



THE ROLE OF IPOMOEA BATATAS LEAVES EXTRACT ON THE TREATMENT OF DIABETES INDUCED BY STREPTOZOTOCIN

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ABSTRACT

Diabetes mellitus (DM) is a disease that is common worldwide. The current work was conducted to assess the possible antidiabetic activity of *Ipomoea batatas* Leaves extract (IBLE) in streptozotocin (STZ) - induced diabetic rats. Fifty male adult albino rats were distributed to five groups (10 rats each) and were studied as following scheme for 4 weeks, group (I) normal control (cont. (-)), group (II) diabetic control rats were given distilled water daily by gastric incubation (cont. (+)), group (III) diabetic rats were treated orally with Gliclazide (GZ) (10 mg/kg), groups (IV) and (V) diabetic rats were treated orally with IBLEat (200 mg/kg) and IBLE (200 mg/kg) combined with GZ (10 mg/kg), respectively. Blood samples and pancreas were collected at the last day of the experimental period for biochemical parameters estimation as well as the histopathological examination. The IBLE administration to diabetic rats reduced significantly blood glucose (BG) level, MDA and anti-inflammatory cytokines (IL-1 β and - TNF- α). On the other hand, the levels of insulin (INS), GSH and SOD were significantly increased compared with cont. (+). Moreover, the extract showed significant amelioration in pancreatic cells structure. These findings demonstrated that IBLE possess antidiabetic properties thus suggesting its beneficial effect in the DM treatment.

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Introduction

Diabetes is a chronic medical disease that prevalence worldwide with the rate of 6.4 % in people aged 20-79 years [1, 2]. It is a metabolic disorder characterized by hyperglycemia, insulin resistance and pancreatic β -cells dysfunction [3, 4]. Diabetes is considered as one of the leading causes of death worldwide [5]. In DM, hyperglycemia exhibit enhancement of oxidative stress, which induced oxidative damage in target organs as kidneys, eyes and nerves with inevitable complications [6, 7]. Life style, genetic and aging are the main causes involved in etiology of DM [8]. In Saudi Arabia the rapid changes over the last 3 decades in the people's lifestyle towards urbanization exhibit exceeding the proportions of DM [9].

Although there have been many hypoglycemic drugs, however, most of them have limited efficacy, expensive, unavailable and have many side effects as drug resistance, dropsy and weight gain [10-12]. Therefore, it is still needed to develop natural, effective, economic and safe hypoglycemic agents. Recently, several studies are focusing on functional foods that have potential effects on the diseases protection and prevention, through their nutraceutical compounds, providing additional physiological benefits and promoting health [13].

Ipomoea batatas L. leaf (Convolvulaceae, Solanales Family) is commonly used as a therapeutic plant. The leaves are high in anthocyanins and polyphenolic compounds, which possess anti-carcinogenesis, antioxidant, anti-inflammatory and anti-mutagenicity activities [13, 14]. The total polyphenols in sweet potato leaves are more than other commercial vegetables [13]. It is used as a remedies for tumors of the mouth and throat, tonic, laxative and fungicide [15]. Several studies demonstrated the beneficial effects of IBLE as hypoglycemic agent [13, 16], and in the treatment of anemia and other related ailments [17]. Therefore, the present study aims to evaluate the possible antidiabetic activity of IBLE in diabetic rats.

Material and Methods

Material

Chemicals and Drugs

Gliclazide was obtained from Alnahdi pharmacy. All chemicals with high analytical grade and streptozotocin were purchased from Sigma, USA. The tested kits for determinations of glucose, insulin, anti-inflammatory cytokines and malondialdehyde (MDA) levels, as well as SOD and GSH enzymes were purchased from Biosystems (Barcelona, Spain).

Plant material

1) *Ipomoea batatas* Leaves were obtained from the local market, Jeddah, Saudi Arabia.

