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Full Length Research Article

Alpha-glucosidase Inhibitory and Antigylcation Effects of Compounds Isolated from *Detarium microcarpum* Stem Bark

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ABSTRACT
Diabetes is a leading cause of death and accounted for about 2 million deaths globally in 2019 alone. The disease is characterized by hyperglycaemia and protein glycation. This study was designed to examine the antidiabetic potential of *Detarium microcarpum* stem bark. The plant material was extracted into 70% methanol by cold maceration. The extract was concentrated *in vacuo* and partitioned into n-hexane, dichloromethane, and ethyl acetate soluble fractions. The crude extract and fractions were subjected to alpha-glucosidase inhibitory assay. The active fractions were subjected to a combination of chromatographic techniques, and the isolated compounds were characterized using spectroscopic data. *In vitro* alpha-glucosidase inhibitory and anti-glycation activities of the isolated compounds were evaluated. The crude extract, dichloromethane, ethyl acetate, and aqueous soluble fractions displayed potent alpha-glucosidase inhibitory activity with IC_{50} values of 8.93±2.03, 24.67±1.32, 12.89±2.41 and 7.69±1.09 µg/mL, respectively. The isolated compounds were identified as methyl gallate, quebrachitol, catechin, catechin gallate, and gallic acid. The compounds all displayed potent alpha-glucosidase inhibitory activity. Methyl gallate and catechin displayed the highest activity with IC_{50} values of 83.43±2.68 and 106.27±2. 98 µM compared to acarbose (377.75±1.34 µM). Catechin and catechin gallate displayed antiglycation activity with IC_{50} values of 108±0.30 and 576.34±22.92 µM, respectively. However, a catechin that displayed the highest activity produced about 50% of the antiglycation activity of rutin (54.59±2.20 µM) used as standard. *Detarium microcarpum* stem bark displayed alpha-glucosidase inhibition and the compounds isolated from the ethyl acetate fraction showed protective effects against glucose-induced protein glycation.
Keywords: Alpha-glucosidase, Diabetes, Antigylcation, *Detarium microcarpum,* Catechin gallate, Catechin

INTRODUCTION
Diabetes mellitus (DM) is a chronic metabolic and endocrine disorder that is characterized by hyperglycaemia and oxidative stress which predisposes affected individuals to long-term health complications such as blindness, kidney failure, diabetic foot, amputation, and death if left untreated (Chawla *et al*., 2016). In the past two centuries, there has been an increase in the number of people living with diabetes, which is projected to rise to 440 million by 2030 (Golden *et al*., 2019). Several therapeutic approaches including the use of alpha-glucoside inhibitors have been explored for the treatment of diabetic hyperglycaemia. Alpha-glucosidase inhibitors are important antidiabetic agents because of their role in ameliorating carbohydrate metabolism. Polysaccharides are normally degraded by amylase to dextrin oligomers and further hydrolysed by alpha-glucosidase into alpha-D-glucose that is available in the bloodstream. Hence, alpha-glucosidase inhibitors reduce the amount of glucose that is available in the bloodstream. Hence, alpha-glucosidase inhibitors reduce the amount of glucose that is available in the bloodstream thereby resulting in a low glycemic state (Nguyen *et al*., 2017). The alpha-glucosidase enzyme is located in the brush border of the small intestine and is required for the breakdown of carbohydrates into absorbable monosaccharides. The alpha-glucosidase inhibitors (AGIs) delay, but do not prevent, the absorption of ingested carbohydrates, reducing the postprandial glucose and insulin peaks. In recent years, several researchers have focused on the AGIs of medicinal plants and natural products such as flavonoids and polyphenols are found to be effective inhibitors of alpha-glucosidase (Andrade-Cetto *et al*., 2008; Zhao *et al*., 2023).

Prolonged DM is associated with oxidative stress which results in an accelerated protein glycation reaction. Hence diabetes mellitus is characterised by increased protein glycation and the subsequent build-up of tissue advanced glycation end products (AGEs) that often contribute towards the pathogenesis of complications of diabetes. Protein glycation furthers the generation of free radicals through the autoxidation of glucose and glycated proteins and via the interaction of AGEs with their cell surface receptors (referred to as RAGE). Glycation resulting in free radicals can damage proteins, lipids, and nucleic acids and contribute towards oxidative stress in diabetes. Hence, the compounds with anti-glycation activity may offer the therapeutic benefit of delaying or preventing the onset of diabetic complications. Although many different compounds are under study, only a few have successfully entered clinical trials and none have yet been approved for clinical use. Whilst the search for new synthetic inhibitors of glycation continues, little attention has been paid to anti-glycation compounds from natural sources (Elosta *et al*., 2012). In this present study, the alpha-glucosidase inhibitory properties of *Detarium microcarpum* stem bark extract were studied and the alpha-glucosidase inhibitory

and antiglycation properties of the isolated compounds were determined.

