STUDY ON ISOLATION OF TRITERPENOID SAPONINS FROM THE LEAVES OF WEIGELA FLORIDA "PINK POPPET"

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ABSTRACT

The *Weigela florida* "Pink Poppet" is a shrub distributed widely in Europe and other regions in the world. This plant has been grown for comfort and ornamental purposes. It belongs to the genus *Weigela*, the family Caprifoliaceae known for the sources of saponins. Therefore, it is necessary to conduct a phytochemical study on the cultivar *W. florida* "Pink Poppet". The research on the leaves of this plant resulted in the isolation and purification of three triterpenoid saponins, which have structural determinations as 3-*O*-α-L-arabinopyranosylhederagenin 28-*O*-β-D-xylopyranosyl-(1→6)-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranosyl ester (**1**), 3-*O*-α-L-arabinopyranosylhederagenin 28-*O*-β-D-glucopyranosyl-(1→6)-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranosyl ester (**2**), and 3-*O*-β-D-glucopyranosyl-(1→2)-α-L-arabinopyranosylhederagenin 28-*O*-α-L-rhamnopyranosyl-(1→2)-[β-D-xylopyranosyl-(1→6)]-β-D-glucopyranosyl ester (**3**). Additionally, in this study, the relationship between the chemical structure and biological activities of the saponins was discussed, which is fundamental for evaluating the biological activities of these compounds in the future.

NGHIÊN CỨU PHÂN LẬP TRITERPENOID SAPONIN TỪ PHẦN LÁ CỦA LOÀI WEIGELA FLORIDA "PINK POPPET"

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TỪ KHÓA

Saponin
Triterpenoid saponin
Weigela florida "Pink Poppet"
Oleanane-type aglycone
Hederagenin

TÓM TẮT

W. florida "Pink Poppet" là một loài cây bụi, có vùng phân bố rộng ở châu Âu và trên thế giới và được trồng với mục đích làm cảnh. Loài thực vật này thuộc chi *Weigela*, họ Kim ngân (Caprifoliaceae) vốn được biết đến là nguồn cung cấp các hợp chất saponin có hoạt tính sinh học, do đó, việc nghiên cứu tách chiết thành phần saponin từ loài thực vật này là cấp thiết. Theo đó, nghiên cứu đã tách chiết được ba hợp chất triterpenoid saponin từ phần lá của loài *W. florida* "Pink Poppet", có cấu trúc hóa học là 3-*O*-α-L-arabinopyranosylhederagenin 28-*O*-β-D-xylopyranosyl-(1→6)-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranosyl ester (**1**), 3-*O*-α-L-arabinopyranosylhederagenin 28-*O*-β-D-glucopyranosyl-(1→6)-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranosyl ester (**2**), và 3-*O*-β-D-glucopyranosyl-(1→2)-α-L-arabinopyranosylhederagenin 28-*O*-α-L-rhamnopyranosyl-(1→2)-[β-D-xylopyranosyl-(1→6)]-β-D-glucopyranosyl ester (**3**). Tiếp đó, mối liên quan giữa cấu trúc hóa học và hoạt tính sinh học của các hợp chất saponin đã được bàn luận, là cơ sở để tiến hành đánh giá hoạt tính sinh học của các hợp chất saponin phân lập được trong các nghiên cứu tiếp theo.

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1. Introduction

Ornamental plants which play an important role in human life possess beautiful flowering and are easy to grow, so they are being planted at homes, workplaces, research institutes... for decoration and improving quality of life [1]. Some of them are used to remove indoor air pollutants such as formaldehyde, benzene, carbon monoxide and some other toxic compounds [2]. Besides, some ornamental plants possessing high content of natural compounds such as phenolics, antioxidant compounds, and carotenoids are planted for medicinal purposes because of their biological activities [3]. This information shows that ornamental plants can be a source of biologically active natural compounds that science has not fully explored.

The genus *Weigela*, belonging to the Caprifoliaceae family, consists of ten species which are mainly distributed in Asia, but many cultivars were produced for many purposes. One of those is that they are used traditionally to treat allergic syndromes and pain [4]-[6]. Among those cultivars, *W. florida* "Pink Poppet" is a shrub with pink flowers and dark green leaves. Previously, studies on some species of genus *Weigela* revealed the identification of triterpenoid saponins which possesses interesting biological activities, some of which showed cytotoxic, anti-inflammatory, stimulatory, and antibody recognition activities [4], [7]-[11]. This evidence led us to carry out the phytochemical study on the leaves of cultivar *W. florida* "Pink Poppet" to achieve the data of saponins in genus *Weigela*. By the way, the isolation and purification resulted in three triterpenoid saponins obtained by various chromatographic and spectroscopic methods (1D and 2D NMR and Mass spectroscopy). A highlight of biological activities on these hederagenin types was also reported due to the data in the literature suggesting to carry out other experiments to achieve an overview of biological activities on these compounds.

