British Journal of Pharmaceutical Research
4(11): 1300-1310, 2014

SCIENCEDOMAIN *international*
www.sciencedomain.org

Anti Diabetic activity of *Terminalia superba* (*Combretaceae*) Stem Bark Extract in Streptozotocin Induced Diabetic Rats

Dzeufiet Djomeni Paul Désiré[1], Nguelefack Télesphore Benoît[2], Azay Jacqueline[3], Cros Gérard[3], Kamtchouing Pierre[1] and Dimo Théophile[1*]

[1]Departement of Animal Biology and Physiology, Faculty of Science, University of Yaounde I, P.O. Box 812, Yaounde, Cameroon.
[2]Department of Animal Biology, Faculty of Science, University of Dschang, BP 67 Dschang, Cameroon.
[3]Laboratory of Pharmacology and Experimental Pathophysiology, University Montpellier I, 34060 Montpellier, France.

Authors' contributions

This work was carried out in collaboration between all authors. Authors DDPD, KP and DT designed the study, wrote the protocol, authors DT and DDPD wrote the first draft of the manuscript. Authors DDPD, NTB, AJ and CG managed the analyses of the study performed the statistical analysis. All authors read and approved the final manuscript.

Original Research Article

Received 24th January 2014
Accepted 9th April 2014
Published 23rd May 2014

ABSTRACT

Aims: The present study was designed to evaluate the antidiabetic activity of the methanol stem bark extract of *Terminalia superb* (*T. superba*), a traditionally used medicinal plant in Cameroon.
Place and Duration of Study: Department of Animal Biology and Physiology, Faculty of Science, University of Yaounde I, Cameroon and Laboratoire de Pharmacologie et Physiopathologie Expérimentales, Université Montpellier I, France. Between Ferbruary 2011 and September 2011.
Methodology: In one set of experiments, repeated doses of *T. superba* extract (37.5–300mg/kg, p.o.) were administrated once daily for 21 days to groups of diabetic rats. In another set of experiments, acute effect of the plant extract (37.5–300mg/kg) in diabetic rats was evaluated.

**Corresponding author: Email: dimo59@yahoo.com;*

Results: Following acute treatment, the plant extract produced a significant reduction in the blood glucose levels in diabetic rats. *T. superba* (75–300mg/kg) significantly decreased the blood glucose levels in glucose loaded rats. Oral administration of *T. superba* extract for 21 days resulted in a 31.43% and 21.42% significant reduction in blood glucose levels at the dose of 75mg/kg and 300mg/kg respectively**.** The plant extract significantly, reduced the plasma urea levels (20%) and induced a significant elevation in plasma insulin in treated rats. The extract did not significantly change elevated plasma cholesterol and triglycerides resulting from diabetic conditions.
Conclusion: The antidiabetic effect of the methanol stem bark extract of *T. superba* seems to be a result of increase in glucose utilization due to stimulatory action on insulin release.

Keywords: Terminalia superb; streptozotocin-diabetic rats; antidiabetic effect.

1. INTRODUCTION

Diabetes mellitus is a metabolic disease of multiple etiologies characterised by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both. In 2013, according to International Diabetes Federation, an estimated 381 million people had diabetes. Its incidence is increasing rapidly, and by 2030, this number is estimated to almost double [1]. In spite of the introduction of hypoglycemic agents, diabetes and related complications continue to be a major health problem. The cost of modern drugs is prohibitive and as a result, many patients in developing countries resort to traditional herbal medicine for their health problems [2,3]. Through the ages, many herbal medicines in different oral formulations have been recommended for diabetes, and confident claims of cure are on record. Many herbs and plants are mentioned in the literature as cures for diabetic conditions, and some of them have been experimentally evaluated and the active principles isolated [4-6].

