Natural Resources for Human Health

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Original Research

View Article Online

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Received 07 December 2021
Revised 25 December 2021
Accepted 25 December 2021
Available online 07 January 2022

Edited by Onur Bender

KEYWORDS:
Acetylation
Chemotaxonomy
Guibourtia ehie
Leguminosae
α-glucosidase inhibitory

Natr Resour Human Health 2022; 2 (3): 306-312
https://doi.org/10.53365/nrfhh/145341
eISSN: 2583-1194

Phytochemical compounds of *Guibourtia ehie* and their antioxidant, urease and α-glucosidase inhibitory activities

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ABSTRACT: Thirteen compounds (**1**– **13**) were isolated and identified during phytochemical analysis of the leaves and stem bark of *Guibourtia ehie* (A. Chev) J. Leonard. Spectroscopic and spectrometric methods and the comparison of their results with those given in the literature were used to ascertain their structures. Furthermore, the acetylation of 3,3′-di-*O*-methylellagic acid 4′-*O*-β-D-xylopyranoside (**2**) afforded a new derivative 3,3′-di-*O*-methylellagic acid 4′-*O*-β-D-(4,2′′,4′′-triacetyl)-xylopyranoside (**2a**). Extracts, fractions, and isolated compounds were assessed for their antioxidant, urease, and α-glucosidase inhibitory activities. Compound **1** demonstrated potent antioxidant activity in the DPPH with an IC_{50} value of 36.4 $\pm$ 0.2 μM, while rhaponticin (**3**), 2,6-dimethoxybenzoquinone (**4**), and taraxerol (**6**) exhibited a strong α-glucosidase inhibitory activity with the IC_{50} values of 35.5 $\pm$ 0.1, 25.5 $\pm$ 0.2 and 43.4 $\pm$ 0.3 μM, respectively. The present study enriches the chemistry of *Guiboutia ehie* and provides further evidence on its bioactive constituents, which might help in the development of hypoglycaemic drugs.

1. INTRODUCTION

The Cameroonian flora represents a significant reservoir of medicinal plants that are used by the local population as first aid in the management of several illnesses like malaria or diabetes due to their cheapness and their availability (Happi et al., 2020; Mbougnia et al., 2021; Wouamba et al., 2020). Diabetes mellitus is a common chronic metabolic disease and remains a global health problem in almost all countries worldwide. Its relationship with oxidative stress is well established and documented (Kasali et al., 2021). Moreover, infection with *Helicobacter pylori* causes stomach inflammation, ulcers, adenocarcinoma, and lymphoma (Kumar et al., 2021), which affect an essential ratio of the population worldwide. Inhibiting urease activity has been proposed as a viable strategy for eradicating *Helicobacter pylori* from the human body (Amin et al., 2013). Our recent research on Cameroonian medicinal plants and their endophytes contributed to identifying lead bioactive compounds with antimicrobial, antiparasitic, antioxidant and cytotoxic potencies (Happi et al., 2015; Jouwa et al., 2020; Makong et al., 2019; Tabekoueng et al., 2020). As a continuity of our research works on Cameroonian medicinal plants, the plant *Guibourtia ehie* has been investigated for its antioxidant compounds and urease and α-glucosidase inhibitors. Indeed, "Bubinga", the common name of the *Guibourtia* of the forests of Central Africa, also nicknamed "the forest giant", is a fetish or sacred tree for the pygmies (Bahuchet, 1985). *Guibourtia ehie* (A. Chev) J. Leonard, also known as *Copaifera ehie* A. Chev is present in Cameroon, Ivory Coast, Gabon, Ghana, Liberia and Nigeria. Various organs of the plant (bark, roots, and fruits) are used for various purposes (Adjanohoun, 1984). The stem bark extract is used to manage gastrointestinal related clinical problems in African ethnomedicine. The decoctions

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of a mixture of stem bark of *G. ehie* and *Tetrapleura tetraptera* are drunk to treat stomach ulcers in Ghana, while the bark and leaves of *G. ehie* are introduced in the decoction of plant mixtures by the local population in South Cameroon for the treatment of hypertension and its related symptoms as well as sexual infections. Phytochemical screening of the plant species highlighted the presence of saponins, flavonoids, alkaloids, sterols, triterpenes, pro-anthocyanidins having good antioxidant, antibacterial and α-glucosidase inhibitory activities (Abdoul-Latif-Fatouma et al., 2017).

