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Benzo[*c*]phenanthridine alkaloids and glycosylated flavonoids from the roots of *Zanthoxylum gilletii* (Rutaceae)

Liliane Clotilde Dzouemo [1], Emmanuel Ngeufa Happi [1,*], Gervais Mouthe Happi [2], Willifred Dongmo Tekapi Tsopgni [1], Jean Duplex Wansi [1]

[1]Department of Chemistry, Faculty of Sciences, University of Douala, P.O. Box 24157, Douala, Cameroon
[2]Department of Chemistry, Higher Teacher Training College Bambili, The University of Bamenda, P.O. Box 39, Bambili, Cameroon

ABSTRACT: The roots of *Zanthoxylum gilletii* have been chemically investigated and led to the isolation and characterization of nine compounds including three benzo[*c*]phenanthridine alkaloids oxychelerythrine (**1**), angoline (**2**) and arnottianamide (**3**); two glycosylated flavonoids hesperidin (**4**) and its analogue neohesperidin (**5**) along with four common specialized metabolites including sesamin (**6**), lupeol (**7**), β-sitosterol (**8**) and its derivative daucosterol (**9**). Their structures were established based on their recorded 1D and 2D-NMR data. Some compounds (**1**, **2**, **3**, **6** and **7**) did not display a cytotoxic activity until the highest concentration of 200 μM against the human cell lines MCF-7 and A549. The chemotaxonomic relevance of this study has been discussed. To the best of our knowledge, except for the five compounds **3**, **6**-**9**, all the four others have been for the first time isolated from *Z. gilletii* (Rutaceae).

1. INTRODUCTION

Rutaceae represents a large plant family which along with Meliaceae and Simaroubaceae families are called Sapindales which are distinguishable by their ability to produce limonoids (Happi et al., 2018; Kemayou et al., 2021). Rutaceae consists to a total of 148 plant genera and 1,487 accepted species including *Zanthoxylum gilletii* (De Wild.) P.G. Waterman (Rutaceae) also known as *Fagara tessmanii* or *Fagara macrophylla* (Gaya et al., 2013; List, 2022). Recent review on the genus *Zanthoxylum* revealed that its plant species display a large variety of bioactive specialized metabolites belonging to various classes of compounds including lignans, alkaloids, flavonoids, coumarins and triterpenoids with a large scale of activities related to cancer, infectious diseases and sickle cell anaemia (Okagu et al., 2021). The plant *Z. gilletii* is widely used in Cameroon as a spice (due to its relevant fragrance and taste) and in African traditional medicine for the cure of numerous diseases *viz* cancer, malaria, inflammation or microbial infections (Zirihi et al., 2009). As part of our search for bioactive natural products with good cytotoxicity or less toxicity (Happi et al., 2021; Makong et al., 2019; Mbougnia et al., 2021), we have investigated the roots of *Z. gilletii* collected in the West region of Cameroon. The chemical investigations of the methanolic extract led to the isolation of nine compounds which were screened for their cytotoxic potency against the two cell lines MCF-7 (human breast adenocarcinoma cell line) and A549 (human lung cancer cell line). The chemotaxonomy relevance of the isolated compounds in this study is also discussed in the paper.

2. MATERIALS AND METHODS

2.1. General instrumentation

Details can be retrieved from the supplementary information associated with this paper (Appendix A).

2.2. Plant material

The roots of *Zanthoxylum gilletii* (De Wild.) P.G. Waterman were harvested at Bana-Tentcheu (GPS coordinates: Latitude 5°07′57″N, Longitude 10°17′41″E, Elevation: 1412 m), West region, Cameroon, in December 2021. Some leaves and bark samples have been used for the identification of the plant has been done by Mr Victor Nana in comparison to some collected leaves with the plant specimen registered under the voucher number 38960 HNC in the National Herbarium of Cameroon database.