Teminalia superba belonging to family Combretaceae is a large tree attaining 50m in high and 1.20m in diameter. It is a species of the dense humid forest, semi-deciduous forest, and also present in easily flooded and secondary forests, widespread in Congo Kinshasa, Guinea, Angola and Cameroon [7]. Traditional medicinal systems advocate several different therapeutic effects of this plant. The stem bark is used in the treatment of gastroenteritis, diabetes, hypertension, female infertility, abdominal pain, miscarriages, bronchial infections, and as an antiseptic [7-10]. Masai women use a tannin material from *T. superba* for curing skin infections and it is also administrated to cattle suffering from gall fever [7]. Trypanocidal properties of *T. superba* extract have been reported previously [11]. While performing field work and interacting with tribal people in the Centre province of Cameroon, it came to our notice that these people use the stem bark to treat diabetes. *T. superba* is rich in tannins, and the stem bark contains traces of alkaloids that are reported to be antidiabetic [4,5]. A high degree of *In vitro* oxygen free radicals scavenging activity of the bark of different plants of the genus Terminalia has also been documented [12]. The present study, evaluates the effect of the stem bark methanol extract of *T. superba* on blood sugar levels and plasma biochemical parameters in streptozotocin diabetic rats.

2. MATERIALS AND METHODS

2.1 Plant Material

The stem bark of *T. superba* was collected in Ngoa-Ekelle II, Yaounde in May. The plant material was identified using the herbarium collection (N°19652/HNC) at the Cameroon national herbarium, Yaounde. The stem bark was sun-dried and ground into a powder and stored at room temperature until use. The powdered material (245g) was macerated in 1 : 1 (v/v) mixture of methanol and dichloromethane for 48h at room temperature. The filtrate was evaporated in a rotating evaporator under reduced pressure until dryness [13] and sequentially fractionated with dichloromethane to obtain 26 g of the methanol extract. In fact, dichloromethane is used to break the membrane but also extract some compounds. Methanol is used because only the compounds soluble in methanol will be extracted of mixture dichloromethane/methanol (1:1). Four grams of this extract were dissolved in 100mL of distilled water to give a final concentration of 40mg/mL.

2.2 Experimental Animals and Induction of Diabetes

42 male Wistar rats weighting 250–280g were used in this study. The rats were housed in an environmentally controlled room with a 12h light: 12h dark cycle and free access was allowed to normal rat chow and tap water. The non fasting rats were made diabetic using streptozotocin (Sigma, St. Louis, MO., USA). The STZ was freshly dissolved in physiological saline and maintained on ice prior to use. The STZ was injected intravenously into the penis vein at a dose of 55 mg/kg in a corresponding volume of 1mL/kg. Diabetes was confirmed in the STZ-treated rats by measuring unfasted blood glucose concentrations 72h post injection using glucose reagent strips with a glucometer 4 Ames (Bayer diagnostic) [14]. Animals showing blood glucose levels above 400mg/dL were considered to be diabetic and were used in the experiment. The rate of success for diabetes induction was 76.19%.

2.3 Experimental Procedure

2.3.1 Oral glucose tolerance test (OGTT)

OGTT was performed on diabetic rats. Rats were deprived of food for at least 16h before and during the experiment, but were allowed free access to tap water. Thirty rats were divided into six equal groups. Two control groups were given either distilled water (10mL/kg) or 500mg/kg metformin while four test groups were given 37.5, 75, 150 or 300mg/kg of extract one hour before glucose load (5g/kg body weight). All the treatments were given orally by gavage. The glucose administration time was considered as time 0. Blood glucose levels from the tail tip were taken 30, 60, 120, 180 and 300min. after glucose administration using a Glucometer 4 Ames, Bayer. Area Under the Curve (AUC) was calculated following this formula:

AUC= Gly 0h x 0.25 + Gly 0.5h x 0.5 + Gly 1h x 0.75 + Gly 2h x 1 + Gly 3h x 1 + Gly 5h x 0.5, with Gly = glycemia and h=hour [14].

2.3.2 Single oral administration of *T. superb* extract

Diabetic rats were randomly assigned to six different groups of six rats each. Reference controls (oral treatment) were distilled water (10mL/kg) and metformin (500mg/kg). The test

groups received the methanol extract of *T. superba* at a dose of 37.5, 75, 150, or 300mg/kg body weight. Blood glucose concentrations were determined using a Glucometer Ames, from the tail tip in non fasted animals at 0 (before extract administration), 1.5, 3, 6, 8 and 10h after plant extract administration [14].