2. EXPERIMENTAL

2.1. General instrumentation

The detailed information about the general instrumentation was given in the supplementary information (Appendix A).

2.2. Plant material

The stem bark and leaves of *Guibourtia ehie* (A. Chev) J. Leonard were collected in December 2018 at Dibombari locality (GPS coordinates: Latitude 4°12′00″N, Longitude 9°39′00″E, Elevation: 14 m), Littoral Region, Cameroon. The identification of the plant was made by Mr. Victor Nana based on morphological comparison of its leaves and branches with the previous plant material in the database of the National Herbarium of Cameroon, where a specimen was kept under the voucher number 43216 HNC.

2.3. Extraction and isolation

MeOH extraction of *G. ehie* stem bark (3.16 kg) and leaves (860.0 g) yielded brown viscous extract (80.2 g) and green viscous extract (30.4 g), respectively, at room temperature for 48 h, after which the filtrates were concentrated under reduced pressure. Each extract (~5 g) was kept for biological assays, and the remaining crude extract was independently subjected to silica gel column chromatography with a gradient of EtOAc in *n*-hexane, followed by a gradient of methanol in EtOAc. The stem bark extract (75.2 g) was fractionated over silica gel to obtain seven main fractions labelled from S_1 to S_7. The fraction S_1 (*n*-hexane-EtOAc, 37:3) gave a total of 104 subfractions and afforded three pure compounds identified as a mixture of β-sitosterol (**11**) and stigmasterol (**12**) (5.6 mg) (from subfractions 5-24) and friedelan-3-one (**7**) (5.7 mg) (from subfractions 86-97). By applying the same method, the second fraction S_2 (*n*-hexane–EtOAc 17:3) gave a total of 94 subfractions of 200 mL each from which taraxerol (**6**) (6.3 mg) (from subfractions 13-21) and lupeol (**5**) (8.3 mg) (from subfractions 57-68) have precipitated as white powders. Furthermore, 2,6-dimethoxylbenzoquinone (**4**) (4.2 mg) was obtained from the third fraction S_3 (*n*-hexane–EtOAc, 4:1) while the last fraction S_7 (EtOAc) was further purified on silica gel column chromatography to yield 113 subfractions from which stigmasterol-3-*O*-β-D-glucopyranoside (**13**) (10.2 mg) (from subfractions 1-18) and ellagic acid (**1**) (7.2 mg) (from subfractions 67-82) as white amorphous and yellowish powders, respectively.

The leaves extract (25.4 g) was fractionated over a silica gel column using the gradient hexane–DCM–EtOAc–MeOH, resulting in six series. The third series, S_3 (hexane–DCM, 1:4), was a combination of 108 fractions (100 mL, each) and afforded lanosterol (**8**) (3.4 mg) (from fractions 34-41). The fourth series S_4 (DCM–EtOAc, 1:1) resulted from the combination of 142 fractions and after purification process yield scopoletin (**9**) (3.4 mg) (from fractions 5-12), pilloin (**10**) (2.8 mg) (from fractions 34-53) and 3,3′-di-*O*-methylellagic acid 4′-*O*-β-D-xylopyranoside (**2**) (24.5 mg) (from fractions 122-135) while the last series S_6 (EtOAc–MeOH, 49:1) with a total of 68 fractions yielded rhaponticin (**3**) (6.4 mg) (from fractions 34-41).

2.4. Acetylation of compound 2

3,3′-di-*O*-methylellagic acid 4′-*O*-β-D-xylopyranoside (**2**) (15.0 mg) was dissolved in pyridine (1.0 mL), and 1.0 mL of acetic anhydride was added. After 10 hours under agitation at room temperature, the reaction was quenched with water, and the medium was partitioned between CH_2Cl_2 and H_2O. The organic layer was reduced to dryness using a rotavapor to afford an oily extract that was further purified over silica gel eluting with hexane-AcOEt (1:19) to yield 3,3′-di-*O*-methylellagic acid 4′-*O*-β-D-(4,2″,4″-triacetyl)-xylopyranoside (**2a**) (8.0 mg) as a yellow powder.