Animals

Adult male Wister albino rats, weighing 190 ± 10 g, had been purchased from King Fahd Medical Research Center. They were kept in standard conditions for laboratory, fed on AIN-93 standard diet [18]. They were kept in compliance with King Fahd Research Center's standard guide.

Methods

2) Extraction of *Ipomoea batatas* leaves

Two hundred grams of air-dried leaves of *Ipomoea batatas* were boiled with 1.5 liters of water for 40 minutes, after which it was rapidly filtered through a muslin cloth. The filtrate was allowed to evaporate for another 45 minutes to give a brownish - black almost solid residue [19].

Phytochemical screening of *Ipomoea batatas* leaves extract

The phytochemical analysis of IBLE had been performed to find the presence of the main chemical constituents, including flavonoids, glycosides, alkaloids, steroids, tannins and saponins using the analysis standard procedures [20].

Induction of diabetes and experimental design

Rats ($n=50$) were kept under control conditions in conventional animal house. They were fed a standard diet with access to water *ad libitum*. Rats were distributed to two main groups; first ($n=10$ rats) serves as control negative group and second group DM rats ($n=40$) were injected intraperitoneally (i.p.) once by STZ (65mg/kg) [21] to induce diabetes, after fasting 12 hrs. Since, the injection of STZ, rats were given glucose solution (10%) in feeding bottles for 24 hrs. to prevent hypoglycemia. Then, after 3 days, fasting blood sample of all surviving rats were collected from the tail vein to analyze glucose level. The diabetic rats were selected for the study should have blood glucose levels (>200 mg/dL) [22].

Five groups of rats were divided as follows:

Group I - Normal rats cont. (-).

Group II – DM control positive cont. (+).

Group III - DM + GZ(10 mg/kg).

Group IV - DM + IBLE (200 mg/kg) [23].

Group V - DM + IBLE (200 mg/kg)+ GZ (10 mg/kg).

After 4 weeks of experimental time, treatments were stopped and rats for each group were sacrificed under light ether anesthesia. Blood samples were collected by heparinized capillary tubes, kept for couple hrs, and centrifuged for 15 min at 3000 rpm. The separated serum was stored at -20°C for subsequent followed analyzes. The pancreas was removed for histopathological studies.

Determination of serum and tissue biomarkers

Blood sugar and insulin were measured using colormetric kits. Pancreatic oxidative stress biomarkers (lipid peroxidation level (MDA), GSH and SOD) were estimated in homogenated pancreatic tissue using ELISA kits, and the anti-inflammatory cytokines (IL- 1β and - TNF- α) were assessed by ELISA kits.

Histopathological examination

The pancreas from all experimental groups were removed after sacrificing the rats. Tissue were fixed in 10% neutral formalin, dehydrated, and embedded in paraffin wax and then stained with hematoxylin-eosin by routine procedures.

Statistical analysis

The SPSS Version 22 was used to analyze the resulting data. Values were expressed as mean \pm SD, and analyzed by one-way variance (ANOVA) followed by t-test. The results at $P \leq 0.05$ were considered as statistically significant.

Results

The phytochemical screening of IBLE exposed that it has great amounts of flavonoids, moderate amounts of saponins, tannins, and alkaloids a few amount of glycosides and steroids as depicted in Table (1).

Table 1: Phytochemical screening of *Ipomoea batatas* leaves extract (IBLE)

Phytochemical	Test results
Flavonoids	+++
Alkaloids	++
Tannins	++
Saponins	++

Steroids	+
Glycosides	+

The following symbol indicated the intensity of active compounds: a small amount (+), a moderate amount (++), and large amount (+++).

Table (2) showed the effect of IBLE and GZ on the BG and INS in STZ-induced diabetes. A significant increase in the BG was observed in the cont. (+) group (235.43 ± 2.32) as compared with the cont. (-) group (110.74 ± 1.29) ($p < 0.005$). Treatment with GZ, IBLE and their mixture significantly decreased BG as compared with the cont. (+) group, their values were 111.49 ± 2.73 , 130.31 ± 2.17 and 110.88 ± 2.62 , respectively versus 235.43 ± 2.32 in cont. (+) group. At the same time the INS is significantly reduced in the cont. (+) group compared with cont. (-) group. While, there were significant increases ($p < 0.005$) in all treated groups versus the cont. (+) group.

