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Effects of *Gmelina arborea* extract on experimentally induced diabetes

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ABSTRACT

Objective: To study the effects of aqueous extract of *Gmelina arborea* bark on normoglycemic levels and streptozotocin (STZ) induced diabetes in rats. **Methods:** After single administration of the aqueous extract, plasma glucose level was determined up to 6 h. In subacute study, the aqueous extract was administered for 28 d and plasma glucose level was determined weekly. The diabetes was induced in rats by the intraperitoneal injection of STZ at a dose of 55 mg/kg body weight. The diabetic animals were divided into four groups containing six in each: Group Ⅰ diabetic control, Group Ⅱ and Ⅲ treated with the aqueous extract respectively at a dose of 250 and 500 mg/kg body weight once daily and Group Ⅳ treated with glibenclamide at a dose of 0.6 mg/kg body weight once daily. In acute study, the aqueous extract and glibenclamide were administered orally to rats. Plasma glucose levels were determined at 30, 60, 120, 240 and 360 min after the administration of the test samples. To study subacute effects, test samples (the aqueous extract and glibenclamide) were administered for 28 d consecutively. The effects of each test sample on plasma glucose level, body weight as well as food and water intake were also monitored weekly. The oral glucose tolerance test and biochemical indicators were estimated on day 28. **Results:** The aqueous extract did not significantly decrease the plasma glucose level in the normoglycemic rats as shown by the acute and subacute assays. However, after oral administration of the aqueous extract, the plasma glucose level was significantly ($P<0.001$) decreased in the diabetic rats in the acute study. The long-term administration of the aqueous extract significantly ($P<0.001$) reduced plasma glucose levels of the diabetic rats. Additionally, the aqueous extract also reduced loss of body weight and significantly decreased food and water intake in the diabetic animals. Nevertheless, no effects on biochemical indicators were observed at the selected doses. **Conclusions:** The aqueous extract of *Gmelina arborea* bark had antihyperglycemic activity against STZ induced diabetes in rats, after single and subacute oral administration. Moreover, it did not show significant glucose lowering effect in normoglycemic rats.

1. Introduction

Diabetes mellitus, a global public health problem, is now emerging as an epidemic world over. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030[1]. The excess global mortality attributable to diabetes in the year 2000 was estimated to be 2.9 million deaths, equivalent to 5.2% of all deaths. In people at 35-64 years of age, 6%-27% of deaths were attributable to diabetes[2]. Despite tremendous advances in medicine during the past century, there is still no cure, which means that effective prevention and treatment is of paramount importance to prevent future increases in disease burden[3,4].

The ethnobotanical information reports that about 800 plants may possess anti-diabetic potential[5]. The World Health Organization Expert Committee on diabetes has recommended that traditional medicinal herbs be further investigated. India has a rich history of using various potent herbs and herbal components for treating diabetes. Many Indian plants have been investigated for their beneficial use in different types of diabetes and have been reported in numerous scientific journals[6].

Gmelina arborea (*G. arborea*) is one of the important medicinal plants in Indian Ayurvedic system of medicine. Its root, fruit, bark and leaves are being used in medicine[7,8]. The plant is used in treatment of diabetes[9-12],

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snake-bite and scorpion sting[13-15].

Different phytoconstituents like flavonoids, lignans, glycosides and alkaloids have been found in the plant. Luteolin[16] and indole alkaloids[17] have been isolated from the leaves of *G. arborea*. Heartwood of the plant showed presence of different lignans such as arboreol, isoarboreol, methyl arboreol, arborone, gmelanone, gummadiol, and 7-oxodihydrogmelinol[18-20]. Iridoid glycosides have been isolated from the leaves[21]. Three iridoid glycosides, 6-*O*-(3″-*O*-benzoyl)-alpha-*L*-rhamnopyranosylcatalpol, 6-*O*-(3″-*O*-*trans*-cinnamoyl)-alpha-*L*-rhamnopyranosylcatalpol and 6-*O*-(3″-*O*-*cis*-cinnamoyl)-alpha-*L*-rhamnopyranosylcatalpol, were isolated from the aerial parts of *G. arborea*[22]. The bark of the plant showed presence of tyrosol [2-(4-hydroxyphenyl) ethanol]; (+)-balanophonin, an 8-5′ neolignan, gmelinol, phenylethanoid glycoside {(-)-*p*-hydroxyphenylethyl [5‴-*O*-(3,4-dimethoxycinnamoyl)-b-*D*-apiofuranosyl(1‴→6′)]-b-*D*-glucopyranoside}, 2,6-dimethoxy-*p*-benzoquinone and 3,4,5-trimethoxyphenol[23].