2. Methodology

2.1. General procedures

An automatic polarimeter (Optical Activity®, England) was used to record optical rotation values. An NMR Inova spectrometer (Agilent Technologies®, USA) was used to perform the 1D and 2D spectra including ^{1}H, ^{13}C, HSQC, ROESY, HMBC, TOCSY, COSY NMR, and further recorded at the temperature of 35°C in pyridine-d_5 (C_5D_5N). HR-ESI-MS was done by a micrOTOF II mass spectrometer (Bruker®, Germany). A microwave apparatus (MARS 6, CEM®, USA) was used to perform the extractions. CC (Column chromatography) were presented ion Sephadex® LH20 (Sigma Aldrich, France). VLC (Vacuum liquid chromatography) was performed on a normal phase (silica gel 60 60-200 µm, Merck®, Germany). MPLC (Medium-pressure liquid chromatography) was carried out on normal phase (silica gel 60, Merck®, Germany) with an M305 pump (Gilson®, USA). HPTLC (High performance thin layer chromatography, Merck®, Germany) and TLC (Thin layer chromatography, Silicycle®, Canada) were precoated silica gel plates $60F_{254}$. A vanillin reagent was used to reveal saponins in samples.

2.2. Plant materials

The leaves of *W. florida* "Pink Poppet" were collected in Jardiland® (Chenove, France) at 47°17'06.4"N, 5°01'28.1"E. The voucher specimen was kept and the work of isolation and extraction was done at the Laboratoire de Pharmacognosie, Université de Bourgogne Franche-Comté, Dijon (Figure 1).

2.3. Extraction and isolation

The extraction on dried leaves (15.6 g) of *W. florida* "Pink Poppet" was carried out by ultrasound assisted-extraction with EtOH/H_2O (75:35) (60°C, 45 min, 3 times with 250 mL each). After removing solvent, the extract (3.9 g) was presented to VLC normal phase with solvent $CHCl_3$/MeOH/H_2O 80:20:2, 70:30:5, 60:32:7 (v/v/v) resulting 4 fractions (A - D).

Fraction B (138.8 mg) was subjected to a MPLC normal phase with solvent $CHCl_3$/MeOH/H_2O 75:25:3 (v/v/v) to give 4 subfractions (B1 - B4). Subfraction B2 was chromatographed again on MPLC normal phase with solvent $CHCl_3$/MeOH/H_2O 80:20:2, 75:25:3 (v/v/v) yielding 3 subfractions (B2.1 - B2.3). Subfraction B2.2 (8.3 mg) was further purified on CC with solvent EtOH 96% affording compound **1** (WeFJG2V3d) (3.2 mg). Fraction C (155.8 mg), rich in saponin, was chromatographed on a MPLC normal phase with solvent $CHCl_3$/MeOH/H_2O 75:25:3, 70:30:5 (v/v/v) resulting compound **2** (WeFJR2) (3.5 mg) among the 6 fractions obtained (C1 - C6). The interesting fractions containing saponins were combined and further presented to MPLC normal phase with solvent $CHCl_3$/MeOH/H_2O 70:30:5 (v/v/v) yielding compound **3** (WeFJ0711) (9.2 mg).

Figure 1. *Morphological characteristic of W. florida "Pink Poppet"*

3. Results and discussion

The aglycone signals of compounds **1-3** by working on spectra ^1H and ^{13}C were quite similar with the signals of hederagenin previously revealed in *Weigela* species proved by the olefinic signals at the C-12 and C-13 positions of the aglycone (124.0 and 145.4 in compound **1**, 124.0 and 145.6 in compound **2**, 124.0 and 143.4 in compound **3**, respectively) [4], [5]. The oligosaccharide chain linked to the positions of C-3 and C-28 in combination with the presence of the alcohol function at the C-23 position of the aglycone was identified as the differences between these compounds. The monosaccharides were revealed by analyzing 2D NMR as α-L-arabinopyranosyl (Ara), β-D-glucopyranosyl (Glc), β-D-xylopyranosyl (Xyl), and α-L-rhamnopyranosyl (Rha) in compounds **1** and **3**, together with Ara, Glc, and Rha in compound **2**. The absolute configurations of the monosaccharides were identified as D for Xyl and Glc, along with L for Ara and Rha. The $^3J_{H\text{-}1,\ H\text{-}2}$ values of Ara, Glc, Xyl (5.0-8.2 Hz) pointed out an α orientation for Ara, and a β orientation for Xyl and Glc. The broad singlet of Rha indicated an α anomeric orientation [12].