2.5. Spectroscopic data of reported compound 2a

3,3′-di-*O*-methylellagic acid 4′-*O*-β-D-(4,2″,4″-triacetyl)-xylopyranoside (**2a**): $C_{27}H_{24}O_{15}$, Yellow powder (MeOH); HR-ESI-MS (*m/z*): 611.1007 $[M+Na]^+$(calcd for $C_{27}H_{24}O_{15}Na^+$, 611.1013); $[\alpha]^{25}{}_D$ = +20 (c = 1.0, $CHCl_3$); UV (MeOH) λ_{max} (log e) 260 (3.43), 292 (3.51), 358 (3.40) nm; IR (KBr) υ_{max} 3500 (OH), 1748 (C=O), 1630 (C=C), 1062 (C-O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 7.90 (1H, s, H-5), 7.80 (1H, s, H-5′), 5.26 (1H, d, J = 5.2 Hz, H-1″), 5.24 (2H, m, H-5″), 5.02 (1H, dd, J = 6.9, 9.7 Hz, H-2″), 4.40 (3H, s, 3′-OCH_3), 4.26 (1H, dd, J = 4.5, 9.9 Hz, H-3″), 4.20 (3H, s, 3-OCH_3), 3.62 (1H, dd, J = 6.2, 10.1 Hz, H-4″), 2.11 (3H, s, 4″-$OCOCH_3$), 2.10 (6H, s, 4-$OCOCH_3$ and 2″-$OCOCH_3$); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 169.9 (4″-$OCOCH_3$), 169.8 (2″-$OCOCH_3$), 169.4 (4-$OCOCH_3$), 158.3 (C-7), 158.1 (C-7′), 150.8 (C-4, C-4′), 143.5 (C-3), 141.5 (C-2), 139.8 (C-2′), 138.9 (C-3′), 115.5 (C-1), 114.1 (C-5′), 113.2 (C-6), 112.4 (C-6′), 111.9 (C-1′), 111.7 (C-5), 99.5 (C-1″), 69.9 (C-3″), 69.6 (C-2″), 68.1 (C-4″), 62.2 (3-OCH_3), 62.2 (3′-OCH_3), 61.9 (C-5″), 20.8 (4-$OCOCH_3$ and 2″-$OCOCH_3$), 20.7 (4″-$OCOCH_3$).

2.6. DPPH radical scavenging activity

As described by Gülcin et al. (2005), the free radical scavenging activity was evaluated using 1,1-diphenyl-2-picrylhydrazil (DPPH). The detailed procedures were given in the supplementary information (Appendix A).

2.7. Urease inhibition assay

The urease inhibition assay was measured using the method described by (Lodhi et al., 2014). The detailed procedures were given in the supplementary information (Appendix A).

2.8. Alpha-glucosidase inhibition assay

The alpha-glucosidase inhibition assay was measured using the method described by Atsumi et al. (1990) and Kurihara et al. (1994). The detailed procedures were given in the supplementary information (Appendix A).

3. RESULTS AND DISCUSSION

3.1. Phytochemical study

Using purification techniques, the chemical study of the methanolic leaves and stem bark extracts of *Guibourtia ehie* led to the isolation of thirteen compounds (Figure 1). Their structures were established as ellagic acid (**1**) (Nkainsa et al., 2020), 3,3′-di-*O*-methylellagic acid 4′-*O*-β-D-xylopyranoside (**2**) (Moharram et al., 2003; Ngoumfo et al., 2008), rhaponticin (**3**) (Park et al., 2018), 2,6-dimethoxylbenzoquinone (**4**) (Harasawa & Tagashira, 1994), lupeol (**5**) (Ahmed, 2019), taraxerol (**6**) (Midori et al., 1999), friedelan-3-one (**7**) (Xie et al., 2013), lanosterol (**8**) (Ishii et al., 2014), scopoletin (**9**) (Napiroon et al., 2018), pilloin (**10**) (Tsai et al., 2018) and three common steroids β-sitosterol (Ododo et al., 2016), stigmasterol (Ibrahim et al., 2015) and its glucoside stigmasterol-3-*O*-β-D-glucopyranoside (Faizi et al., 2001) by comparing their 1D-NMR and ESI- or EI-MS with those reported in the literature (Figure 1). The isolated steroids were directly identified by comparison of their R*f* on TLC profiles with those of the reference compounds available in the laboratory.

