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Original Article

Bioassay-guided Antidiabetic Study of Chromatographic Fractions of *Boswellia Dalzielii* Hutch. Leaf Extract

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ABSTRACT

Background: *Boswellia dalzielli* Hutch. (Burseraceae) is a medicinal plant, which is used locally by the local dwellers for the management and treatment of microbial-related diseases, neurological conditions, stomach spasms, diabetes, etc.

Objectives: This study aimed at isolating a phytochemical of anti-diabetic potentials from the leaf of *Boswellia dalzielii* in alloxan-induced diabetic rats.

Methods: The n-butanol fraction of the leaf of *B. dalzielii* was fractionated using column chromatography. Fractions obtained were screened phytochemically and by antidiabetic study.

Results: Encoded column fraction B4 (150 mg/kg) produced a maximum reduction (72.45%) in fasting blood glucose (FBG) of animals after 7 hours, which was significantly ($P<0.05$) different from the controls (alloxan-induced diabetic rats) and was better than glibenclamide (52.67%). The re-column fractions obtained from fraction B4 were pooled based on similar R_f values and encoded B41-B48, and subjected to further antidiabetic evaluation on alloxan-induced mice. Eight sub-fraction with doses of 50 mg/kg each were administered to all the groups. Fraction B44 had the highest reduction of FBG by 65.63%, whose effect was significantly higher than the non-treated diabetic mice (negative control) and glibenclamide (52.68%) at 2.0 mg. Further purification of sub-fraction B44 with Sephadex LH-20 yielded encoded fractions A, B, and C. Isolate C showed the highest inhibition of glycemia (22.85%) when the dose of 10 mg/kg was administered (p.o).

Conclusion: The antidiabetic effect of the plant in laboratory animals (rats and mice) may be due to the presence of the isolated phenolic compounds.

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Introduction

Nature has been the source of medicine since ancient times [1]. The ethnobotanical study has led researchers to explore medicinal plants used by the natives to understand how they work, improve the preparations, and find a standard remedy. Medicinal plants have been used for centuries in traditional systems of medicine for the treatment and management of diabetes as complementary and alternative remedies [2], making them an interesting source of potential drug-candidate compounds [3]. These plants have played a vital role in the treatment of disease conditions, which include epilepsy, obesity, cardiovascular diseases, diabetes, microbial-related diseases, etc. [4-6].

Diabetes mellitus (DM) is a metabolic disorder of the endocrine system that precipitates disturbances in glucose, lipid, and protein homeostasis [7]. This condition is increasing rapidly worldwide. It is secondary to a deficiency of the number of pancreatic β-cells of the islets of Langerhans or resistance of tissue cells to insulin [8]. People suffering from this disease cannot produce or properly use insulin, and persistently have high blood glucose. DM is generally characterized by medical conditions, such as hyperglycemia, glucosuria, polyuria, body weight loss, disability, coma, and even death [9]. The currently, available treatment for diabetes includes insulin and various oral hypoglycaemic agents, which include sulfonylureas, metformin, glucosidase inhibitors, troglitazone, etc. These agents however are reported to produce serious adverse effects, such as liver problems, lactic acidosis, and diarrhea [10]. However, due to appalling scientific reports of these side effects [11], the effectiveness of these compounds has been debatable and there is a demand for new compounds for the treatment of DM [12]. In the last few years, there has been a growing interest in the traditional system of herbal medicine in the care and management of diabetes and diabetes-related diseases globally, due to their natural origin and fewer side effects [13-15]. DM is currently affecting around 422 million people [15] and the number of those affected is increasing daily. By 2030, this number is predicted to reach 366 million populations worldwide. Several plant species have been used for the prevention or management of DM by the Native Americans, Chinese, South Americans, Asian Indians, and Africans [16-19], and about 800 of them have been reported to possess antidiabetic properties [17, 18].

