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A novel poly-oxygenated flavone glucoside from aerial parts of the Brazilian plant *Neoglaziovia variegata* (Bromeliaceae)

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Abstract

Neoglaziovia variegata is endemic to northeastern Brazil. The drought resistant plant produces edible fruits and is used as a fibre plant by rural communities in the Caatinga region where a variety of products are made from the white, soft and flexible fibres. Extracts of *N. variegata* have been reported to be of low toxicity and to exhibit antinociceptive effect, photoprotective potential, antioxidant effect, gastroprotective effects and antibacterial effect against both Gram-positive and Gram-negative bacteria, however, the chemical constituents of this species are mainly unknown. The novel poly-oxygenated flavone glucoside 5,6,7,4'-tetrahydroxy-3',5'-dimethoxy-flavone 7-*O*-*β*-glucopyranoside in addition to the rare poly-oxygenated flavone 5,4'-dihydroxy-6,7,3'-trimethoxyflavone 4'-O-β-glucopyranoside and the flavonol quercetin 3-*O*-(6''-rhamnopyranosyl-*β*-glucopyranoside) have been characterised from the leaves of *N. variegata*.

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5,6,7,4'-tetrahydroxy-3',5'-dimethoxy-flavone, which comprises the core structure of the novel compound, is a new flavonoid aglycone in nature. The structure determinations were based on extensive use of 2D NMR spectroscopic techniques and high-resolution mass spectrometry. Both substances exhibited toxicity towards MOLM-13 acute myeloid leukaemia cells.

Keywords: Biochemistry, Cell biology, Food analysis, Food science, Molecular biology, Natural product chemistry

1. Introduction

Extensive regional droughts are already a major problem on all inhabited continents and severe regional droughts are expected to become an increasing and extended problem in the future. Consequently, extended use of available drought resistant food plants should be encouraged. *Neoglaziovia variegata* (Arruda) Mez (Portuguese: caroá) (Fig. 1) is an excellent candidate in that respect, as an established drought resistant edible plant from the semi-arid Caatinga region. From a food safety perspective, increased utilization of this plant would necessitate detailed knowledge about its chemical constituents. However, in current literature only limited information is available about the chemical composition of *N. variegata* (Oliveira-Júnior et al., 2015; Juvik et al., 2017). *N. variegata* is one of only three species in the genus *Neoglaziovia*, a close relative to *Ananas* in the Bromeliaceae (Schulte et al., 2009), all of which are endemic to northeastern Brazil. *N. variegata* is characterized by reddish flowers with inferior ovaries in raceme inflorescences, which produces edible fleshy berry fruits at the beginning of the rainy season (Mayo, 1992). The plant was first described by the Brazilian cleric, physician and scientist Manuel Arruda da Câmara (1752−1810), while the genus is named after the French botanist

Fig. 1. *Neoglaziovia variegata* photographed in Petrolina, Brazil 2013. Photo: JRGS Almeida.

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Auguste Francois Marie Glaziou (1828−1906). *N. variegata* is used as a fiber plant by rural communities in the Caatinga region where a variety of products are made from the white, soft and flexible fibres (Almeida et al., 2008; Oliveira-Júnior et al., 2012; Silveira et al., 2010; Silveira et al., 2009). Ethanol extracts of *N. variegata* have been reported to be of low toxicity *in vivo* in mice (Lima-Saraiva et al., 2012), and to exhibit antinociceptive effect in experimental models in mice (Lima-Saraiva et al., 2012), photoprotective potential, antioxidant effect (Oliveira-Júnior et al., 2012; Lima-Saraiva et al., 2012), gastroprotective effects in a mice model of gastric ulcer (Machado et al., 2013) and antibacterial effect against both Gram-positive (Oliveira-Júnior et al., 2012) and Gram-negative bacteria (Oliveira-Júnior et al., 2012; Silva et al., 2014). Only limited information about the natural products of *N. variegata* is available in current literature. Recently we identified several non-polar natural products from *N. variegata* (Juvik et al., 2017) including the fatty acids *n*-hexadecanoic acid (palmitic acid), (9*Z*)-octadec-9-enoic acid (oleic acid) and octadecanoic acid (stearic acid), the very long chain (VLC) alkanes *n*-nonacosane and *n*-triacontane, the vitamins α- and β-tocopherol, as well as the plant sterols campesterol, ergostanol, stigmasta-4,22-dien-3-*β*-ol, *β*-sitosterol and stigmastanol. Oliveira-Junior et al. (2015) tentatively identified the flavonols quercetin 3-glucoside and quercetin 3-rhamnoside and the phenolic acids *p*-coumaric acid, caffeic acid, vanilic acid and protocatechuic acid from *N. variegata* (Oliveira-Júnior et al., 2015). However, at present, no compounds unique to *N. variegata* have hitherto been identified and the potential anticancer activity of natural products from this plant source has not been revealed. In this paper we report on isolation, characterization and antileukaemic activity of two flavonoids from *N. variegata*, including a novel natural product.

