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Chemical constituents of *Citrus grandis* (L.) Osbeck (Rutaceae) and their α-glucosidase inhibitory activity

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ABSTRACT: The chemical investigation of the methanolic bark extract of *Citrus grandis* (L.) Osbeck (Rutaceae) led to the isolation of one saponin named aridanin (**1**) isolated for the first time in the genus *Citrus*, together with seventeen known compounds including eight acridone-type alkaloids, two limonoids, two coumarins, one sugar, one lactam derivative, and three common steroids. Their structures were conclusively established using 1D- and 2D-NMR spectral data. The isolated compounds **1-9** were tested for their α-glucosidase inhibitory activity and the results showed that they all have potency higher than the reference acarbose (IC_{50} = 218.2 ± 2.8 μM) and aridanin was the strongest one which could be due to its sugar unit as usually observed for triterpene saponins. Furthermore, the structure-activity relationship of the tested compounds has been discussed as well as the chemotaxonomic significance of the study. The present study enriches the chemistry of Citrus with three additional compounds (**1**, **14**, **15**) and classifies the plant *C. grandis* as a good source of leads for the development of anti-diabetic drugs.

1. INTRODUCTION

Before the COVID-19 pandemic that has greatly weakened the healthcare system worldwide, *Diabetes mellitus* was already reported almost a decade ago as a growing public health concern with a record of 415 million affected people and 5 million deaths as documented by the International Diabetes Federation (2015). Two types of diabetes are known so far, amongst which the type-2 identified by insulin resistance has the greatest incidence with almost 90% of cases recorded in the affected population (Alberti et al., 2004). Insulin is well-reported as the key hormone in tackling the progress of diabetes and several strategies have been developed for the treatment of diabetic patients including the stimulation of the secretion of insulin, the improvement of the sensitivity of insulin as well as the reduction of the absorption of glucose at the level of the intestine (Defronzo, 1999; Inzucchi, 2002; Stumvoll et al., 2005). The role of the enzyme α-glucosidase is to catalyse the hydrolysis of the terminal α-glucose residues during the digestion process of dietary starch at the level of the small intestine where absorption into the blood takes place (Chiba, 1997). The inhibition of α-glucosidase is therefore important to reduce the absorption of carbohydrates from diet.

Commonly known as pomelo, *Citrus grandis* (L.) Osbeck is a tropical and subtropical small tree or shrub about 5 m tall belonging to the Rutaceae family (Chen & Mato, 2000). The grapefruit is a berry whose skin is very thick, smooth or grainy, varying from light yellow to light green, while its leaves are alternate, shiny, light green, pubescent on the reverse side, and large (16 cm long by 7 cm wide) (Fang et al., 2003). The plant *C. grandis* is mainly found in tropical countries and sometimes in temperate zones where it is used in traditional medicine of Africa and Asia against tiredness, lack of vitality, stomach aches, acne or mild skin disorders, while the fruit pulp is consumed as juice but can also be used to make salads or other desserts (Aumeeruddy-Elalfi et al., 2016). Various extracts of this species have demonstrated a wide range of pharmacological activities such as antioxidant, anti-inflammatory, antimicrobial and anticancer effects (Mokbel & Hashinaga, 2006). The previous chemical studies of the plant display acridone-type alkaloids, coumarins, flavones and terpenoids as the most encountered classes of compounds from its investigated organs (Wu et al., 1983, 1988). In the course of our research on secondary metabolites from Cameroonian medicinal plants with α-glucosidase inhibitory potency (Bongmo et al., 2022), we have carried out the chemical study of the bark of *C. grandis* as well as the evaluation of the α-glucosidase inhibitory activities of some isolated compounds. The results helped to discuss the structure-activity of the compounds as well as classified the plant

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species as a good source of lead compounds for the discovery of new potent drugs against diabetes and related diseases.