Table 2: Antidiabetic effect of *Ipomoea batatas* leaves extract on blood glucose and insulin levels in diabetic rats.

Groups	BG(mg/dl)	INS(mg/dl)
Cont (-)	110.74 ± 1.29^c	2.99 ± 1.09^a
Cont(+)	235.43 ± 2.32^a	0.79 ± 0.05^c
GZ	111.49 ± 2.73^c	2.89 ± 1.28^a
IBLE (200 mg/kg)	130.31 ± 2.17^b	1.82 ± 0.08^b
IBLE (200 mg/kg)+GZ	110.88 ± 2.62^c	2.96 ± 1.19^a

Values are presented as mean \pm SD.

Values with different superscript letters within a column are significantly different at $P < 0.05$.

As shown in Table (3), in diabetic group, MDA (the marker of lipid peroxidation) revealed a significant elevation ($p < 0.005$) versus the cont. (-) group. Moreover, a significant reduction in the pancreatic MDA was detected with GZ, IBLE and IBLE + GZ treated groups as compared with diabetic rats with mean values 79.93 ± 2.35 , 84.86 ± 2.42 and 75.52 ± 2.62 , respectively versus 130.31 ± 2.17 in cont. (+). The most effective treatment was seen in the group treated with GZ + IBLE (200 mg/kg). Concerning GSH and SOD, results presented a significant decrease ($p < 0.05$) in both with mean values 36.65 ± 2.67 and 39.43 ± 2.83 respectively in cont (+) group compared with the 36.65 ± 2.67 and 64.28 ± 3.53 respectively of the cont. (-) group; whereas treated rats with GZ, IBLE and their mixture displayed significant elevation compared to the group of cont. (+).

Table 3. Antidiabetic effect of *Ipomoea batatas* leaves extract (IBLE) and gliclazide (GZ) on MDA, GSH and SOD levels in diabetic rats.

Groups	MDA (μ mol/g tissue)	GSH (mg/g tissue)	SOD (U/g tissue)
Cont (-)	74.26 ± 3.23^c	58.16 ± 2.53^a	64.28 ± 3.53^a
Cont(+)	130.31 ± 2.17^a	36.65 ± 2.67^c	39.43 ± 2.83^c
GZ	79.93 ± 2.17^a	60.63 ± 1.98^a	61.93 ± 2.66^a
IBLE (200 mg/kg)	84.86 ± 2.42^b	64.59 ± 2.18^b	56.72 ± 2.09^b
IBLE (200 mg/kg)+GZ	75.52 ± 2.62^c	58.67 ± 1.88^a	63.89 ± 2.89^a

Values are presented as mean \pm SD.

Values with different superscript letters within a column are significantly different at $P < 0.05$.

From information recorded in table (4) it might be recognized that rats injected by STZ (65 mg/kg i.p) had significant ($P < 0.05$) increases in the activities of the IL-1 β and - TNF- α (59.26 ± 0.81 and 60.39 ± 0.92 respectively) as compared to cont. (-) group (23.74 ± 1.05 and 13.62 ± 1.02 respectively). Administration of GZ, IBLE and their mixture for 4 weeks induced significant decreases ($P < 0.05$) in both anti-inflammatory cytokines marker level in all treated groups as compared to cont. (+) group. In addition, there was no significant difference found in the anti-inflammatory cytokines (IL-1 β and - TNF- α) between both GZ group and the mixture group.

Table 4: Antidiabetic effect of *Ipomoea batatas* leaves extract on IL-1 and TNF- α level in diabetic rats.