MATERIALS AND METHODS

Plant Collection, Authentication and Preparation

The stem bark of *Detarium microcarpum* was collected from the main campus of the University of Ilorin and authenticated at the Forest Herbarium Ibadan (FHI) where a voucher specimen was deposited and a voucher number (FHI 111953) was issued. The plant material was air-dried at room temperature and pulverised into fine powder.

Extraction and Fractionation Procedure

Ten (10) kg of *D. microcarpum* fine powder was extracted into 25L of 70% methanol for 72 h, filtered, concentrated *in a vacuum* and stored until needed for further use. Ten kilograms of *D. microcarpum* stem bark yielded 17% $^{w}/_{w}$ of extract following extraction with 25L of 70% methanol. The crude extract (1000 g) was partitioned successively into n-hexane, dichloromethane and ethyl acetate soluble fractions and the crude extract yielded 0.3, 4.8 and 45.6 % $^{w}/_{w}$ of n-hexane, dichloromethane and ethyl acetate soluble fractions, respectively. While the aqueous residue yielded 35.6% $^{w}/_{w}$. The fractions and aqueous residue were concentrated *in vacuo*. The crude extract and fractions were stored in the refrigerator until further use.

Isolation of Antiglycation Compounds

The dichloromethane fraction (35 g) of *D. microcarpum* was chromatographed using a glass column (6 x 60 cm) with silica gel (60-120 microns) as the adsorbent (1050 g) using gradient elution using two solvents combination system of n-hexane, dichloromethane and methanol in order of increasing polarity as mobile phase. Column fractions obtained were pooled into seven sub-fractions using their TLC profile. Sub-fraction 4 (273 mg) was purified by dissolving in methanol and passed through a column of sephadex LH-20 using 100% methanol as the mobile phase, 265 mg of the pure compound was obtained and labelled as Compound **1**. Sub-fraction 5 (681 mg) was chromatographed using silica gel (mesh size 40-60 µm) in a long column (1.5 x 50 cm). The column was packed in C_6H_{14}:EtOAc (20:80) and eluted by gradient elution using two solvents combination system of hexane, ethyl acetate and methanol in order of increasing polarity as mobile phase, column fractions obtained were pooled into seven fractions (A-G) as shown in Figure 2. Sub-fraction G (93 mg) was purified by recrystallization in a less polar solvent (acetone) to obtain a pure compound (33 mg) labelled Compound **2**. Thereafter, forty grams (40 g) of ethyl acetate fraction of *D. microcarpum* was chromatographed using a glass column (7 x 60 cm) with silica gel (60-120 microns) as the stationary phase and eluted using two solvents combination system of n-hexane, ethyl acetate and methanol in order of increasing polarity as mobile phase as shown in Figure 2. The fraction was further fractionated into seven sub-fractions (1-7). Sub-fraction 3 (10 g) was further chromatographed using two solvents combination system of n-hexane, ethyl acetate and methanol in order of increasing polarity as mobile phase using silica gel (mesh size 60-120 µm) as the stationary phase and a column (3 x 50 cm) as the stationary support. Fractions obtained were pooled into five fractions (A-D). sub-fraction A (160 mg) was purified by dissolving in methanol and passed through the Sephadex LH-20 column (2 x 20 cm) and the pure compound labelled as compound **3** (20 mg) and a mixture (100 mg) labelled A1 were obtained. The mixture (100 mg) was further purified by passing through a narrower and longer Sephadex LH-20 column (1 x 50 cm) to obtain two pure compounds labelled as compound **4** (28 mg) and compound **5** (31 mg). Compounds isolated were characterized using a combination of mass and NMR spectroscopic techniques. Spectroscopic data obtained were compared to those available in the literature. Mass spectrometric data were generated using EI- MS and FAB-MS (positive and negative modes) techniques using ONE JEOL JMS HX-110 and TWO JEOL JMS-600H mass spectrometers, respectively. anti-glycation activities of the isolated compounds were evaluated as shown in Figure 1.