Table 1
IC_{50} values of antioxidant, urease and α-glucosidase inhibition assays

Samples	$IC_{50} \pm$ SEM (μM)		
	DPPH assay	Urease inhibitory	α-Glucosidase inhibitory
SBE	61.2 ± 0.1	81.3 ± 0.7	14.1 ± 0.5
LE	63.4 ± 0.1	80.7 ± 0.4	18.2 ± 0.8
FLE 1	75.5 ± 0.1	25.2 ± 0.8	12.4 ± 0.7
FLE 2	89.1 ± 0.1	86.3 ± 0.1	10.3 ± 0.2
1	36.4 ± 0.2	n.t	n.t
2	-	-	84.3 ± 0.2
2a	-	75.3 ± 0.5	75.2 ± 0.9
3	85.3 ± 0.4	89.2 ± 0.2	35.5 ± 0.1
4	-	-	25.5 ± 0.2
6	89.2 ± 0.5	-	43.4 ± 0.3
7	-	-	89.1 ± 0.1
BHA	44.2 ± 0.2	-	-
Thiourea	-	22.4 ± 0.2	-
DNJ	-	-	3.9 ± 0.7

SBE: Stem bark extract; LE: Leaves extract; FLE 1: the first fraction leaves extract (DCM/AcOEt 1:1); FLE 2: the second fraction leaves extract (AcOEt); DNJ: 1-deoxynojirimycin, n.t: not tested.

In looking for significant activity, 3′-di-*O*-methylellagic acid 4′-*O*-β-D-xylopyranoside (**2**) obtained in sufficient amount was chemically modified by acetylation reaction to afford compound **2a**, a yellow powder with an optical rotation $\alpha^{25}{}_D$ = +20 (*c* = 1.0, $CHCl_3$). It's (+)-HR-ESI-MS showed the sodium adduct ion $[M+Na]^+$ at *m/z* 611.1007 (calcd. for $C_{27}H_{24}O_{15}Na^+$, 611.1013) consistent with the molecular formula $C_{27}H_{24}O_{15}$ suggesting the acetylation of three hydroxyl groups of compound **2** (Figure 1). This observation was further confirmed with the ^{1}H NMR spectrum of **2a** (Table 1 , Figure 3S Appendix A), which showed in the upfield region, the signals of three additional methyl groups deshielded by an ester carbonyl at δ2.11 (3H, s, 4′′-$COCH_3$), 2.10 (3H, s, 2′′-$COCH_3$) and 2.10 (3H, s, 4-$COCH_3$) compared to that of **2** (Figure 3S Appendix A). In addition, the ^{13}C, Dept-135 and Dept-90 NMR spectra (Figure 4S-6S Appendix A , Table 1) displayed extra resonances, including signals of three carbonyl groups at δ 169.4, 169.8 and 169.9. The careful analysis of the HSQC spectrum (Figure 8S Appendix A) allowed us to establish the correlations between protons at δ 5.02 (1H, dd, *J* = 6.9, 9.7 Hz, H-2′′), δ 3.62 (1H, dd, *J* = 6.2, 10.1 Hz, H-4′′) and the carbonyl groups at δ 169.8 (2′′-$COCH_3$) and δ169.9 (4′′-$COCH_3$), respectively. These observations suggested that the initial hydroxyl groups at C-2′′ and C-4′′ in the sugar moiety of **2** have been acetylated in **2a**. The third acetoxy group was attached to hydroxyl at C-4 based on HMBC cross-peaks between the aromatic proton at δ 7.90 (1H, s, H-5) with the ester carbonyl group at δ 169.4 (4-$COCH_3$) in long-range correlation (Figure 9S Appendix A). Thus, the structure of compound **2a** was determined as 3,3′-di-*O*-methylellagic acid 4′-*O*-β-D-(4,2′′,4′′-triacetyl)-xylopyranoside as shown in (Figure 1).