Bowellia dalzielii locally called Hano or Arrarabi in the Hausa language (meaning to prevent bad luck), is a popular plant in the Northern part of Nigeria due to its ethnic medicinal value. The decocted root bark is used traditionally by the Hausa-Fulanis in Sokoto, Nigeria to treat diabetes [20]. A bark decoction is used as an antiseptic wash for sores in Ivory Coast and is an ingredient of a complicated prescription for leprosy [21]. In the northern part of Nigeria, the stem bark is boiled and taken for the treatment of fever and rheumatism, and management of snake bites [21].

Scientific studies have revealed that the plant possesses antibacterial, antibiotic, antifungal, and antiseptic properties, making it a valuable ingredient in natural medicine [22]. The antidiabetic effect of the plant has also been reported by Bobboi and Olusegun [23], Balogun et al. [24], and Yakubu et al. [4]. Phytochemicals, which include boswellic acid, gallic acid, protocatechuic acid, and incensole have been isolated from the stem bark of the plant [25, 26]. Yakubu et al. [4, 27] reported the antidiabetic activity of the crude methanolic as well as the polarity-graded partitioned fractions. They reported that the n-butanol portion had the most promising antidiabetic effect making it a choice for further studies. To the best of our knowledge, there has not been any scientific report on the bioassay-guided isolation of the phytochemical(s) responsible for the antidiabetic effect of the plant. Thus, there is a need to investigate the chemicals within *B. dalzielii* leaf for its antidiabetic efficacy with the view of isolating a possible novel lead for the cure of diabetes.

