ABSTRACT
The methanolic extract of *Mussaenda pubescens* Dryand leaves exhibited significant anti-osteoclastogenic activity. Chemical investigation of *M. pubescens* led to the isolation of one new cycloartane saponin, mussaendoside X (1) along with eight known compounds: heinsiagenin A 3-O-[α-L-rhamnopyranosyl-(1→2)]-O-β-D-glucopyranosyl-(1→2)]-O-β-D-glucopyranoside (2), mussaendoside O (3), heinsiagenin A 3-O-[α-L-rhamnopyranosyl-(1→2)]-O-β-D-glucopyranosyl-(1→2)]-O-β-D-glucopyranosyl-(1→4)-O-β-D-glucopyranoside (4), mussaendoside G (5), mussaendoside U (6), shanzhiside methyl ester (7), barlerin (8) and musaenoside (9). Their structures were elucidated by extensive spectroscopic methods including 1D- and 2D-NMR as well as MS analysis and comparison with the literature. Cycloartane saponins 1–6 positively suppressed osteoclast formation in an anti-osteoclastogenic screening assay. Consequently, treatment of RANKL-stimulated RAW 264.7 cells with compounds 1–4 significantly decreased the number of osteoclasts in a concentration-dependent manner. Six compounds from *M. pubescens*, with the new cycloartane, mussaendoside X, were shown for the first time as potential effective inhibitors of osteoclastogenesis.

1. Introduction
Osteoblasts, osteoclasts, osteocytes and lining cells are the four types of cells that make up bone. The damaged bone is eliminated by osteoclasts and replaced by new bone created by osteoblasts in the process of bone remodelling (Feng and McDonald...
An imbalance between bone formation and resorption can result in too much bone (osteopetrosis) or too little bone (osteoporosis) (Lazner et al. 1999). Bisphosphonates and estrogen therapy are popular and effective in treating osteoporosis, but they have a number of adverse effects (Kennel and Drake 2009; Baron et al. 2011). As a result, new, safer anti-osteoporosis medications are desperately needed. Previous studies indicated that receptor activator of nuclear factor kappa B ligand (RANKL) is produced by osteoclasts and interacts with a receptor activator of nuclear factor kappa B (RANK) on osteoclasts and promotes their change into completed osteoclasts. In addition, the RANK/RANKL interaction promotes bone resorption (Kostenuik et al. 2009). This opens up many options for future research in terms of evaluating anti-osteoporotic activity by affecting osteoclast formation in vitro.

For thousands of years, traditional herbs have been used in folklore with few side effects. As a result, finding chemicals from herbal sources that contain anti-osteoporotic properties have raised concerns (Sun et al. 2017; Wang et al. 2020; Wei et al. 2021). *Mussaenda* is a genus of flowering plants in the family Rubiaceae and includes 188 accepted species. *Mussaenda* species native to the African and Asian tropics and subtropics are important sources of oriental medicine. *Mussaenda pubescens* Dryand has been used in traditional medicine for the treatment of some inflammatory diseases, such as laryngopharyngitis and acute gastroenteritis (Chi 1999). Phytochemical studies of *M. pubescens* have revealed the presence of N-triterpene cycloartane saponins (Zhao et al. 1994; Weimin et al. 1995, 1996; Zhao et al. 1996b, 1997), phenolics, and iridoids (Hien et al. 2017).

In the search for anti-osteoclastogenic activity in Vietnamese traditional plants, the methanol extract of *M. pubescens* leaves was found to inhibit strongly the progression of osteoclastogenesis by 98.51% at a concentration of 25 μg/mL (Huong et al. 2021). The plant was selected for further chemical investigation. This paper reports the isolation, structural elucidation and anti-osteoclastogenic activity of one new saponin and eight known compounds from *M. pubescens*.