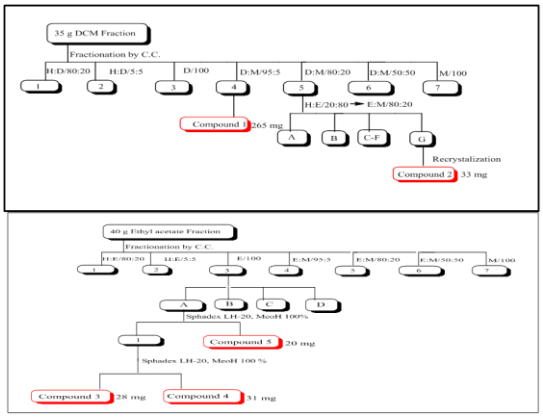

Figure 1: Isolation of compounds from fractions of *Detarium microcarpum* stem bark.

Alpha-glucosidase Inhibitory Assay

The alpha-glucosidase inhibitory activity of the extracts and fractions of *D. microcarpum* were determined using the method described by Elya and co-workers (2012). One (1) mg of alpha-glucosidase (*Saccharomyces cervisiae*, Sigma-Aldrich) was dissolved in 100 mL of phosphate buffer (pH 6.8) containing 200 mg of bovine serum albumin. Thereafter 10 µL of test extract/fractions (50 µg/mL) in 70% DMSO was premixed with 490 µL of phosphate buffer pH 6.8 and 250 µL of 5 mM p-nitrophenyl α-D-glucopyranoside (Sigma Aldrich). The mixture was incubated for 5 mins at 37 ^{o}C. Thereafter, 250 µL α-glucosidase (0.15 unit/mL) enzymes were added into the pre-incubated mixture and further incubated at 37°C for 15 min and the reaction was

terminated by adding 2000 µL Na_2CO_3 200 mM. The inhibition of the α-glucosidase inhibitory activity of the test samples was measured by estimating the amount of p-nitrophenol spectrophotometrically at 400 nm using Spectrophotometer (Spectra Max plus 384). Acarbose and 70% DMSO were used as positive and negative controls, respectively. Acarbose (0.1 mg/mL) was used as the positive control. Extract/ fractions with over 50% at 50 µg/mL are considered active and 10 µL of test extract/fractions in various concentrations (0.52-33 µg/mL) in 70% DMSO was premixed with 490 µL of phosphate buffer pH 6.8 and 250 µL of 5 mM p-nitrophenyl α-D-glucopyranoside (Sigma Aldrich). The mixture was incubated for 5 mins at 37 °C. Thereafter, 250 µL α-glucosidase (0.15 unit/mL) enzyme was added into the pre-incubated mixture and further incubated at 37°C for 15 min and the reaction was terminated by adding 2000 µL Na_2CO_3 200 mM. The inhibition of the α-glucosidase inhibitory activity of the test samples was measured by estimating the amount of p-nitrophenol spectrophotometrically at 400 nm using Spectrophotometer (Spectra Max plus 384). Acarbose and 70%DMSO were used as positive and negative controls, respectively. The IC_{50} value showed the concentration of the extract required to inhibit 50% of α-glucosidase activity and it was determined from a non-linear regression curve plotted using GraphPad prism version 6.0. The experiment was repeated in three replicates (Elya *et al*., 2012). The same process was repeated for the isolated compounds at 1 µM.

Antiglycation/Immunomodulation Assay

The antiglycation activity of the compounds was determined Bovine Serum Albumin assay described by Perera and co-workers (2013). Bovine Serum Albumin (Sigma–Aldrich) 500 µL (1 mg/ml concentration) was incubated with 400µL glucose (500 mM final concentration) and 100 µL of various concentrations (0.063, 0.125, 0.25, 0.5 and 1 µM) of the test compound. Phosphate buffer saline was used as the sample control and rutin (Sigma–Aldrich) was used as the positive control. The reaction was allowed to proceed at 60 °C for 24 hours. The reaction was terminated by the addition of 10 µL of 100% (W/V) trichloroacetic acid (TCA) (Sigma–Aldrich). The whole mixture was allowed to stand for 10 mins at 4 °C before it was centrifuged for 4 minutes at 13000 rpm. The sediment obtained was redissolved with alkaline phosphate buffer saline (pH 10) and was quantified for the relative amount of glycated BSA based on fluoresce intensity by Fluorescent Microplate Reader (Spectra Max). The excitation and emission wavelengths used were 370 nm and 440 nm respectively. Each sample was analyzed in five concentrations and in triplicates. The IC_{50} value showed the concentration of the extract required for the 50% inhibition was determined from a non-linear regression curve plotted using GraphPad Prism version 6.0. (Perera *et al*., 2013).