2. MATERIAL AND METHODS

2.1. General experimental procedures

The extraction of the plant material was done using methanol to obtain crude extract while *n*-hexane, ethyl acetate and methanol were used as pure or binary mixtures at different polarities for the purification of compounds. Column chromatography was carried out on silica gel 230–400 mesh and 70–230 mesh (Merck, Darmstadt, Germany). Thin-layer chromatography (TLC) was performed on pre-coated silica gel (60 F_{254}) aluminium foil (Merck, Darmstadt, Germany) and compound spots were detected by spraying with diluted sulphuric acid before heating the plate at about 80 °C. NMR spectra were recorded on a Bruker ARX 500 spectrometer (Bruker, Brussels, Belgium) in deuterated solvents. Chemical shifts were reported in δ (ppm) using tetramethylsilane (TMS) (Sigma-Aldrich) as an internal standard, while coupling constants (J) were measured in Hz.

2.2. Plant material

The bark of *Citrus grandis* (L.) Osbeck was collected in March 2020 in Ndobong, the locality of Douala in the Littoral region of Cameroon. The authentication was done by the botanist Mr Victor Nana by comparison with the sample available in the databank of National Herbarium of Cameroon under the voucher 25860/HNC.

2.3. Extraction and isolation

The air-dried and powdered bark of *C. grandis* (3.39 kg) was macerated twice at room temperature with 5L of methanol for 48 h, each. Then, the solvent was removed under reduced pressure to yield (147.93 g) of a green paste extract. Part of the extract (~138.93 g) was dissolved in water and partitioned using *n*-hexane, dichloromethane, ethyl acetate (EtOAc) and *n*-butanol to afford five main fractions indexed F_1 (3.0 g; n-hexane, 100:0 v/v), F_2 (10.0 g; CH_2Cl_2, 100:0 v/v), F_3 (15.0 g; EtOAc, 100:0 v/v), F_4 (48.0 g; n-butanol, 100:0 v/v).

Fraction F1 was mainly oils and was not further investigated while fraction F_2 was chromatographed on a silica gel column eluting with mixtures of *n*-hexane/EtOAc and EtOAc/MeOH of increasing polarities to obtain the non-separable mixture of compounds **14** and **15** (22.5 mg; *n*-hexane/EtOAc, 39:1 v/v), compound **3** (4.1 mg; *n*-hexane/EtOAc, 37:3, v/v), compound **2** (50.7 mg; *n*-hexane/EtOAc, 9:1, v/v), compound **10** (15.9 mg; *n*-hexane/EtOAc, 3:2, v/v) and compound **11** (20.6 mg; *n*-hexane/EtOAc, 1:3, v/v).

Fraction F_3 was further purified using silica gel column chromatography eluting with mixtures of *n*-hexane/EtOAc of increasing polarities to obtain compound **4** (30.0 mg; *n*-hexane/EtOAc, 9:1, v/v), compound **5** (25.0 mg; *n*-hexane/EtOAc, 7:1, v/v), compound **6** (13.0 mg; *n*-hexane/EtOAc, 17:3, v/v), compound **7** (50.0 mg; *n*-hexane/EtOAc, 37:3, v/v), compounds **8** (8.0 mg; *n*-hexane/EtOAc, 37:3, v/v), compound **9** (5.0 mg; *n*-hexane/EtOAc, 37:3, v/v).

The fourth fraction F_4 was also subjected to successive silica gel column chromatography and eluted with a mixture of EtOAc/MeOH of increasing polarities to yield compound **16** (52.8 mg; EtOAc/MeOH, 39:1, v/v), compound **1** (12.4 mg; EtOAc/MeOH, 39:1, v/v), compound **12** (70.5 mg; EtOAc/MeOH, 1:1, v/v) and compound **13** (30.0 mg; EtOAc/MeOH, 1:1, v/v).