2.3.3 Sub-acute effect of *T. superb*

Streptozotocin diabetic rats were divided into six groups of five animals each. Subacute study was carried out by oral administration of stem bark extract of *T. superba* for 21 consecutive days with a single feeding. Basal glycaemia was determined in non fasted animals 72h post STZ injection. The vehicle (distilled water, 10mL/kg), metformin (500 mg/kg) and the plant extract (37.5, 75, 150 and 300mg/kg) were orally administrated once daily for three weeks. Food and water intakes were monitored every day between 8.00 and 9.00a.m. for 3 weeks. Blood glucose concentration and body weight were closely monitored twice a week. On the 15th day, the effect of the plant extract on OGTT in rats was evaluated as described above.

2.3.4 Biochemical analysis

At the end of the treatment (21st day), the animals were sacrificed by decapitation and the blood samples were collected. The samples were centrifugated and the plasma obtained was aliquoted and frozen at -20ºC for less than 3 day for biochemical analysis. Plasma glucose, triglyceride, cholesterol and urea were determined using an automatic plasma analyser (Hitachi 704). Plasma insulin was evaluated by the radio immunological method of Herbert et al. [15] using rat insulin as standard.

2.4 Statistical Analysis

Data were expressed as mean ± SEM. The statistical analysis was performed using analysis of variance (ANOVA) and Student's *t* test. The values were considered significantly different when the p-value was less than 0.05.

3. RESULTS

3.1 Oral Glucose Tolerance Tests

Fig. 1 shows the changes in the blood glucose levels during OGTT in untreated diabetic and diabetic animals treated orally with *T. superba* extract and metformin at the beginning of treatment (day 1). At day 1, *T. superba* extract at the dose of 75, 150 and 300mg/kg significantly depressed the increase in blood glucose caused by OGTT. One hour after glucose administration, the blood glucose level of diabetic rats was 525.28±3.80mg/dL while the blood glucose of those who received *T. superba* at the doses of 75, 150 and 300mg/kg was respectively 435.80±21.21, 454.82±5.48 and 467.80±6.05mg/dL. *T. superba* at 37.5mg/kg was not effective. For metformin (500mg/kg), used as reference drug, the blood glucose level was 227.80±21.65mg/dL one hour after glucose administration.

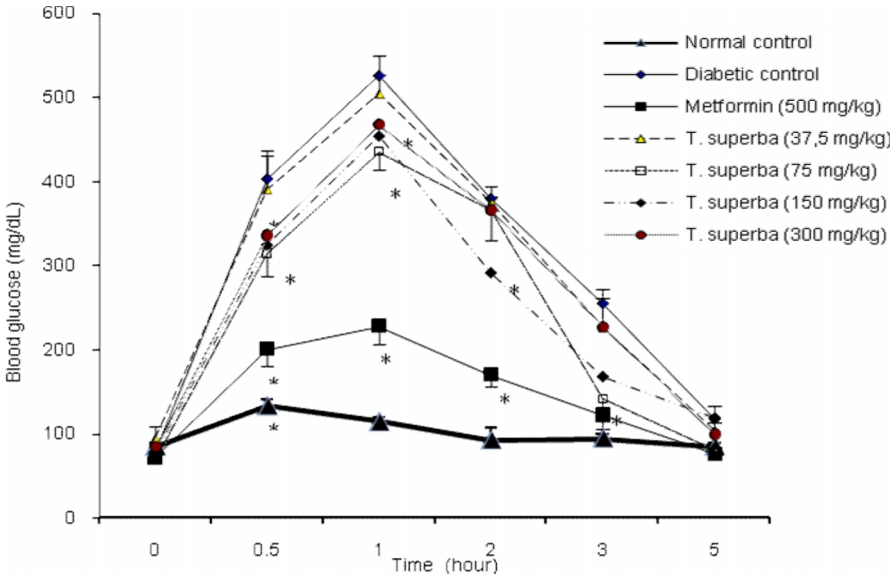

Fig. 1. Effect of the methanol extract of *T. superba* on blood glucose levels of STZ-diabetic rats after feeding glucose (5g/kg) on day 1 of treatment

*Each point represents mean±SEM of 6 values; *p<0.05 compared to diabetic control rats*

Fig. 2 compares the changes in the mean glucose concentration calculated from the area under the curve (AUC) in diabetic animals treated with *T. superba* extract once a day during 2 weeks from day 1. In untreated diabetic animals, 10% increase in blood glucose concentration was observed after 2 weeks. The mean glucose concentration in the OGTT appeared to be lower in diabetic rats treated with the plant extract as compared to the initial blood glucose concentration (day 1). But the difference between blood glucose levels at different time did not reach statistical significance at the dose of 37.5mg/kg.

