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In vitro α-glucosidase inhibitory activity of isolated compounds and semisynthetic derivative from aerial parts of *Erythrina senegalensis* DC

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ABSTRACT

The current study was conducted to isolate the phytoconstituents from *Erythrina senegalensis* leaves and stem bark and evaluate their inhibitory activity against α-glucosidase, digestive enzyme related to diabetes mellitus. Phytochemical investigation of the leaves resulted in the isolation of three saponins (3–5), two triterpenoids (7 and 8) and two steroids (10a and 10b) as inseparable mixture, while one saponin (6), one triterpenoid (9) and one mixture of two cinnamates (2a and 2b) were isolated from the stem bark. Except for compounds 2 b, 7, 8, 10a and 10 b all the isolated compounds are reported here for the first time from the genus *Erythrina*. Acetylation of the mixture of two cinnamates (2a and 2b) led to a new diester derivative (1) trivially called erythrinamate. The extracts and pure compounds (3, 4, 6) showed good α-glucosidase inhibitory activity compared to the standard drug acarbose. The findings suggest that saponins of *E. senegalensis* could be used to develop potential anti-hyperglycemic drugs.

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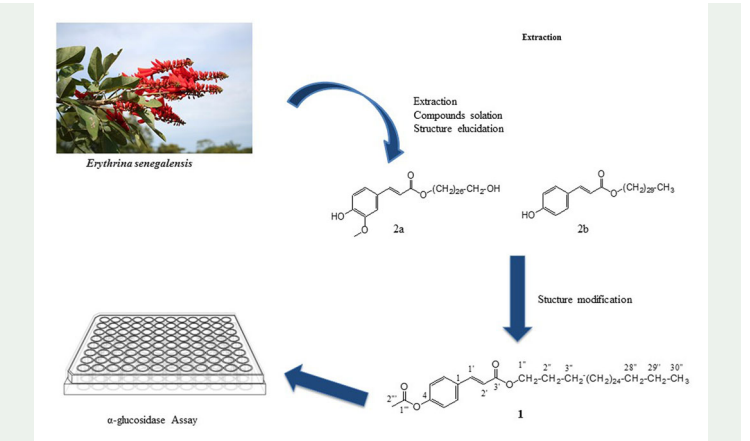


1. Introduction

Human illnesses such as cancer, respiratory defects, cardiovascular diseases and diabetes are usually refered to as non-communicable diseases and they are amongst the leading causes of deaths (Zimmet et al. 2014). Diabetes and its related ailments fall within the top ten causes of death, with a global increasing prevalence that is estimated to rise from 9.3% world's population to about 10.2% and 10.9% by 2030 and 2045 respectively (Saeedi et al. 2019; Khodakarami et al. 2022). Diabetes Mellitus (DM) also called diabetes, is a chronic metabolic disorder characterized by an increase in the serum blood glucose levels. Diabetes develops when the cells of the body become unable to efficiently metabolize sugar, resulting from either the inability of the pancrease to produce sufficient insulin (the peptide hormone which regulates blood glucose) or inability of the body to use its produced insulin (Salehi et al. 2019). Therefore, diabetes can result from defects in insulin secretion (Type 1 DM) or insulin action (Type 2 DM), or both. Most diabetic patients suffer from type 2 DM, is non-insulin-dependent diabetes, and it results from insulin resistance in which the body is unable to use the insulin produces effectively, leading to hyperglycemia (Tripathy and Chavez 2010). The chronic hyperglycemia resulted from diabetes can lead to irreversible damage, dysfunction and failure of various organs such as kidneys, blood vessels, heart, eyes and nervous system (El Barky et al. 2017) and this can possibly result to disabilities and untimely death. Many drugs are clinically available for the management of type 2DM, capable of exercising hypoglycemic effects and lowering blood glucose levels through different mechanisms and they can be classified as classes biguanides, sulfonylureas, thiazolidinediones, α-amylase and α-glucosidase inhibitors (Salehi et al. 2019). The α-amylase and α-glucosidase inhibitors, such as miglitol and acarbose, block the action of enzymes responsible for carbohydrate hydrolysis by binding around the carbohydrate-binding region and interfering with their ability to hydrolyze the carbohydrates into monosaccharides, thereby reducing postprandial blood sugar levels (Nyemb et al. 2022; Khan et al. 2022; Tamfu et al. 2022a, 2022b). Acarbose is a medication clinically used in the treatment of diabetes but this one possesses side effects

including abdominal distention and diarrhea (Kifle et al. 2021). Up to date, there is a need to search for an alternative medication in decreasing serum blood glucose level in patients they suffering from diabetes. Naturals products, both compounds and extracts, from various medicinal plants are suitable alternatives for diabetes therapy since they are easily available, cheap and have little side effects, and most of them act as α-amylase and α-glucosidase inhibitors or insulin supplements (Chokki et al. 2020; Beddiar et al. 2021; Okoduwa et al. 2021; Alam et al. 2022; Ansari et al. 2022). Among the medicinal plants with confirmed antidiabetic effect is *Erythrina senegalensis* DC. (Bilanda et al. 2020; Fahmy et al. 2020).

