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Antioxidant potential of flavonoid glycosides from *Manniophyton fulvum* Müll. (Euphorbiaceae): Identification and molecular modeling

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ABSTRACT

Chemical investigation of the leaves of *Manniophyton fulvum* led to the isolation of seven flavonoid glycosides: myricetin-3-*O*-β-D-rhamnoside (**1**), kaempferol-3-*O*-β-D-rhamnoside (**2**), quercetin-3-*O*-β-D-glucoside (**3**), quercetin-3-*O*-β-D-rhamnoside (**4**), quercetin-3-*O*-β-D-galactoside (**5**), rutin (**6**) and quercetin (**7**). The structures of the compounds were established by spectroscopic analyses as well as by comparison with published data. Some of the compounds showed strong antioxidant activity which validates the traditional use of the plant. An attempted correlation between the computed HOMO-LUMO energies and the measured antioxidant activities was established. We have also estimated the cardiotoxicity of the compounds by calculating the predicted logarithm of the human Ether-'a-go-go Related Gene (loghERG) using the QikProp program. These purified flavonoids are new potential lead compounds for the development of antioxidant drugs.

Introduction

Manniophyton fulvum Johannes Müll. is a tropical liana of the Euphorbiaceae, which is abundant in many countries of Central and West Africa. It grows as a shrub or woody climber in primary and secondary forests. The stem, leaf, root, and bark of this plant have been used in the traditional folklore of the Congo Basin to treat diarrhea, stomach ache, cough, bronchitis, oxidative stress, and inflammation [1,2]. Preliminary chemical screening of the crude extracts of the leaves of *Manniophyton fulvum* exhibited significant antioxidant activity [1]. Also, a previous study had indicated that the crude extract

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of the plant exhibited antimalarial, cytotoxic, antiviral, anti-inflammatory, antidiarrheal and aphrodisiac properties [3–5]. To the best of our knowledge, chemical investigations of the twigs of this plant species collected in the South of Cameroon, in the Loukounje district near Ndoumale revealed the presence of new pentacyclic triterpenoids and other classes of compounds with cytotoxicity activity against HeLa cells [2]. However, the probability of getting new lead compounds is still very high since bioactive compounds are often present at the level of parts per million in the complex matrices of the raw plant material [6]. Also, there is no data reported in the literature on the antioxidant activity and the human Ether-à-go-go related gene (hERG) channel blocking profile of pure compounds isolated from this plant species.

Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbitals (LUMO) are known to be key orbitals responsible for the chemical reactivity of molecules. Hence their computed values could be used to attempt an explanation of the antioxidant profiles of molecules. Cardiotoxicity caused by the inhibition of hERG is a major liability within the drug development process. To avoid such a severe adverse effects, all potential drug candidates should be screened early enough during the drug discovery process. Thus in our continuing efforts to search for bioactive natural products from Cameroonian medicinal plants, seven flavonoid glycosides were isolated from this plant species. Their structures were established by means of extensive nuclear magnetic resonance spectroscopic analyses, and chemical methods. All isolated compounds were tested for their antioxidant activity on 2, 2- diphenyl-1-picrylhydrazyl hydrate (*DPPH*) stable radical [1]. A majority of the tested compounds had low hERG channel blocking profiles and significant antioxidant activities.

Materials and methods

General experimental procedures

Column chromatography was performed with glass columns using either silica gel 60–200 mesh or Sephadex LH-20. Fractions were monitored by TLC using various solvent systems, and the cyanidin test was used to test for the presence of flavonoids. The ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, with TMS used as the internal reference. The ^{1}H and ^{13}C NMR chemical shifts are expressed in ppm relative to TMS. Chemical shifts were recorded in δ (ppm) and the coupling constants (J) are in Hertz. Thin-layer chromatography (TLC) was performed on Merck silica gel plates. TLC plates were visualized with a UV-lamp (UVGL-58) at 254 or 366 nm and later exposed to iodine.