2. Experimental

2.1. Plant material

Leaves of *Neoglaziovia variegata* were collected within the municipality borders of the city of Petrolina, State of Pernambuco, Brazil, in January 2013. A voucher specimen was deposited in the Herbarium Vale do São Francisco (HVASF) of the Federal University of Vale do São Francisco. *N. variegata* leaves were collected at the coordinates 08°59′16.90″ S and 40°35′20.60″ W and the voucher specimen is no. 6441. Identification of the collected plant species was done by the botanist André Paviotti Fontana from Centro de Recuperação de Áreas Degradadas da Caatinga (CRAD). Prior to shipment to Norway the leaves were dried in an oven with air circulation at a temperature of 50 °C for seven days. After drying, the plant materials were powdered in a mill.

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2.2. Extraction

1.7 kg dried leaves of *N. variegata* were extracted (two times) with 5 L methanol-water 70:30; v/v for 24 h. The combined extracts were concentrated on rotavapor. The resulting dark brown concentrated aqueous extract (1.4 L) was purified to partition against equal volumes of petroleum ether and ethyl acetate. The aqueous phase was then concentrated on rotavapor prior to separation by column chromatography, as described below.

2.3. Amberlite XAD-7 column chromatography

The concentrated aqueous phase from liquid-liquid partition was applied to the matrix surface of the column (column dimensions: 5 × 105 cm). The mobile phase consisted of 5 L distilled water (fractions 1−5), followed by 1 L MeOH-H_2O 10:90; v/v (fraction 6), 1 L MeOH-H_2O 25:75; v/v (Fraction 7), 3 L MeOH-H_2O 50:50; v/v (fractions 8−12) and 4 L MeOH (fractions 13−16). 1−1.5 mL of each fraction was directly transferred to HPLC vials for later determination of their content and purity, as described below.

2.4. Sephadex LH-20 column chromatography

Fraction 14 from XAD-7 column chromatography of the aqueous phase was further separated on a Sephadex LH-20 column (column dimensions: 3 × 50 cm) using varying proportions of methanol, super distilled water and trifluoroacetic acid (TFA). The gradient consisted of 142 mL methanol-water-TFA 20:80:0.2; v/v/v (fractions 1−12), followed by 550 mL methanol-water-TFA 50:50:0.2; v/v/v (fractions 13−43), 200 mL methanol-water-TFA 70:30:0.2; v/v/v (fractions 44−105) and 375 mL methanol-water-TFA 80:20:0.2; v/v/v (fractions 106−109). Each fraction was analyzed by HPLC. Pure **1** (78.5 mg) was isolated in fractions 87−89, whereas **3** (9.3 mg) was isolated in fractions 64 and 65. Fractions 80−82 were combined and further purified by preparative HPLC.

2.5. Preparative HPLC

The HPLC instrument (Dionex UltiMate 3000) was equipped with a 250 × 22 mm, C_{18} Altech column (5 μm particle size). Two solvents were used for elution; A (H_2O-TFA 99.5:1; v/v) and B (methanol-TFA 99.5:1; v/v). The elution profiles of the applied HPLC gradient consisted of isocratic elution with 10% B-90% A for the first 18 min, followed by linear gradient (10% B-40% B) for the next 46 min and isocratic elution (40% B) for 40 min. The sample was dissolved in a total of 1 mL of A-B (50:50 v/v). Portions of 100 μL of the sample were manually injected into the HPLC column. Each peak in the chromatogram was separately collected in vials.

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1−1.5 mL of each of the collected fractions was transferred to HPLC vials for later identifications using analytical HPLC. Pure **2** (2.1 mg) was isolated in fraction 1.