3.2. Antioxidant property

The extracts, fractions and the major compounds obtained were submitted for antioxidant activity in the DPPH (Table 1). Briefly, the stem bark and leaves extracts and leaf fractions showed weak activity with effectiveness in the range of IC_{50} value from 61.2 to 89.1 μM. As expected for the phenolic constituents, ellagic acid (**1**) displayed a strong potency with an IC_{50} value of 36.42 μM more active than the standard butylhydroxyanisole (BHA) (IC_{50} = 44.2 ± 0.2 μM) while its derivatives 3,3′-di-*O*-methylellagic acid 4′-*O*-β-D-xylopyranoside (**2**) and 3,3′-di-*O*-methylellagic acid 4′-*O*-β-D-(4,2′′,4′′-triacetyl)-xylopyranoside (**2a**) were not active. Another phenolic rhaponticin (**3**), was slightly active (IC_{50} = 85.3 ± 0.4 μM) whereas 2,6-dimethoxylbenzoquinone (**4**) was not active. Taking together, we can partially conclude based on our results that the potency in antioxidant activity for the phenolic compounds, especially the ellagic acid derivatives, increases with the availability of the phenolic hydroxyl groups in their core structures. The more the phenolic compound is substituted on its hydroxyl functions, the less it is active. Previous investigations reported that ellagic acid (**1**) demon-