Plant material

The mature fresh leaves of *Manniophyton fulvum* Müll. was collected from the Democratic Republic of Congo (DRC), Kinshasa. A voucher specimen (06/2455/b) was kept at the Institute of Pharmacy, University of Kinshasa XI.

Extraction and isolation

The dried and powdered leaves of *Manniophyton fulvum* (23.0 g) was defatted with hexane and then extracted by maceration at room temperature with methanol until exhaustion. The mixture was filtered, and the filtrate concentrated by rotary evaporation to afford eleven (11.0 g) of a dark greenish extract. The concentrate was recovered with a minimum volume of dichloromethane and kept open at room temperature until all the residual solvent had evaporated. This was subjected to normal phase silica gel column chromatography and elution with a gradient of ethyl acetate in hexane as mobile phase. A total of 75 fractions were collected (50 mL each). The fractions were combined based on similar TLC profiles [silica 60 F254 gel-coated glass sheets with *n*-hexane and ethyl acetate to give six pooled fractions (A-F). Several runs using the preparative TLC of D, E and F yielded compounds **1** (25.0 mg), **2** (30.0 mg), and **3** (14.2 mg), respectively, using hexane in ethyl acetate as mobile phase. Similarly, Fraction A (40.5 mg) was purified using preparative TLC to give compounds **5** (10.3 mg) and **7** (18.0 mg). A total of thirty fractions were collected (2 mL each) and regrouped on the basis of similar TLC profiles. Fraction C (200.0 mg) was dissolved in dichloromethane and was then passed through a Sephadex LH-20. The column was eluted with pure dichloromethane to afford compounds **4** (45.0 mg) and **6** (60.0 mg).

Antioxidant activity (DPPH) assay

The free radical scavenging activity of the pure compounds was evaluated as described by Nia et al. [1] with slight modifications. Briefly, the test samples were dissolved in dimethyl sulfoxide and then added to *DPPH* methanolic solution, to give final concentrations and ascorbic acid was used as a standard. All the analyses were carried out in triplicate and the results were statistically significant compared to the Waller-Duncan test. The free radical scavenging activity of the compounds demonstrates the hydrogen donating ability on reaction to the stable free radical which results in the discoloration of the *DPPH* free radical from purple to yellow. Among quercetin-3-*O*-glycosides, quercetin-3-*O*-β-D-galactoside (**5**) exhibited a slightly higher *DPPH* value than quercetin-3-*O*-β-D-glucoside (**3**). Both flavonoids have adjacent phenolic hydroxyl groups at ring B which is responsible for their antioxidant activity reported in literature [7,8].

