., 2012).

Herbal agents are prescribed widely because of their effectiveness, fewer side effects and relatively low cost (Venkatesh et al., 2003). Therefore, investigation on such agents from traditional medicinal plants has become more important (Suba et al., 2004). Many traditional plants with anti-diabetic effects have been identified but only a few have been evaluated scientifically for their efficacy. However, the major drawback in the usage of herbal medicine in modern medical practices includes lack of scientific and clinical data proving their efficacy and safety.

Several pieces of research state that coumarins possess a variety of biochemical and pharmacological properties that may be effective against diabetes and its complications, some of which are of potential therapeutic interest (Li et al., 2017). Umbelliferone (UMB), a derivative of coumarin, benzopyrene in nature and is mainly extracted from *Citrus aurantium* (Wu et al., 1992) with 7-hydroxycoumarin as a pharmacologically active agent (Plate 1).

Umbelliferone has been shown to exhibit pharmacological activities against various health-related conditions, including conditions related to pro-oxidants and reactive oxygen species such as inflammation, degenerative diseases, microbial infections, and cancer cells (Mazimba, 2017). The parent compound coumarin has been reported to reduce or decrease blood glucose, elevated plasma insulin, protein profile, and cause hypolipidemic effect (Ramesh and Pugalendi, 2005). UMB’s are also known to enhance insulin sensitivity and promote GLUT4 translocation through the activation of PPARγ (Naowaboot et al., 2015).

With this knowledge, the present study was carried out to evaluate the antidiabetic efficacy of UMB, (a coumarin compound) given alone or in combination and to compare the efficiency with a proven allopathic antidiabetic drug glibenclamide.

**Materials and Methods**

**Animals:** Genetically normal adult male *Wistar albino* rats weighing 170-200 g were procured and were maintained under standard laboratory conditions and offered *ad libitum* of standard commercial rat feed (Amruth Feeds, Bangalore) and clean reverse osmosis drinking water. The experiment was carried out after obtaining permission from Institutional Animal Ethics Committee, Veterinary College, Hebbal, Bengaluru vide Ref No. VCS / IAEC/ 23/ 2017-18 dt 22.12.2017.

**Chemicals:** Streptozotocin (STZ) and Umbelliferone, (Cat No.: H24003) was purchased from Sigma chemicals, USA.
Umbelliferone (7-hydroxycoumarin), Glibenclamide (Glyenil®, 5 mg) was procured from a local chemist. All the other chemicals were of analytical grade obtained from Merck, Trivitron, India and HIMEDIA, India.

**Experimental induction of diabetes mellitus (DM)**

The rats were fasted overnight and injected with freshly prepared streptozotocin (Sigma chemicals, USA) at a dose of 45 mg/ kg b. wt. intraperitoneally in 0.09 M citrate buffer solution procured from M/s Sigma chemicals, USA (Cat- C2488), having a pH 4.5 to induce diabetes mellitus (Babu and Prince, 2004). The control Group I control received citrate buffer alone. The diabetic state was confirmed by estimating the random glucose levels after 72 hours of STZ injection using Accu-chek® (M/s Roche, India) using strips. The blood was collected from the tail vein by using an Insulin syringe bearing 31’ G needle. The animals with a glucose level above 200 mg/dl were considered diabetic and selected for the study.

**Experimental design**

The rats were randomly divided into six different groups with eighteen animals in each as given below. The UMB and glibenclamide were administered orally by a gavaging needle once a day using vehicle solution. The rats of Group I and II were gavaged only with distilled water.

| Group I (NC)          | Normal control: |
|-----------------------|-----------------|
| Group II (DC)         | Diabetic control: R.O water |
| Group III (GC)        | Glibenclamide (GC) @ 600 μg/kg b. wt. |
| Group IV (U-20)       | UMB @ 20 mg/ kg b. wt. |
| Group V (U-40)        | UMB @ 40 mg/ kg b. wt. |
| Group VI (U-20 + GC)  | UMBandGC @ 20 mg/kg body and 600 μg/ kg b. wt. |

To study the progressive effects of the treatments given to different groups, six rats from each group were sacrificed humanly under ketamine anaesthesia on 15th and 30th and the remaining rats on the 45th day of experimentation. Blood samples were collected in both EDTA and serum vacutainer containing clot activator. Several parameters including body weight, AST, ALT and serum glucose were analysed. During necropsy, Pancreatic tissue was preserved using Neutral Buffered Formalin at pH 7.4 and was subjected to histopathology and immunohistochemistry.

**Biochemical estimation**

Serum Glucose was estimated as per the kit manufacturers (Trivitron, Labsystems) protocol.

