ANTIDIABETIC AND HYPOLIPIDEMIC EFFECTS OF *CANARIUM SCHWEINFURTHII* HEXANE BARK EXTRACT IN STREPTOZOTOCIN-DIABETIC RATS

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Summary

Canarium schweinfurthii (Burseraceae) is empirically used in Cameroon to treat various ailments, including diabetes mellitus. In the present work, the anti-diabetic effects of the hexane extract of *C. schweinfurthii* stem bark was evaluate in streptozotocin (STZ)-induced diabetes rats. Hypoglycemic and hypolipidemic effects of the plant extract where also evaluated. Acute (5h) and sub-chronic (14 days) treatments were undertaken using graded doses of the hexane bark extract in normal and diabetic rats. Diabetic groups treated with extract were compared with standard insulin. In normal and diabetic rats, the extract (75 and 150 mg/kg) produced a significant ($P<0.001$) hypoglycaemic effect 2 hours post-dosing during acute treatment. Daily treatment of diabetic rats with hexane extract (38, 75 and 150 mg/kg p.o) significantly decreased blood glucose levels by 72.17, 79.91 and 73.68 %, respectively, while insulin (10 UI/kg) given subcutaneously and once daily, had 71.1 % reduction as compared to initial values. Similarly, the body weight gains were 2.4, 9.4 and 7.9 %, respectively, and were comparable to the normal rats. Still with the same doses, there was 34.1, 46.1, 40.1 % ($P<0.001$) significant decrease in food consumption and 42.9, 60.6 and 52.5 % ($P<0.001$) in fluid intake by diabetic rats treated with the respective doses of the plant extract. The insulin treated rats showed 40.1 % and 64.9 % decrease in food and fluid intake as compared to diabetic control rats, 138.7 % and 504.7% respectively, at the end of the second week of experimentation.

Treatment with *C. schweinfurthii* extract resulted in significant decrease ($P<0.01$) in total cholesterol and serum triglycerides levels in diabetic rats. Decreases in aminotransferase (ASAT and ALAT) levels in diabetic-treated rats were also observed. These results showed that the plant extract can reverse hyperglycemia, polyphagia, polydipsia and hyperlipidemia provoked by streptozotocin, and thus, it have anti-diabetic properties.

Keywords: *Canarium schweinfurthii*; streptozotocin; hypoglycemic; hypolipidemic; antidiabetic effect

Introduction

Diabetes mellitus is a chronic metabolic disease cause by an absolute or relative lack of insulin and or reduced insulin activity, which results in hyperglycemia and abnormalities in carbohydrate, protein and fat metabolism. Though different types of oral hypoglycemic agents are available along with insulin for the treatment of diabetes mellitus, there is a growing interest in herbal remedies due to the side effets associated with these therapeutic agents [1]. The investigation of anti-diabetic agents of plant origin which are used in traditional medicine is thus of great importance.

Canarium schweinfurthii Engl. (Burceraceae) is a forest region plant, wide spread over all Africa, from Senegal to Democratic Republic of Congo, Sudan and Ethiopia. *C. schweinfurthii* locally known as "*Bete*" is a big tree up to 40 m high and 1.5 m diameter with cylindrical bole scaly bark exuding resin, with buttresses not much developed [2]. The stem bark decoction of *C. schweinfurthii* is used as a remedy for roundworms, colic, stomach pains, pains after child birth, gale, dysentery and gonorrhoea [3]. Many plant species are known in folk medicine of different cultures to be use for their hypoglycaemic properties and therefore used for treatments of diabetes mellitus [4, 5]. In the west province of Cameroon, the stem bark maceration of *C. schweinfurthii* is used by traditional healers for the management of diabetes mellitus but apart from our previous study on *Canarium schweinfurthii* methanol/methylene chloride extract (Kamtchouing et al., 2006), limited information is available on the hypoglycaemic activity of this plant.

The aim of this study was to evaluate how the extract of *C. schweinfurthii* influences the biochemical disturbance in streptozotocin-induced diabetic male rats. For this purpose, we have estimated the effects of the hexane stem bark extract of *C. schweinfurthii* in normal and diabetic rats.