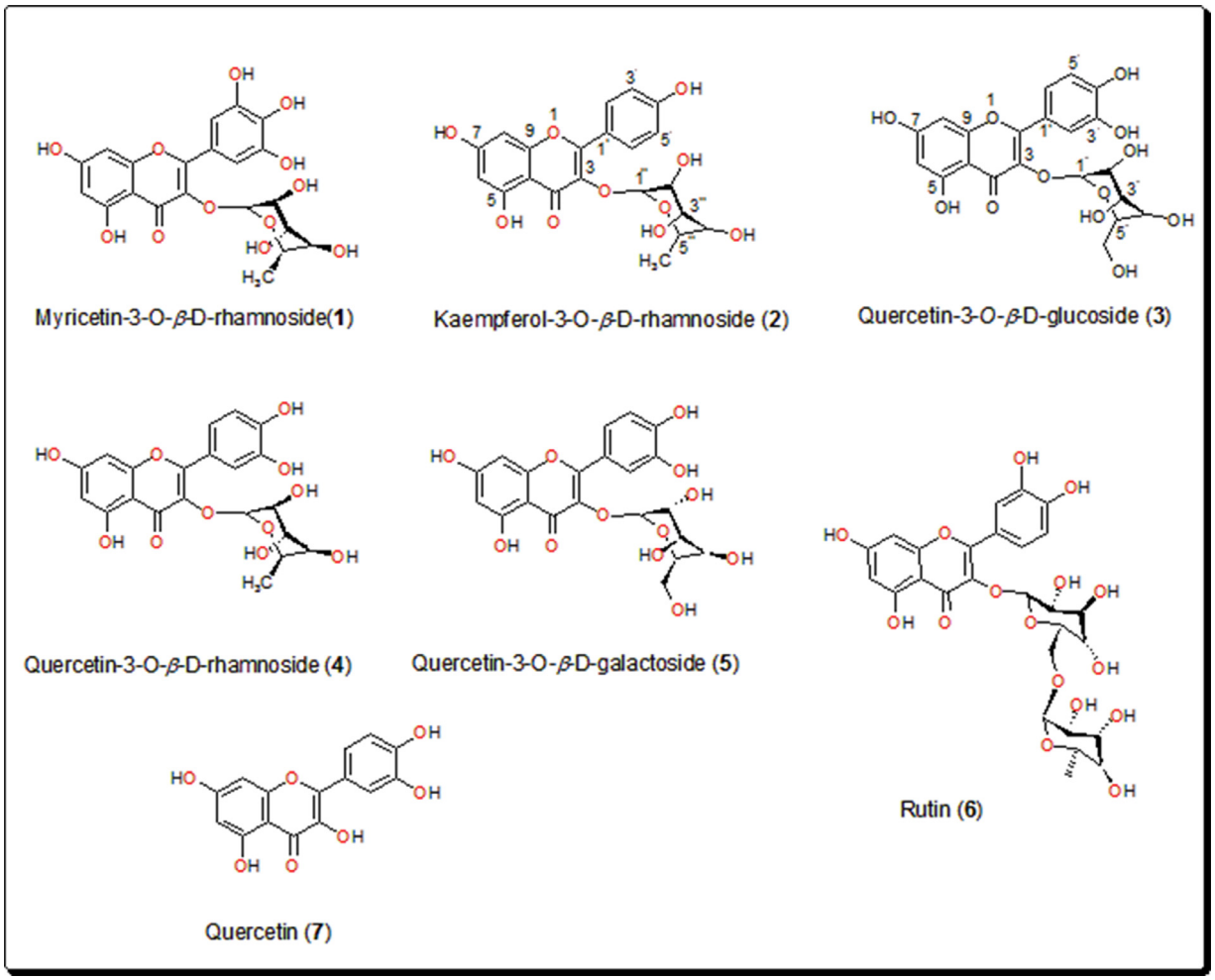

Fig. 1. Chemical structures of compounds 1–7.

Molecular modeling

Gaussian 09, Rev D.01 and B.01 [9] were used to carry out the DFT calculations. Geometries of all species were fully optimized at the M06-2X level with the aug-cc-pVDZ basis set for all atoms. Minima were confirmed by the lack of any imaginary frequencies. The predicted inhibitory concentration (logarithm of IC_{50}) values for the blockage of the channels (loghERG) were calculated by using the QikProp program (Schrodinger 2018) running in normal mode, implementing the methods developed by Jorgensen and Duffy [10].

Results and discussion

Isolated flavonoid glycosides

The seven compounds (**1–7**) (Fig. 1) were obtained as yellow, amorphous powders and they gave positive reactions for flavonoids [7,8,11–16]. They were isolated and purified from the extracts of *Manniophyton fulvum* by successive chemical fractionation followed by a series of chromatographic steps. Their ^{1}H and ^{13}C NMR spectra showed the characteristics of flavonoid scaffold when compared with published data in the literature. The compounds were identified by comparison of experimental and reported spectroscopic data as quercetin-3-*O*-*β*-D-glucoside [7,11], kaempferol-3-*O*-*β*-D-rhamnoside [12], myricetin-3-*O*-*β*-D-rhamnoside [12,13], quercetin [7,14,15], quercetin-3-*O*-*β*-D-galactoside [15], quercetin-3-*O*-*β*-D-rhamnoside [7,8] and rutin [16].

