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Antihyperglycaemic and Antilipidaemic Activities of the Methanol Seed Extract of Passion Fruit (Passiflora edulis var. flavicarpa) in Alloxan Induced Diabetic Rats

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Abstract
The present study was undertaken to evaluate the antihyperglycaemic and antilipidaemic effect of methanol extract of seeds of *Passiflora edulis var. flavicarpa* in alloxan induced diabetic rats. Alloxan was administered as a single dose (120mg/kg, b.wt) to induce diabetes mellitus. Thirty albino rats were randomly divided into six groups of five rats each. Group I served as normal control. Group II served as diabetic control. Group III served as diabetic rats treated with oral hypoglycemic agent glibenclamide (2.5mg/kg). Groups IV, V and VI were diabetic rats orally administered with extract of the seeds (100, 200 and 400 mg/kg). The study was carried out for 28 days. On the 29th day, after an overnight fast, blood samples were obtained by cardiac puncture under inhaled chlorofoam anesthesia for the determination of the fasting blood glucose (FBS), serum triglyceride (TG), total cholesterol (TC), and high density cholesterol (HDL-C). The low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C), atherogenic index (AI) were also calculated**.** The extracts of the seeds at the dose of 100, 200 and 400mg/kg reduced the blood glucose level by 46.89%, 52.13% and 57.52% respectively as compared to standard drug glibenclamide (2.5mg/kg) which showed 66.18% reduction in the diabetic rats. The extract also reduced the elevated lipid profile parameters such as TG, LDL-C, VLDL-C, and TC, increased the reduced level of HDL-C. The result suggests that methanol extract of the seeds of *Passiflora edulis var. flavicarpa* possesses antihyperglycaemic and antilipidaemic properties.
Keywords*: Passiflora edulis var. flavicarpa*., Antihyperglyceamia., Antilipidaemia., Alloxan., Glibenclamide.

Introduction

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia with disturbances of carbohydrates, lipid and protein metabolism resulting from defects in insulin secretion, insulin action or both [26]. The resulting hyperglycemia may lead to acute metabolic complication including ketoacidosis and in the long term contribute to chronic micro vascular complications [29] such as neuropathy, nephropathy, retinopathy etc., and macro vascular complications which include cardiovascular diseases such as heart attacks, strokes and insufficiency in blood flow to legs as well. The global burden of diabetes has risen dramatically over the last two decades and diabetes is expected to affect more than 500 million adults worldwide by 2030 [36].

Passion fruit (*Passiflora edulis*) belongs to the *Passifloraceae* family and is originally from the tropical America, featuring over 500 species worldwide among which is the yellow passion fruit (*Passiflora edulis var flavicarpa*). Several studies have reported that the genus *Passiflora* has been used as an aid in the treatment (or control) of diabetes, mainly due to the presence of soluble fibers such as pectin [15, 35]. In the present study, we investigate the anti- diabetic effect of methanol seed extract of (*Passiflora edulis var. flavicarpa)* passion fruit in alloxan induced diabetic rats.

2. Materials and Methods

Plant Collection

Matured fresh passion fruits (*Passiflora edulis var. flavicarpa*) were obtained from Vandeikya Local Government Area of Benue State, Nigeria. The fruits were identified by a Taxonomist in the Botany unit, Biological Science Department, Usmanu Danfodiyo University, Sokoto and a voucher specimen was deposited at the Herbarium of the same department with a voucher specific number UDUH/ANS/0059.

Preparation of extract

The fruits were washed with distilled water and the residual moisture evaporated at room temperature. The seeds were removed from the pulp of the fruit, air dried for one to three weeks and pulverized into fine powder using wooden pestle and mortar. About 200g of the powdered sample was extracted with 2 litres of methanol at room temperature for 72hours and filtered through Whatman No. 1 filter paper. The filtrate was concentrated to dryness using rotary evaporator and the yield calculated.

Preliminary phytochemical screening

The methanol extract of *Passiflora edulis var. flavicarpa* seeds were screened for various bioactive compounds including flavonoids, saponins, alkaloids and tannins [9, 14, 30 and 32].

Acute oral toxicity studies

Acute oral toxicity study was carried out according to Organization for Economic and Cultural Development method [20].