2. Results and discussion

The methanolic extract of *M. pubescens* leaves was suspended in water and then partitioned with *n*-hexane and ethyl acetate (EtOAc) to obtain layers. Using various chromatography methods, nine compounds were isolated. The known compounds were identified as heinsiagenin A 3-O-[α-L-rhamnopyranosyl-(1→2)-O-β-D-glucopyranosyl-(1→2)]-O-β-D-glucopyranoside (2), mussaendoside O (3) (Zhao et al. 1994), heinsiagenin A 3-O-[α-L-rhamnopyranosyl-(1→2)-O-β-D-glucopyranosyl-(1→2)]-O-β-D-glucopyranoside (4), mussaendoside G (5) (Weimin et al. 1996), mussaendoside U (6) (Zhao et al. 1997), shanzhisolide methyl ester (7), barlerin (8) and musaenoside (9) (Hien et al. 2017) (Supplementary material, Figure S1). Their structures were elucidated by extensive spectroscopic methods including 1D- and 2D-NMR as well as MS analysis and by comparison with the literature.

Compound 1 was obtained as an amorphous powder and its molecular formula determined to be C_{78}H_{125}O_{37}N by high-resolution electrospray ionization mass (HR-ESI-MS) at m/z 1702.7586 [M + Cl]^{-} (Calcd. for [C_{78}H_{125}O_{37}NCl]^{-}, 1702.7624). The $^1$H-NMR
The spectrum of 1 (CD$_3$OD) showed the signals of three olefinic protons at $\delta_H$ 5.97 (dd, $J = 9.0$, 15.0 Hz), 6.37 (dd, $J = 11.0$, 15.0 Hz), and 6.91 (d, $J = 11.0$ Hz), two protons of the cyclopropane ring at $\delta_H$ 0.40 (br s) and 0.61 (br s), six methyl groups at $\delta_H$ 0.96 (s), 0.97 (s), 1.08 (d, $J = 6.5$ Hz), 1.09 (s), 1.13 (s) and 1.99 (s), indicating the presence of a cycloartane aglycone, seven anomeric protons at $\delta_H$ 4.35 (d, $J = 7.5$ Hz), 4.38 (d, $J = 8.0$ Hz), 4.61 (d, $J = 7.0$ Hz), 4.85 (d, $J = 8.0$ Hz), 4.94 (d, $J = 1.5$ Hz), 5.22 (br s) and 5.23 (d, $J = 8.0$ Hz) assigned to seven monosaccharide moieties. Two methyl groups at $\delta_H$ 0.85 (d, $J = 7.0$ Hz) and 1.38 (d, $J = 6.5$ Hz), and one N-methine proton at $\delta_H$ 5.08 (d, $J = 7.0$ Hz) suggested the presence of a 4-hydroxyisoleucine $\gamma$-lactone. The $^{13}$C-NMR, DEPT and HSQC spectra revealed signals of 78 carbons, including two carbonyls, six non-protonated carbons and 46 methine, 14 methylene and 9 methyl carbons. The $^1$H- and $^{13}$C-NMR data of 1 were found to be similar to those of mussaglaoside C (6) (Thu et al. 2019), a compound previously reported from M. glabra. The structural difference between 1 and mussaglaoside C is the addition of a glucopyranosyl moiety (Figure 1). The HMBC correlations between H-26 ($\delta_H$ 1.99) and C-24 ($\delta_C$ 136.4)/C-25 ($\delta_C$ 128.6)/C-27 ($\delta_C$ 172.7), between H-24 ($\delta_H$ 6.91) and C-22 ($\delta_C$ 149.8)/C-23 ($\delta_C$ 124.5)/C-25 ($\delta_C$ 