2.6. Analytical HPLC

The HPLC instrument (Dionex) was equipped with a HP 1050 multidiode array detector, a 20 μL loop and a 250 × 4.6 mm, 5 μm Thermo Scientific Hypersil GOLD column. Two solvents were used for elution; A (water-TFA 99.5:1; v/v) and B (acetonitrile-TFA 99.5:1; v/v). The elution profile of the applied HPLC gradient is shown in Fig. S1. The analytical HPLC pump system was purged with both solution A and solution B for 15 min each with a flow of 5 mL/min. The column was thereafter equilibrated with a flow of 1 mL/min in 30 min with acetonitrile-super distilled water (10:90 v/v). 20 μL of each sample was injected with an autoinjector. The elution profiles consisted of isocratic elution (10% B in A) for the first 4 min, followed by linear gradient (10% B-14% B) for the next 10 min, isocratic elution (14% B) for the next 4 min, linear gradient (14% B-18% B) for the next 10 min, linear gradient (18% B-28% B) for the next 10 min, linear gradient (28% B-40% B) for the next 4 min and isocratic elution (40% B) for 10 min. The flow rate was 1 mL/min.

2.7. Spectroscopy

High-resolution mass spectra were recorded using a JEOL AccuTOF JMS T100LC instrument fitted with an electrospray ion source. The spectrum was recorded over the mass range 50−1000 *m/z*.

UV-Vis absorption spectra were recorded on-line during HPLC analysis over the wavelength range 240−600 nm in steps of 2 nm.

NMR samples were prepared by dissolving the isolated compounds in hexadeuterated dimethylsulfoxide (99.9 atom % D, Sigma-Aldrich). The 1D ^{1}H and the 2D ^{1}H-^{13}C HMBC, ^{1}H-^{13}C HSQC, 2D ^{1}H-^{1}H COSY and ^{1}H-^{1}H ROESY NMR experiments were obtained at 600.13 MHz and 150.90 MHz for ^{1}H and ^{13}C, respectively, at 298K on a Bruker 600 MHz instrument equipped with a cryogenic probe.

2.8. Cytotoxicity towards MOLM-13 human acute myeloid leukaemia cells and normal rat kidney (NRK) epithelial cells

Pure rutin (**1**) and 5,6,7,4'-tetrahydroxy-3',5'-dimethoxy-flavone 7-*O*-*β*-glucopyranoside (**2**) were isolated from aerial parts of *N. variegata* as described above. The stock solutions were prepared by dissolving compounds **1** and **2** in DMSO to a final concentration of 100 mM and stored at -80 °C. Normal rat kidney epithelial cells (NRK, ATCC no.: CRL-6509) were cultured in DMEM (Sigma-Aldrich, St. Lous, MO, USA) supplemented with 10% fetal bovine serum (FBS, Invitrogen, Carlsbad,

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CA). When the cells reached 80% confluence, they were detached by mild trypsin treatment (0.33 mg mL^{-1} trypsin for 5 min at 37 °C), centrifuged (160 x g, 4 min) and reseeded in fresh medium to 25% confluence. The AML cell line MOLM-13 (Matsuo et al., 1997; Quentmeier et al., 2003) were cultured in RPMI 1640 medium (Sigma-Aldrich) enriched with 10% FBS. The cells were kept in suspension cultures at a density between 150,000 and 600,000 cells/mL. Both NRK and MOLM-13 cell lines were cultured in media supplemented with 50 IU/mL penicillin and 0.05 mg/mL streptomycin (both from Cambrex, Belgium) in a humidified atmosphere (37 °C, 5% CO_2).

For experiments with compounds **1** and **2**, the NRK cells were seeded in 96 wells tissue culture plates (5,000 cells/well, 0.1 mL) and left overnight to attach, while the MOLM-13 cells were seeded in 96 wells tissue culture plates at 15,000 cells/well in 0.1 ml on the day of the experiment. Compounds dissolved in DMSO were diluted in cell culture medium with supplements, but without cells, and added to the cells at different concentrations, and the cells incubated with the compounds for 72 h. Resazurin (Sigma-Aldrich) was then added to the cells, and left to incubate in the dark for 45 min before metabolic conversion into the fluorescent reporter dye resorufin was recorded at 530/590 Ex/Em filters using a Wallac Envision 2103 Multilabel Reader (Perkin Elmer, Waltham, MA, USA). The cells were next fixed in 2% buffered formaldehyde (pH 7.4) with 0.01 mg mL^{-1} of the DNA-specific fluorescent dye, Hoechst 33342 (Sigma-Aldrich). The cells were also studied under differential interference contrast and fluorescent microscopy to confirm the presence of apoptotic and/or necrotic cells, as previously described (Oftedal et al., 2010; Myhren et al., 2014). Cells with only DMSO added were used as control, and 1% DMSO gave less than 5% reduction in resazurin signal, and less than 3% apoptotic nuclei in the cell culture. EC_{50} values were determined by four-parameter regression analysis of the data of metabolic activity using the SPSS Statistics software ver. 25 (IBM Corp., Armonk NY, USA).