Experimental animals

Thirty (30) albino rats of both sexes weighing 115-120g were used for this study. The rats were purchased from Nigerian institute for Trypanosomiasis Research, Kaduna state. They were kept in a well-ventilated room under supervision in the animal house of Biochemistry Department, Usmanu Danfodiyo University, Sokoto with free access to feeds and tap water ad libitum.

Induction of diabetes mellitus

Diabetes mellitus was induced in all rats except the positive control by injecting with a single dose of 120mg/kg b.w of alloxan monohydrate [31]. Diabetes mellitus was confirmed by measuring the blood glucose level with the aid of a glucometer. Only rats that had fasting blood glucose level >7.0 mmol/l (126mg/dl) were included in the study.

Experimental design

A number of thirty (30) rats were divided into six (6) main groups of five (5) rats each as follows:
Group I: Non diabetic non – treated (positive control)
Group II: Diabetic non – treated (negative control)
Group III: Diabetic treated with 2.5mg/kg bw of Glibenclamide (drug control)
Group IV: Diabetic treated with 100mg/kg bw of the methanolic extracts of the seed in addition to normal diet.
Group V: Diabetic treated with 200mg/kg bw of the methanolic extracts of the seed in addition to normal diet.
Group VI: Diabetic treated with 400mg/kg bw of the methanolic extracts of the seed in addition to normal diet.
The experiment was conducted for 28 days.

Blood collection

The animals were humanely sacrificed 24hrs after the last treatment and the blood of the animals was collected, centrifuged and the serum separated for biochemical analysis.

Biochemical analysis

Serum glucose was determined using the glucose oxidase method of Barham and Trinder, [4], Serum total cholesterol was determined by the enzymatic method of Allain *et al.*, [2], serum triglycerides was determined by the method of Trinder [33]. Serum high density lipoprotein cholesterol was determined by enzymatic method of Burstein *et al*., [6], serum low density lipoprotein cholesterol and VLDL Cholesterol were calculated using Friedewald formula [12] while atherogenic index (AIX) was calculated as the ratio of LDL-C to HDL-C [19].

Data analysis

The data obtained were represented as Mean ± SEM. Results were analysed statistically by One way ANOVA followed by Duncan's, multiple comparison test using the statistical package – SPSS version 20. Values were considered statistically significant at $p<0.05$.

3. Results

Preliminary phytochemical screening

The results of phytochemical screening of methanol extract of *Passiflora edulis var. flavicarpa* seeds revealed the presence of flavonoids, alkaloids, saponins, tannins, steroids, volatile oils, glycosides, saponin glycosides, balsams, terpenes and cyanogenic glycosides while anthraquinones, cardiac glycosides and resins were not detected. (Table 1)

Table 1: Phytochemical Screening of methanol seed extract of *Passiflora edulis var. flavicarpa.*

Phytochemical constituents	Status
Flavonoids	+
Alkaloids	+
Saponins	+
Tannins	+
Steroids	+
Anthraquinones	-
Volatile oils	+
Glycosides	+
Cardiac glycosides	-
Saponin glycosides	+
Balsams	+
Terpenes	+
Resins	-
Cyanogenic glycosides	+

Key:
+=Present
-=Absent

Acute Oral Toxicity Study

The oral administration of methanol seed extract of *Passiflora edulis var flavicarpa* at a single dose of 5000mg/Kg body weight did not cause rat mortality during the 48 h and 14 day observation and there was no indication of toxicity, behavioural or physiological changes. Thus, the result indicated that the LD_{50} of the methanol seed extract is greater than 5000mg/Kg.

Body weight

Table 2 shows the body weight changes of the alloxan-induced diabetic rats treated with methanol seed extract of *Passiflora edulis var flavicarpa* for 28 days. The result showed that alloxan injection decreased body weight of the animals. Treatment with the extract however alleviated the decrease in weights of the rats as a result of alloxan injection.

Table 2: Body weight (g) of alloxan induced diabetic rats treated with methanol seed extract of *Passiflora edulis var. flavicarpa* for 28 days.