3.2 Acute Effect of *T. superba* Extract

The percentage change of blood glucose concentrations of control and STZ-diabetic rats following single oral administration of *T. superba* extract at different time intervals are shown in Fig. 3. The fall in blood glucose level was time-dependent and the greater fall was observed 10h after plant extract administration. The vehicle (distilled water) did not affect significantly the blood glucose levels of the control diabetic rats. The fall in blood glucose concentrations in *T. superba*–treated rats increased with increasing doses of the plant extract, from 30.92% at the dose of 37.5mg/kg to 77.74% at the dose of 300 mg/kg at the end of 10 h, as compared to diabetic control rats. Metformin (500 mg/kg) caused a reduction in blood glucose concentration from 36.72% at 1.5h to 82.59% at 10h.

3.2.1 Effects of treatments on body weight, water and food intake

Table 1 summarizes some general features of the experimental rats. The body weights were significantly less in the untreated and *T. Superba* treated diabetic groups than in the untreated normal group. Compared with normal rats, diabetic animals showed polydipsia and hyperphagia by the end of the study period. In untreated STZ diabetic rats, 21.95% decrease in body weight, 186% and 140% significant increase in water and food intake,

respectively, were observed after 21 days. However, the animals gained weight after treatment with the plant extract and metformin with a maximum increase in body weight of 15% at the dose of 75mg/kg as compared to the initial value. Food and water intakes of *T. Superba* treated diabetic rats (75 –300mg/kg) were reduced significantly as in the metformin treated group when compared to untreated diabetic rats Table 1.

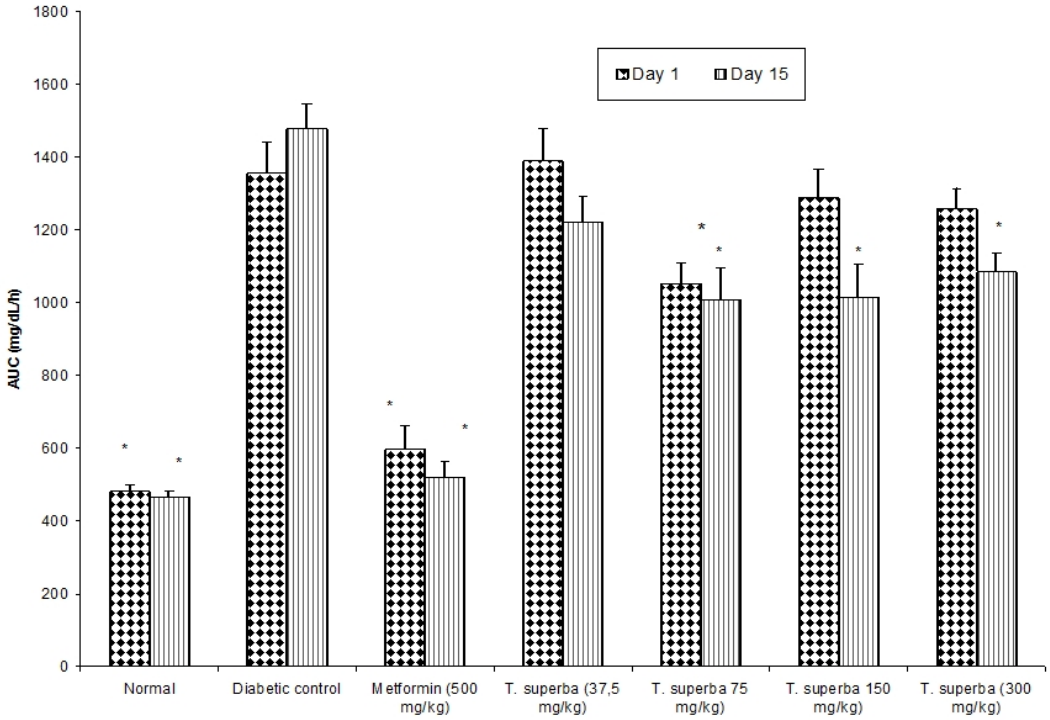

Fig. 2. Effect of *T. superba* extract on blood glucose levels on day 1 and 15 of treatment