Various pharmacological activities of *G. arborea* like wound-healing[24], antidiarrhoeal[25] antioxidant activity[26,27] and antiulcer activity[28] have been reported. The toxicity studies of aqueous and methanol extracts of the plant have been reported[29,30]. In order to establish scientific basis for use of the bark of the plant, the present study evaluated its effects on streptozotocin [STZ; 2-deoxy-2-(3-methyl-3-nitrosourea) 1-*D*-glucopyranose] induced diabetes in experimental animals.

2. Materials and methods

2.1. Plant material

The bark of the *G. arborea* was collected in the month of November from Jawhar (District-Thane), Maharashtra, India. It was identified and authenticated by P.S.N. Rao of the Botanical Survey of India, Pune, India. A voucher specimen (b-03) of the stem bark is deposited in the department for future reference. The plant material was air-dried at room temperature and ground into a fine powder. The powdered bark was used to prepare the aqueous extract.

2.2. Preparation and doses of aqueous extract of G. arborea bark

The aqueous extract of *G. arborea* bark was prepared by cold maceration technique. Powdered bark (500 g) was macerated with 5 L of distilled water for 7 d, with frequent shaking. After 7 d, the aqueous extract was filtered and the marc was subjected to maceration with distilled water again for complete extraction. After filtration, the aqueous extracts were combined and concentrated with the help of a rotary vacuum evaporator under reduced pressure. The aqueous extract was dried in a vacuum dryer and stored in a refrigerator. The yield of the aqueous extract was found to be 20% (w/w), with respect to the powdered bark. The aqueous extract is reported safe up to a dose of 5 000 mg/kg body weight[29]. The doses of extract for the present study were chosen such that they were 1/10 and 1/20 of its safe dose.

2.3. Experimental animals

Experiments were performed in Wistar rats that were 6-8 weeks old and weighed 170-200 g at the start of the study. The animals were procured from Haffkine Institute (Mumbai, India) and housed three per cage in an animal house with controlled temperature of (25±2) °C, relative humidity of (75±5)% and 12 h light/dark cycle for an acclimatization period of 7 d, before carrying out the experiments. Food (Amrut Feeds, Maharashtra, India) and water were provided to each rat *ad libitum*. All experimental protocols were approved by the Institutional Animal Ethics Committee, constituted as per the norms of Committee for the Purpose of Control and Supervision of Experiments on Animals, and complied with the NIH guidelines for care and use of experimental animals.

2.4. Acute and subacute assay in normoglycemic rats

The freshly prepared aqueous extract of *G. arborea* bark was administered orally at doses of 250 and 500 mg/kg body weight. Rats in the control group were administered with an equal volume of distilled water. Plasma was collected from orbital sinuses at 1-hour time interval for up to 6 h after the treatment. Plasma glucose levels were determined using GOD-POD kit (Transasia Biomedicals Ltd., India)[31,32]. In the long-term study, the above test samples were administered orally once daily for 4 weeks. Plasma glucose levels were determined once every week.

2.5. Induction of diabetes

Diabetes was induced in the rats by the intraperitoneal injection of STZ at a dose of 55 mg/kg body weight (dissolved in 0.01 mol/L ice cold sodium citrate buffer, pH 4.4). After 48 h post the injection, the plasma glucose levels were measured. Each animal with a plasma glucose level above 250 mg/dL was considered to be diabetic[33].

2.6. Grouping of diabetic rats

The animals were divided into four groups: Group Ⅰ diabetic control (n=6), Group Ⅱ and Ⅲ, the aqueous extract treated (250 and 500 mg/kg body weight once daily) (n=6) and

Group Ⅳ glibenclamide (0.6 mg/kg body weight once daily). Along with these groups, there was also one age matched control group (n=6).

2.7. Acute assay in diabetic rats

In acute assay, the aqueous extract of *G. arborea* bark and glibenclamide were administered orally by using an oral feeding needle. Plasma glucose levels were determined at 30, 60, 120, 240 and 360 min after the administration of the test samples.