3. Results and discussion

The methanolic extract of aerial parts of *Neoglaziovia variegata* was concentrated under reduced pressure and fractionated by extraction with petroleum ether and ethyl acetate. The ethyl acetate phase was further separated by gradient XAD-7 adsorption chromatography, Sephadex LH-20 gel filtration chromatography and preparative HPLC. Following this strategy, two pure flavonoids were isolated.

Compounds **1** and **3** were identified as quercetin 3-*O*-(6''-*O*-α-rhamnopyranosyl-β-D-glucopyranoside) (rutin) and 5,4'-dihydroxy-6,7,3'-trimethoxyflavone 4'-O-β-D-glucopyranoside by a combination of 1D ^{1}H NMR, 1D ^{1}H selective TOCSY, 1D ^{13}C CAPT, 2D ^{1}H-^{13}C HSQC, 2D ^{1}H-^{13}C HSQC-TOCSY, 2D ^{1}H-^{13}C HMBC and 2D

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^{1}H COSY NMR experiments. Compound **3** is also known as the rare polymethoxylated flavone cirsilineol 4'-glucoside, which was originally isolated from *Cirsium lineare* (Morita et al., 1973). The ^{1}H and ^{13}C NMR data of **1** were in agreement with previously published NMR data on rutin (Slimestad et al., 2008).

The downfield region of the 1D ^{1}H NMR spectrum of **2** showed three 1H singlets belonging to phenolic OH groups at δ 12.67 (5-OH), δ 9.33 (4'-OH) and δ 8.54 (6-OH). The aromatic region of the 1D ^{1}H NMR spectrum of **2** exhibited a 2H singlet at δ 7.32 (H-2'/6′) and two 1H singlets at δ 7.11 (H-8) and δ 7.01 (H-3). The presence of a further singlet at δ 3.86, integrating for 6H, which corresponds to two identical methoxy groups (3'/5'-OCH_3) confirmed the identity of the aglycone of **2** to be 5,6,4'-trihydroxy-3',5'-dimethoxyflavone. The crosspeak at δ 3.86/148.7 (3',5'-OCH3/C-3',5') observed in the HMBC spectrum of **2** (Fig. 2) confirmed the substitution positions of the methoxy groups. The glycosyl substituent of **2** was identified as β-glucopyranosyl by the seven ^{1}H resonances in the spectral region δ 4.97−3.15, which correlated to six carbon signals in the 2D ^{1}H-^{13}C HSQC spectrum (Fig. 2 and Table 1). The large anomeric coupling constant (7.7 Hz) confirmed the β-configuration of the glucosyl substituent. In theory, such large coupling constant would also be present for an α-L-glucopyranosyl unit. However, this may be unlikely because it is the β-anomer of this sugar that is invariably found in flavonoid glycosides (Veitch and Grayer, 2006). The crosspeak at δ 4.97/151.3 (H-1''/C-7) observed in the 2D ^{1}H-^{13}C HMBC spectrum (Fig. 2) confirmed the identity of **2** to be the novel flavonoid 5,6,7,4'-tetrahydroxy-3',5'-dimethoxy-flavone 7-*O*-*β*-D-glucopyranoside. A molecular ion at *m/z* 509.12923 observed in the high-resolution mass spectrum of **2**, corresponding to $C_{23}H_{25}O_{13}$ (Calculated: 509.12951; mass difference -0.55 ppm), confirmed this identification. 5,6,7,4'-tetrahydroxy-3',5'-dimethoxy-flavone,