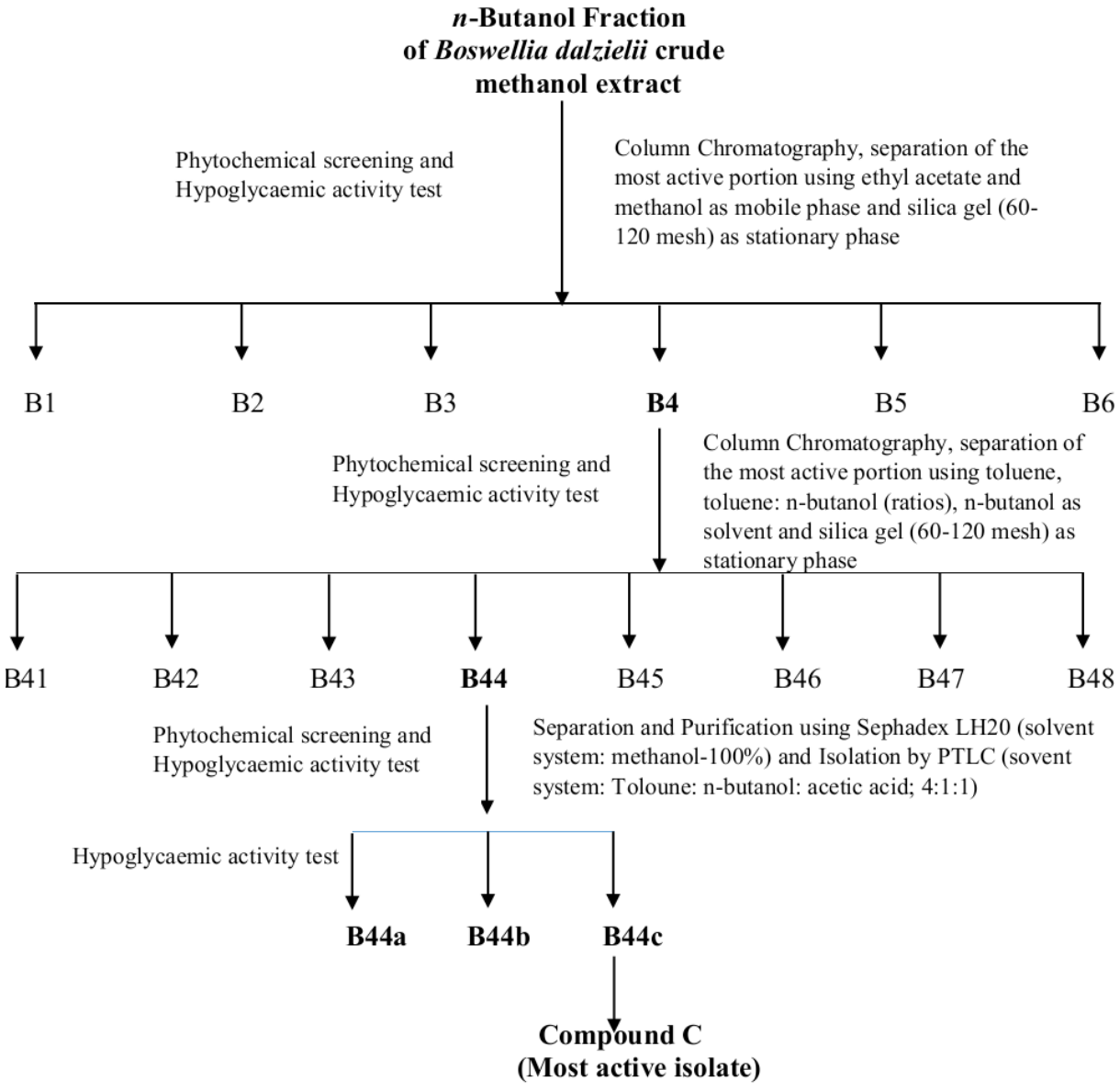
Materials and Methods

Sample collection, identification, and preparation

The fresh leaves of B. dalzielii were collected from Gulantabar, a village in Song Local Government Area of Adamawa State, Nigeria. The plant leaf was given a voucher specimen of UMC/DC/341 and deposited at the herbarium of the Postgraduate Research Laboratory of Chemistry Department, University of Maiduguri, Maiduguri, Borno State. The fresh plant sample was cleaned and shade-dried for ten days. The air-dried plant material was ground using a mortar and pestle and kept in a desiccator until required for use.

Plant extraction

The pulverized leaf material (2 kg) of the leaf was macerated using 22.5 liters of 85% methanol for 72 hours with periodic shaking and allowed to stand at room temperature for proper dissolution of soluble plant chemicals. The liquid mixture of the extract was filtered using



Figute 1. Bioassay directed hypoglycaemic studies/compound isolation

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a clean white muslin cloth followed by filtration using Whatman No. 1 filter paper (200 mm in diameter). The crude extract was concentrated to dryness at reduced pressure.

Partitioning of Methanol Extract of *B. dalzielii*

As earlier reported by Yakubu et al. [27], the crude methanol extract (300 g) of the leaf was partitioned using n-hexane, chloroform, ethyl acetate, and n-butanol.

Fractionation and isolation

The n-butanol partitioned portion of *B. dalzielii* was fractionated by column chromatography and Thin Layer Chromatography (TLC) for the isolation of the phytochemical(s) responsible for the antidiabetic efficacy. The flow chart of the experiments is shown in Figure 1.

The n-butanol fraction of the methanol crude leaf extract of *B. dalzielii* was subjected to further separation using the column chromatographic technique. Silica gel 60-120 mesh (Quikelem, India) was used as the stationary phase. The eluting solvent initially was 100% ethyl acetate and the polarity was gradually increased at 90:10, ethyl acetate: methanol ratio until 0:100 ethyl acetate: methanol ratio was used. Thirty sub-fractions were collected. The column fractions were monitored

for similarities of the fractions based on retardation factor (R_f) values using the TLC technique, and afforded six pooled fractions encoded B1, B2, B3, B4, B5, and B6. This method was used to further purify 10 g of column pooled fraction B4, which afforded 30 re-columned fractions. The fractions were also monitored using TLC plates, and re-pooled based on R_f similarity. The pooled fractions were encoded, which afforded B41, B42, B43, B44, B45, B46, B47, and B48.

Fraction B44 (0.3g) was further purified using an equilibrated Sephadex LH-20 fixed column chromatographic technique. A total of three sub-fractions were obtained and encoded A, B, and C. A preparative TLC was used to isolate a single compound from the sub-fraction C.