Materials and methods

1. Collection of the plant material and preparation of the hexane extract of C. schweinfurthii

C. schweinfurthii stem bark was collected in Batchingou, west province, Cameroon, in August. The botanical identification was performed at the national herbarium Yaounde, Cameroon by comparison with voucher specimens N° 19652/HNC collected by Leuwenberg (N° 8763**).**

The fresh plant material was dried at room temperature and ground into a powder. 900 g of this powder were extracted four times at room temperature (with occasional stirring) in 3 L of hexane for 24 hours. The extract was filtered and concentrated using a rotavapor. A brownish residue was obtained, with a yield of 3.83%.

2. Preliminary phytochemical tests

Phytochemical properties of the hexane extract of *C. schweinfurthii* were tested by the method of Odebiyi, and Sofowora [6], using the following chemicals and reagents : alkaloids with Mayerand Dragendoff's reagents, tannin ($FeCl_3$), Saponin (frothing test), Flavonoids (chip of magnesium and HCl), glycosides (NaCl, and fehling's solutions A and B), steroids (ether ethylic, sulfuric acid and anhydride acetic), Anthraquines (Ether-chloroform and NaOH), phenols ($Fecl_3$ and $K_3Fe(CN)_6$) and polyphenols ($K_3Fe(CN)_6$).

3. Animals

Adult healthy male albino Wistar rats weighing between 200 and 250 g were used in this experiment. They were maintained under standard conditions (12 h light and 12 h dark cycle; 25 ± 3°C; 30-65% humidity), raised on a standard Laboratory diet and were given tap water *ad libitum*. They where fasted overnight prior to blood glucose determination or STZ injection but were allowed free access to water.

4. Induction of diabetes mellitus

Diabetes was induced by a single intravenous injection of freshly prepared streptozotocin (50 mg/kg in 0.9% saline solution), which produced type 1 diabetes mellitus after 72 h of injection. The diabetic state was maintained throughout the experimental schedule.

5. Hypoglycaemic activity of C. schweinfurthii on fasting blood glucose levels in healthy rats

Thirty healthy 12 h fasted rats were divided into 6 groups of 5 animals each. Group I and II served as controls and received a single dose of corn oil (0.25 mL/ 100 g body weight) and isulin, 10UI/kg, respectively. The other groups received a single dose of 38, 75, 150 and 300

mg/kg body weight of the hexane extract of *C. schweinfurthii* dissolved in corn oil (0.25 mL/100 g body weight). Blood samples were collected from the tip of the tail and the serum glucose was estimated (GOD/POD method) using commercial kit (Randox Laboratories, San Diego-USA) at 0 (prior to plant extract administration), 1, 2, 3 and 5 h.

6. Hypoglycaemic activity of C. schweinfurthii on fasting blood glucose levels in diabetic rats

6.1. Acute treatment

Thirty diabetic rats were divided into 6 groups of 5 animals each. They were submitted to the same treatment as previously described for healthy rats.

6.2. Sub-chronic treatment

Animals were divided into 6 groups of 5 rats each. Group I: normal control rats administered corn oil daily for 14 days; Group II: diabetic control rats administered corn oil for 14 days; Group III: diabetic rats administered insulin 10 UI/kg daily for 14 days. The 3 other diabetic groups were administered daily the hexane extract of *C. schweinfurthii* at the dose of 38, 75 and 150 mg/kg, respectively. Changes in body weight were monitored. Fasting serum glucose levels were estimated as described previously on days 1 (before the test compounds), 8 and 15 of extract administration.

At the end of the treatment, rats were sacrificed by decapitation, and the free-running fasted blood was collected. Serum was separated for the determination of serum total protein, total cholesterol and triglycerides levels. Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) activity were also analysed. All those parameters were determined using commercial diagnostic kits, Randox Laboratories, San Diego-USA.

7. Statistical analysis

The results are presented as mean ± SEM. Differences between means were assessed by one-way analysis of variance (ANOVA) followed by Dunnett's test using Stat-Direct software. Values of $p < 0.05$ were taken to imply statistical significance.

Results

1. Phytochemistry

Triterpenes steroids, saponins, lipids and glycosides were identified whereas tannins, coumarin, alkaloids, phenols and anthraquines were absent.