The free radical-scavenging capacity of the isolated compounds was tested by their ability to bleach the stable *DPPH*. The *DPPH* values of flavonol-3-*O*-rhamnosides were ranked as kaempferol-3-*O*-*β*-D-rhamnoside (**2**) greater than myricetin-3-*O*-*β*-D-rhamnoside (**3**), exhibiting higher *DPPH* scavenging activity than the quercetin glycosides (Table 1) [9]. Quercetin and

Table 1
IC_{50} values of isolated compounds for *DPPH* radical scavenging activity (mean ± SD, $n = 3$) ($p < 0.5$).

Secondary metabolites	Antioxidant activity (*DPPH*) IC_{50} (μM)
Myricetin-3-*O*-β-D-rhamnoside (**1**)	3.0 ± 0.1
Kaempferol-3-*O*-β-D-rhamnoside (2)	0.2 ± 0.1
Quercetin-3-*O*-β-D-glucoside (**3**)	12.0 ± 0.1
Quercetin-3-*O*-β-D-rhamnoside (**4**)	ND
Quercetin-3-*O*-β-D-galactoside (5)	11.0 ± 0.1
Rutin (**6**)	16.0 ± 0.1
Quercetin (**7**)	9.0 ± 0.1

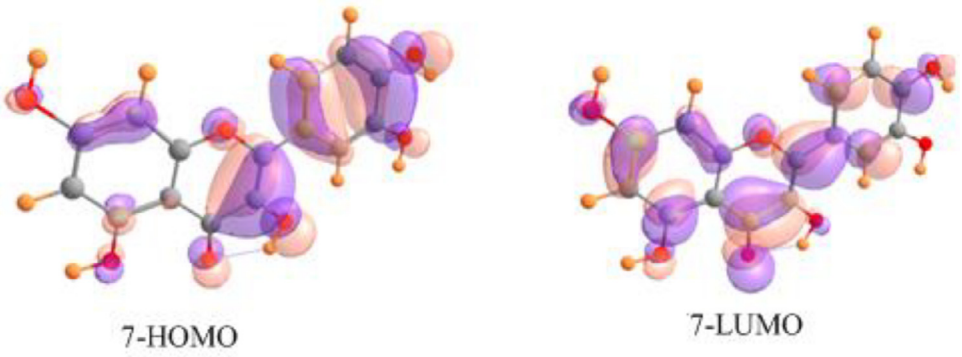

Fig. 2. HOMO (left), LUMO (right) representation of 7 computed at the M06-2X/aug-cc-pVDZ level of theory.

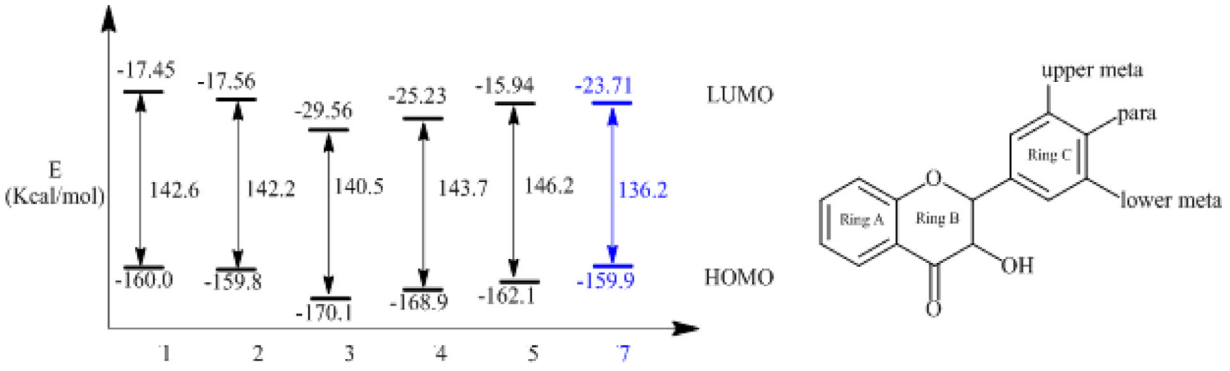

Fig. 3. HOMO-LUMO energy gap of compounds derived from the 3D models (1–5 and 7).