formula:

% Inhibition = [1 - (Absorbance of test samples/Absorbance of control)] × 100

Statistical Analysis

Data obtained were expressed as means ± SEM of values obtained in triplicates from three independent experiments. Statistical differences between treated groups and standards were evaluated using a one-way analysis of variance (ANOVA). A p-value <0.05 was considered to be significant. Data were analysed using GraphPad Prism Version 6.0 Software.

RESULTS

Alpha-glucosidase Inhibitory Activity of *D. microcarpum* Extract and Fractions

The crude extract of *D. microcarpum* displayed powerful inhibition of the alpha-glucosidase enzyme. At 0.5 mg/mL, the crude extract inhibited alpha-glucosidase enzyme up to 99.8% with an IC_{50} of 8.93±2.03 µg/mL. Similarly, dichloromethane (99.82% inhibition), ethyl acetate (98.76% inhibition) and aqueous (99.89% inhibition) soluble fractions displayed potent alpha-glucosidase inhibitory activity with an IC_{50} value of 24.67±1.32, 12.89±2.41 and 7.69±1.09 µg/mL, respectively. Interestingly, the activity of the crude extract and active fractions of *D. microcarpum* displayed more potent activity than acarbose (IC_{50}= 377.75±1.34 µg/mL) a standard alpha-glucosidase inhibitor as shown in Table 1.

Isolation and Structural Elucidation of Bioactive Compounds

Compound **1** was isolated as a white crystalline solid from dichloromethane faction and identified as methyl gallate with the following spectroscopic data; ^{1}H NMR (in CD_3OD): 7.03 (2H, s) and 3.81 (3H, s), ^{13}C NMR (in CD_3OD) and 2D NMR Data (including COSY, HMBC and DEPT-90, DEPT-135 were used to assign protons to carbon): 121.45 (C-1), 110.04 (C-2), 146.54 (C-3), 140.30 (C-4), 145.51 (C-5), 110.04 (C-6), 169.02 (C-7), 52.24 (C-8). EI-MS *m/z*: 184 (M^+).

Compound **2** was isolated as a white crystalline solid from dichloromethane faction and identified as quebrachitol with following spectroscopic data; ^{1}H NMR (C_5D_5N): 4.17 (1h, t), 4.75 (1H, m), 4.8 (1H, m), 4.65 (1H, t), 4.80 (1H, m), 4.75 (1H, m), 3.92 (3H, s), 6.44 (2 OH, b s), 6.61 (2 OH, b s), 6.71 (1 OH, b, s), ^{13}C NMR (C_5D_5N): 85.81 (C-1), 73.06 (C-2), 72.26 (C-3), 74.67 (C-4), 74.17 (C-5), 73.74 (C-6), 60.73 (C-7). EI-MS m/z: 194 (M^+).

Table 1: Alpha-glucosides inhibitory activity of *D. microcarpum* extract and fractions

SAMPLE	PERCENTAGE YIELD (% w/w)	CONC. (mg/mL)	% INHIBITION ±SEM	IC_{50} ± SEM (µg/mL)
Crude Extract	17.0	0.5	99.8±0.01	8.93±2.03
Hexane fraction	0.3	0.5	0±0.0	
Dichloromethane fraction	4.8	0.5	99.82±0.53	24.67±1.32
Ethyl acetate fraction	45.6	0.5	98.76±0.81	12.89±2.41
Aqueous residue	35.6	0.5	99.89±0.11	7.69±1.09
Acarbose (Standards)	-	0.1	59.02±1.02	377.75±1.34