* Corresponding author.
E-mail address: ngeufa@yahoo.fr (Emmanuel Ngeufa Happi)

2.3. Extraction and isolation

The air-dried and powdered roots of *Zanthoxylum gilletii* (~3 kg) were macerated twice in methanol at room temperature for 48 h, each, to give a dark brown gum as crude extract (63.2 g) after removing of solvent. Small amount (~3.8 g) of the crude extract was kept for further investigations (biological tests and chemical analyses) and the remaining extract was suspended in water (100 ml) and partitioned with *n*-hexane, dichloromethane and ethyl acetate (500 ml, each), as well as *n*-butanol (200 ml), to afford four main fractions A (12.7 g), B (22.3 g), C (10.4 g) and D (4.7 g), respectively.

Fraction A was mainly a yellowish oil and fats. Its purification by silica gel column chromatography (230-400 mesh, 5.0 x 75.0 cm) using an increasing polarity of ethyl acetate (EtOAc) (0 to 40%) in *n*-hexane (n-Hex). The process led to the isolation of two common compounds namely lupeol (**7**) (5.8 mg) and β-sitosterol (**8**) (13.6 mg) at the polarities n-Hex/AcOEt 19:1 and n-Hex/AcOEt 9:1, respectively.

However, dichloromethane-soluble fraction B was further purified using silica gel column chromatography eluting with increasing polarity of ethyl acetate (EtOAc) (10 to 70%) in *n*-hexane (n-Hex). A total of 221 sub-fractions (ca. 100 ml each) were collected and combined into 7 series B1–B7 based on their TLC profiles. Arnottianamide (**3**, 4.6 mg), sesamin (**6**, 12.7 mg) and angoline (**2**, 3.2 mg) were obtained as powders from series B3 (n-Hex/AcOEt 3:1), B4 (n-Hex/AcOEt 7:3) and B5 (n-Hex/AcOEt 3:2), respectively.

Furthermore, the series B7 (2.4 g, n-Hex/AcOEt 1:1), the ethyl acetate soluble fraction C and the *n*-butanol soluble fraction D displayed similar TLC profiles and were combined, then further chromatographed over silica gel column eluting with increasing polarity of methanol (MeOH) (0 to 30%) in dichloromethane (DCM). Following the collection of a total of 237 sub-fractions (ca. 100 ml each), combined into six series D1 – D6, oxychelerythrine (**1 ,** 6.2 mg) was recrystallised from series D3 (DCM/MeOH 37:3), hesperidin (**4**) and its analogue neohesperidin (**5**) (8.2 mg) were obtained as an unseparated mixture of yellow powders from series D4 (DCM/MeOH 4:1) with the relative proportion 1:1 in the mixture based on the heights of ^{13}C NMR peaks of corresponding carbon atoms in the two compounds as displayed on Figures 1S and 2S (see Appendix A), while the common steroid daucosterol (**9**, 12.2 mg) was precipitated as a white powder from D2 (DCM/MeOH 9:1).

2.4. Physical aspects and spectral data of isolated compounds

Further details on the spectral data of isolated compounds are available in the supplementary information (Appendix A).

2.5. Cytotoxicity activity

The detailed protocol for the biological test is given in the supplementary information associated with this paper (Appendix A).

3. RESULTS AND DISCUSSION

3.1. Phytochemical study

The chemical study of the roots of *Zanthoxylum gilletii* led to the isolation of nine compounds (Figure 1 for compounds **1**-**5** and Figure 2 for compounds **6**-**9**). The structures of the isolated compounds have been established using their spectroscopic data, as well as the comparison of these data with those reported in the literature. The nine isolated compounds have been identified as oxychelerythrine (**1**) (Fuchino et al., 2010), angoline (**2**) (Lee et al., 1998), arnottianamide (**3**) (Yang et al., 2009), hesperidin (**4**) (Tine et al., 2020), neohesperidin (**5**) (D.I. Hamdan et al., 2014), sesamin (**6**) (Yang et al., 2009), lupeol (**7**) (Jouwa et al., 2020; Tsopgni et al., 2019; Wouamba, Happi, Lenta, et al., 2020; Wouamba, Happi, Pouofo, et al., 2020), β-sitosterol (**8**) (Keugwa et al., 2021) and its derivative daucosterol (**9**) (Happi et al., 2020).