*Values are mean±SEM of 6 values, *p<0.05, in comparison with diabetic untreated animals on corresponding day (on day 1, treated groups are compared with diabetic untreated animals and the same comparison is done on day 15)*

3.3 Effect of *T. superba* Extract on Biochemical Variables

The results obtained in untreated and diabetic-treated rats are shown in Table 1. Plasma glucose concentrations were consistently higher (36.97±1.66mM) in the untreated diabetic rats. In the *T. Superba* treated diabetic rats, glycaemia fell to 25.35±2.03–29.05 ± 3.51mM for doses 75-300mg/kg after 21 days but remained significantly higher ($p<0.05$) than the non diabetic control rats. *T. superba* extract showed 31.43% and 21.42% antidiabetic activity at the dose of 75mg/kg and 300 mg/kg, respectively. Daily metformin (500 mg/kg) administration for 21 days produced a statistically significant hypoglycaemic effect of 29% (26.07±1.27 vs 36.97±1.66mM).

Table 1. Effects of three weeks oral administration of *T. superba* extract on physical and biochemical parameters in nonfasting STZ- diabetic rats

Treatment	Initial body weight (g)	Final body weight (g)	Fluid intake (ml/rat/day)	Food intake (g/rat/day)	Glucose (mm)	Cholesterol (mm)	Triglyceride (mm)	Urea (mm)	Insulin (pm)
Non diabetic	289.25±6.21	308.16±7.72*	19.11±0.21*	20.76±0.36*	6.61±0.16*	1.24±0.02*	0.88±0.04*	4.16±0.16*	296.91±20.40*
Diabetic	293.20±12.23	240.50±15.63	226.83±22.28†	50.06±2.78†	36.97±1.66†	2.06±0.12†	1.98±0.16†	7.66±0.50†	69.89±10.12†
Extract (37.5mg/kg)	255.35±12.54	226.00±18.60	189.70±10.17†	45.19±1.73†	35.72±1.50†	1.39±0.07*	1.45±0.19†	6.16±0.16*	74.83±5.04†
Extract (75mg/kg)	288.01±13.02	259.00±20.60	113.73±9.86*†	35.63±5.97*†	25.35±2.03*†	1.55±0.12	1.70±0.17†	6.50±0.50†	195.98±12.90*
Extract (150mg/kg)	251.90±12.03	221.66±12.57	127.55±14.68*†	38.76±3.74*†	28.67±3.43*†	1.63±0.10	1.53±0.12†	6.08±0.08*	129.62±9.57*
Extract (300mg/kg)	249.25±9.48	220.33±13.06	183.70±10.19*†	42.98±2.80*†	29.05±3.51†	1.58±0.07	1.62±0.13†	6.06±0.16*	106.24±16.02†
Metformin (500mg/kg)	275.33±12.08	249.50±15.60	86.35±10.72*†	27.66±1.09*	26.07±1.27*†	1.65±0.07	2.18±0.80†	6.00±0.05*	186.24±14.92*

*Results are expressed as mean±SEM, n=6. *p<0.05 as compared with diabetic untreated group; †p<0.05 as compared with normal control group*