Compound **1** was isolated in a white powder. The formula of **1** was established as $C_{52}H_{84}O_{21}$ by mass spectrum in positive-ion mode with a pseudo-molecular peak at *m/z* 1067.5389 $[M + Na]^+$, revealing a molecular weight of 1044. The structure of aglycon was identified by analyzing spectra NMR ^1H, ^{13}C, HSQC and HMBC. In the spectrum of HSQC, characteristic signals of an oleanane-type aglycone were shown including six methyl groups with singlet signals at δ_H 0.82/δ_C 14.8, δ_H 0.95/δ_C 17.5, δ_H 1.05/δ_C 18.8, δ_H 1.16/δ_C 27.2, δ_H 0.79/δ_C 34.3, δ_H 0.86/δ_C 25.1, one olefinic proton at δ_H 5.40 (br t, J = 3.6 Hz) corresponds to proton H-12, proved by the ^{13}C NMR spectrum with five tertiary carbons (CH), eleven secondary carbons (CH_2), six primary carbons (CH_3) and eight quaternary carbons (C) (Table 1). The observed downfield shift at δ_C 83.4 for C-3 and upfield shift at δ_C 178.0 for C-28 suggested that compound **1** was an oleanane-type aglycone.

The sugar part of **1** in the HSQC spectrum showed the cross-peaks at δ_H 4.79 (d, J = 7.6 Hz)/δ_C 106.5, δ_H 6.03 (d, J = 8.2 Hz)/δ_C 95.9, δ_H 6.36 (br s)/δ_C 102.7, δ_H 4.94 (d, J = 7.0 Hz)/δ_C 107.6 deal with the presence of four sugar moieties as Xyl, Glc, Rha and Ara (Table 2). An HMBC correlation between δ_H 4.94 (Ara H-1) and δ_C 83.4 (C-3), together with a ROESY correlation at δ_H 4.94 (Ara H-1)/δ_H 4.16 (dd, J = 11.1, 4.1 Hz, H-3) proved that the α-L-arabinopyranosyl moiety attached to the C-3 position of the aglycone. The signals at δ_C 95.9 of Glc C-1 and δ_C 178.0 of C-28 position of the aglycone revealed a linkage of Glc this position which was in agreement with the literature data [4], [7], [11]. The HMBC correlations at δ_H 4.79 (Xyl H-1)/δ_C 70.0 (Glc C-6) and δ_H 6.36 (Rha H-1)/δ_C 96.0 (Glc C-1), together with the ROESY correlations at δ_H 4.79 (Xyl H-1)/δ_H 4.20 (Glc H-6) and δ_H 6.36 (Rha H-1)/δ_H 4.28 (Glc H-2) confirmed the linkage as β-D-xylopyranosyl-(1→6)-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranosyl. Based on the above results and compared to the literature, the structure of **1** was elucidated as 3-*O*-α-L-arabinopyranosylhederagenin 28-*O*-β-D-xylopyranosyl-(1→6)-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranosyl ester (Figure 2). This compound was previously isolated from the aerial parts of *Lonicera japonica* [13].