Recently, we reported that the root wood of this plant contained triterpens, pterocarpans and saponins which act as α-glucosidase inhibitors (Djoko et al. 2021). Until now, there are no studies of the antidiabetic effects of pure molecules from *Erythrina senegalensis* leaves and stem bark. Therefore, this study reports the inhibitory effect of eleven isolated compounds (soyasaponin I, kaikasaponin III, daucosterol, sericoside, β-amyrine, oleanolic acid, sericic acid, β-sitosterol, stigmasterol, erythrinasinate B and erythrinasinate X) on α-glucosidase activity. In continuation of our search for antidiabetic agents from natural origin, we identified four saponins (3, 4, 5 and 6) from *E. senegalensis* that showed potential inhibitory activity against α-glucosidase.

2. Results and discussion

2.1. Chemical compounds

Various chemical compounds with structures given on Figure 1 were obtained from the ethyl acetate and methanol extracts from the leaves of *E. senegalensis* through column chromatography. The compounds include erythrinasinate B (**2 b**) (Wandji et al. 1990), soyasaponin I (**3**) (Sakamoto et al. 1992), kaikasaponin III (**4**) (Sakamoto et al. 1992), daucosterol (**5**) (Nyemb et al. 2018a), sericoside (**6**) (Bombardelli et al. 1974), β-amyrin (**7**) (Mahamat et al. 2020), oleanolic acid (**8**) (Seebacher et al. 2003; Venditti et al. 2016), sericic acid (**9**), β-sitosterol (**10a**) and stigmasterol (**10b**) (Nyemb et al. 2018a; 2018b) which were identified by NMR spectroscopic analysis and comparing with relevant reported data. A new derivative, compound **1**, was obtained through the acetylation of the mixture **2a + 2b** and was characterized using NMR and MS experiments.

2.2. α-Glucosidase inhibitory activity

The α-glucosidase inhibitory potential of the extracts and isolated compounds are given on Tables 1 and 2. The percentage inhibitions evaluated at 10 mM for pure compounds indicates that some of those compounds could be exploited for their α-glucosidase potential and find application in the management of diabetic conditions. At 200 μg/ml, the ethyl acetate (62.2%) and methanol extract (67.1%) showed good α-glucosidase inhibitory activity, and their IC_{50} values were found to be 97.6 ± 1.0 μg/ml and 83.2 ± 0.8 μg/ml respectively (Table 1). Some *Erythrina* species are used for the management of diabetic ailments, and have shown potential to remedy type 2 diabetes, usually attributed to the intake of flavonoids and other constituents contained in the