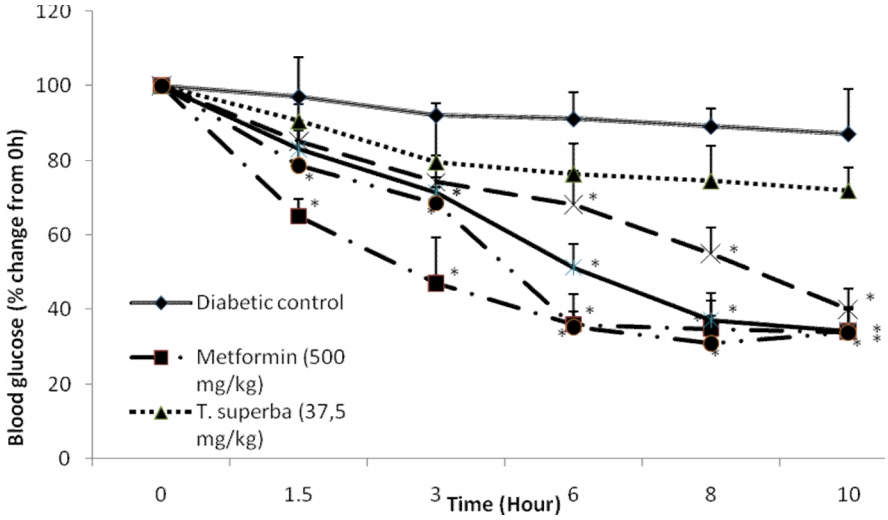

Fig. 3. Effect of a single oral administration of the methanol stem bark extract of *T. superba* on unfasting blood glucose levels (% change) of STZ-diabetic rats

*Data are expressed as means±SEM, n=6 rats per group. *p<0.05 when compared to untreated diabetic rats*

Plasma cholesterol and triglyceride levels in non treated diabetic animals were significantly higher than in control animals, but not significantly different between diabetic control and *T. superba* treated diabetic rats. The induction of diabetes resulted in elevated plasma urea levels which were significantly reduced by the plant extract. Three weeks after STZ injection, plasma insulin was 75.46% less in non treated diabetic rats in comparison with normal animals (69.89±10.12 vs 296.91±20.40pM) but was significantly increased in diabetic treated rats with *T. superba* extract at 75 and 150mg/kg as compared to untreated diabetic control animals (respectively 195.98±12.90 and 129.62±9.57 vs 296.91±20.40pM).

4. DISCUSSION

For the study of antidiabetic agents, STZ induced hyperglycaemia in rodents is considered to be a good preliminary screening model and is widely used [14]. STZ causes hyperglycaemia and massive reduction in insulin release by selective destruction of the beta-cells of the pancreas [15]. STZ is known to damage acutely pancreatic beta-cells through methylation of DNA, which leads to strand breaks and activates poly (ADP-ribose) polymerase for DNA repair [16]. In our study, we observed a significant increase in the plasma insulin levels when STZ diabetic rats were treated with the methanol extract of *T. superba*. This could be due to potentiation of the insulin effect of plasma by increasing the pancreatic secretion of insulin from existing beta-cells of islets of Langerhans or its release from bound insulin.

The most common lipid abnormalities in diabetes are hypertriglyceridemia and hypercholesterolemia [17,18]. Repeated administration of the plant extract for 21 days slightly, but not significantly, reduced plasma cholesterol and triglyceride levels. The effect of *T. superba* on diabetic hypertriglyceridemia and hypercholesterolemia could be through its control of hyperglycaemia. It is possible that the slight reduction of plasma lipid levels observed are related to a direct effect of *T. superba* extract on cholesterol metabolism. High urea levels in STZ-induced diabetes have classically been interpreted as the sign of a certain degree of renal failure associated with diabetes [17,19]. Our studies, however, have

shown that plasma urea levels were significantly reduced by the plant extract. The reduction of the level of plasma urea in diabetic rats suggests that *T. superba* exerts its hypoglycaemic effect through the inhibition of gluconeogenesis, as is the case with biguanides [20]. Thus, the improvement in the impaired plasma urea levels associated with STZ-diabetes with *T. superba* extract treatment in the present investigation could be attributed to its antidiabetic action resulting in the alleviation of the altered metabolic status of the diabetic animals.

Food intake and water intake were reduced in treated as compared to non-treated diabetic rats. Food and fluid intake were decreased in parallel to the reduction of hyperglycaemia and did not reach values lower than those of non-diabetic animals. These observations could indicate that the correction of excessive food and water intake are induced by the correction of the diabetic state. The body weight was decreased in STZ-diabetic rats [21-23]. Administration of *T. superba* extract reduced the intensity of body weights lost in STZ-diabetic rats, especially at the dose of 75mg/Kg. The ability of *T. superba* to protect massive body weight loss seems to be due to its ability to reduce glycaemia.