2.4. α-glucosidase inhibitory activity

The triterpenoid (**1**) and the eight acridone-type alkaloids (**2**– **9**) isolated during this study have been evaluated for their α-glucosidase inhibitory activity following the modified protocol previously described by Kim et al. (2008) with acarbose as the positive control. Each test sample (20 μM) in various concentrations and 20 μM of α-glucosidase (0.3 U/mL) in 20 μL phosphate buffer (pH 7.0) were incubated at 37°C for 10 min. Then, 20 μL of p-nitrophenyl-a-D-glucopyranoside (2.5 mM) was added followed by another incubation at 37°C for 30 min. After adding a solution of Na_2CO_3 to quench the reaction, the UV-vis spectrophotometer was used to measure the absorbance at 405 nm and then quantify the enzymatic activity. The concentration of the sample that inhibited 50% of α-glucosidase activity (IC_{50}) was calculated following the formula % Inhibition = $(A_{blank} - A_{test})x100/A_{blank}$.

2.5. Statistical analysis

The data were subjected to one-way analysis of variance (ANOVA) and results were presented as means ± SD of the replicated values. Significant differences for multiple comparisons were determined by the Waller Ducan Post Hoc test at $p \leq 0.05$ using the Statistical Package for the Social Sciences (SPSS, Version 16.0) program. Activity values were obtained from sigmoidal dose-response curves of concentration versus response.

3. RESULTS AND DISCUSSION

3.1. Phytochemical study

The successive fractionation of the crude methanolic extract of *C. grandis* led to the isolation of eighteen compounds (Figure 1). The structural elucidation of the isolated compounds has been done with the aid of their spectrometric data including 1D-, 2D-NMR and MS, as well as by their comparison with those found in the literature (Supplementary information is given in Appendix A). This exercise allowed us to identify the isolates as one triterpenoid called aridanin (**1**) (Sikam et al., 2022). Eight acridone-type alkaloids namely 5-hydroxynoracronycine (**2**) (Wu et al., 1983), glycocitrin-I (**3**) (Kawaii et al., 1999), citracridone I (**4**) (Hiroshi et al., 1983), natsucitrine-II (**5**) (Motoharu et al., 1985), citpressines I and II (**6** and **7**) (Wu et al., 1983), baiyumine-A (**8**) (Wu, 1987), grandisinine (**9**) (Wu et al., 1983). Additionally, two limonoids