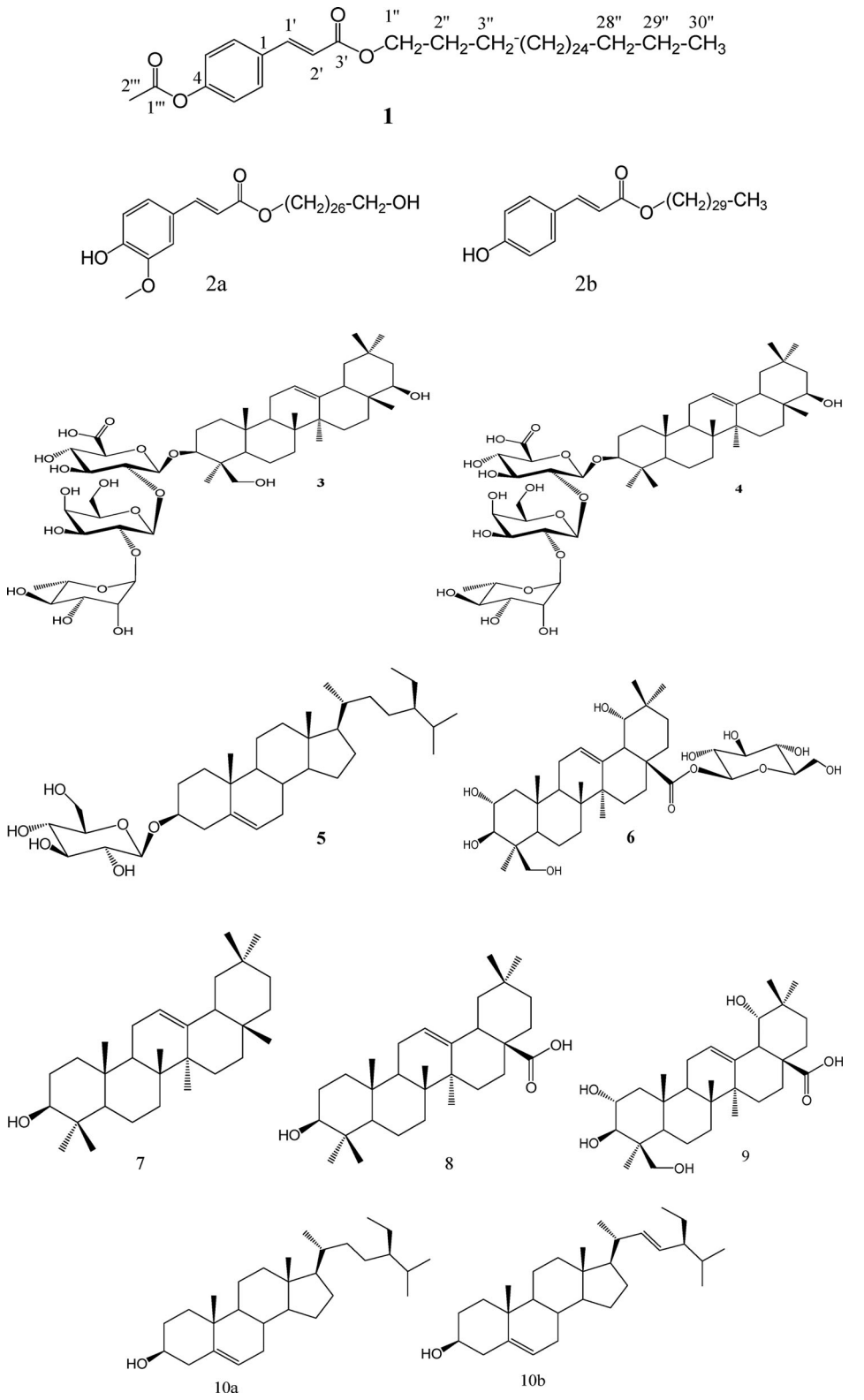


Figure 1. Structures of compound isolated from *E. senegalensis* leaves and stem bark.

Table 1. α-glucosidase inhibition by extracts and compounds mixture.

Samples	%inh. (2 mg/ml)	IC_{50} (μg/ml)
EtOAc	62.2	**97.6 ± 1.0**
MeOH	67.1	**83.2 ± 0.8**
2a and 2b	38.3	/
10 + 11	28.7	/

Table 2. α-glucosidase inhibition by tested compounds.

Samples	%inh. (10 mM)	IC_{50} (μM)
1	40.1	/
3	59.1	0.12 ± 0.0
4	55.9	0.15 ± 0.0
5	51.8	0.26 ± 0.0
6	60.5	0.10 ± 0.0
7	41.8	/
8	50.2	0.32 ± 0.0
9	52.5	0.30 ± 0.0
Acarbose	69.0	0.20 ± 0.0

various species of *Erythrina* (Kumar et al. 2011; Ndinteh 2016). Precisely, extracts of *E. senegalensis* has shown specific and significant ability to reduce blood glucose levels, that is, reverse hyperglycemia, and other related pathologies in diabetic rat models and the activity was attributed to the presence of some chemical constituents (Djoko et al. 2021).