Compound 3 was isolated as a white amorphous powder from ethyl acetate fraction and identified as catechin with following spectroscopic data; ^{1}H NMR (CD_3OD): 4.562 (1H, d, J_2 = 7.2), 3.989 (1H, ddd $J_{3a,4b}$= 5.6, $J_{3a,4a}$ 8.0, $J_{3a,2a}$ = 7.6), 2.524 (1H, dd, $J_{4a,b}$ = 16.4; $J_{4b,3}$ = 5.6), 2.865 (1H, dd, $J_{4b,a}$ = 16.4; $J_{4a,3}$ = 5.6), 5.846 (1H, d $J_{6,8}$ = 2.0), 5.919 (1H, d $J_{8,6}$ = 2.0), 6.829 (1H, d $J_{2',6'}$ = 2.0), 6.762 (1H, d $J_{5',6'}$ = 8.0), 6.72 (1H, dd $J_{6',2'}$ = 1.6, $J_{6',5'}$ = 8.0). EI-MS m/z: 290 (M^+).

Compound **4** was isolated as a colourless crystalline solid from ethyl acetate fraction and identified as catechin gallate with the following spectroscopic data; ^{1}H NMR (in C_5D_5N): 5.44 (1H, bs), 6.10 (1H, bs), 3.64 (1H, dd, $J_{4a,b}$ = 4.8; $J_{4a,3}$ = 17.2), 3.46 (1H, dd, $J_{4b,a}$ = 4.8; $J_{4b,3}$ = 17.2), 6.65 (1H, d $J_{6,8}$ = 2), 6.66 (1H, d $J_{8,6}$ = 2), 7.13 (1H, d, $J_{3',2'}$ 8), 7.67 (1H, d, $J_{6',2'}$ = 2), 7.84 (1H, s), 7.84 (2H, s). ^{13}C NMR NMR (in C_5D_5N): 78.29 (C-2), 69.27 (C-3), 26.94 (C-4), 157.34 (C-5), 96.93 (C-6), 158.50 (C-7), 95.75 (C-8), 158.68 (C-9), 99.04 (C-10), 130.65 (C-1'), 118.98 (C-2'), 146.98 (C-3'), 147.44 (C-4'), 116.18 (C-4'), 115.63 (C-5'), 121.14 (C-1"), 110.27 (C-2"), 1.47.44 (C-3"), 140.95 (C-4"), 147.44 (C-5"), 110.27 (C-6"), 166.69 (C-7").FAB+ MS M/Z: 443.1 (M^++1).

Compound **5** was isolated as a white crystalline solid from ethyl acetate fraction and identified as catechin gallate with the following spectroscopic data; ^{1}H NMR (in C_5D_5N): 8.078 (1H, s), 8.078 (1H, s) FAB+ MS M/Z: 170.1 (M^++1).

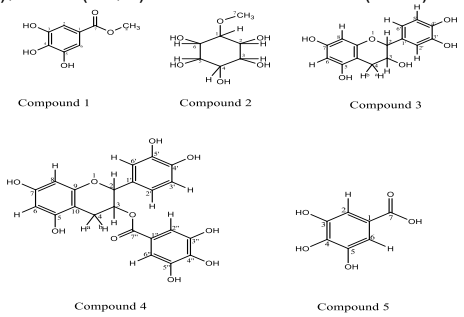

Figure 2: Structure of compounds isolated from *Detarium microcarpum* stem bark

Alpha-glucosidase Inhibitory Activity of Isolated Compounds

The compounds isolated from *D. microcarpum* displayed alpha-glucosidase activity better than acarbose as shown in Figure 3. Methyl gallate and gallic acid displayed the highest activity with an IC50 of 83.43±2.68 and 106.27±2.98 µM, respectively compared to acarbose (377.75±1.34 µM) used as the positive control. However, quebrachitol (328.79±5.38µM) displayed similar activity to acarbose.

Antiglycation/ Immunomodulatory Assay

Compounds isolated from the dichloromethane fraction displayed weak antiglycation activity compared to those isolated from the ethyl acetate fraction. The activities of the compounds were compared to rutin (standard drug). Interestingly only catechin and catechin gallate displayed over 50% antiglycation activity at 1 µM with IC_{50} values of 108±0.30 and 576.34±22.92 µM compared to rutin with an IC50 of 54.59±2.20 µM. However, gallic acid displayed a negative antiglycation effect while quebrachitol displayed a weak antiglycation effect as shown in Table 2.