The formula of compound **2** was obtained as $C_{53}H_{86}O_{22}$ proved by mass spectroscopy in the positive-ion mode which displayed a pseudo-molecular ion peak at *m/z* 1097.5513 $[M + Na]^+$ and thus a molecular weight of 1190. This molecular weight differs from **1** by only 30 amu, correlating to the presence of a hexosyl group instead of 5-deoxypentosyl one in **1**. The HSQC spectrum of monosaccharide moieties of **2** showed five cross-peaks at δ_H 4.90 (d, J = 7.6 Hz)/δ_C 106.2, δ_H 4.94 (d, J = 7.0 Hz)/δ_C 107.7, δ_H 6.00 (d, J = 8.2 Hz)/δ_C 96.0 and δ_H 6.37 (br s)/δ_C 102.7, revealing the identification of four sugar moieties which were further determined as Glc I, Ara, Glc II and Rha (Table 2). The spectra data NMR of **2** were the same as **1** with the appearance of the Ara (δ_H 4.94/δ_C 107.7) correlated to the C-3 position, and the sequence α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranosyl correlated to the C-28 position of the aglycone. The difference was pointed out at the C-6 position of the Glc I part with the downfield shift at δ_H 4.61 ppm. Another Glc linked to the C-6 position of Glc I was determined by the HMBC correlation at δ_H 4.90 (Glc II H-1)/ δ_C 70.4 (Glc I C-6) and by the ROESY correlation at δ_H/δ_H 4.90 (Glc II H-1)/4.61 (Glc I H-6). Based on these results, the structure of **2** was elucidated as 3-*O*-α-L-arabinopyranosylhederagenin 28-*O*-β-D-glucopyranosyl-(1→6)-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranosyl ester (Figure 2). This compound was previously isolated from the aerial parts of *Weigela subsessilis* [9].

The mass spectrum showed a pseudo-molecular ion peak for compound **3** at *m/z* 1229.5954 $[M+Na]^+$, revealing a molecular formula of $C_{58}H_{94}O_{26}$ and a molecular weight of 1206. The difference of molecular weight between compounds **3** and **1** was 162 amu indicating to the addition of one 6-deoxyhexosyl group. The HSQC spectrum of sugar region of **3** showed five cross-peaks at δ_H 5.11 (d, J = 5.9 Hz)/δ_C 105.1, δ_H 4.78 (d, J = 7.6 Hz)/δ_C 106.5, δ_H 5.14 (d, J = 7.6 Hz)/δ_C 106.5, δ_H 6.01 (d, J = 7.6 Hz)/δ_C 95.9 and δ_H 6.35 (br s)/δ_C 102.7, indicating the presence of five sugar units. They were characterized as Ara, Xyl, Glc I, Glc II, and Rha, respectively (Table 2). The data of **3** was compared to **1** revealing the similar structure of sequence: 3-*O*-α-L-arabinopyranosylhederagenin 28-*O*-β-D-xylopyranosyl-(1→6)-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranosyl ester (Tables 1 and 2). The difference of these two compounds was identified as another terminal sugar moiety, β-D-glucopyranosyl moiety, linked to the C-2 position of Ara moiety. This conclusion was determined by an HMBC correlation at δ_H 5.14 (Glc I H-1)/δ_C 81.5 (Ara C-2) and a ROESY cross-peak at δ_H 5.14 (Glc I H-1)/δ_H 4.54 (Ara H-2). Based on these observations and further, in comparison with the literature, the structure of **3** was revealed as 3-*O*-β-D-glucopyranosyl-(1→2)-α-L-arabinopyranosylhederagenin 28-*O*-β-D-xylopyranosyl-(1→6)-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranosyl ester which was previously isolated from the leaves of *W. stelzneri* (Figure 2) [4].

Table 1. *^{1}H and ^{13}C NMR data of the aglycone portion of **1-3** (C_5D_5N, δ in ppm, J in Hz)*

	1		**2**		**3**	
	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
1	40.1	0.97 m, 1.52 m	40.0	0.95 m, 1.52 m	40.0	0.91 m, 1.48 m
2	27.3	1.92 m, 2.16 m	27.4	1.92 m, 2.17 m	27.2	1.90 m, 2.07 m
3	83.4	4.16 dd (11.1, 4.1)	83.4	4.16 dd (11.1, 3.5)	83.6	4.08
4	44.6	–	44.8	–	44.7	–
5	48.8	1.59 d (12.3)	48.4	1.59 d (11.7)	48.9	1.52 d (11.7)
6	19.5	1.32, 1.63	19.4	1.32, 1.63	19.6	1.31, 1.62
7	34.1	1.61, 1.65	34.3	1.62, 1.65	34.2	1.60, 1.63
8	41.2	–	41.2	–	41.2	–
9	49.4	1.71	49.4	1.70	49.4	1.67
10	38.2	–	38.2	–	38.1	–
11	25.1	1.85, 1.95	25.1	1.86, 1.93	25.1	1.82, 1.94
12	124.0	5.39 t-like	124.0	5.48 t-like	124.0	5.38 t-like
13	145.4	–	145.6	–	143.4	–
14	43.5	–	43.6	–	43.5	–
15	29.8	1.44 m, 2.00	30.0	1.49 m, 1.97	29.8	1.44 m, 1.98
16	24.7	1.96, 2.08	24.8	1.98, 2.09	24.6	1.97, 2.06
17	47.6	–	47.6	–	47.6	–
18	43.2	3.08	43.2	3.06	43.2	3.08
19	47.6	1.15, 1.68	47.8	1.14, 1.68	47.6	1.14, 1.67
20	31.9	–	31.9	–	31.9	–
21	35.2	1.10 m, 1.28 m	35.2	1.07 m, 1.26 m	35.2	1.09 m, 1.27 m
22	33.5	1.74, 1.98	33.5	1.74, 1.92	33.5	1.73, 1.97
23	65.4	3.55, 4.16	65.5	3.55, 4.15	65.6	3.57, 4.15
24	14.8	0.82 s	14.8	0.82 s	14.6	0.91 s
25	17.5	0.95 s	17.5	0.93 s	17.4	0.93 s
26	18.8	1.05 s	18.8	1.05 s	18.8	1.04 s
27	27.2	1.16 s	27.1	1.16 s	27.2	1.14 s
28	178.0	–	178.8	–	178.0	–
29	34.3	0.79 s	34.3	0.78 s	34.4	0.79 s
30	25.1	0.86 s	25.0	0.81 s	25.1	0.85 s