2.8. Subacute assay in diabetic rats

The aqueous extract of *G. arborea* bark and glibenclamide were administered for 28 d consecutively. Plasma glucose levels were determined on day 7, 14, 21 and 28 after the administration of the test samples. The effects of each test sample on plasma glucose level, body weight as well as food and water intake were also monitored on the same days. The oral glucose tolerance test (OGTT) was performed on day 28. Different biochemical indicators like cholesterol, high density lipoproteins, triglycerides (TG), aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total proteins, albumin, bilirubin, creatinine and blood urea nitrogen (BUN) were determined using diagnostic kits (Transasia Biomedicals Ltd., India) with autoanalyser (Erba Chem 7, Germany).

2.9. Statistical analysis

The differences between the experimental and control groups were determined using the statistical software Sigmastat Ver. 2.03 for Windows. Significant differences between the experimental groups were assessed by student's t test. All data are expressed as mean±SEM. P-value less than 0.05 was considered to be significant.

3. Results

3.1. Acute and subacute effects of the aqueous extract on basal plasma glucose level

The acute effect of the aqueous extract on the basal plasma glucose level in the normoglycemic rats is shown in Figure 1. The single oral administration of the aqueous extract at a dose of 250 or 500 mg/kg body weight did not affect the plasma glucose levels in the normal rats compared with that in the control rats which received distilled water. The repeated administration of the aqueous extract for 28 d also did not show any effect on the plasma glucose levels in the normoglycemic rats when compared with that in the control rats (Figure 2).

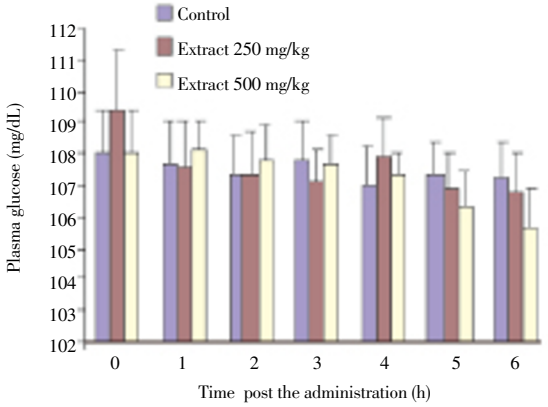

Figure 1. Effect of the aqueous extract of *G. arborea* bark on plasma glucose levels in normoglycemic rats after single oral administration.

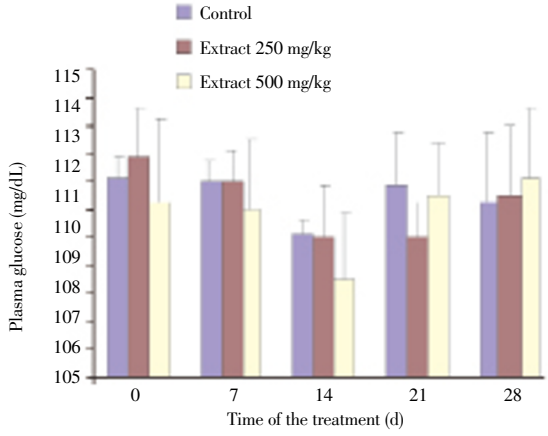

Figure 2. Effect of the aqueous extract of *G. arborea* bark on plasma glucose levels in normoglycemic rats after repeated administration for 28 d.

3.2. Antidiabetic activity of the aqueous extract against hyperglycemia in diabetic rats

After the acute administration of the aqueous extract of *G. arborea* (250 and 500 mg/kg body weight) as well as glibenclamide (0.6 mg/kg body weight), the plasma glucose levels were significantly reduced at 2, 4 and 6 h in the STZ induced diabetic rats (Table 1). The diabetic rats treated with the aqueous extract at a dose of 500 mg/kg body weight showed maximum reduction in the serum glucose level at 6 h when compared with the diabetic control.

The effect of the aqueous extract on the plasma glucose level after 28-day administration is shown in Table 2. Significant reduction (P<0.05) in the plasma glucose levels was observed on day 7 at the selected dose levels. The glucose level was further reduced on day 14 and day 21 after the administration of the aqueous extract and glibenclamide. The diabetic rats treated with the aqueous extract at doses of 250 and 500 mg/kg body weight showed maximum decreases in the plasma glucose levels on day 28 when compared

Table 1
Effect of the aqueous extract of *G. arborea* bark on plasma glucose level in streptozotocin induced diabetic rats after single administration (mg/dL).