Preliminary phytochemical screening

The column chromatographic fractions and sub-fractions were screened qualitatively for phytochemical constituents using standard procedures as described by Evans [28].

Experimental animals

All the experiments performed on laboratory animals in this study followed standard procedures for the treatment of animals. The International Guiding Principle for Biomedical Research involving animals was followed [29]. An Ethical approval (Reference ID: HREC:2021-009) was granted by the Health Research Ethics Committee, University of Maiduguri, Maiduguri, Borno State.

A total of 32 Wistar strained rats (100-180 g) and 46 mice (20-25 g) of both sexes were purchased from the Animal House of the Faculty of Pharmacy, University of Maiduguri. They were housed in clean, sterilized plastic, well-ventilated cages with a wood sawdust as beddings under 12 hours light/12 hours dark cycle conditions of normal room temperature and humidity in the Veterinary Physiology and Biochemistry Laboratory, Faculty of Veterinary Medicine, University of Maiduguri, Maiduguri, for the analysis. They were fed with standard food and water. The animals were allowed to acclimatize for 48 hours before the commencement of the experiment.

Column fractions and alloxan preparation

The column fractions and alloxan (2 g each or the equivalent) were dissolved in 10 mLor its equivalent of distilled water to give a stock solution of 200 mg/mL

$$\text{Volume to be administered} = \frac{\text{Dose x Body Weight in Kg}}{\text{The concentration of the Extract in mg}}$$

Antidiabetic study of column fractions and isolates

The method described by Emordi et al. [30] with a modification was adopted in this study. The acclimatized laboratory animals were fasted for 12 hours and subsequently injected (i.p.) with alloxan monohydrate in ice-cold 0.9% saline (NaCl) solution, at a dose of 150 mg/kg body weight. Animals with a blood glucose of 200 mg/dL or more after 48 hours were selected for the study. The diabetic rats were segregated into nine groups. Groups 1-7 were treated orally with 200 mg/kg each of B1 to B6, respectively. Groups 8, 9, and 10 received (p.o) 2 ml/kg normal saline, glibenclamide (2 mg/kg), and 150 mg/kg alloxan monohydrate solution. At the end of the fasting period, taken as zero time (0 hour), blood was withdrawn from the tip of the tail of each animal and the fasting blood glucose (FBG) was estimated with a blood glucometer (Accu-Check, Roche, Germany). The same procedure described above using mice was repeated for re-columned fractions as well as sub-fractions.

Statistical analysis

The results of the pharmacological study were analyzed using GraphPad Prism software, Version 8 for windows (Graphpad Software, 2016). One-way analysis of variance (ANOVA) followed by Dunnet's Multiple Comparison test was used to analyze and compare the results at a 95% confidence level.

Results

Phytochemical constituents of column fractions

Table 1 presents the phytochemical constituents of the column fractions of the leaf extract of *B. dalzielii*. The results showed that column fractions B2-B6 contained flavonoids, tannins, and saponins, while steroids were absent in the fractions; flavonoids, tannins, saponins, steroids, cardenolides, and terpenoids were present in fraction B1, cardenolides were present in fractions B2-B4, but were absent in fractions B5 and B6.

Phytochemical screening of re-column fraction B4 of *B. dalzielii* leaf

Table 2 presents the result of phytochemical screening carried out on the column chromatographic fractions obtained from the fraction B4 of n-butanol partitioned portions of *B. dalzielii*. The re-column pooled fraction B44 had most of the prominent phytochemicals, which were flavonoids, glycosides, tannins, and saponins.