quercetin glycosides (compounds **3, 5, 6, 7**) also displayed antioxidant activity which is consistent with reported activities of these flavonoids in the literature (Table 1) [12].

Description of reactivity based on frontier molecular orbitals

The Frontier Molecular Orbital (FMO) is a chemical descriptors predispose to quantitatively predict chemical reactivity. The Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbitals (LUMO), (Fig. 2), are key orbitals responsible for the chemical reactivity of molecules. However, the LUMO (right) is distributed all over the molecule. A quantitative analysis of these orbital involves the computation of the HOMO-LUMO energy gap as shown in Fig. 3.

HOMO is the molecular orbital containing the valence electrons with the highest energy. On the other hand, the LUMO is perceived as the electrophilic part of a molecule. The difference in energy between these orbitals is known as the HOMO-LUMO energy gap, an essential structural stability indicator that helps to characterize the chemical reactivity and kinetic stability of a molecule [18]. Molecules with low polarizability, are generally associated with low chemical reactivity and high energy gap. Such molecules are said to be kinetically stable. Fig. 2 shows the FMO of compound **7** the unsubstituted

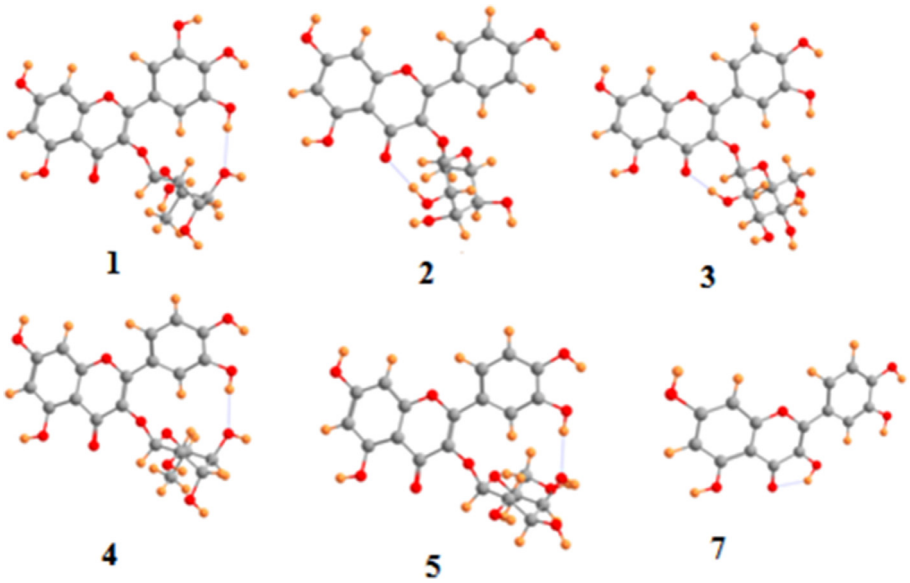

Fig. 4. Geometry optimized (3D) models for compounds 1 to 5 and 7 (1–5 and 7) showing intramolecular hydrogen bond. These structures were optimized at M06-2X/aug-cc-pVDZ level of theory.

Table 2
Computed loghERG channel profile of the compounds and the recommended range for 95% of known drugs.

Compounds	1	2	3	4	5	6	7
loghERG	**−**5.09	−4.88	−4.49	−4.67	−5.13	−4.99	−5.02

Predicted IC_{50} value for blockage of hERG K^+ channels (concern < -5).

fragment. It is worth mentioning that a similar pattern was observed for compounds **1**–**5**. These results show that the HOMO (Left) of this series of molecule reside above and below the plane of ring C.