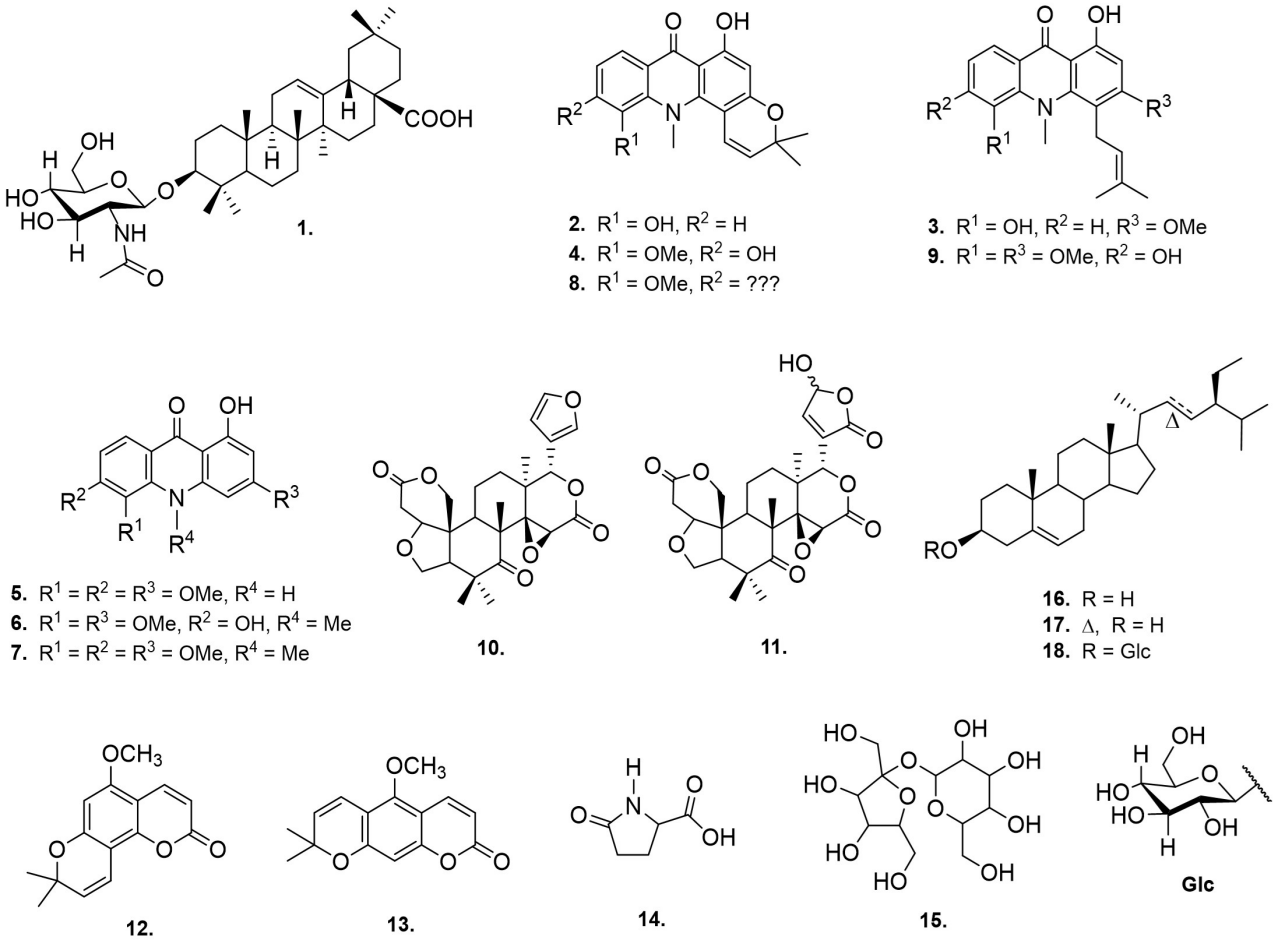

Figure 1. Structures of compounds (**1**– **18**) isolated from *Citrus grandis.*

identified as limonin (**10**) (Khalil et al., 2002) and limonexic acid (**11**) (Sook-Young et al., 1999); two coumarins named 5-methoxyseselin (**12**) (Wu et al., 1983), xanthoxyletin (**13**) (Ju et al., 2001), one lactam derivative pidolic acid (**14**) (Kaneko et al., 2011), one sugar sucrose (**15**) (Jones et al., 1979), and three common steroids viz β-sitosterol (**16**), stigmasterol (**17**) (Habib et al., 2007) and β-sitosterol-3-O-β-D-glucoside (**18**) (Peshin & Kar, 2017), have been also isolated.

3.2. α-glucosidase inhibitory activity

Amongst the isolated compounds in this study, the triterpenoid aridanin (**1**) was isolated for the first time and was tested for its α-glucosidase inhibitory potency along with the acridone-type alkaloids **2**-**9**. The results are consigned in Table 1. All the tested compounds displayed a stronger α-glucosidase inhibitory activity than acarbose used as the reference compound (IC_{50} = 218.2 ± 2.8 μM). Compound **1** was the most active one and its potency is in agreement with the literature showing that triterpene saponins are significant inhibitors of α-glucosidase due to the presence of their sugar units (Zhang et al., 2018).

Recently, we have published a comprehensive review on the chemistry, occurrence and pharmacological properties of aridanin (**1**), a lead compound found in the spice *Tetrapleura tetraptera* (Fabaceae) and several other medicinal plants (Sikam et al., 2023). From the literature survey, we reported that aridanin (**1**) displayed some significant pharmacological activities including molluscicidal potency by reducing the level of glycogen of *Biomphalaria glabrata* during a period of exposure up to 4 weeks; while its antischistosomal potency

Table 1
α-Glucosidase inhibitory assay of the isolated compounds **1**– **9.**

Compounds	IC_{50} (μM)
1	2.4 ± 0.4
2	13.8 ± 0.6
3	39.8 ± 0.7
4	11.6 ± 1.3
5	60.4 ± 1.8
6	42.7 ± 0.9
7	51.5 ± 1.2
8	32.4 ± 1.1
9	21.8 ± 0.8
Acarbose	218.2 ± 2.8

was observed through the ability of the compound to diminish the transmission of schistosomiasis by dropping the cercariae production (Adewunmi et al., 1988; Adewunmi & Furu, 1989). Additionally, aridanin (**1**) also showed antibacterial, cytotoxic, trypanocidal and antiviral activities, which further support its importance in the development of new potent drugs (Sikam et al., 2023).