T. superba extract significantly decreased the blood glucose levels in glucose loaded rats. This may be due to restoration of delayed insulin response or due to inhibition of intestinal absorption of glucose or to an enhancement of glucose utilisation. In this context, other workers have reported that *Coccinia grandis*, [24] *Averrhoa bilimbi* [21] and *Securigera securida* [25] has significant antidiabetic and glucose tolerance effects in experimentally induced diabetic rats. Previous studies reported the presence of tannin and alkaloids in *T. superba* extracts. Those compounds might be at least in part, responsible for the antidiabetic activity of the plant extract as reported by Ravichandiran et al. [26], who showed that tannin supplementation had a favourable effect on plasma glucose and lipid profile concentrations and Agrawal et al. [27], who reported the antidiabetic activity of alkaloids of *Aerva lanata* [28].

In the present study, we used a range of doses for the plant extract (37.5-300mg/kg). The results showed that the effect of the plant extract was not dose dependant. The maximum effect for almost all parameters assessed was obtained at the dose of 75mg/kg. This may indicate that *T. superba* is active at low doses and that the increase in doses could lead to the reduction of the antidiabetic effect. This can be explain by the fact that plant extract contains many active compound which at certain doses may have antagonistic effect and then hindering the antidiabetic effect evaluated in the present study [14].

5. CONCLUSION

The antidiabetic activity of *T. superba* extract seems to be a result of increase in glucose utilization due to a stimulatory effect on insulin release. The antidiabetic effect observed in the present study is of much importance and there is a need for further studies to elucidate the exact mechanism of the antihyperglycemic effect of *T. superba.*

CONSENT

Not applicable.

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed. All experiments have been examined and approved by the Cameroon National Ethics Committee (Ref. N°. FWIRB 00001954).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27(5):1047–53. Doi:10.2337/dia care.27.5.1047. PMID: 15111519.
2. Chibuike I, Conrad CJ, Chinedu I, Kelechi UO, Monday UO. Evaluation of the Antioxidant activities of *Psidium guajava* and *Aloe vera* British Journal of Pharm Res. 2014;4(3):397-406.
3. Ravichandra VD, Padmaa M. Evaluation of Anti-diabetic potentials of methanol extract of *Ficus hispida* Linn. Leaves against Alloxan Induced Diabetic Rats British J Pharm Res. 2014;4(3):315-24.
4. Marles RJ, Farnsworth NR. Antidiabetic plants and their active constituent. Phytomedicine. 1995;2:137–189.
5. Nagappa AN, Thakurdesai PA, Venkat Rao N, Singh J. Anti diabetic activity of *Terminalia catappa* Linn fruits. J. Ethnopharmacol. 2003;88:45–50.
6. Anzana P, Morshedul A, Anwarul H, Amrita B, Liaquat A, and Begum R. Study of the Hypoglycemic Effect of *Tamarindus indica* Linn. Seeds on Non-Diabetic and Diabetic Model Rats. British J Pharm Res. 2013;3(4):1094-1105.
7. Berhaut J. Flore illustrée du Sénégal: Dicitylédones. Tome II, Balanophoracées. Dakar; 1974. In French.
8. Adjanohoun JE, Aboubakar N, Dramane K. Ebot M, Ekpere JA, Enow-Orock EG, et al. Traditional medicine and pharmacopoeia. Contribution to ethnobotanical and floristic studies in Cameroon. Organization of African Unity Scientific, Technical and Research Commission. Centre National de Production de Manuels Scolaires, Porto-Novo, Benin; 1996.
9. Burkill HM. The useful plants of west tropical Africa.2nd edition, vol. 1, Royal Botanic Garden, Kew, Great Britain; 1985.
10. Tom EN, Demougeot C, Mtopi OB, Dimo T, Djomeni PD, Bilanda DC, Girard C, Berthelot A. The aqueous extract of *Terminalia superba* (*Combretaceae*) prevents glucose-induced hypertension in rats. J Ethnopharmacol. 2011;133(2):828-33.
11. Adewunmi CO, Agbedahunsi JM, Adebajo AC, Aladesanmi AJ, Murphy N, Wando J. Ethno-veterinary medicine : screening of Nigerian medicinal plants for trypanocidal properties. J. Ethnopharmacol. 2001;77:19-24.
12. Gauthaman K, Maulik M, Kumari R, Manchanda SC, Dinda AK, Maulik SK. Effect of chronic treatment with bark of *Terminalia arjuna*: A study on the isolated ischemic-perused rat heart J. Ethnopharmacol. 2001;75:197-201.
13. Dimo T, Rakotonirina SV, Tan PV, Azay J, Dongo E, Cros G. Leaf methanol extract of *Bidens pilosa* prevents and attenuates the hypertension induced by high-fructose diet in wistar rats. J. Ethnopharmacol. 2002;83:183-91.
14. Dzeufiet DPD, Tedong L, Dimo T, Assongalem EA, Sokeng DS, Kamtchouing P. Hypoglycaemic effect of the metylene chloride/methanol root extracts of *Ceiba pentandra* in normal and diabetic rats. Indian J Pharmacol. 2006;38(3):194-97.
15. Herbert V, Lau KS, Gottlieb CW, Bleicher SJ. Coated charcoal immunoassay of insulin. J. Clin. Endocrinol. Metab. 1965;25:1375-84.