**Bodyweight**

The rats were weighed on the day of the start of the experiment and on 3rd, 15th, 30th and 45th day of the study before the necropsy.

**Histology**

The representative tissue samples of 3-5 mm thickness were collected in 10 per cent NBF for histopathological examination. The tissues were processed by the routine paraffin embedding technique. Sections of 4 μm thickness were cut and subjected to the H&E staining (Luna, 1968).

**Immunohistochemistry**

The sections of the pancreas were subjected to immunohistochemistry for demonstrating insulin in the β-cells of islets of Langerhans using a mouse monoclonal IgG1k (2D11-H5-Santacruz -sc-8033) antibody raised against amino acids 1-84 representing full-length Insulin. These primary antibodies were detected by (Secondary) mouse IgG kappa binding protein (m-IgGκ BP) conjugated to
Horseradish Peroxidase (HRP) (Santacruz - sc-516102). The tissue sections were subjected to Heat induced epitope retrieval using citrate buffer pH 6.0. After staining, number of insulin positive cells in 1000 beta cells were counted under high magnification and was expressed in percentage.

**Statistical analysis**

Statistical analysis was performed using the statistical software GraphPad Prism, version 5 for windows. Mean values and standard error were calculated and all values were expressed as Mean (± SE). The data were analysed by two-way analysis of variance (ANOVA).

**Results and Discussion**

The present study was conducted to evaluate the antidiabetic efficacy of umbelliferone in streptozocin induced diabetes mellitus in rats and to compare the hypoglycemic effect with that of an oral hypoglycaemic agent, glibenclamide.

**Bodyweight**

The mean (± SE) b. wt. of all the rats in the experimental groups was recorded (Table 1 and Fig. 1) Group I (normal control) rats showed a gradual increase from day 3 to day 45. Whereas the rats in the remaining group showed an improvement by the end of the study period, excluding Group II, when compared to diabetic control, however, values were lesser in comparison to normal control and the improvement was statistically comparable at P≥ 0.05.

Serum biochemistry

**Serum glucose**

The mean (± SE) serum glucose levels are presented in the table 2 and Fig. 2. In the normal control animals showed no significant (P≥ 0.05) variation in glucose levels throughout the experiment.

The diabetic rats of Group II revealed a significant increase (P≤ 0.001) in the serum glucose levels when compared to normal control rats at all tested intervals of the experimental period. In Group III diabetic rats, serum glucose levels showed a gradual and significant reduction (P≤ 0.001) from day 3 to 45th day of the experiment when compared to the normal control rats and showed a significantly lower values when compared with Group II rats on 30th and 45th day (P≤ 0.001).

In the present study, the serum glucose levels were significantly lowered in the glibenclamide treatment group compared to diabetic control rats. Insulin secretion by the β cells in response to glibenclamide treatment could be responsible for the reduction in serum glucose levels which further improves sensitivity of β cells to glucose and potentiates insulin secretion (Ling et al., 2006). In the present study, the serum glucose
levels failed to reach the normal levels in spite of treatment with Glibenclamide as also observed by several workers (Erejuwa et al., 2011). This could be due to failure of β - cells population to attain optimum secretory functional activity in response to the Glibenclamide treatment as evidenced by microscopic and by immunohistochemistry in the present study.

Similar decline in serum glucose levels was observed in Group IV, V and VI with significant decrease in values was observed on 30th day onwards when compared with Group II. However, the values were on a higher side when compared to normal control rats. The mean serum glucose values were comparable with no significant difference when compared to glibenclamide treated group as well as the UMB treated group except on 45th day when compared with Group III vs Group V and VI.

The observations made in the present study are similar to previous reports (Ramesh and Pugalendi, 2005). The increased body weight could be attributed to the better utilization of nutrients, glucose, amino acids, fatty acids and other macromolecular components due to improved insulin release by the β cells on treatment with UMB. In addition, the hepatoprotective property of the extract and induction of various metabolic enzymes also could be responsible which improved uptake of nutrients and their metabolism (Devipriya et al., 2007).

Sim et al., (2015) reported that UMB supplementation caused decline in lipid profiles due to increased plasma adiponectin levels. Since, adiponectin is an adipokine secreted from adipose tissue that can influence circulating plasma glucose and lipid levels (Kandasamy et al., 2012) which can influence circulating plasma glucose and lipid levels. He also suggested that the concentration of plasma adiponectin independently predicts the progression of diabetes and that adiponectin deficiency may contribute to the development of insulin resistance/T2D and observed that mice receiving adiponectin gene therapy showed lower blood glucose, decreased insulin and improved peripheral insulin sensitivity, improved glucose tolerance and reduced hepatic gluconeogenesis compared with control mice.