A comparison of compounds **1** and **2** reveals that the absence of the upper meta hydroxyl group in **2** (at positions 3' and 5') does not affect the chemical reactivity and the kinetic stability of the molecules. Replacement of the X-sugar moiety in compound **2** with Y-sugar to yield compound **3** leads to the disruption of the intramolecular hydrogen bond between sugar X and the lower meta hydroxyl group, resulting in a drop in antioxidant activity (0.2 to 12.0 microM). A new intramolecular hydrogen bond is created between sugar Y and the carbonyl group of ring B. The effect of this sugar ring swap involving compounds **2** and **3** led to an increased reactivity of the flavonoid **2**. The reactivity decreases after the replacement of the lower meta hydroxyl group to yield compound **4**. Thus compound **4** has a higher energy gap (stable) and should have lower *DPPH* scavenging activity than **3**. The addition of a sugar moiety to compound **7** to generate compounds **1**–**5** (Fig. 4) generally increases the energy gap of some of the flavonoids hence, rendering them more polarizable, less reactive and kinetically stable.

HERG channel blocking profile assessment

Inhibition of the hERG potassium channel has been shown to induce long-QT syndrome by inhibiting the repolarisation of cardiac cells [17]. Due to the withdrawal of several drugs from the market because of hERG-related cardiotoxicity, this voltage-gate potassium channel becomes an important descriptor in early drug discovery [17]. Also the inclusion of the hERG channel prediction values is often a good initial assessment of the toxicity profiles of drug-like molecules.The predicted IC_{50} values for the blockage of the channels (loghERG) were calculated by using the QikProp program [10]. Our results (Table 2) showed that 4 out of the 7 compounds had loghERG channel profile within the recommended range for 95% of known drugs. Aromatic rings in these compounds are the fundamental features responsible for the inhibition of hERG channel [17]. The hERG channel blocking profile of a majority of the flavonoids derivatives were encouraging, those that violated this parameter only falling along the boundary cutoff value. These compounds should thus be considered for further investigations. Our findings, overall, are significant and establish the potential of these compounds as leads for antioxidant drug discovery.

^{13}C NMR data of the compounds

Quercetin-3-O-β-D-glucoside (3)

^{13}C NMR (MeOH-d_4, 400 MHz): δ 158.0 (C-2), 135.1 (C-3), 180.0 (C-4), 162.8 (C-5), 100.0 (C-6), 165.0 (C-7), 94.9 (C-8), 159.9 (C-9), 105.1 (C-10), 122.1 (C-1′), 115.6 (C-2′), 146.0 (C- 3′),150.0 (C-4′),121.9 (C-5′),118.9 (C-6′), 105.0 (C-1″), 73.6 (C-2″), 75.3 (C-3″), 70.6 (C-4″), 76.8 (C-5″), 62.5 (C-6″).

Kaempferol-3-O-*β-D-rhamnoside* (***2***)

^{13}C NMR (MeOH-d_4, 400 MHz): δ 158.6 (C-2), 136.3 (C-3), 179.7 (C-4), 163.2 (C-5), 99.9 (C-6), 166.0 (C-7), 94.8 (C-8), 159.3 (C-9), 106.0 (C-10), 122.6 (C-1′), 131.9 (C- 2′),116.6 (C- 3′),161.6 (C- 4′),116.6 (C- 5′),131.9 (C- 6′), 103.5 (C-1″), 72.0 (C-2″), 72.2 (C-3″), 72.1 (C-4″), 73.1 (C-5″), 17.7 (C-6″).