DISCUSSION

Medicinal plants have been used since the known history of man for the treatment of various types of ailments including diabetes (Siddiqui *et al*., 2022) and the anti-diabetic activities of several medicinal plants used in ethnomedicine (including *D. microcarpum*) have been evaluated and established (Dogara, 2022). In another earlier report, the root bark extract and fractions of *D. microcarpum* were reported to demonstrate *in vivo* anti-diabetic activity with methanol fraction displaying the most potent anti-diabetic activity (Okolo *et al*., 2012). However, there is limited information on anti-diabetic activities and likely mechanisms of anti-diabetic action of bioactive compounds isolated from *D. microcarpum* stem bark.

In this study, the anti-diabetic activity of *D. microcarpum* stem bark was evaluated and the methanol extract displayed anti-diabetic activity by inhibiting alpha-glucosidases enzyme responsible for hydrolysis of starch to simple sugars in a magnitude similar to the reference standard (acarbose) used as positive control. Similarly, in an earlier report, leaf extract and fractions of *D. microcarpum* were reported to exhibit alpha-glucosidase inhibition. However, it was reported that the leaf extract displayed weak alpha-glucosidase inhibition compared to acarbose (David *et al*., 2017).

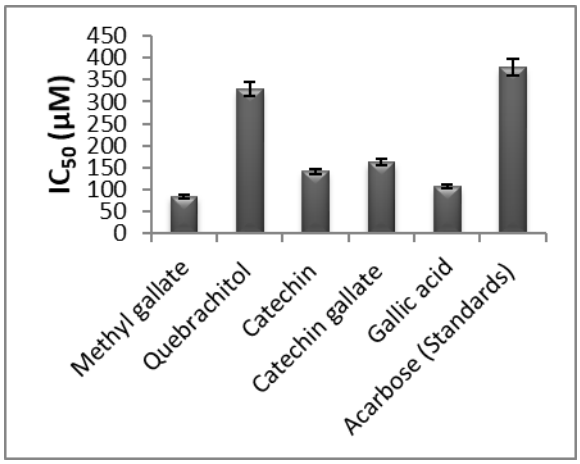

Figure 3: Alpha-glucosides inhibitory activity of isolated compounds from *D. microcarpum*

Table 2: Antigylcation effects of phenolic compounds

SAMPLE	CONC. (µM)	% INHIBITION ± SEM	IC_{50}± SEM (µM)
Methyl gallate	1	39.52±3.33	-
Quebrachitol	1	3.9±0.53	-
Catechin	1	85.34±5.32	108±0.30
Catechin gallate	1	60.19±3.33	576.34±22.92
Gallic acid	1	-17.54±2.58	-
Rutin (Standards)	1	90.97±2.33	54.59±2.20

Five bioactive compounds were isolated from *D. microcarpum* stem bark and were evaluated for their anti-diabetic activity by evaluating their alpha-glucosidase inhibitory and antiglycation activities. Compounds with antiglycation activities have been reported to possess great therapeutic potential for treating diabetes and its complications (Yagi *et al.*, 2013). Methyl gallate, gallic acid, catechin and catechin gallate all displayed significantly higher alpha-glucosidase inhibitory activities than the positive control (acarbose). In previous studies, methyl gallate and gallic acid have been reported to display potent antidiabetic activity (Choudhary *et al*., 2022). Catechin and catechin gallate isolated from the ethyl acetate fraction of *D. microcarpum* displayed high antiglycation activity compared to methyl gallate and quebrachitol isolated from the dichloromethane fraction. Catechin (108±0.30 µM) displayed better anti-glycation activity than catechin gallate (576.34±22.92 µM). However, both catechin and catechin gallate are less active compared to rutin (54.59±2.20 µM). Several polyphenolic compounds including catechin and catechin gallate have been reported to alleviate hyperglycemia and reduce advanced glycation endpoint (Sampath *et al*., 2017, Yagi *et al*., 2013).

CONCLUSION

This study revealed that the methanol extract of *D. microcarpum* stem bark displayed anti-diabetic activity by inhibiting alpha-glucosidase and the compounds isolated from the ethyl acetate fraction of *D. microcarpum* stem bark all displayed alpha-glucosidase enzymes inhibitory effects and antiglycation effects. The alpha-glucosidase inhibitory and antiglycation effects are suggestive of possible mechanisms of the antidiabetic activities of *D. microcarpum* stem bark. Further studies are needed to buttress the antidiabetic mechanism of *D. microcarpum* extract.

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CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.

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