Table 2. *^{1}H and ^{13}C NMR data of the sugar portion of **1-3** in (C_5D_5N, δ in ppm, J in Hz)*

	1		**2**		**3**	
	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
Ara-1	107.6	4.94 d (7.0)	107.7	4.94 (7.0)	105.1	5.11 d (5.9)
2	74.1	4.38	74.1	4.38	81.5	4.54
3	75.6	4.09	75.7	4.09	74.6	4.25
4	70.6	4.22	70.7	4.23	69.5	4.27
5	68.0	3.69 dd (11.1, 1.2), 4.23	68.0	3.69 dd (11.1, 1.2), 4.22	68.1	3.55 dd (11.1, 1.2), 4.22
Rha-1	102.7	6.36 br s	102.7	6.37 br s	102.7	6.35 br s
2	73.1	4.72 br s	73.1	4.73 br s	73.1	4.72 br s
3	73.5	4.48 dd (9.4, 3.5)	74.8	4.48 dd (9.4, 2.3)	73.5	4.48 dd (9.4, 2.9)
4	74.8	4.28 dd (9.4, 9.4)	73.7	4.28 dd (9.4, 8.8)	74.8	4.29 dd (9.4, 9.4)
5	71.2	4.43 dq (9.4, 6.4)	71.1	4.44 dq (8.8, 5.9)	71.2	4.42 dq (9.4, 6.4)
6	20.0	1.68 d (6.4)	19.9	1.69 d (5.9)	20.0	1.68 d (6.4)
Xyl-1	106.5	4.79 d (7.6)			106.5	4.78 (7.6)
2	75.8	3.90			75.8	3.89
3	78.9	4.07			79.0	4.07
4	72.1	4.09			72.1	4.09
5	68.1	3.55 t (10.0), 4.24			68.1	3.55 t (10.5), 4.22
Glc I-1	95.9	6.03 d (8.2)	96.0	6.00 d (8.2)	106.5	5.14 d (7.6)
2	77.1	4.28	76.9	4.29	77.1	4.01

	1		2		3	
	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
3	80.2	4.18	80.2	4.19	79.2	4.12
4	71.9	4.27	72.0	4.25	72.5	4.1
5	78.6	4.01 m	79.0	4.02 m	79.4	3.78 m
6	70.0	4.20, 4.55	70.4	4.20, 4.61	63.6	4.24, 4.39
Glc II-1			106.2	4.90 d (7.6)	95.9	6.01 d (7.6)
2			76.1	3.91	77.1	4.27
3			79.2	4.14	80.2	4.18
4			72.6	4.08	71.9	4.26
5			79.4	3.82 m	78.6	4.01 m
6			63.6	4.23, 4.39	70.0	4.20, 4.55