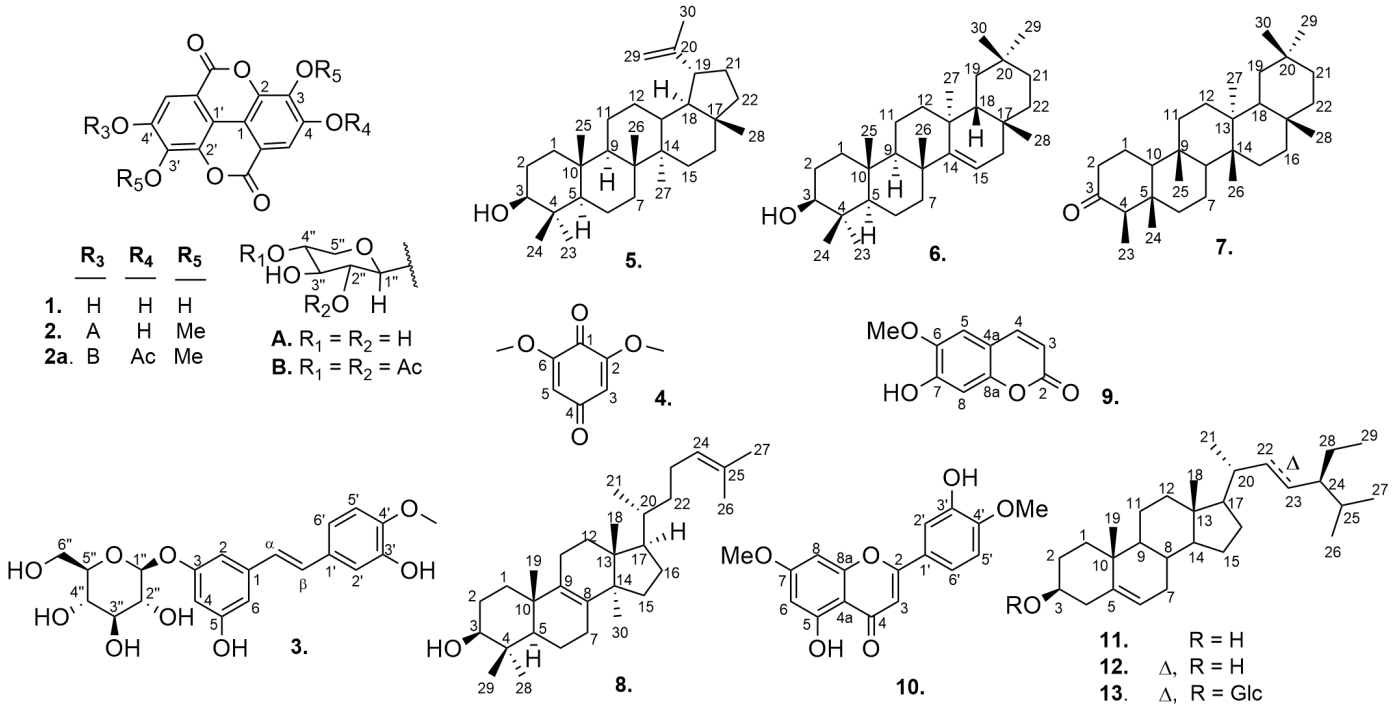

Figure 1. Chemical structures of compounds **1**– **13** isolated from *G. ehie*

strated a high DPPH radical scavenging, lipid peroxidation inhibition, and a high reactivity towards HO● , oxygen, and nitrogen species. Furthermore, it significantly increases the activities of SOD (superoxide dismutase), CAT (catalase) and GPX (glutathione peroxidase) in V79-4 cells (Galano et al., 2014; Han et al., 2006; Priyadarsini et al., 2002; Tošovi & Bren, 2020). Similarly, rhaponticin (**3**) significantly reduced oxidative stress by decreasing the level of malondialdehyde and increasing the activity of SOD, CAT and GPX in diabetic rats (Shi et al., 2020). Lastly, the triterpene taraxerone (**6**) exhibited a weak activity with an IC_{50} of 89.2 ± 0.5 μM.

3.3. Urease inhibition activity

The evaluation of extracts, fractions and pure compounds for their urease inhibitory activity showed that except the DCM/AcOEt (1:1) fraction of leaves extract which had an activity close to the reference thiourea 25.2 ± 0.8 μM and 22.4 ± 0.2 μM, respectively, the stem bark and leaves crude extracts, compounds 3,3′-di-*O*-methylellagic acid 4′-*O*-β-D-(4,2″,4″-triacetyl)-xylopyranoside (**2a**) and rhaponticin (**3**) were slightly active with IC_{50} values in the range of 75.3 to 89.2 μM. The other tested compounds 2,6-dimethoxylbenzoquinone (**4**), lupeol (**5**), friedelan-3-one (**7**) and lanosterol (**8**), were inactive (Table 1). Our result can be supported by the literature, which reports that the urease inhibition ability of medical plants is attributed to their large classes of phytoconstituents, including phenolic compounds, saponins, cardiac glycosides and gallocatechin derivatives (Modolo et al., 2015)

3.4. Alpha-Glucosidase inhibition activity

In the α-glucosidase inhibitory assay, the crude extracts and leaves fractions of *G. ehie* exhibited promising results with intense activities in the range of 10.3 to 18.2 μM, which were less active than the reference (1-deoxynojirimycin, IC_{50} = 3.9 ± 0.7 μM). 2,6-dimethoxylbenzoquinone (**4**) was the most potent among the tested compounds, followed by rhaponticin (**3**) and taraxerol (**6**) with IC_{50} values of 25.5 ± 0.2, 35.5 ± 0.1 and 43.4 ± 0.3 μM, respectively. Several compounds from various classes have been reported in the literature as alpha-glucosidase inhibitors. For instance, Atta-Ur-Rahman et al. (2008) isolated cichoridiol, a taraxane-type triterpenoid close to taraxerl (**6**), displaying a significant alpha-glucosidase inhibitory activity. These results suggested that the extracts of *G. ehie* might be of great importance in the formulation of ameliorated traditional medicine for the treatment of diabetes and other diseases related to the inhibition of α-glucosidase, but further analyses are necessary to support this partial conclusion. Furthermore, rhaponticin (**3**), 2,6-dimethoxybenzoquinone (**4**), and taraxerol (**6**) deserve further investigations for the development of new antidiabetic drugs.

3.5. Chemotaxonomic significance

This study led to the isolation of thirteen compounds, including ellagic acid (**1**) and its derivative 3,3′-di-*O*-methylellagic acid 4′-*O*-β-D-xylopyranoside (**2**), rhaponticin (**3**), 2,6-dimethoxybenzoquinone (**4**), lupeol (**5**), taraxerol (**6**), friedelan-3-one (**7**), lanosterol (**8**), scopoletin (**9**), pilloin (**10**), as well as the common steroids β-sitosterol (**11**), stigmasterol