Myricetin-3-O-*β-D-rhamnoside (1)*

^{13}C NMR (MeOH-d_4, 100 MHz): δ 159.5 (C-2), 137.9 (C-3), 179.7 (C-4), 163.2 (C-5), 99.8 (C-6), 165.9 (C-7), 94.7 (C-8), 159.5 (C-9), 105.9 (C-10), 121.9 (C-1′), 109.6 (C-2′), 146.5 (C-3′), 136.3 (C-4′), 146.5 (C-5′), 109.9 (C-6′), 103.7 (C-1″), 71.9 (C-2″), 72.0 (C-3), 72.1 (C-4″), 73.4 (C-5″), 17.7 (C-6″).

Quercetin (7)

^{13}C NMR (MeOH-d_4, 100 MHz): δ 147.9 (C-2), 137.2 (C-3), 177.3 (C-4), 162.5 (C-5), 99.2 (C-6), 165.6 (C-7), 94.4 (C-8), 158.2 (C-9), 104.5 (C-10), 124.2 (C-1′), 115.9 (C-2′), 146.2 (C-3′), 148.8 (C-4′), 116.2 (C-5′), 121.3 (C-6′).

Quercetin-3-O- *β-D-galactoside* (***5***)

^{13}C NMR (MeOH-d_4, 100 MHz): δ 158.5 (C-2), 135.6 (C-3), 179.5 (C-4), 163.1 (C-5), 99.8 (C-6), 166.0 (C-7), 94.6 (C-8), 159.0 (C-9), 104.0 (C-10), 123.0 (C-1′), 117.5 (C-2′), 146.0 (C-3′), 149.2 (C-4′), 116.0 (C-5′), 123.0 (C-6′), 104.1 (C-1″), 78.4 (C-2″), 75.6 (C-3″), 71.3 (C-4″), 78.3 (C-5″), 62.6 (C-6″).

Quercetin-3-O-*β-D-rhamnoside (4)*

^{13}C NMR (MeOH-d_4, 100 MHz): δ 158.5 (C-2), 136.3 (C-3), 179.7 (C-4), 163.2 (C-5), 99.9 (C-6), 165.9 (C-7), 94.8 (C-8), 159.3 (C-9), 105.9 (C-10), 122.9 (C-1′), 116.4 (C-2′), 146.4 (C-3′), 149.8 (C-4′), 117.0 (C-5′), 123.0 (C-6′), 103.6 (C-1″), 71.9 (C-2″), 72.2 (C-3″), 73.3 (C-4″), 72.1 (C-5″), 17.7 (C-6″).

Rutin (6)

^{13}C NMR (MeOH-d_4, 100 MHz): δ 157.1 (C-2), 134.2 (C-3), 177.9 (C-4), 157.9 (C-5), 98.5 (C-6), 164.6 (C-7), 93.5 (C-8), 161.6 (C-9), 104.2 (C-10), 122.2 (C-1′), 114.6 (C-2′), 144.4 (C-3′), 148.4 (C-4′), 116.3 (C-5′), 121.7 (C-6′), 101.0 (C-1″), 74.3 (C-2″), 76.8 (C-3″), 72.5 (C-4″), 75.8 (C-5″), 67.1 (C-6″), 103.3 (C-1‴), 69.9 (C-2‴), 70.7 (C-3‴), 70.8 (C-4‴), 68.3 (C-5‴), 16.5 (C-6‴).

Declaration of Competing Interests

The authors declare no conflict of interest.

CRediT authorship contribution statement

Smith B. Babiaka: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing - original draft, Writing - review & editing. **Rene Nia:** Conceptualization, Methodology, Writing - review & editing. **Kennedy O. Abuga:** Conceptualization, Project administration, Resources, Supervision, Writing - review & editing. **James A. Mbah:** Methodology, Project administration, Resources, Supervision, Writing - review & editing. **Vincent de Paul N. Nziko:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing - original draft, Writing - review & editing. **Dietrich H. Paper:** Conceptualization, Writing - review & editing. **Fidele Ntie-Kang:** Conceptualization, Formal analysis, Funding acquisition, Resources, Software, Supervision, Validation, Writing - original draft, Writing - review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.sciaf.2020.e00423.

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