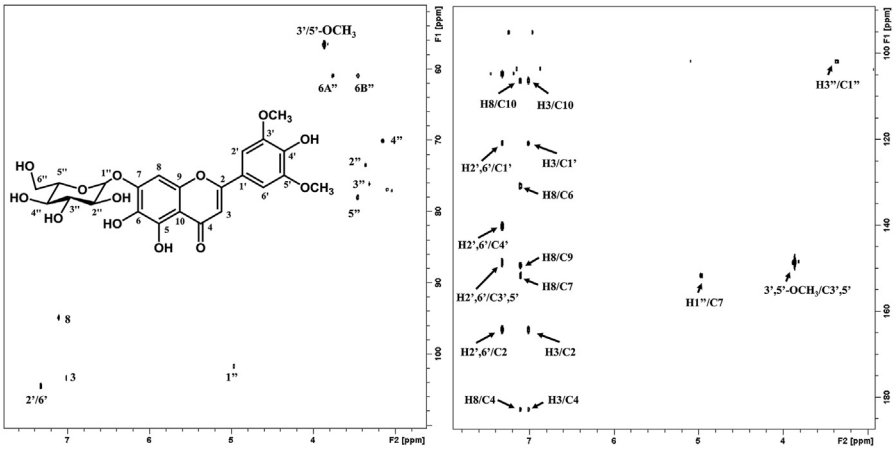

Fig. 2. Expanded regions of the HSQC spectrum (left) and HMBC spectrum (right) of 5,6,7,4'-tetrahydroxy-3',5'-dimethoxy-flavone 7-*O*-β-glucopyranoside (**2**) with assigned crosspeaks.

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Table 1. ^{1}H and ^{13}C chemical shift values (ppm) and coupling constants of 5,6,7,4'-tetrahydroxy-3',5'-dimethoxy-flavone 7-*O*-*β*-glucopyranoside (2) and 5,4'-dihydroxy-6,7,3'-trimethoxyflavone 4'-glucoside (3) in DMSO-D_6 at 298 K.

	2 δ ^{1}H	**2** δ ^{13}C	**3** δ ^{1}H	**3** δ ^{13}C
2		164.0		163.57
3	7.01 s	103.0	7.06 s	104.04
4		182.5		182.5
5		146.5		152.17
6		130.5		132.05
7		151.3		158.86
8	7.11 s	94.8	6.99 s	91.88
9		148.9		152.85
10		106.0		105.33
1'		120.5		124.07
2'	7.32 s	104.4	7.63 d 2.1	110.32
3'		148.3		149.33
4'		139.9		149.96
5'		148.3	7.25 d 8.7	115.15
6'	7.32 s	104.4	7.69 dd 2.1, 8.7	120.00
5-OH	12.67 s			
6-OH	8.54 s			
4'-OH	9.33 s			
6-OCH_3			3.73	60.17
7-OCH_3			3.92	56.61
3'/5'-OCH_3	3.86 s	56.5	3.90 s	56.17
7-*O*-*β*-glucopyranoside			4'-*O*-*β*-glucopyranoside	
1''	4.97 d 7.7	101.6	5.08 d 7.7	99.59
2''	3.36 dd 7.7, 9.2	73.4	3.30 m	73.23
3''	3.31 t 9.0	76.1	3.30 m	76.97
4''	3.15 t 9.0	70.0	3.18m	69.73
5''	3.46 m	78.0	3.39 m	77.30
6A''	3.76 m	60.9	3.68 dd 1.9, 11.9	60.74
6B''	3.46 m		3.46 dd 5.8, 11.9	

s = singlet; d = doublet; dd = double doublet; t = triplet; m = multiplet.

which comprises the core structure of the novel compound is a new flavonoid aglycone in nature, however, this aglycone has previously been synthesized (Horie et al., 1992). The ^{1}H NMR data of the aglycone of **2** reported by Horie et al. (1992) were relatively similar to that of **2** with exception of the chemical shift value of H-8, which

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occur 0.45 ppm downfield because of the substituent effect of the glucosyl substituent.

We next evaluated the cytotoxic potential of rutin (**1**) and the novel flavonoid 5,6,7,4'-tetrahydroxy-3',5'-dimethoxy-flavone 7-*O*-*β*-D-glucopyranoside (**2**) towards the MOLM-13 human acute myeloid leukaemia, and NRK rat kidney epithelial cell lines (Fig. 3). Both compounds showed cytotoxic activity towards MOLM-13 cells, but rutin was far more potent than 5,6,7,4'-tetrahydroxy-3',5'-dimethoxy-flavone 7-*O*-*β*-D-glucopyranoside (EC_{50} 40 ± 12 and 920 ± 150 μM, respectively, Fig. 3A). The NRK cells showed less response to exposure to either compound. These cells were unaffected by the highest concentration of 5,6,7,4'-tetrahydroxy-3',5'-dimethoxy-flavone 7-*O*-*β*-D-glucopyranoside, and the EC_{50} value for rutin was 245 ± 19 μM (Fig. 3B). Cirsilineol 4'-glucoside exhibited AML cell cytotoxicity with EC_{50} of around 100 μM after 24 h of incubation (Supplementary Fig. S1).