The compounds isolated from the tested extracts were equally evaluated for the potential α-glucosidase inhibitory activity. Amongst the compounds tested, Compound **6** showed highest percentage inhibition (60.5%) at the dose of 10 mM with an IC_{50} value of 0.10 ± 0.01 μM, followed by Compound **3** (59.1%) with an IC_{50} value 0.12 ± 0.01 μM (Table 2). The saponosides compounds **3**, **4** and **6** showed better activity than other isolated compounds. The structural features combining sugar moiety with various hydroxyl groups on the aglycone in saponins **3**, **4** and **6** seem to be responsible for the increased α-glucosidase inhibitory activity. However, saponin **4** shares the same sugar chain with **3** without a hydroxyl group at C-24 of the aglycone. Saponin **4** was less active than **3**, and in turn, compound **3** was less active than compound **6**, thereby suggesting that the additional hydroxyl groups played an important role in enhancing the antidiabetic activity. It has been proven through molecular docking studies that presence of several polar hydroxyl groups intervenes in the stabilization of compounds in the active sites of digestive enzymes through the electron-donating hydroxyl groups and hydrogen-bonding interactions inside the pocket with polar and charged amino acids (Swilam et al. 2022). Sericoside and seric acid have the same aglycon in terms of their structure. However, sericoside (compound **6**) was more active than seric acid (compound **9**), which could be due to the presence of a glucose moiety in its structure. Acetylation of the compound **2** into compound **1** led to an increase in activity and this has been explained that esterification of the hydroxyl group could improve antidiabetic and offer new potential and enhanced therapeutic molecules against type 2 diabetes mellitus (Ahmed et al. 2018; Tamfu et al. 2022b). The present study

provided evidence for further development of *E. senegalensis* in the treatment of diabetes mellitus.

3. Experimental

3.1. General experimental procedure

Column chromatography (CC) was performed on silica gel 60 (70–230 mesh, Merck), and Thin Layer Chromatography (TLC) was performed on silica gel pre-coated plates F-254 Merck (20 × 20 cm). Spots were visualized under UV light (254 and 365 nm), sprayed with diluted sulphuric acid, then heated. The ^{1}H and ^{13}C NMR data were recorded on spectrometer Bruker Avance AV-500 and 600, and tetramethylsilane (TMS) was used as standard. An iTecan Microplate reader was used in the α-Glucosidase inhibitory assay.

3.2. Materials

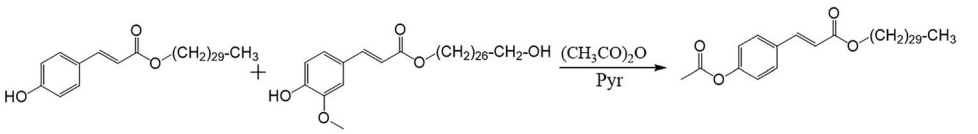
The leaves and stem bark of *Erythrina senegalensis* were collected in Ngaoundere, in the Adamawa Region during the month of July 2020. The plant was identified at the National Herbarium of Cameroon (NHC) with the voucher number: N° 50119 NHC.

3.3. Extraction and isolation procedure

The leaves and stem bark of *E. senegalensis* were collected, dried at room temperature then ground into powder. The ground leaves of *E. senegalensis* (1 Kg) was immersed in methanol (4 L) and kept for 72 h, while the ground stem bark (0.5 Kg) was combined with 3 L ethyl acetate. The resulting solutions were evaporated using a rotary evaporator to obtain 45 g and 18 g of methanol and ethyl acetate crude extract respectively. Twenty-five g of methanol and 17 g of ethyl acetate extracts were separated through column chromatography on silica gel using gradient system of hexane/ethyl acetate (0 → 100%) and ethyl acetate/methanol (0 → 100%) as solvent elution. From the methanol extract, a total of 370 fractions were obtained and grouped into eighteen subfractions (A-R) according to their TLC profile. Subfractions B, C, E, H, M and N crystallized and were filtered and washed to obtain compound **10** and **11** (14 mg), **7** (12.3 mg), **8** (9 mg), **5** (9.2 mg), **4** (20 mg) and **3** (12 mg) respectively. From the ethyl acetate extract, a total of 262 fractions were collected and grouped into thirteen subfractions (A-M) affording 16 mg, 8.4 mg and 7.3 mg of compounds **2a** and **2b** in mixture, **9** and **6** respectively.

3.4. Preparation of compound 1

A solution of the mixture **2a + 2b** (7 mg) in dry chloroform (3 ml) poured in a two necked round bottom flask provided with moisture trap. Acetic anhydride (2 ml) and pyridin (2 ml) were added by charging funnel and the reaction mixture was kept under stirring at room temperature for 24 hrs. Compound **1** selectively crystallized from the reaction mixture upon addition of 10 mL of methanol. The crystals were washed with



Scheme 1. Acetylation of the mixture **2a + 2b** to compound **1**.

few drops of methanol to give 5.3 mg of compound **1**. The reaction conditions are reported below (Scheme 1)