2. Hypoglycaemic effect of C. schweinfurthii on normoglycaemic rats

The effect of *C. schweinfurthii* on blood glucose levels in fasting normal rats is shown in Figure 1. A single administration of *C. schweinfurthii* extract at the doses of 38, 75 and 150 mg/kg exhibited a significant hypoglycaemic effect after 2 hours. The maximum hypoglycaemic effect (33.80 % of reduction, $p<0.001$) was observed 2 h after treatment with the dose of 75 mg/kg. There after, the blood glucose level started to increase but remain lower. At this concentration, the plant extract wasn't more effective than insulin (10 UI/kg) which produced a significant ($P<0.001$) reduction in blood glucose level by 66.8% with respect to the initial value. *C. schweinfurthii*-treated groups also showed a significant ($P<0.05$) hypoglycaemic effect as compared to the untreated control group.

3. Hypoglycaemic effect of C. schweinfurthii *on diabetic rats*

3.1. Acute treatment

In diabetic rats, the extract produced a significant ($P<0.001$) hypoglycaemic effect at the doses 38, 75 and 150 mg/kg compared to the diabetic control rats. The blood glucose levels were reduced by 36, 43 and 35% respectively, 2 h post dosing (Figure 2). Insulin produced the most hypoglycaemic effect (85% reduction as compare to initial value).

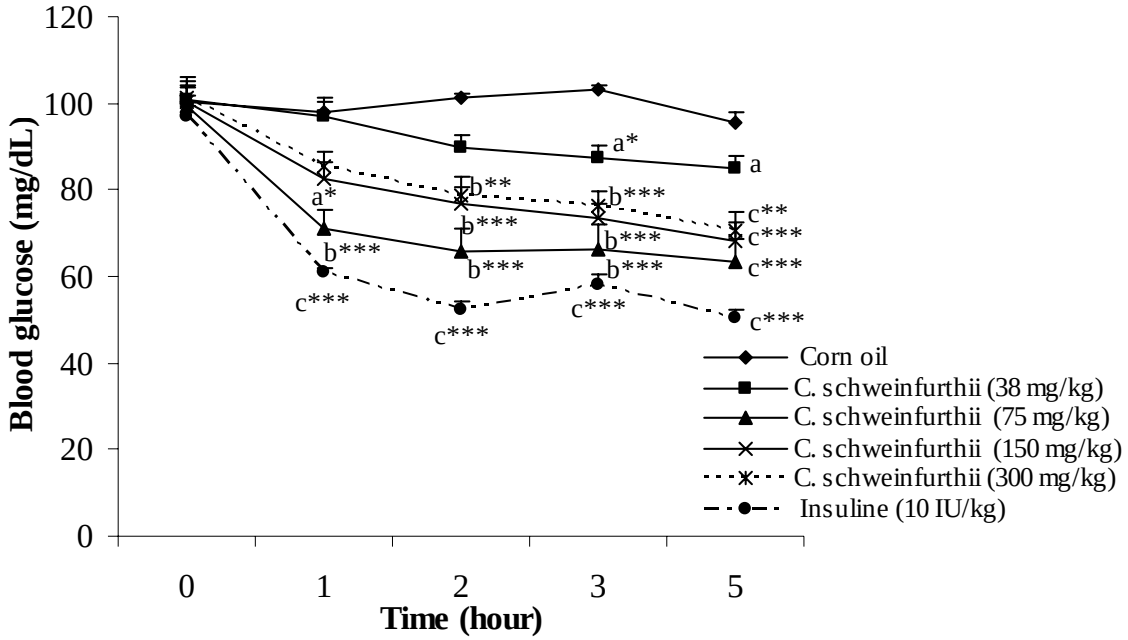

Figure 1: Effect of the hexane extract of *C. schweinfurthii* on serum glucose levels in normal rats. Values are given as means ± SEM, n=5; * $p<0.05$, ** $p<0.01$, *** $p<0.001$; significantly different from normal control; [a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$; significantly different from initial value.