Table 1. Phytochemical constituents of column chromatography fractions of *B. dalzielii* leaf extract

S/N	Phytochemical Test	B1	B2	B3	B4	B5	B6
	Test tor carbohydrates						
	General test-Molisch	+	+	+	+	+	+
	Test for reducing sugar, Fehling's test	-	+	+	+	+	+
	Test for combined reducing sugar	-	-	-	+	+	+
2	Test for tannins						
	Ferric chloride test	+	+	+	+	+	+
	Lead acetate	+	+	+	+	+	+
3	Test for steroids/triterpenes						
	Salkwoski test	+	-	-	-	-	-
4	Test for flavonoids						
	Shinoda's test	+	+	+	+	+	+
	Ferric chloride test	+	+	+	+	+	+
	Lead acetate test	+	+	+	+	+	+
	Sodium hydroxide test	-	-	-	-	-	-
5	Test for Saponnins						
	Frothing test	-	+	+	+	+	+
6	Test for cardiac glycoside nucleus/cardenolides						
	Keller-Killian's test	+	+	+	+	-	-
7	Test for terpenoids	+	-	-	-	-	-

+: Present; -: Absent

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Effect of column fraction of n-butanol partitioned portion of *B. dalzielii* on alloxan-induced diabetic Wistar strain rats

The column fractions, which were pooled based on the similarities of their R_f values encoded B1-B6 were subjected to further antihyperglycaemic evaluation on alloxan-induced rats. Six fractions of the dose of 150 mg/kg were administered to all the groups. Fraction B4 caused a significant reduction of FBG by 72.45%, while fraction B3 showed the lowest FBG reduction (16.02%). The effect was significantly higher than the effect of the non-treated diabetic rats (negative control) and standard drug glibenclamide (52.68%) at 2.0 mg concentration (Table 3).

Effect of column fraction of n-butanol partitioned portion of *B. dalzielii* on alloxan-induced diabetic mice

The re-column fractions, which were pooled based on the similarities of their R_f values encoded B41-B48 were subjected to further antihyperglycaemic evaluation in alloxan-induced diabetic mice. Eight fractions of the dose of 50 mg/kg were administered to all the groups. Fraction B44 showed the highest reduction of FBG by 65.63%, while fraction B47 had an FBS reduction of 13.52 as the lowest. The effect was significantly higher than the effect of the non-treated diabetic rats (negative control) and standard drug glibenclamide (52.68%) at 2.0 mg concentration (Table 4).

Table 2. Phytochemical constituents of Column chromatography fractions of *B. dalzielii* leaf extract

S/N	Phytochemical Test	$B4_1$	$B4_2$	$B4_3$	$B4_4$	$B4_5$	$B4_6$	$B4_7$	$B4_8$
1	Test tor carbohydrates								
	General test-Molisch	-	-	-	-	-	+	+	+
	Test for reducing sugar-Fehling's test	-	-	-	-	-	+	+	+
2	Test fortannins								
	Ferric chloride test	-	-	+	+	+	+	+	+
	Lead acetate		-	-	+	+	+	+	+
3	Test for flavonoids								
	Shinoda's test	-	-	-	+	+	+	+	+
	Ferric chloride test	-	-	-	+	+	+	+	+
	Lead acetate test	-	-	+	+	+	+	+	+
4	Test for saponins								
	Frothing test	-	-	+	+	+	-	-	-
5	Test for cardiac glycoside nucleus/cardenolides								
	Keller-Killiani's test	+	+	+	+	-	-	-	-

+: Present; -: Absent

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Table 3. Effect of column fractions of *B. dalzielii* leaf extract on alloxan-induced diabetic rats

S/N	Treatment (150 mg/kg)	Basal FBG (mg/dL)	Mean±SD Fasting Blood Glucose (FBG) Concentration (mg /dL) Time (hour) After Treatment					% Inhibition of Glycemia
			0	1	3	5	7	
1	Normal	73.50±5.24	73.00±4.92	75.75±5.02	72.75±4.33	70.50±5.64	78.00±2.74	-
2	D.C	73.50±5.24	263.00±16.50	286.50±25.18	262.00±10.80	253.80±4.33	249.00±9.25	5.32
3	B1	75.00±3.24	293.00±18.40	263.00±24.16	215.50±16.78	180.80±58.98	147.50±24.47*	49.66
4	B2	72.00±4.08	391.30±17.32	370.30±19.12	335.80±32.39	333.80±27.63	284.30±45.90*	27.34
5	B3	72.25±3.47	452.00±8.50	428.50±69.32	432.00±66.20	376.30±55.25	379.30±67.33*	16.02
6	B4	77.00±3.51	433.50±57.39	330.30±36.24	249.00±43.27	170.30±33.65	119.00±26.50*	72.45
7	B5	72.50±3.47	307.80±24.57	267.70±34.68	271.50±24.46	240.30±33.65	227.80±31.51*	25.99
8	B6	80.50±3.48	463.00±41.98	422.30±50.68	407.30±47.49	378.00±43.56	333.50±29.77*	27.95
9	Glibenclamide (2.0 mg)	73.25±1.90	307.50±32.69	305.00±32.16	240.30±46.48	215.30±4.33	145.50±28.93*	52.68