Group	Time post the administration (min)					
	0	30	60	120	240	360
Normal control	110.88±3.21	111.48±2.54	108.57±1.88	109.47±2.34	112.57±1.87	111.35±2.12
Diabetic control	450.37±5.51	446.41±5.00	443.88±6.12	448.73±5.37	445.75±5.01	446.83±6.12
Diabetic+Extract (250 mg/kg)	434.72±10.07	432.15±10.02	429.12±9.14	418.38±10.26*	413.88±9.81*	410.97±9.66*
Diabetic+Extract (500 mg/kg)	433.65±10.06	431.30±9.84	427.65±9.89	416.62±9.39*	411.83±9.52**	407.98±9.87**
Diabetic+Glibenclamide	441.95±10.56	432.08±10.40	417.12±11.03*	414.37±11.30*	407.27±11.33**	399.57±11.98**

The values are expressed as mean±SEM. *P<0.05; **P<0.01 (compared with the diabetic control).

Table 2
Effect of the aqueous extract of *G. arborea* bark on plasma glucose level in streptozotocin induced diabetic rats after consecutive administration for 28 d (mg/dL).

Group	Days of the treatment (d)				
	0	7	14	21	28
Normal control	110.88±3.21	108.69±2.71	109.07±2.37	110.12±2.17	110.47±2.11
Diabetic control	450.37±5.51	456.78±5.12	455.82±4.71	454.38±3.64	455.13±3.91
Diabetic+Extract (250 mg/kg)	434.72±10.07	428.73±7.27*	415.05±8.50**	399.01±6.01***	392.96±4.55***
Diabetic+Extract (500 mg/kg)	433.65±10.06	423.02±11.19*	409.72±10.96***	389.18±10.29***	384.07±10.06***
Diabetic+Glibenclamide	441.95±10.56	382.18±11.69***	352.08±12.17***	313.68±12.42***	283.95±11.19***

The values are expressed as mean±SEM. *P<0.05; **P<0.01; ***P<0.001 (compared with the diabetic control).

with the diabetic control. The glibenclamide group showed maximum reduction in the glucose level on day 28 when compared with the aqueous extract treated and diabetic control groups.

3.3. Effect of the aqueous extract on oral glucose tolerance of STZ induced diabetic rats

The OGTT was performed in the diabetic rats previously treated with the extract for 28 d. The plasma glucose levels in the diabetic control and experimental groups before and after the oral administration of glucose are shown in Figure 3. The aqueous extract significantly (P<0.001) reduced the increased plasma glucose levels in the OGTT.

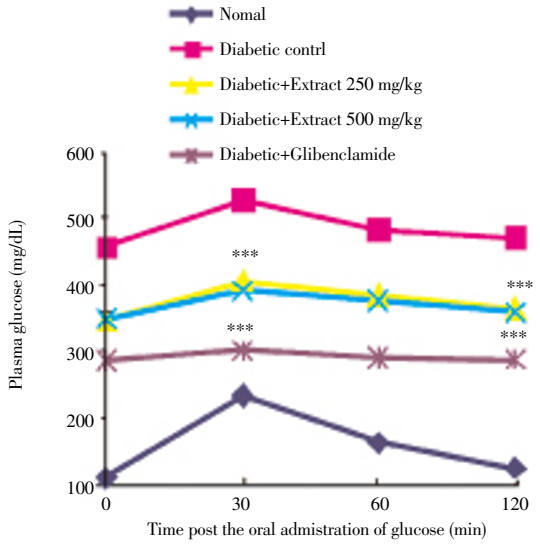

Figure 3. Effect of the aqueous extract of *G. arborea* bark on oral glucose tolerance of streptozotocin induced diabetic rats.
***P<0.001 compared with the diabetic control.

3.4. Effect of the aqueous extract on body weight, food intake and fluid intake in STZ induced diabetic rats

The treatment with the aqueous extract at the selected doses decreased loss of body weight in the STZ induced diabetic animals (Figure 4). The subacute treatment with the aqueous extract for 28 d also lowered their food consumption and water intake significantly when compared with that in the diabetic control rats (Figures 5 & 6).