128.6)/C-26 ($\delta_C$ 13.0)/C-27 ($\delta_C$ 172.7) suggested the location of two double bonds at C-22/C-23 and C-24/C-25. The large coupling constant between H-22 and H-23 ($J = 15.0$ Hz) and the NOE correlation between H-23 ($\delta_H$ 6.37) and H-26 ($\delta_H$ 1.99) demonstrated the configurations of both double bonds to be $E$. The $^{13}$C-NMR chemical shifts of hil 3-Me ($\delta_C$ 8.0) and hil 4-Me ($\delta_C$ 15.7) indicated the configuration of the 4-hydroxyisoleucine $\gamma$-lactone as [2$^S$,3$R$,4$^R$] by comparison with those of mussaglaoside C [hil 2$^S$,3$R$,4$^R$] [hil 3-Me ($\delta_C$ 8.1) and hil 4-Me ($\delta_C$ 15.7)] and mussaglaoside E [hil 2$^S$,3$R$,4$^S$] [hil 3-Me ($\delta_C$ 12.4) and hil 4-Me ($\delta_C$ 19.9)] (Thu et al. 2019). The 4-hydroxyisoleucine $\gamma$-lactone bonded with C-27 of cycloartane was confirmed by the HMBC correlation between hil H-2 ($\delta_H$ 5.08) and C-27 ($\delta_C$ 172.7). The position of an oxygenated group at C-3 was confirmed by the HMBC correlations between H-28 ($\delta_H$ 1.13)/H-29 ($\delta_H$ 0.96) and C-3 ($\delta_C$ 92.6) (Supplementary material, Figure S2). Moreover, the axial orientation of H-3 ($\alpha$-configuration) was based on the multiplicity of H-3 ($\delta_H$.
3.16, dd, J = 4.0, 12.0 Hz) and the NOESY correlation between H-3 (δH 3.16) and H-5 (δH 1.33). Acid hydrolysis of 1 gave L-rhamnose and D-glucose (identified as trimethylsilyl derivatives by gas chromatography). In addition, the monosaccharides were determined to be β-D-glucopyranosyl and α-L-rhamnopyranosyl based on the multiplicity of H-1 of gluc I: δH 4.38 (d, J = 8.0 Hz), gluc II: δH 4.85 (d, J = 8.0 Hz), gluc III: δH 5.23 (d, J = 8.0 Hz), gluc IV: δH 4.61 (d, J = 7.0 Hz), gluc V: δH 4.35 (d, J = 7.5 Hz), rha I: δH 4.94 (d, J = 1.5 Hz) and rha II: δH 5.22 (br s). The HMBC correlations from rha I H-1 (δH 4.94) to gluc I C-4 (δC 80.3), from gluc II H-1 (δH 4.85) to gluc I C-2 (δC 77.6), from rha II H-1 (δH 5.22) to gluc II C-2 (δC 79.3), from gluc III H-1 (δH 5.23) to gluc II C-6 (δC 70.4), from gluc IV H-1 (δH 4.61) to gluc III C-2 (δC 83.6), from gluc V H-1 (δH 4.35) to gluc III C-6 (δC 69.5) and from gluc I H-1 (δH 4.38) to C-3 (δC 92.6) indicated the sugar linkages to be β-D-glucopyranosyl-(1→6)-O-[β-D-glucopyranosyl-(1→2)]-O-β-D-glucopyranosyl-(1→6)-O-[α-L-rhamnopyranosyl-(1→2)]-O-β-D-glucopyranosyl-(1→2)-[O-α-L-rhamnopyranosyl(1→4)].

Consequently, the structure of 1 was determined to be heinsiagenin A 3-[O-β-D-glucopyranosyl-(1→6)-O-[β-D-glucopyranosyl-(1→2)]-O-β-D-glucopyranosyl-(1→6)-O-[α-L-rhamnopyranosyl-(1→2)]-O-β-D-glucopyranosyl-(1→2)-[O-α-L-rhamnopyranosyl(1→4)]-O-β-D-glucopyranoside and named mussaendoside X.