Groups	IL-1 (pg/ml)	TNF- α (pg/ml)
Cont (-)	23.74 ± 1.05^c	13.62 ± 1.02^c
Cont(+)	59.26 ± 0.81^a	60.39 ± 0.92^a
GZ	24.49 ± 1.07^c	14.69 ± 1.12^c
IBLE (200 mg/kg)	30.11 ± 1.01^b	22.77 ± 1.08^b
IBLE (200 mg/kg)+GZ	23.96 ± 1.02^c	14.09 ± 1.01^c

Values are presented as mean \pm SD.

Histopathological results

The negative control group's pancreas revealed a normal pancreatic cells (Fig. A). Meanwhile, the positive control group's pancreas showed necrosis of cells of islets of Langerhan's (Fig. B). pancreas cells of GZ treated diabetic rats showed normal pancreatic blood vessels (Fig. C). While, the IBLE group treated with two hundred mg/kg of diabetic rats, pancreas revealed slight hypertrophy of Langerhans islets (Fig. D). Pancreas sections of rats given the mixture, did not show any change in histopathology (Fig. E).

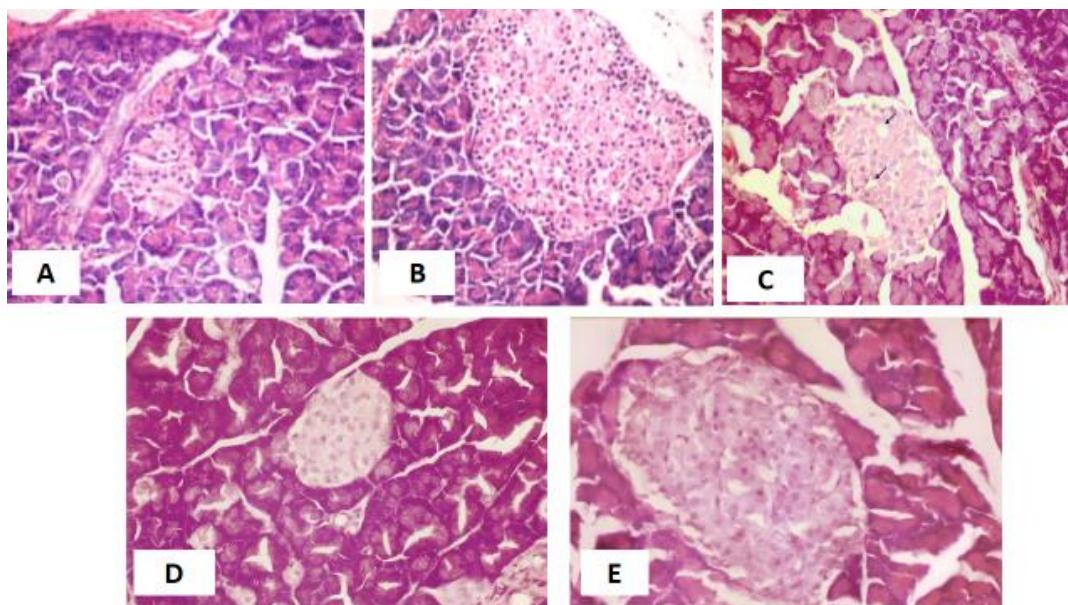


Fig.1: Photomicrography showing H&E-stained sections of pancreas in different groups. Pancreas of control negative rats showing normal pancreatic cells (A). In diabetic rats, pancreas sections showing necrosis of cells of Langerhan's (B), pancreas cells GZ treated diabetic rats showed normal pancreatic blood vessels (C). The IBLE group treated with two hundred mg/kg of diabetic rats, pancreas revealed slight hypertrophy of Langerhans islets (D), Pancreas sections of rats given the mixture., did not show any change in histopathology (E). (x400)

Discussion

Diabetes is characterized by disarrangements in all macro-nutrients metabolism induced *via* partial or complete insufficient insulin action and/or secretion [24, 25]. Managements and control of blood glucose is rarely achieved in spite of surplus hypoglycemic drugs [26]. Several plants showed hypoglycemic effects in human and animal studies [27, 28]. Several researches demonstrated that hyperglycemia induces oxidative stress and increases production of ROS [29, 30]. *Ipmoea batatas* leaves extract used a potential source of natural antioxidants, which attributed to its high contents of flavonoid contents [31]. In this study, IBLE has great amounts of flavonoids with moderate amounts of saponins, tannins, and alkaloids.