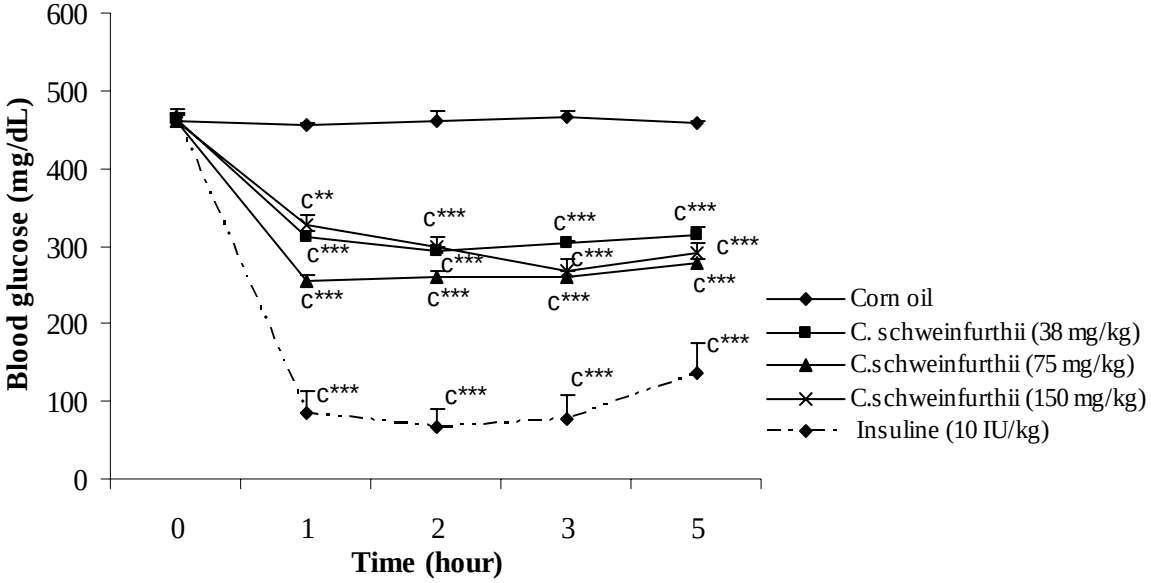

Figure 2: Effect of the hexane extract of *C. schweinfurthii* on serum glucose levels in streptozotocin-diabetic rats. Values are given as means ± SEM, n=5; * p<0.05, ** p<0.01, *** p<0.001; significantly different from diabetic control; ^{c} p<0.001; significantly different from initial value.

3.2. Sub-chronic treatment

During the experiment, diabetic control animals showed a progressive decrease in body weight. In diabetic rats treated with *C. schweinfurthii* extract, there was a significant (P<0.01) weight gains at the end of the treatment. Insulin (10 IU/kg) also provoked a significant (P<0.01) increase in body weight (Table 1).

Table1: Effects of *Canarium schweinfurthii* extract on the body weight, food and fluid intakes in STZ-induced diabetic rats.

Treatment	Body weight (g)		Food intake (g/rat/day)		Fluid intake (mL/rat/day)	
	Initial	Final	Initial	Final	Initial	Final
Normal control	225.94± 9.63	247.97± 7.35**	16.16 ± 0.59***	16.59 ± 1.20***	19.03 ± 0.65***	18.62 ± 1.38***
Diabetic control	223.20± 3.89	193.60± 3.21	36.04 ± 0.86	39.6 ± 1.02	97.40 ± 2.96	112.60 ± 2.29
C. schweinfurthii (38 mg/kg)	226.77± 7.26	244.93± 8.92**	27.31 ± 1.01***	23.71 ± 0.86***	66.82 ± 1.85***	39.51 ± 2.05***
C. schweinfurthii (75 mg/kg)	225.71± 1.50	231.11± 1.69**	29.69 ± 1.03**	26.08 ± 0.84***	87.60 ± 2.97	64.20 ± 1.31***
C. schweinfurthii (150 mg/kg)	224.32± 5.09	245.41± 4.19**	24.93 ± 0.99***	21.34 ± 0.89***	82.80 ± 3.76*	44.40 ± 1.34***
Insulin (10 IU/kg)	224.29± 5.78	242.03± 8.91**	27.31 ± 1.01***	23.71 ± 0.86***	85.20 ± 3.36*	53.50 ± 1.35***

Values are expressed as means ± S.E.M.; n=5; $^{*}P< 0.05$, $^{**}P< 0.01$, $^{***}P< 0.001$, significantly different compared to diabetic control.