(**12**) and stigmasterol-3-*O*-β-D-glucopyranoside (**13**). The isolation of these secondary metabolites is not uncommon since the report on previous phytochemical investigations of some *Guibourtia* species like *Guibourtia ehie*, *G. coleosperma*, and *G. tesmanii* demonstrated the presence of tannins, triterpenoids, saponins and sterols (Dushimemaria et al., 2017). All of these compounds have been reported from *G. ehie* for the first time, allowing us to gain a better understanding of this species' chemistry. The stilbene glycoside rhaponticin (**3**) was reported from G. tessmannii (Kathryn et al., 2005). Compound **3** was also isolated from a Leguminosae plant *Trigonella foenum-graecum* (Idris et al., 2021), indicating a close relationship between genus *Guibourtia* and *Trigonella*; however, further investigation must be done to support these observations. Lanosterol (**8**) was identified using gas chromatography-mass spectrometry from *G. colosperma* (Preez et al., 2020). Lupeol (**5**), taraxerol (**6**) and friedelan-3-one (**7**) are isolated for the first time from the *Guibourtia* genus but were previously detected in other genera from Leguminosae (Fabaceae) family. Indeed, lupeol (**5**) was reported from *Dalbergia hainanensis* (Zhang et al., 2003), Cassia abbreviate (Mutasa & Kahn, 1995), *Caesalpinia sappan* (Oswal & Garg, 1993), *Caesalpinia pulcherrima* (Chiang et al., 2003) while friedelan-3-one (**7**) was reported from *Caesalpinia digyna* (Srinivasan et al., 2011), *Pterocarpus santalinoides* (Ichiko et al., 2016), and *Pterocarpus erinaceus* (Ouedraogo et al., 2011). Taraxerol (**6**) was isolated from *Dalbergia hainanensis* (Zhang et al., 2003) and *D. spinosa* (Anjaneyulu et al., 2005). These findings indicated the close phylogenetic relationship between the genera *Guibourtia*, *Cassia*, *Milletia*, *Dalbergia* and *Caesalpinia* belonging to the same plant family. Finally, 3,3'-Di-*O*-methylellagicacid-4'-*O*-β-D-xylopyranoside (**2**), scopoletin (**9**) and 2,6-dimethoxybenzoquinone (**4**) can also be found in some species across the Leguminosae (Fabaceae) family. Therefore, compound **2** was reported from *Acacia farnesiana* (Hussein et al., 2002), while compound **4** was previously obtained from *Senna alata* (synonym of *Cassia alata*) (Chimi et al., 2021), and compound **9** was already obtained from twigs and leaves of *Caesalpinia spinosa* (He et al., 2015). Additionally, pilloin (**10**) was identified by GS-MS from Dalbergia melanoxylon (Yin et al., 2018). Hence, this evidence further supports the taxonomy of the plant species *G. ehie* and enriches its chemistry.

4. CONCLUDING REMARKS

The chemical investigation of leaves and stem bark of the Cameroonian medicinal plant *Guibourtia ehie* afforded thirteen compounds including ten compounds **1**– **10** reported for the first time from the species *G. ehie* while five including 3,3′-di-*O*-methyl ellagic acid 4′-*O*-β-D-xylopyranoside (**2**), 2,6-dimethoxylbenzoquinone (**4**), lupeol (**5**), taraxerol (**6**), and friedelan-3-one (**7**) were previously-reported from the genus Guibourtia. In addition to enhancing the chemistry of *G. ehie*, the present works revealed the pharmacological importance of chemical constituents of the plant. Indeed, some exciting activities have been observed for the extracts, fractions and pure compounds. The most important was the significant α-glucosidase inhibitory activity of extracts, fractions, as well as rhaponticin (**3**), 2,6-dimethoxybenzoquinone (**4**), and taraxerol (**6**), which deserve further attention in pharmacological investigations for the development of new potent hypoglycemic drugs.

CONFLICTS OF INTEREST

The authors have not declared a conflict of interest.

ACKNOWLEDGMENTS

The TWAS-ICCBS 2019 programme Fellowship has given the authors the chance to conduct the above research. Thanks to the ICCBS Center, BLVL obtained excellent training from November 15, 2019 to September 14, 2020. A special thanks go out to the YaBiNaPA Graduate School in Cameroon for allowing us to conduct our research there.

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A. APPENDIX. SUPPLEMENTARY INFORMATION

Supplementary information to this article can be found online at https://doi.org/10.53365/nrfhh/145341.

AUTHOR CONTRIBUTIONS

ABN and JDW conceived and directed the project, described the isolated compounds' structures, and reviewed the manuscript. The laboratory work was performed, and LVLB, GMH, and GBT wrote the manuscript. ML performed the biological activity experiments, whereas AFKW revised the text extensively for biological content. The NMR and MS measurements were performed by the MSA and MIC research groups, who also revised the final version of the publication.

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