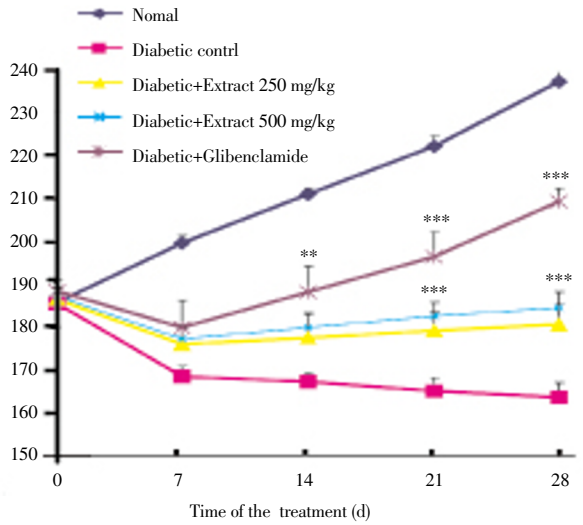

Figure 4. Effect of the aqueous extract of *G. arborea* bark on body weight of streptozotocin induced diabetic rats.
**P<0.01; ***P<0.001 (compared with the diabetic control).

3.5. Effect of the aqueous extract on biochemical indicators in STZ induced diabetic rats

The effect of the aqueous extract on different biochemical

indicators is presented in Table 3. The STZ induced diabetic rats showed significantly (P<0.001) increased levels of cholesterol and TG when compared with the normal control. The levels of high density lipoproteins were significantly (P<0.01) decreased in the diabetic rats when compared with those in the normal control. The reference drug glibenclamide significantly decreased the elevated cholesterol (P<0.05) and TG levels (P<0.01) in the diabetic rats when compared with that in the diabetic control group. The diabetic rats treated with the aqueous extract did not show any significant decrease in the levels of cholesterol and TG when compared with the diabetic control.

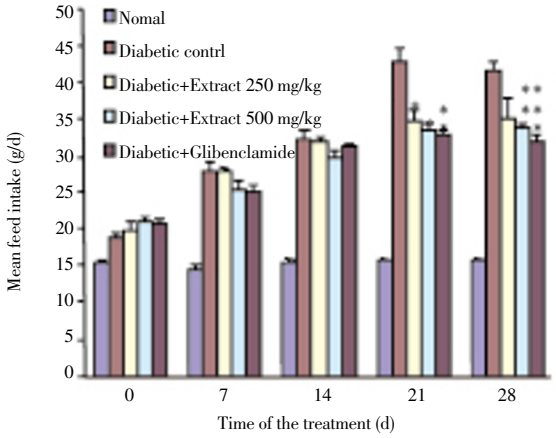

Figure 5. Effect of the aqueous extract of *G. arborea* bark on feed intake in streptozotocin induced diabetic rats.
$^{*}P$<0.05; $^{**}P$<0.01; $^{***}P$<0.001 (compared with the diabetic control).

The diabetic rats showed significant increases in the liver indicators like aspartate aminotransferase (P<0.001), alanine aminotransferase (P<0.05), and alkaline phosphatase (P<0.001). The contents of total proteins and albumin were significantly decreased (P<0.05) in the untreated diabetic rats. The aqueous extract at the selected doses did not show any effect on these indicators. The diabetic rats exhibited significant (P<0.05) increases in the BUN and creatinine levels, while these two indicators were not significantly reduced in the diabetic rats treated with the aqueous extract.

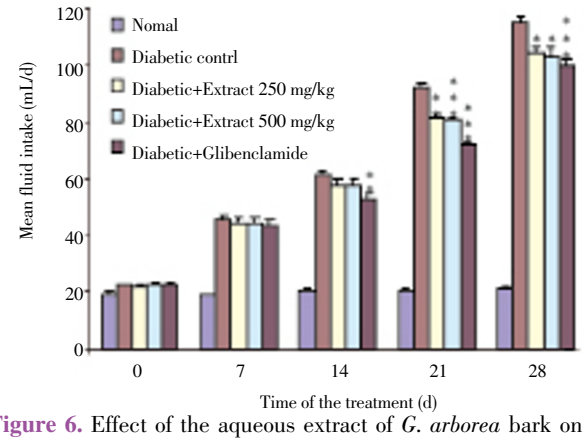

Figure 6. Effect of the aqueous extract of *G. arborea* bark on fluid intake in streptozotocin induced diabetic rats.
$^{*}P$<0.05; $^{**}P$<0.01; $^{***}P$<0.001 (compared with the diabetic control).

4. Discussion

The present study was designed to assess the effect of the aqueous extract of *G. arborea* bark in the normoglycemic rats and STZ induced diabetic rats. The acute administration of the extract failed to decrease the normal plasma glucose levels in the experimental animals. The repeated administration of the extract for 28 d did not significantly reduce the normal plasma glucose levels. The studies in the normoglycemic rats indicated that the aqueous extract did not have glucose lowering effect, *i.e.*, hypoglycemic activity,

Table 3
Effect of the aqueous extract of *G. arborea* bark on biochemical indicators in streptozotocin induced diabetic rats.