Table 1 also shows the effects of the plant extract on food and fluid intakes of diabetic rats. When compared to the normal control, the untreated diabetic rats had severe polyphagia and polydipsia at the end of the second week of the experiment with respective increase in food and fluid intakes of 138.7% and 504.7% rats. However, in *C. Schweinfurthii*-treated rats (38 mg/kg, 75 mg/kg and 150 mg/kg), food intake was significantly (P<0.001) reduced by 34.1%, 46.1% and 40.1%, respectively, when compared with diabetic control rats. Insulin-treated rats also had their food intake reduced by 40.1% (P<0.001). Fluid intakes was significantly (P<0.001) decreased by 42.9%, 60.6% and 52.5% (P<0.001) in *C. Schweinfurthii*-treated diabetic rats at doses of 38 mg/kg, 75 mg/kg and 150 mg/kg, respectively compared with diabetic control rats. Diabetic rats treated with 10 UI/kg of insulin also showed a significant reduction of water intake (64.9%; P<0.001). In diabetic rats, the glucose lowering activity of *C. schweinfurthii* (38, 75 and 150 mg/kg) was statistically significant (P<0.001) as compared to untreated rats (72.2, 79.9 and 73.7% reduction respectively) and was more pronounced than in rats treated with the standard drug (71.1% reduction) (Table 2).

Table 2: Blood glucose level (mg/dL) of rats 3 days post STZ administered and after 14 days of treatment with *C. Schweinfurthii* hexane bark extracts

Treatment	Blood glucose (mg/dL)		Net variation (%)
	Initial	Final	
Normal control	85.00 ± 1.62	88.60 ± 1.63 ***	+ 4.3
Diabetic control	437.60 ± 3.55	472.40 ± 17.69	+ 7.9
C. schweinfurthii (38 mg/kg)	436.20 ± 4.58	121.40 ± 7.17 ***	- 72.2
C. schweinfurthii (75 mg/kg)	433.16 ± 2.31	87.00 ± 8.12 ***	- 79.9
C. schweinfurthii (150 mg/kg)	433.61 ± 4.52	114.13 ± 19.75 ***	- 73.7
Insulin (10 IU/kg)	434.60 ± 1.59	125.40 ± 14.73 ***	- 71.1

Values are expressed as mean ± S.E.M.; n=5; += increase; -= decrease; *** p<0.001, significantly different as compared to diabetic control rats.

Significant differences were also observed in serum total protein, ALT and AST, total cholesterol and triglycerides levels; but no significant change was observed in serum creatinine (Table 3). Streptozotocin diabetic untreated rats showed a high activity of ALT and AST (P<0.001), significant (P<0.001) hypercholesterolemia and hypertriglyceridemia as compared with normal control and diabetic treated rats.

Table 3: Changes in serum constituents of rats after sub-chronic treatment with *C. schweinfurthii* hexane bark extract

Treatment	Total protein (mg/mL)	Creatinine (mg/L)	ALT (UI/L)	AST (UI/L)	Triglycerides (mg/dL)	Total cholesterol (mg/dL)
Normal control	81.88±3.08[b]	5.74± 0.53	34.34±2.77[c]	57.61±2.67[c]	57.10±4.55[c]	87.91±8.87[c]
Diabetic control	59.44±0.80**	6.63 ± 0.53	128.20±2.34***	144.80±8.82***	173.20±8.84***	159.19±2.95***
C. schweinfurthii (75 mg/kg)	88.81±7.73[c]	5.01 ± 0.49	32.28±2.57[c]	50.31±2.39[c]	54.29±6.53 [c]	65.68±1.73[c]
C .schweinfurthii (150 mg/kg)	85.94±3.43[b]	6.25 ± 0.80	32.06±0.24 [c]	47.60±0.46[c]	90.33±3.36**[c]	73.15±1.65[c]
Insulin (10 UI/kg)	86.39±0.77[b]	6.74 ± 0.44	70.40±7.55***[c]	88.00±1.98**[c]	88.40±1.22**[c]	73.80±81.86[c]

Value are given as means ± SEM, n=5; * $p<0.05$, ** $p<0.01$, *** $p<0.001$; significantly different from normal control; [b] $p<0.01$, [c] $p<0.001$; significantly different from diabetic control.

Discussion

In the present work, we investigated the hypoglycemic, antihyperglycaemic and anti-lipemic effects of the hexane extract of *C. schweinfurthii* in STZ-induced diabetic rats. The metabolic disturbances were corrected after administration of the plant extract for 2 weeks, as shown by the normalisation of fasting blood glucose levels, reduction of polyphagia and polydipsia as well as weight gain in diabetic treated rats.