Group	BAI	Week 0	Week 1	Week 2	Week 3	Week 4
Normal	119.50±2.53	117.75±2.29	125.25±2.84	131.00±2.94	135.25±3.68	141.25±4.39
Diabetic	121.00±5.29	119.00±5.51	114.00±2.31	112.00±0.58	110.00±2.31	109.33±1.20
Glibenclamide	127.00±6.51	124.33±6.69	129.00±4.04	135.00±2.89	143.00±0.58	149.33±1.45
100mg/kg	124.00±4.58	122.33±4.26	123.67±4.70	129.00±3.46	131.00±8.18	134.33±0.88
200mg/kg	121.67±7.62	118.33±7.69	126.00±2.31	131.00±1.15	139.00±2.89	142.00±1.15
400mg/kg	126.33±3.18	123.67±2.91	134.67±0.88	139.67±1.76	144.00±2.31	148.00±3.53

Values are expressed as mean ± Standard Error of Mean of five replicates.

The effect of methanol seed extract of *Passiflora edulis var. flavicarpa* on serum levels of glucose is shown in table 3. The result shows that there is significant decrease ($p< 0.05$) in the treatment groups compared with the diabetic control.

Table 3: **Serum glucose level (in mmol/l) in alloxan induced diabetic rats before and after oral administration of methanol seed extract of *Passiflora edulis var flavicarpa.***

Group	Before Treatment	After Treatment	% Increase or Decrease in Blood Glucose
Normal	4.72±0.24	5.30±0.12[a]	-12.29
Diabetic	15.40±1.23	19.96±0.07[c]	-29.61
Glibenclamide	15.64±0.68	5.29±0.35[a]	66.18
100mg/kg	13.33±0.61	7.08±0.77[b]	46.89
200mg/kg	16.67±1.24	7.98±0.49[b]	52.13
400mg/kg	13.70±0.54	5.82±1.29[a]	57.52

Values are expressed as mean ± Standard Error of Mean of five replicates. Mean Value Having Different Superscript Letters in rows are significantly different ($p<0.05$) (One way ANOVA followed by Duncan's, multiple comparison test).

The effect of methanol seed extract of *Passiflora edulis var. flavicarpa* on serum levels of lipid profile

is shown in table 4. The result shows that there is significant decrease in ($p<0.05$) TG, TC, LDL-C, VLDL-C and Aix compared with the diabetic control while the HDL-C was significantly increased ($p<0.05$).

Table 4: Effect of methanol seed extract of *Passiflora edulis var flavicarpa* on serum lipid profile (mg/dl) in alloxan induced diabetic rats.

Group	TG	TC	HDL-C	LDL-C	VLDL	Aix
Normal	73.91±8.32[a]	68.61±5.49[a]	41.07±4.10[c]	12.76 ±0.10[a]	14.78±1.67[a]	0.31±0.06[a]
Diabetic	197.10±10.03[c]	110.08±9.41[b]	21.43±1.90[a]	49.23±5.20[c]	39.42±6.68[c]	2.30±0.21[c]
Glibenclamide	81.16±7.67[a]	68.21±8.63[a]	34.13±2.89[b]	17.84±0.48[a]	16.23±1.53[a]	0.52±0.01[a]
100mg/kg	145.65±8.40[b]	76.74±8.47[a]	29.77±2.97[b]	17.86±0.45[a]	29.12±3.36[b]	0.60±0.06[b]
200mg/kg	110.87±7.79[b]	75.58±8.36[a]	30.36±2.72[b]	23.04±3.78[b]	22.18±2.60[a]	0.76±0.03[b]
400mg/kg	95.65±7.97[a]	63.57±4.10[a]	32.51±4.17[b]	11.93±1.64[a]	19.13±2.66[a]	0.37±0.02[a]

Values are expressed as mean ± Standard Error of Mean of five replicates. Mean Value Having Different Superscript Letters in rows are significantly different ($p<0.05$) (One way ANOVA followed by Duncan's, multiple comparison test).

Legend: TG= Triglycerides; TC= Total Cholesterol; HDL-C = High density lipoprotein cholesterol; LDL-C = Low density lipoprotein cholesterol; VLDL-C = Very low density lipoprotein cholesterol; and Aix=Atherogenic Index.

4. Discussion

One of the most potent methods to induce experimental diabetes mellitus is chemical induction by Alloxan [11]. Alloxan is a toxic glucose analogue, which selectively destroys insulin-producing cells (β-cell) in the pancreas [13]. Alloxan monohydrate induces diabetes through the generation of a redox cycle with the formation of superoxide radicals which undergo dismutation to hydrogen peroxide. These radicals accumulate in the cytosol simultaneously with calcium and cause rapid destruction of the pancreatic β-cells [16] which leads to hyperglycemia and thus inducing diabetes.