Indicator	Normal control	Diabetic control	Diabetic+Extract (250 mg/kg)	Diabetic+Extract (500 mg/kg)	Diabetic+Glibenclamide
Cholesterol	86.38±1.83	105.78±2.78†††	102.90±1.71	101.91±3.43	91.13±2.57**
HDL	45.33±0.97	38.96±1.51††	38.36±1.40	40.28±1.93	43.35±2.32
TG	90.55±1.79	101.93±1.57†††	99.16±2.30	98.36±1.21	84.30±1.68***
Bilirubin	0.40±0.04	0.41±0.01	0.39±0.01	0.39±0.01	0.39±0.03
AST	177.33±3.95	238.66±11.42†††	236.83±9.38	228.66±6.27	213.00±6.66
ALT	53.81±3.32	62.33±1.74†	62.50±2.32	62.16±2.23	64.16±2.63
ALP	91.50±2.95	129.50±6.88†††	125.66±2.25	125.00±4.28	114.00±5.17
TP	5.26±0.17	4.75±0.190	5.10±0.36	5.13±0.23	4.93±0.15
Albumin	2.96±0.11	2.53±0.20	2.98±0.19	2.93±0.09	3.00±0.17
BUN	21.03±0.68	51.81±1.70†††	47.30±1.71	46.51±1.78	39.98±2.63**
Creatinine	0.473±0.033	0.765±0.021†††	0.728±0.015	0.716±0.011	0.475±0.030***

The values are expressed as mean±SEM. $^{\dagger}P$<0.05; $^{\dagger\dagger}P$<0.01; $^{\dagger\dagger\dagger}P$<0.001 (compared with the normal control). $^{*}P$<0.05; $^{**}P$<0.01; $^{***}P$<0.001 (compared with the diabetic control). HDL: High density lipoproteins; TG: triglycerides; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; TP: Total proteins; BUN: Blood urea nitrogen.

in the normal rats. STZ is a broad spectrum antibiotic which is used for beta-cell necrosis and to induce diabetic state in experimental animals. At the intracellular level, major phenomenon responsible for beta-cell death is free radical generation and nitric oxide production[34]. The aqueous extract of *G. arborea* bark has been reported for significant antioxidant activity[27]. Thus, the possible mechanism of action of the extract may be related to its free radical scavenging activity and protection of beta-cells.

In this study, the higher dose of the extract produced the maximum anti-diabetic effect, which suggests that the dose of 500 mg/kg body weight may be the effective antidiabetic dose of the crude extract. However, the reference drug glibenclamide was better in activity when compared to the extract at the test doses, which may be attributed to the crude nature of the plant extract.

Medicinal plants and herbal extracts containing saponins, glycosides and phenolics have been reported to demonstrate antidiabetic activities. Preliminary phytochemical screening has also shown that *G. arborea* contains all the above phytoconstituents. It is therefore possible that the phytochemicals present in the plant may be responsible for the observed antidiabetic activity.

In the STZ induced diabetic rats, the increased food consumption and decreased body weight were observed. The polyphagic condition and loss of weight are due to excessive break-down of tissue proteins[35]. Hakim *et al* have stated that decreased body weight in diabetic rats could be due to dehydration and catabolism of fats and proteins[36-40]. Increased catabolic reactions leading to muscle wasting might also be the cause for the reduced weight gain in diabetic rats[41]. The administration of the aqueous extract to the diabetic rats decreased food consumption and increased body weight, possibly due to a better control of the hyperglycemic state in the diabetic rats. Decreased levels of plasma glucose could increase body weight in STZ-diabetic rats[42,43]. Induction of diabetes markedly increases feed and water intake in the diabetic rats. The treatment with the aqueous extract significantly ($P<0.05$) reduced the feed and water intake.

The diabetic rats showed increases in lipid indexes and liver enzymes. The treatment with the extract did not change these indicators significantly when compared with that in the diabetic control. The STZ treatment led to significant ($P<0.001$) increase in kidney biomarkers like BUN and creatinine when compared with that in the normal control. The aqueous extract did not show any significant changes in these two indicators after the 28-day administration.

In conclusion, *G. arborea* shows a remarkable anti-diabetic potential in the present study. However, further study is required to isolate and characterize the antidiabetic bioactive compounds and to establish the exact mechanism(s) of action.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

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