***Erythrinamate (1)*:** *white powder, ESI-MS: m/z:* 648.1 $[M + Na\text{-}H]^+$ (calcd. 648.5090 for $[C_{41}H_{69}O_4Na]^+$). ^1H NMR (500 MHz, $CDCl_3$): 7.59 (2H, d, $J = 8.5$ Hz, H-2 and H-6), 7.14 (2H, d, $J = 8.5$ Hz, H-3 and H-5), 7.68 (1H, d, $J = 16.0$ Hz, H-1′), 6.42 (1H, d, $J = 16.0$ Hz, H-2′), 4.23 (1H, t, $J = 6.0$ Hz, H-1″), 1.73 (1H, quintuplet, $J = 6.0$ Hz, H-2″), 1.41-1.45 (1H, m, H-3″), 1.29 (48H, m, H-4″-H-27″), 1.58 (2H, m. H-28″), 1.32 (2H, m, H-29″), 0.91 (3H, t, $J = 6.5$ Hz, H-30″), 2.34 (3H, s, H-2‴). ^{13}C NMR (125 MHz, $CDCl_3$): 132.2 (C-1), 122.1 (C-2), 129.1 (C-3), 152.0 (C-4), 129.1 (C-5), 122.1 (C-6), 143.4 (C-1′), 118.5 (C-2′), 166.9 (C-3′), 64.8 (C-1″), 28.7 (C-2″), 25.9 (C-3″), 29.7 (C-4″-27″), 31.9 (C-28″), 22.6 (C-29″), 14.1 (C-30″), 169.1 (C-1‴), 21.1 (C-2‴).

3.5. In vitro α-Glucosidase inhibition assay

The α-Glucosidase inhibition was determined as described elsewhere (Chokki et al. 2020). 20 µl sodium phosphate buffer (pH 5.0), 20 µl *p*-nitrophenyl-α-D-glucopyranoside (Sigma Chemical Co., 1 mg/ml) and 10 µl of the sample at different concentrations (dissolved in DMSO) were mixed and incubated in a 96-well plate at 37 °C for 10 min, followed by the addition of 10 µl α-glucosidase solution from almonds (Sigma Chemical Co., 5 mg/ml) and further incubation at 37 °C for 30 min. The reaction was terminated by adding 140 µl of sodium carbonate buffer, pH = 10. Absorbance was determined at 410 nm using a microplate reader (iTecan Microplate). To the control and blank were added 10 µl DMSO instead of the sample solution. The system without α-glucosidase was used as blank, and acarbose was used as positive control. The α-glucosidase inhibitory activity was expressed as the percentage of inhibition and calculated using the equation below:

$$\%\ \text{inhibition of}\ \alpha - \text{glucosidase} = 100\left(1 - \frac{\text{ODSample} - \text{ODblank/Sample}}{\text{ODcontrol} - \text{ODblank}}\right)$$

A preliminary screening was firstly done on all the sample in order to determine the percentage of inhibition. Extracts and compound mixtures were tested at a concentration of 2 mg/ml while pure compounds were evaluated at a concentration of 10 mM. Further, only samples that inhibited at least 50% of enzyme were considered for IC_{50} determination.

4. Conclusion

Metabolic diseases such as diabetes mellitus constitutes a life-threatening ailment and it is considered as one of the most important public health problems in all nations.

Some available drugs are used to lower glucose levels in the blood of patients with type 2 diabetes but often, are unavailable or cause secondary side effects. For this reason, the search for new and natural therapeutics that can be used in the management of diabetes including inhibitors of carbohydrate digestive enzymes such as α-glucosidase inhibitors, is an urgent need. *E. senegalensis* is a traditional plant which is used to for diabetic patients with few reports on the antidiabetic potential of crude extracts of this plant, but the chemicals constituents responsible for this activity could also be of interest. In this study, crude extracts and isolated compounds from the aerial parts of *E. senegalensis* were evaluated for the α-glucosidase inhibition. The activity of the tested samples ranged from moderate to good as compared to the standard acarbose used. The extracts were more active than the pure compounds. Four saponins were identified and they showed good potential inhibitory activity of α-glucosidase, indicating that they can lower postprandial glucose levels in the blood. A cinnamate derivative (**1**) was obtained through hemisynthesis, and it was observed that acetylation slightly increases inhibition of α-glucosidase. This study suggests that *E. senegalensis* could be exploited for pharmaceutical development of natural antidiabetic therapies.

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Disclosure statement

We the authors declare that there is no conflict of interest related to this work.

Supplemental material

Please see supplementary document for the MS, 1D and 2D NMR spectra of compound **1**.

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