From our findings, after alloxan induction (Week 0) the diabetic rats showed moderate reduction in body weight. However, after seven days and thereafter of administration of the extract, the body weight of diabetic treated rats started to increase, whereas, diabetic non-treated rats showed gradual reduction in body weight during the experimental period. This result has similarities with the findings of [1, 5] who found that body weight of all the treated groups were significantly ($P<0.05$) increased with neem treatment compared to diabetic animals. They suggested that this may be due to some constituents of the neem extract which may have mimicked or stimulated the actions of growth factors hence its ability to enhance the repair and regeneration of damaged pancreatic tissue. Increase in body weight may as well be explained by increased insulin secretion or increased food consumption [21]. The decrease in body weight of alloxan induced diabetic rats can be attributed to gluconeogenesis which is associated with increased muscle wasting and loss of tissue proteins [10, 24].

Also, from our study, the result showed that the methanol extract of Passiflora edulis var. flavicarpa seeds reduced fasting serum glucose level of treated rats in a dose dependent manner. Alloxan induced diabetic rats treated with the seed extract (100, 200 and 400mg/kg) showed significant ($p<0.05$) reduction in fasting serum glucose levels by 46.89%, 52.13% and 57.52% respectively as compared to standard drug glibenclamide which showed 66.18% reduction. In a similar study, Ramos and colleagues demonstrated a significant reduction in fasting blood glucose levels and triglycerides in individuals with altered glucose metabolism upon supplementation with yellow passion fruit peel during their study [25]. The possible mechanism of action of the hypoglycaemic effect of the seed extract could be similar with the hypoglycaemic effect of sulphonylureas such as glibenclamide which promote or stimulate insulin secretion. Aside from stimulating insulin secretion, another possible mechanism of action could be through reducing endogenous glucose production and improving glucose utilization in the peripheral tissues thus improving the glycemic control mechanisms. The hypoglyceamic property of the extract can also be attributed to the presence of some phytochemicals present in the extract. As per literatures, alkaloids, steroids and tannins are to known to reduce blood glucose level in diabetic conditions [27]. Generally alkaloids have been said to inhibit α- glucosidase and decrease glucose transport through the intestinal epithelium [18, 22]. Also, flavonoids inhibit glucose-6-phophatase activity in the liver thereby suppressing gluconeogenesis and glycogenolysis and consequently reduce the hyperglycaemia [8].

Dyslipidemia is a frequent complication noted in chemical induced diabetes [17, 23 and 34] and presents a serious risk of vascular disease. In normal physiologic condition, insulin activates lipoprotein lipase, an enzyme which is involved in the hydrolysis of triglycerides. Insulin also inhibits lipolysis through inhibition of the enzyme carnitine palmitoyl transferase 1 in the presence of high levels of malonyl-CoA. However in the absence of insulin, lipolysis is increased which causes hyperlipidemia.

In addition to the hypoglycemic effect of the methanol seed extract, it also caused a decrease in the concentration of serum triacylglycerides and total cholesterol in the diabetic treated rats. Other elevated lipid

profile parameters such as LDL-C, VLDL-C, AIX were also reduced significantly ($p < 0.05$) in diabetic treated with the extract compared with the non-treated diabetic rats. Ramos *et al.,* [25] used a flour of yellow passion fruit peel and also found beneficial effects on the lipid profile of individuals with altered glucose metabolism. In another study, there was reduction in glycemia and lipid profile of offsprings of diabetic rats fed with passion fruit juice [3].

The possible mechanism of action of the methanol seed extract might be through enhancing the activity of enzymes involved in bile acid synthesis and its excretion and in this way cause a decrease in serum cholesterol and triglyceride concentrations [28]. It can also be attributed to the presence of some phytochemicals present in the extract such as tannins, saponins, flavonoids which are known to exert hypocholesterolemic effect. Other authors have suggested that the insoluble fiber-rich fraction prepared from *P. edulis* seeds and rinds could potentially be hypocholesterolemic [7, 37].

5. Conclusion

The present study suggests that the methanol seed extract of *Passiflora edulis var. flavicarpa* has hypoglycaemic and antilipidaemic effect on alloxan induced diabetic rats. Further studies need to be done to isolate and identify the active principle responsible for its anti-diabetic activity and to ascertain a possible mechanism of action of the extract.

6. References

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