A limited number of poly-oxygenated flavonoids have previously been identified from plants belonging to Bromeliaceae (Bringmann et al., 2000; Flagg et al.,

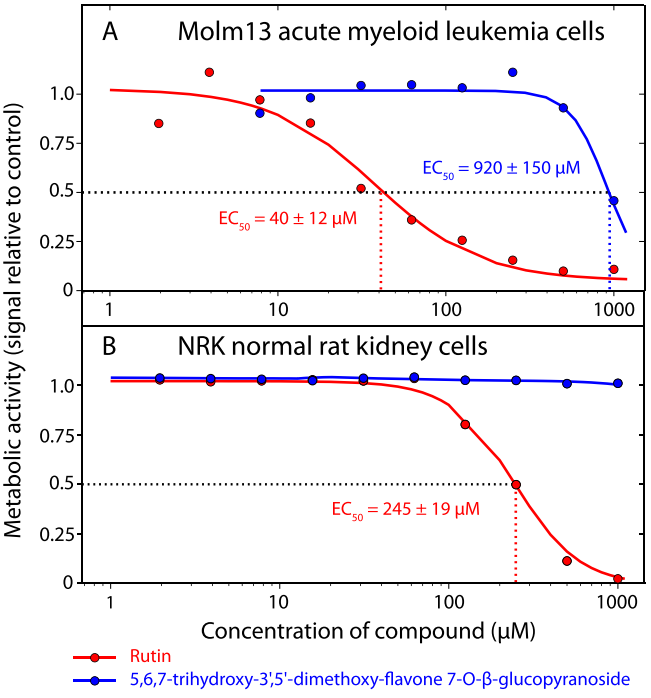

Fig. 3. Cytotoxic activity of rutin and 5,6,7,4'-tetrahydroxy-3',5'-dimethoxy-flavone 7-*O*-β-glucopyranoside towards mammalian cell lines. Molm13 acute myeloid leukaemia cells (A) and NRK rat kidney epithelial cells (B) were treated with various concentrations of either rutin or 5,6,7,4'-tetrahydroxy-3',5'-dimethoxy-flavone 7-*O*-β-glucopyranoside for 48 h before viability of the cells were assessed by metabolic conversion of resazurin to the fluorescent reporter resorufin. The data are average of two parallel experiments and a curve fitted from four-parameter regression analyses. The dotted vertical lines indicate the EC_{50} values. Note the higher activity (lower EC_{50}) of both compounds in Molm13 cells compared to the NRK cells.

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2000; Lowe et al., 2017). Several studies have shown that rutin has anticancer effects (Lin et al., 2012). ben Sghaier et al. (2016) concluded that rutin might have potential as anticancer agent against lung and colorectal carcinogenesis (ben Sghaier, Pagano, Mousslim, Ammaria, Kovacic & Luis). Lin et al. determined that rutin inhibits human leukaemia tumor growth in a murine xenograft model *in vivo* where human leukaemia HL-60 cells were implanted into mice. They concluded that rutin may be useful in treating leukaemia, however, they underlined that much more confirmative research is needed (Lin et al., 2012).

4. Conclusion

In this paper, we report on the first identification of a poly-oxygenated flavone glucoside from *N. variegata* whose core structure is based on the novel flavone aglycone 5,6,7,4'-tetrahydroxy-3',5'-dimethoxy-flavone. The selective cytotoxicity of rutin towards MOLM-13 acute myeloid leukaemia cells reported in this paper further supports the anticancer potential of rutin or analogues of this in future cancer treatment.

Declarations

Author contribution statement

Ayaan Hamdi Haji Ibrahim, Bendik Rathe: Performed the experiments; Analyzed and interpreted the data.

Lars Herfindal, Torgils Fossen: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Heidi Lie Andersen: Conceived and designed the experiments; Wrote the paper.

Jackson Roberto Guedes da Silva Almeida: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

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Additional information

Supplementary content related to this article has been published online at https://doi.org/10.1016/j.heliyon.2019.e01369.

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