Amongst the acridone-type alkaloids, compound **4** was the most active with an IC_{50} value of 11.6 ± 1.3 μM followed by compounds **2** (13.8 ± 0.6 μM) and **8** (32.4 ± 1.1 μM) (Table 1). The three compounds share the same core structure and a comparison of their potencies indicated that the activity increases with the number of oxygen attached to the aromatic nucleus. Furthermore, the hypothesis has been established when comparing the activity of compounds **3** and **9**. Finally, the interpretation of the potencies recorded for compounds **5**-**7** allowed us to partially conclude that the methyl group attached to N-atom might play a key role in improving the α-glucosidase inhibitory activity of the acridone-type alkaloids. Taken together, the level of oxidation of the aromatic ring and the presence of the N-methyl group contribute to improving the activity of the tested alkaloids. This might help in choosing the chemical transformations to be done on other compounds to increase their potency.

3.3. Chemotaxonomic significance of this study

Eighteen compounds were isolated during the phytochemical investigations of the bark of *C. grandis*, including one triterpenic saponin **1**, eight acridone alkaloids **2**-**9**, two limonoids **10** and **11**, two coumarins **12** and **13**, one lactam derivative **14**, one sugar **15** and three steroids **16**-**18**. Except for compounds **1**, **14** and **15** isolated for the first time from this species to the best of our knowledge, the other compounds have been already isolated from *C. grandis*. Moreover, compound **4** has been previously reported from the bark of *Citrus aurantium* and *C. clementina* (Bissim et al., 2019), compound **8** from C. depressa (Wu, 1987), compound **5** from *C. natsudaidai* (Motaharu et al., 1985), limonin from *C. limon*, *C. reticulata* and *C. nippokoreana* (Khalil et al., 2002; Nsangou et al., 2021; Sook-Young et al., 1999), and finally compound **13** from *C. decumana* and *Zanthoxylum americanum* (Ju et al., 2001). The presence of acridone alkaloids in *C. grandis* species is not a surprise, because that subclass of alkaloids is considered as the chemomarkers of *Citrus*. This work therefore brings a significant contribution to the chemotaxonomic knowledge of the species *C. grandis*, further identified here as a new source of aridanin (**1**) which was already reported from several other plant families (Sikam et al., 2023).

4. CONCLUSION

The extensive phytochemical investigation on the bark extract of *C. grandis* led to the isolation and characterization of eighteen compounds (**1**-**18**) including one oleanane-type triterpene saponin named aridanin (**1**) isolated for the first time in genus *Citrus*. Compounds **1**-**9** were evaluated for their α-glucosidase inhibitory activity using acarbose as a reference compound. All the tested compounds displayed stronger potency than the reference and compound **1** was the most active one, which could be due to its sugar unit in agreement with the other triterpene saponins found in the literature. The presence of the N-methyl group and the oxidation level of the aromatic rings of the acridone alkaloids were found to contribute to their potency. In addition, the chemotaxonomic significance of the isolated compounds was also discussed. The present report is part of our ongoing project on the structure elucidation of bioactive compounds from medicinal plants of the Cameroonian pharmacopoeia and provides further insights on the classification of Citrus plants as a good source of potential candidates in the development of new anti-diabetic drugs.

CONFLICTS OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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A. APPENDIX. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.53365/nrfhh/186019.

AUTHOR CONTRIBUTIONS

R.L.B.N.N.: Conceptualization, Investigation, Methodology, Writing - original draft. G.B.T.: Formal analysis, Writing - review & editing. G.M.H.: Methodology, Investigation, writing – original draft. J.D.W.: Methodology, Validation, Resource, Writing - review & editing.

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