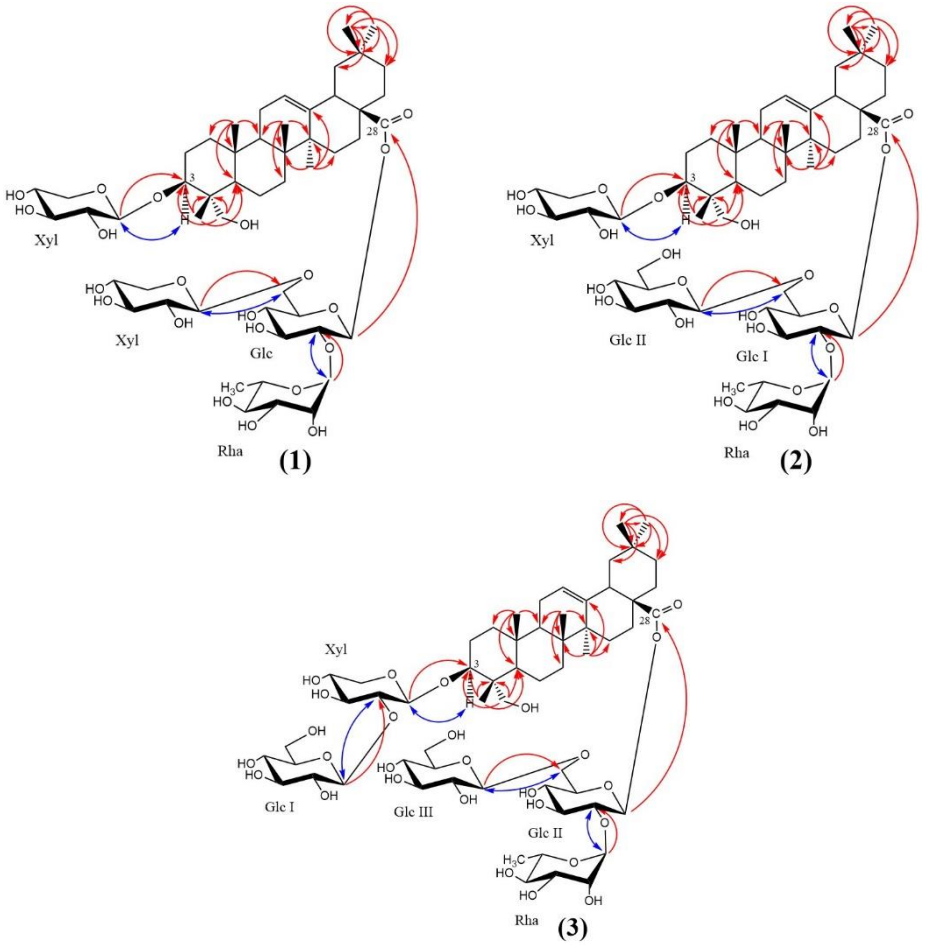

Figure 2. *The structure of compounds **1-3***

The biological activity of triterpenoid glycosides was previously carried out on cytotoxicity against cancer cell lines of hederagenin types isolated from *W. florida* "Jean's Gold" and also displayed for those of hederagenin types from other *Weigela* species [4], [14]. According to biological data in the literature, the biological activities were evaluated against three cancer cell lines CT26 (mouse colon cancer), B16 (mouse melanoma), HepG2 (human liver cancer) for the compound **1** and **3**, and SW480 (human colorectal), EMT6 (mouse mammary) for the compound **2**. The results showed inactive effects on both cell lines due to the presence of an ester group at the C-28 position and an alcohol function at the C-23 position of the aglycon which was previously concluded by Bang et al. (2005) [15]. Furtherly, the anti-inflammatory activity of

those of hederagenin types was measured against acute and chronic inflammation, which further showed good results in comparison to aspirin [16]. Based on the evidence above, it could be interesting to carry out other experiments to achieve an overview of biological activities on hederagenin type compounds.

4. Conclusion

The study of phytochemistry on the leaves of *W. florida* "Pink Poppet" was resulted in the revelation of three triterpenoid saponins including 3-*O*-α-L-arabinopyranosylhederagenin 28-*O*-β-D-xylopyranosyl-(1→6)-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranosyl ester, 3-*O*-α-L-arabinopyranosylhederagenin 28-*O*-β-D-glucopyranosyl-(1→6)-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranosyl ester, and 3-*O*-β-D-glucopyranosyl-(1→2)-α-L-arabinopyranosylhederagenin 28-*O*-β-D-xylopyranosyl-(1→6)-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranosyl ester. These compounds were previously isolated from other *Weigela* species, but this is the first isolation on *W. florida* "Pink Poppet". A summary of biological activities on these hederagenin types was also reported due to the data in the literature suggesting to carry out other experiments to achieve an overview of biological activities on these compounds.

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