Table 1 The Mean (± SE) body weight values of treatment and control groups at different intervals of time

| Groups          | Body weight - Days post treatment |
|-----------------|----------------------------------|
|                 | Day 3     | Day 15    | Day 30    | Day 45    |
| Group I (NC)    | 165.83±2.71a | 195.8±3.75b | 224.1±9.52b | 311.6±7.60c |
| Group II (DC)   | 170±2.23a  | 150.8±2.78a | 128.3±4.77a | 120.8±3.27d |
| Group III (GC)  | 181.66±3.0a | 157.5±6.29a | 155.83±3.27ab | 215±15.43a |
| Group IV (U20)  | 170.0±2.88a | 153.3±2.10a | 160±2.58a  | 225±19.10ab |
| Group V (U40)   | 172.5±3.09a | 149.1±0.83a | 153.3±8.02a | 241.6±15.5b |
| Group VI (U20 +GC) | 176.6±4.941a | 140±4.28a | 168.3±8.72a | 233.3±17.8ab |

Note: Values bearing different superscripts between rows within a column vary significantly (p≤0.05), Values bearing different superscript in capital letters between the row vary significantly (p≤0.05)
Table 2: The Mean (± SE) serum glucose (mg/dL) values of treatment and control groups at different intervals of time

| Groups          | Serum glucose - Days post treatment |
|-----------------|-------------------------------------|
|                 | Day 3      | Day 15    | Day 30     | Day 45     |
| Group I (NC)    | 112.33±4.72aX | 114.16±3.40aX | 108.66±3.63aX | 105.83±2.83aX |
| Group II (DC)   | 338.33±7.06bX | 340.5±4.94bX  | 321.58±6.61bX  | 382.08±4.39bY |
| Group III (GC)  | 343.16±5.05bX | 281.75±4.54cY | 230.50±5.57cZ  | 174.66±5.23cW |
| Group IV (U20)  | 350.33±4.92bX | 313.25±14.17bY | 269.58±8.72dZ  | 239.91±2.67dW |
| Group V (U40)   | 352.16±8.19bX | 284.3±12.72cY | 207.3±5.54cZ   | 187.66±4.88cZ |
| Group VI (U20+GC)| 349.91±4.35bX | 269.16±10.75cY | 211.3±8.48cZ   | 170.16±4.67cW |

Note: Values bearing different superscripts between rows within a column vary significantly (p≤0.05), Values bearing different superscript in capital letters between the row vary significantly (p<0.05)

Table 3: The Mean (± SE) percentage positivity of insulin secreting cells of treatment and control groups at different intervals of time

| Groups          | Insulin positive cells - Days Post Treatment |
|-----------------|--------------------------------------------|
|                 | 15       | 30    | 45    |
| Group I (NC)    | 73±1.39  | 75.66±2.10 | 75.0±0.89 |
| Group II (DC)   | 4.66±0.42 | 3.5±0.22c | 4.83±0.40 |
| Group III (GC)  | 14.33±0.55 | 41.16±2.22 | 60.0±2.09 |
| Group IV (U20)  | 12.5±0.76b | 35.00±0.73 | 47.75±1.14 |
| Group V (U40)   | 17.0±0.73 | 44.83±1.13 | 63.5±1.8 |
| Group VI (U20+GC)| 12.33±0.66 | 45.16±2.25 | 61.16±1.86 |

NOTE: Values bearing different superscripts between rows within a column vary significantly (p≤0.05), Values bearing different superscript in capital letters between the row vary significantly (p<0.05)
Fig. 2. The Mean (± SE) serum glucose (mg/dL) values of treatment and control groups at different intervals of time.

Fig. 3. The Mean (± SE) percentage positivity of insulin secreting cells of treatment and control groups at different intervals of time.

Plate 1. Structure of Umbelliferone.
Plate 2. Normal pancreas showing well-formed islet -200X
Plate 3. Gp. III - 45th day – β cell destruction -400X
Plate 4. Gp. III – 45th day – Better morphology –200X
Plate 5. Gp. IV - 45th day – Improvement in islets – 200X
Plate 6. Gp. V - 45th day – Regeneration in islets – 200X
Plate 7. Gp. VI - 45th day – Bigger islets – 400X
Plate 8. Gp. I - 45th day – Insulin positive β cells – 400X
Plate 9. Gp. II - 45th day – Few Insulin positive β cells – 400X
Plate 10. Gp. III - 45th day – Insulin positive β cells – 400X
Plate 11. Gp. IV - 45th day – Few Insulin positive β cells – 400X
Plate 12. Gp. V - 45th day – Insulin positive β cells – 400X
Histopathology

Group I

Control rats examined during 15th, 30th and 45th days of the experiment showed normal appearance of acini and islets of Langerhans in the pancreas (Plate 2).