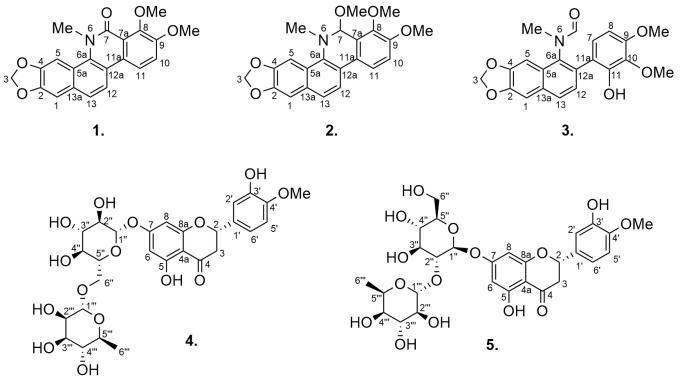

Figure 1. Benzo[c]phenanthridine alkaloids and flavonoids from the roots of *Zanthoxylum gilletii*

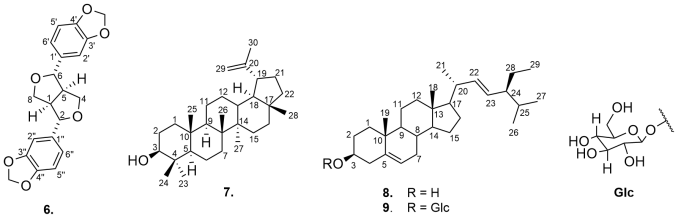

Figure 2. Structures of sesamin (**6**), lupeol (**7**), β-sitosterol (**8**) and daucosterol (**9**) isolated from the roots of *Zanthoxylum gilletii*.

3.2. Cytotoxicity of some isolated compounds

Five compounds including the three benzo[*c*]phenanthridine alkaloids (**1**-**3**) and the two major compounds sesamin (**6**) and lupeol (**7**) were evaluated for their cytotoxicity against the human breast adenocarcinoma cell line (MCF-7) and the human lung cancer cell line (A549) using doxorubicin as reference. The recorded results showed that all the tested compounds did not display an activity until the highest concentration of 200 μM (IC_{50} > 200 μM).

3.3. Chemotaxonomic significance of the study

The chemical investigations of the methanol extract of *Z. gilletii* roots resulted in the identification of nine compounds namely oxychelerythrine (**1**), angoline (**2**), arnottianamide (**3**), the mixture hesperidin (**4**) and neohesperidin (**5**), as well as the four common compounds sesamin (**6**), lupeol (**7**), β-sitosterol (**8**) and daucosterol (**9**).

The literature survey on the previous chemical studies of the genus *Zanthoxylum* indicated that, to the best of our knowledge, it is the frist report of compounds **1**, **2**, **4** and **5** from the plant species *Z. gilletii* but have been already isolated from other species in the genus and the family Rutaceae.

Benzo[c]phenanthridine alkaloids are well-known to be found in the family Rutaceae (Laines-Hidalgo et al., 2022). Therefore, the isolation of the three benzo[*c*]phenanthridine alkaloids **1**-**3** further supported the classification of the plant as belonging to the family Rutaceae.

Moreover, the literature indicated that oxychelerythrine (**1**) has been reported from *Z. nitidum*, *Z. schinifolium* and *Z. capense* (Cabral et al., 2015); angoline (**2**) from *Z. nitidum* or *Z. thomense* (J. Liu et al., 2014; Simeray et al., 1985), while arnottianamide (**3**) was obtained from roots of *Z. gilletii*, *Z. nitidum* and *Z. leprieurii* (Adesina & Reisch, 1988; Zeng et al., 2022). This may suggest that benzo[*c*]phenanthridine alkaloids might be considered as markers compounds for the genus *Zanthoxylum*.