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Results are expressed as Mean±SEM (n=4). *P<0.05 compared to the control group (One-way ANOVA followed by Dunnet's t-test, 2-sided).% Inhibition of glycemia denotes the percentage reduction of blood glucose from 0 hour.

Basal FBG:FBG before induction of diabetes; DC=Diabetic Control.

Table 4. Effect of re-column fractions of the n-butanol partitioned portion of *B. dalzielii* extract on alloxan-induced diabetic mice

S/N	Treatment (50 mg/kg)	Basal FBG (mg/dL)	Mean±SD Fasting Blood Glucose (FBG) Concentration (mg/dL) Time (hour) After Treatment					% Inhibition of Glycaemia
			0	1	3	5	7	
1	Normal	73.50±5.24	73.00±4.92	75.75±5.02	72.75±4.33	70.50±5.64	78.00±2.74	-
2	D.C	73.50±5.24	263.00±16.50	286.50±25.18	262.00±10.80	253.80±4.33	249.00±9.25	5.32
3	B41	79.48±22.35	249.79±4.12	233.89±12.03	230.00±5.23	231.04±6.98	221.98±23.01	11.12
4	B42	69.40±43.76	434.31±12.01	421.34±13.67	401.23±32.76	389.78±43.76	300.90±33.12	30.71
5	B43	71.40±38.76	307.80±24.57	267.70±34.68	271.50±24.46	240.30±33.65	227.80±31.51*	26.00
6	B44	72.01±42.06	433.50±57.39	330.30±36.24	249.00±43.27	200.30±33.65	149.00±26.50*	65.63
7	B45	62.89±24.12	495.00±39.26	358.00±52.49	352.80±48.52	225.00±50.74	200.50±39.02*	59.50
8	B46	66.78±23.90	465.50±38.17	419.00±38.76	413.50±41.65	402.80±42.06	376.30±40.91*	19.18
9	B47	77.10±12.43	503.30±4.73	495.50±40.40	486.00±36.22	471.00±41.24	435.30±42.85*	13.52
10	B48	79.20±13.00	489.03±22.35	399.12±17.45	373.00±32.12	349.12±13.67	300.11±12.19	38.63
11	Glibenclamide (2.0 mg)	73.25±1.90	307.50±32.69	305.00±32.16	240.30±46.48	215.30±4.33	145.50±28.93*	52.68

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Results are expressed as Mean±SEM (n=4). *P<0.05 compared to the control group (One-way ANOVA followed by Dunnet's t-test, 2-sided).% Inhibition of glycemia denotes the percentage reduction of blood glucose from 0 hour.

Basal FBG: FBG before induction of diabetes; DC: Diabetic control.

Table 5. Effect of sephadex column isolates of the n-butanol partitioned portion of crude methanol extract of *B. dalzielii* extract on alloxan-induced diabetic mice

S/N	Treatment (10 mg/kg)	Basal FBG (mg/dL)	Mean±SD Fasting Blood Glucose (FBG) Concentration (m dl) Time (hour) After Treatment					% Inhibition of Glycaemia
			0	1	3	5	7	
1	Normal	73	73	75	72	70	78	-
2	D.C	71	263	286	262	253	249	5.32
3	A	72	207	210	206	200	196	5.31
4	B	71	234	231	231	225	220	5.98
5	C	78	280	270	252	231	216	22.85
6	Glibenclamide (2.0 mg)	78	207	205	190	175	145	29.95