Group II

In diabetic rats belonging to Group II, on 15th day to 45th days post-STZ injection, the pancreas showed numerous lobules with loss of architecture with congestive changes. The acini were lined by highly vacuolated, degenerating, apoptotic and necrotic cells. Islets of Langerhans were reduced in number per lobule with depletion of β cells and an increase in the number of alpha cells. The persisting beta cells were characterised by the loss of cytoplasmic granularity, cytoplasmic vacuolations and necrosis. The microscopic feature of islets in diabetic rats indicated progressive destruction of β cells from day 15 onwards (Plate 3).

Group III

In Glibenclamide treatment group there was a declining trend in the severity of the lesions in the pancreas from day 15 onwards up to day 45 of the study. The islets appeared increased which were either round or oval-shaped with a compact arrangement of beta cells at the core and alpha cells at the periphery by day 45 (Plate 4). The beta cells appeared round with mild to moderate cytoplasmic granularity.

Groups IV

The present study showed a step by step reconstruction of the normal architecture of acini and islets in pancreas from day 15 to day 45 post-treatment. The exocrine portion of acini revealed improvements which were comparable to glibenclamide treatment. On day 15, acinar epithelium showed necrosis and vacuolar degenerative changes. By 45th day post-treatment most of the acini showed normal architecture with few of the lobules containing hyperplastic acinar cells (Plate 5). Further, the islets showed considerable improvement in its cellularity with a mild to moderate increase in the β cells which was demonstrated in immunohistochemistry.

Groups V

In UMB @ 40mg/kg b. wt. group, the endocrine pancreas on day 15 post-treatment was characterized by the presence of few islets which were of small to moderate size with an irregular shape with vacuolar degeneration, necrosis and apoptotic cells.

From 30th day to 45th day post STZ treatment, the islets which were considerably larger compared to day 15 and revealed near to
normal architecture with increased cellularity and showed greater number of alpha cells and few normally appearing beta cells showing mild granular cytoplasm. However, a few cells with cytoplasmic vacuolations still persisted in few islets (Plate 6).

**Groups VI**

The current group showed a progressive reconstruction of normal architecture of acini and islets in pancreas from day 15 to day 45 post treatment.

On day 15 many lobules showed vacuolated, degenerated, necrotic cells and multi focal apoptotic cells. Neovascularisation was evident on day 15. On day 45, the lobules revealed bigger sized islets and more compact arrangement when compared to individual treatment groups (Plate 7). There was a tendency to form new islets near the blood vessels, which was a consistent feature. The histological architecture showed a near to normal architecture characterized by increased cellularity with a greater number of islets per lobule compared to days 15 and 30. However, normal α: β ratio was not attained as showed in the normal control animals. Most of the beta cells were located at the central core, whereas the α cells showed a peripheral placement (Plate 47-50).

**Immunohistochemistry**

In the present study immunohistochemical demonstration of insulin was carried out to identify and enumerate β-cells in various treatment groups using monoclonal insulin antibody.

The mean (± SE) percentage positive cells for insulin are presented in the table 3 and Fig: 3. In the normal control group, most of the islets revealed intensely stained positive cells in large number. The α-cells and acini of exocrine pancreas were negative and the IHC positive β-cells revealed densely stained cytoplasmic granules that were compactly arranged and limited to the regular membrane (Plate 8).

The islets of pancreas in diabetic rats revealed a drastic reduction in the number of insulin positive cells. Most of the IHC positive cells appeared swollen and irregular with scattering of granular material in the cytoplasm indicating degenerating cells (Plate 9).

In the glibenclamide treated diabetic rats, there was a progressive increase in number of insulin positive cells. The improvement was significantly higher (P≤ 0.001) compared to diabetic control group at 30th and 45th days of observation and were not comparable with normal control with significantly lesser values (Plate 10).

In umbelliferone @ 20mg/kg b. wt. group, the islets showed a progressive improvement in the insulin positive cells at regular intervals post treatment (Plate 11). In umbelliferone @ 40mg/kg b. wt. treated rats also showed progressive improvement in the insulin positive cells at regular intervals post treatment (Plate 12). Similar to the glibenclamide and Group V treated rats, the rats in the combination group (Group VI) also showed progressive improvement in the insulin positive cells at regular intervals post treatment (Plate 13). However, in comparison to normal control rats the values were significantly less and with glibenclamide group, the values were comparable on 15th and 30th day without significant variation.

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