16. Rathi SS, Grover JK, Vats V. The effect of *Momordica charantia* and *Mucuna pruriens* in experimental diabetes and their effect on key metabolic enzymes involved in carbohydrate metabolism. Phytother Res. 2002;16:236–43.
17. Matsuda M, Kawasaki F, Mikami Y, Takeuchi Y, Saito M, Eto M, Kaku K. Rescue of beta-cell exhaustion by diazoxide after the development of diabetes mellitus in rats with streptozotocin-induced diabetes. EJP. 2002;45(3):141–48.
18. Cam CM, Pederson RA, Brownsey RW, McNeill HJ. Long-term effectiveness of oral vanadyl sulfate in STZ-diabetic rats. Diabetologia. 1993;36:218–24.
19. Omobola AK, David AO, Olarinde SA, Julius BF. Effects of *Momordica charantia* on serum lipid profile, serum protein levels and selected markers of cardiovascular damage in diabetic rats. British J Pharm Res. 2014;4(4):429-42.
20. Sachdewa A, Khemani LD. Effect of *Hibiscus rosa sinensis* Linn ethanol flower extract on blood glucose and lipid profile in streptozotocin induced diabetes in rats. J Ethnopharmacol. 2003;89:61–6.
21. Pepato M, Baviera AM, Vendranini RC, Perez MPMS, Kettulhut IC, Brunetti IL. *Cissus sicyodes* princess vine; in the long-term treatment of streptozotocin-diabetic rats Biotechnol. Appl. Biochem. 2003;37:15-20.
22. Pushparaj PN, Tan HKB, Tan CH. The mechanism of hypoglycemic action of the semi-purified fractions of *Averrhoa bilimbi* in streptozotocin-induced diabetic rats. Life Scie. 2001;70:535–47.
23. Maghrani M, Lemhadri A, Jouad H, Michel JB, Eddouks M. Effect of the desert plant *Retama raetam* on glycaemia in normal and streptozotocin-induced diabetic rats. J. Ethnopharmacol. 2003;87:21–5.
24. Oyesola OO, Tope O, Omobolanle I, Ogundele, Chijioke M, and Sunday A. *In vitro* antioxidant, antihyperglycaemic and antihyperlipidaemic activities of ethanol extract of *Lawsonia inermis* Leaves. British J Pharm Res. 2014;4(3):301-14.
25. Hosseinzadeh H, Ramezani M, Danaei AR. Antihyperglycaemic effect and acute toxicity of *Securigera securidaca* L. seed extract in mice. Phytother Res. 2002;16:745–47.
26. Mamun Al-Amin, Muhammad NU, Ashfique R, Siddiqul I. Effect of Ethanol Extract of *Coccinia grandis* Lin leaf on Glucose and Cholesterol Lowering Activity. British J Pharm Res. 2013;3(4):1070-78.
27. Ravichandiran V, Nirmala S, Nazeer AKFH. Protective effect of tannins from *Ficus racemosa* in hypercholesterolemia and diabetes induced vascular tissue damage in rats. Asian Pacific J Trop Med. 2012;5(5):367–73. Doi.org/10.1016/S1995-7645 (12) 60061-3.
28. Agrawal R, Sethiya NK, Mishra SH. Antidiabetic activity of alkaloids of *Aerva lanata* roots on streptozotocin-nicotinamide induced type-II diabetes in rats. Pharm Biol. 2013;5(5):635-42. Doi: 10.3109/13880209.2012.761244.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=526&id=14&aid=4665