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% Inhibition of glycemia denotes the percentage reduction of blood glucose from 0 hour. Basal FBG: FBG before induction of diabetes; DC: Diabetic control. (n=1)

Effect of sephadex column fractions of n-butanol partitioned portion of *B. dalzielii* on alloxan-induced diabetic mice

The isolates obtained from the Sephadex column chromatographic separation of fraction B44b yielded encoded isolates A, B, and C. The isolates (10 mg/kg) were administered to all the treatment groups. Isolate C had the highest percentage of inhibition of glycemia (22.85). Although the effect was higher than that of the non-treated diabetic (negative control) rats, it was more effective than the standard drug glibenclamide (29.95%) at 2.0 mg concentration (Table 5).

Discussion

The useful remedies of medicinal plants for the treatment of DM and its complication have been attributed to polyphenolics [31], saponins, flavonoids, glycosides, and steroidal compounds present in the plants, which has the ability to reduce the glucose and cholesterol levels in the blood. The use of natural medicinal plants or herbal products for DM has been described in ancient literature. The phytochemical study of the leaf-portioned fractions of *B. dalzielii* revealed chemical constituents, which include flavonoids, cardiac glycosides, tannins, saponins, terpenoids, and alkaloids. The presence of these phytochemicals in the plant parts is in agreement with the report by Balogun et al. [24]. Several reports have shown that flavonoids [32], steroids, terpenoids, or phenolic acids are bioactive antidiabetic principles [33]. The blood glucose-lowering effect of the plant extracts may be attributed to the presence of total phenols, flavonoids, alkaloids, tannins, terpenoids, and saponins that have been known to confer hypoglycemic activity [34].

Chromatography is one of the most effective methods for the isolation of plant chemicals. Alemika et al. [25, 26] isolated phytochemicals from the stem bark and showed the important role of chromatography in the isolation of bioactive chemicals from plants. It was deployed in this study and could significantly separate the phytochemicals and isolate the bioactive compounds. Through bioactivity-guided fractionation, this study demonstrated that the most active sub-fraction was compound C, which was obtained from the series of column fractionations. This study revealed that the blood glucose levels of the diabetic rats treated with the n-butanol column fractions of *B. dalzielii* significantly lowered after 7 hours. This glucose control was sustained till the end of the study. There was a remarkable increase in the antidiabetic activity of the fractions as the compounds were further purified. The hypoglycaemic effect of the extract supports the findings of Bobboi and Olusegun [23] who reported the hypoglycaemic activity of the aqueous stem bark extract of *B. dalzielii* on laboratory rats. Interestingly, the antidiabetic activities of the plant parts are in agreement with the folkloric usage of the plant root and stem in the management of diabetes. Traditionally, the stem and root are macerated in water, and the infusion is used for diabetes, especially for severe diabetes [20].

There is increasing evidence to suggest that free radicals play a role in beta cell damage [35]. The possible phenolic compound isolated responsible for the antidiabetic effect in column sub-fraction C could have acted by inducing pancreatic beta cell regeneration, repair, and revitalization.

Conclusion

The following conclusions could be drawn: the leaf of *B. dalzielii* contains phytochemicals of medicinal importance, which probably are responsible for its effect against DM by decreasing blood glucose levels. As the extract is further purified, the antidiabetic activity increased. Through bioactivity-guided fractionation of the n-butanol partitioned portion, this study demonstrated the significance and role of chromatography in the isolation of bioactive compounds. The most active sub-fraction was compound C, which was obtained from an n-butanol fraction of methanol leaf extract containing phenolic compound(s), a class of phytochemicals responsible for the antidiabetic effect of the leaf of *B. dalzielii.*

Ethical Considerations

Compliance with ethical guidelines

All experimental protocols were in accordance with the National Institutes of Health (NIH) guidelines and approved by the Health Research Ethics Com-mittee, University of Maiduguri, Maiduguri, Borno State (Code: HREC:2021-009)

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflicts of interest.

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