Streptozotocin, as an antibiotic, has diabetogenic action *via* destruction of pancreatic β - cells [32]. Injection of STZ in this study induced increase in BG and decrease in INS compared with the cont. (-). This agrees with many investigations, where STZ produced insulin-deficient, hyperglycemia, polyuria and polydispisa; this effect is explained by partial destruction of pancreatic islets and triggering an inflammatory that causes further loss of the functions of β -cells [33-35].

The current results showed that administration of GZor IBLE to diabetic rats significantly decreased BG and increased INS; while IBLE+GZ was the most effective treatment than either IBLE or GZ alone, it revealed significant hypoglycemia and hyperinsulinemia versus the cont. (+) group. Previous researches have showed that IBLE possess hypoglycemic effects, due to its content of saponins in its phytochemical results, which exhibit decline in glucose levels [14, 36]. This could be explained by its effects as stimulatory of insulin release and uptake of peripheral BG, thus in turn reversed the STZ induced hyperglycemia [14]. The same effects of IBLE was showed in alloxan-diabetic rats and explained by its active compounds that stimulate or modify insulin receptors, inhibit INS antagonist, and modify structure of glucose transport protein [14, 36-38].

Diabetes induced oxidative stress as evidenced by significant elevation in pancreatic MDA, serum IL-1 β and TNF- α levels with significant reduction in pancreatic antioxidant activities (GSH and SOD) versus cont. (-). These results agree with several studies, that revealed hyperglycemia induces increased in oxidative stress and damage *via* increase in carbonyl stress, peroxy and hydroxyl radicals [39, 40]. Moreover, Motilla *et al.* [41] and Vijayakumar *et al.* [42] showed that the increased

in MDA in plasma and tissues attributed to increase ROS production. Oxidative stress in diabetes coexists with a decline in antioxidant enzyme activities [43, 44]. Plasma and tissue total antioxidant capacity were significantly decreased compared to control un-diabetic [45]. The elevated levels of the inflammatory cytokines explained as a consequence of insulin resistance and hyperglycemia in diabetes [30, 46].

Administration of IBLE to diabetic rats showed antioxidant and anti-inflammatory effects as evidenced by significantly decreased pancreatic MDA and serum IL-1 β and TNF- α , with significant increase in pancreatic GSH and SOD versus cont. (+). These effects of IBLE could be explained through the bioactive compounds which have anti-inflammatory and antioxidant actions [47, 48]. The IBLE showed presence of various flavonoid compounds that have wide bioactivity as antioxidant, anti-inflammatory and suppression effect on adhesion molecules, and it inhibit TNF- α via a mechanism involving NF- κ B [49, 50].

The positive control group's pancreas showed necrosis of cells of islets of Langerhan's, slight hypertrophy of Langerhans islets in the IBLE treated diabetic rats, while treatment with IBLE+ GZ showed apparent normal structure of pancreas. The STZ is toxic to cells by damaging DNA, which induces activation of poly-ribosylation [14, 51]. The possible explanation of IBLE could be due to the phenolic and flavonoid compounds which scavenge ROS and regenerate the β -cells damage [14, 51-53].

Conclusion

IBLE is high in phytochemicals which possess many biological benefits. Hyperglycemia, hypoinsulinemia, oxidative stress, inflammatory and pancreatic histopathological changes in cont. (+) were attenuated by the administration of IBLE, which effectively control diabetes metabolic disorders

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