In a single dose study, our results showed that *C. schweinfurthii* significantly decreased blood glucose levels in normal and diabetic rats but was less effective than insulin (10 UI/kg). These observations were different in the multiple dose study, where treatment with the hexane extract of *C. schweinfurthii* resulted in a progressive and significant decrease in blood glucose levels of diabetic rats.

During acute treatment, *C. schweinfurthii* extract reduced the blood glucose of normal rats, suggesting that its hypoglycaemic action may be due to stimulation of insulin secretion by beta cells. *C. schweinfurthii* and sulfonylurea actions may thus be similar. This hypothesis is supported by the fact that in single dose study, *C. schweinfurthii* extract was not effective in STZ diabetic rats where pancreatic β-cells were almost completely destroyed. Similar results had been obtained by Dzeufiet et al., [7] with *Ceiba pentandra* extract on rats. However, in the multiple dose study (14 days), *C. schweinfurthii* hexane extract was able to normalize metabolic disturbances, as shown by the normalisation of fasting blood glucose levels, reduction in polyphagia and polydipsia as well as weight gain in diabetic treated rats. The lower dose (75 mg/kg) appeared to have greater potency than the higher dose (150 mg/kg) in normalization of metabolic disturbances. The progressive reduction of blood glucose levels may be due to the ability of the plant extract to revitalise or regenerate β-cells,

leading to a progressive increase in insulin secretion. More over, the phytochemical test of the plant extract revealed the presence of glycosides and saponins. Those compounds isolated from *Ficus hispida* [8], *Cissus sicyodes* [9] and *Trigonella foenum-graecum* [10] are reported to poses hypoglycaemic activity. The glucose lowering activity of *C. schweinfurthii* may be related to the combination of those two compounds.

Induction of diabetes with STZ is associated with the characteristic loss of body weight which is due to increased muscle wasting in diabetes [11]. This assumption warrants the fact that the body weight of diabetic control rats showed a significant decrease and a low proteinemia was registered whereas diabetic rats treated with the hexane extract or insulin showed body weight gains and their proteinemia was not affected as compared to the normal control group. The weight gain may be due to the protective effect of the plant extract in controlling muscle wasting i.e. reversal of gluconeogenesis.

In the present work, there was no significant change in serum creatinine both in control and treated diabetic rats. The duration of the STZ-induced diabetes (14 days) may not be sufficient to cause renal disease which is responsible of the increase of creatinemia in severe diabetes [12]. The serum transaminase (ALT and AST) levels were elevated in STZ- induced diabetic rats (128.20 and 144.80 Vs 34.34 and 57.61 UI/L in normal rats). The increase of gluconeogenesis and ketogenesis related to the diabetic condition may be due to high level activiy of these transaminases [13, 14]. The restoration of ALT and AST activities to their respective normal levels after treatment with the hexane extract of *C. schweinfurthii* strengthens the antidiabetogenic effect of this extract. Moreover, ALT and AST levels also act as indicators of liver function and restoration of normal levels of these parameters indicates normal functioning of the liver.

Elevation of serum lipid concentration in diabetes is well documented [15]. In insulin deficient diabetics, the plasma free fatty acid concentration is elevated as a result of increased free fatty acid outflow from fat depots, where the balance of the free fatty acid esterification-triglyceride lipolysis circle is displaced in favour of lipolysis [16]. Hypercholesterolemia and hypertriglyceridemia have been reported to occur in STZ–diabetic rats [17, 18] and the significant increase observed in our experiment was in accordance with those studies. Under normal circumstances, insulin activates the enzyme lipoprotein lipase and hydrolyses triglycerides. However, in insulin deficient subjects, it fails to activate the enzyme and causes hypertriglyceridemia [19]. In our study, treatment with *C. schweinfurthii* hexane extract caused a decrease in total cholesterol and triglycerides levels. This significant control of serum lipid levels may be directly attributed to improvements in insulin levels upon *C. schweinfurthii* therapy.

Thus it may be concluded from the result of the present investigation that *C. schweinfurthii* stem barks possess anti-diabetic properties and can be useful for the treatment

of diabetes. Further investigations to find out the active principle(s) and to elucidate the exact mechanism of action are, therefore, required to be undertaken. Longer duration studies on *Canarium schweinfurthii* and its isolated compounds on chronic models of diabetes are necessary to develop a potent antidiabetic drug.

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