To identify the anti-osteoclastogenic effect of the isolated compounds, we examined them on RANKL-induced RAW 264.7 cells at the screening concentration of 10 μM. Cycloartane saponins 1–6 exhibited strong inhibitory effects against RANKL-induced osteoclast formation (Supplementary material, Figure S13). The cell viability assay revealed that all compounds had no impact on cell growth (Supplementary material, Figure S14). This result ruled out the possibility that the test compounds induced cell toxicity. Therefore, the concentration-dependent effects of the saponins were examined. As expected, treatment of RAW 264.7 cells with compounds 1–4 decreased significantly the number of osteoclasts in a concentration-dependent manner (Supplementary material, Figures S15 and S16), suggesting that the saponins 1–4 suppress the RANKL-induced formation of mature osteoclasts. Compounds 5–6 moderately inhibited osteoclastogenesis at a concentration of 10 μM; therefore, these compounds were selected to evaluate the concentration-dependent effects at 3, 10 and 30 μM. As shown in Figures S14 and S15 (Supplementary material), compounds 5–6 exhibited significant effects in reducing the formation of osteoclasts only at the highest concentration (30 μM). Bone remodelling is modulated by the essential roles of bone-resorbing osteoclasts and bone-formation osteoblasts. In particular, the hyperactivity of osteoclasts results in several bone-related diseases, such as osteoporosis, rheumatoid arthritis or bone metastasis. In recent years, natural products have been used widely in the treatment of bone-loss-related diseases (Sethi and Aggarwal 2007; An et al. 2016). M. pubescens is a rich source of triterpenes and saponins (Weimin et al. 1996; Zhao et al. 1996a, 1996b, 1997). Saponins have been reported to exhibit several biological effects, including anti-inflammatory and anti-osteoclastogenic.
activities. For example, triterpenoid saponin W3 from *Anemone flaccida* inhibits osteoclast differentiation through suppressing RANKL-induced MAPKs and NF-κB pathways (Kong et al. 2015). The present study found for the first time that the cycloartane saponins from *M. pubescens* inhibited RANKL-induced osteoclast differentiation in macrophages. Further studies should be performed to identify the molecular mechanism underlying the anti-osteoclastogenic activity of these cycloartane saponins.

3. Experimental

3.1. General

NMR spectra were recorded on a Bruker 500 MHz (Bruker, MA, USA). HR-ESI-MS spectra were recorded on an AGILENT 6550 iFunnel Q-TOF LC/MS system (Agilent Technologies, Inc, CA, USA). Optical rotations were determined on a Jasco DIP-370 automatic polarimeter (Jasco, Tokyo, Japan). Gas chromatography was recorded on Shimazu GC-2010 pro (Toyko, Japan). Column chromatography (CC) was performed on silica gel (Kieselgel 60, 70–230 mesh and 230–400 mesh, Merck, Darmstadt, Germany), RP-18 gel (30–50 μm, Fuji Silysia Chemical Ltd., Japan) or HP-20 diaion (Mitsubishi Chemical Corporation, Japan). For thin layer chromatography (TLC), pre-coated silica gel 60 F254 (0.25 mm, Merck) and RP-18 F254S (0.25 mm, Merck, Darmstadt, Germany) plates were used. Spots were visualized by spraying with 10% aqueous H₂SO₄, followed by heating. RAW 264.7 cells (murine macrophages) were purchased from the American Type Culture Collection (Manassas, VA, USA).

3.2. Plant materials

The leaves of *Mussaenda pubescens* Dryand were collected in Vinhphuc province, Vietnam in May, 2019, and identified by Dr. Nguyen The Cuong, Institute of Ecology and Biological Resources, VAST. A voucher specimen (ML-29) was deposited at the University of Science and Technology Hanoi, VAST.