Further chemotaxonomic insights of the study have been deduced from the presence of the other compounds isolated during the current investigation of the roots of *Z. gilletii*. Unsurpingsly, the lignan sesamin has been isolated during our investigation as one of the major compounds and it has been mainly reported from several species of the genus *Zanthoxylum* including *Z. chalybeum*, *Z. paracanthum*, *Z. leprieurii, Z. rigidum*, *Z. paracanthum*, *Z. zanthoxyloides*, *Z. nitidum* and *Z. heitzii* (Andima et al., 2020; Chakthong et al., 2019; Kaigongi et al., 2020; Muema et al., 2021; Oloya et al., 2021; Omosa et al., 2022; Santos et al., 2020; Wangensteen et al., 2016).

Additionnally, the compounds identified as lupeol, β-sitosterol, daucosterol are mainly distributed in the plant kingdom and within the family Rutaceae, they have been isolated from *Z. acanthopodium*, *Z. schinofolium*, *Z. tessmannii* or *Citrus aurantium* (Bissim et al., 2019; Cheng et al., 2002; Kenmoe et al., 2019). Finally, flavonoids are usually obtained from several plants and more particularly from the genus *Zanthoxylum*. Hesperidin (**4**) was previously isolated from *Z. scandens*, *Z. leprieurii*, *Z. zanthoxyloides* and *Z. myriacanthum* var. pubescens (Ngoumfo et al., 2010; Nguyen et al., 2002; Queiroz et al., 2006; Zhang et al., 2017), while neohesperidin (**5**) was reported from *Z. dissitum* (S. Liu et al., 2009) but more from some Rutaceae plants including *Murraya tetramera* and *Citrus pyriformis* (D. Hamdan et al., 2011; Zhou et al., 2014).

Taken together, all the isolated compounds from the roots of *Z. gilletii* provide significant insights into the taxonomy of the plant and extend the knowledge of its chemistry.

4. CONCLUDING REMARKS

The present paper deals with the chemical study of the methanol soluble extract of *Z. gilletii* roots and the cytotoxic evaluation of the isolated compounds against the tumour cell lines MCF-7 and A549. Nine compounds have been identified using their spectral data as three alkaloids **1**-**3**, two glycosylated flavonoids **4** and **5**, as well as four other common compounds including sesamin (**6**), lupeol (**7**), β-sitosterol (**8**) and daucosterol (**9**). The results from biological tests showed that compounds **1**– **3**, **6** and **7** did not display any cytotoxicity against the two selected cell lines until the concentration of 200 μM. Furthermore, the chemotaxonomic study of the isolated compounds further supports the classification of the plants by the presence of benzo[*c*]phenanthridine alkaloids majorly reported from Rutaceae, Fumariaceae and Papaveraceae; sesamin (**6**) abundantly distributed in the genus *Zanthoxylum* as well as lupeol (**7**) which is largely found in the family Rutaceae. The plant deserves further study for its minor compounds and another batch of biological activities with different cell lines in order to identify the most potent metabolites that can be classified as lead compounds for the development of new drugs for the local population. However, this study furnishes four additional compounds which enrich the chemistry of the plant *Z. gilletii*.

CONFLICTS OF INTEREST

The authors disclose that they have no competing interests.

ORCID

Liliane Clotilde Dzouemo	0000-0003-4967-4316
Emmanuel Ngeufa Happi	0000-0002-2276-3709
Gervais Mouthe Happi	0000-0001-9659-6125
Willifred Dongmo Tekapi Tsopgni	0000-0002-1644-8171
Jean Duplex Wansi	0000-0002-5111-4361

A. APPENDIX. SUPPLEMENTARY INFORMATION

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AUTHOR CONTRIBUTIONS

Research concept and design : LCD, GMH; Collection of data : WDTT; Data analysis and interpretation: LCD; Writing the article : GMH, LCD; Supervision, critical revision and final approval of the article : ENH, JDW.

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