3.3. Extraction and isolation

The dried powder of leaves of *M. pubescens* (2.0 kg) was sonicated three times (30 min each) with hot methanol (MeOH) at 45 °C and then evaporated under reduced pressure to yield 200 g of a dark solid extract. The extract was suspended in water and partitioned successively with *n*-hexane and ethyl acetate (EtOAc) giving *n*-hexane (MP1, 84 g), EtOAc (MP2, 12 g) and water layers (MP3). The water layer was chromatographed on a Diaion HP-20 column eluting with water to remove sugar components and the concentration of MeOH in water increased (50%, 75% and 100%) to obtain three fractions, MP3A–MP3C, respectively. The fraction MP3A was chromatographed by silica gel column chromatography (CC) eluting with CH₂Cl₂/MeOH (20/1, 10/1, 5/1, 2.5/1, v/v) to give four fractions, MP3A1–MP3A4. The fraction MP3A2 was chromatographed by RP-18 CC eluting with MeOH/water (1/2, v/v) to give four fractions, MP3A2A–MP3A2D. The MP3A2A fraction was chromatographed on a silica gel column eluting with CH₂Cl₂/MeOH (7/1, v/v) to yield compound 9 (15.0 mg). MP3A2C was
further chromatographed by silica gel CC eluting with CH$_2$Cl$_2$/MeOH (8/1, v/v) to yield compound 8 (400 mg). The fraction MP3A3 was chromatographed by RP-18 CC using MeOH/water (1/2, v/v) to give three fractions, MP3A3A–MP3A3C. The fraction MP3A3B was chromatographed by RP-18 CC eluting with acetone/water (1/4, v/v) to yield compound 7 (500 mg). The fraction MP3C was chromatographed by silica gel CC eluting with CH$_2$Cl$_2$/MeOH (20/1, 10/1, 5/1, 2.5/1, v/v) to give fractions, MP3C1–MP3C4. MP3C4 was subjected to RP-18 CC eluting with acetone/water (1.2/1, v/v) to give six fractions, MP3C4A–MP3C4F. The fraction MP3C4A was chromatographed by silica gel CC eluting with CH$_2$Cl$_2$/acetone/water (1/6/1, v/v/v) to yield compound 1 (6.0 mg). The fraction MP3C4C was chromatographed by silica gel CC eluting with CH$_2$Cl$_2$/acetone/water (1/5/1, v/v/v) to yield compounds 5 (20.0 mg) and 6 (25.0 mg). The fractions MP3C4D–MP3C4F were chromatographed by RP-18 CC using MeOH/acetone/water (3.5/0.1/1, v/v/v) to yield compounds 2 (10.0 mg), 3 (80.0 mg) and 4 (9.0 mg).

### 3.3.1. Mussaglaoside F (1)

White amorphous powder. [$\alpha$]$_D^{25}$ = +38.0 (c 1.0 MeOH). HR-ESI-MS m/z: 1702.7586 [M + Cl]$^-$ (Calcd. for [C$_{78}$H$_{125}$O$_{37}$NCl]$^-$, 1702.7624). ¹H- and ¹³C-NMR (CD$_3$OD): see Table S1 (Supplementary material).

### 3.4. Acid hydrolysis

Compound (1, 2.0 mg) was separately dissolved in 1.0 N HCl (dioxane – H$_2$O, 1:1, v/v, 1.0 mL) and heated to 80°C in a water bath for 3 h. Acidic solution was neutralized with Ag$_2$CO$_3$ with the solvent thoroughly removed under a N$_2$ stream overnight. After extraction with CHCl$_3$, the aqueous layer was concentrated to dryness using N$_2$. The residue was dissolved in dry pyridine (0.1 mL), followed by addition of L-cysteine methyl ester hydrochloride in pyridine (0.06 M, 0.1 mL). The reaction mixture was heated at 60°C for 2 h. Trimethylsilylimidazole solution (0.1 mL) was then added, followed by heating at 60°C for 1.5 h. The dried product was partitioned with n-hexane and H$_2$O (0.1 mL each), and the organic layer was analyzed by gas chromatography: column DB-5 (0.32 mm ID × 30 m length), detector FID, column temp 210°C, injector temp 270°C, detector temp 300°C, carrier gas He (2 mL/min). Under these conditions, the standard sugars gave peaks at t$_R$ (min) 14.11 and 14.26 for D- and L-glucose and 4.50 for L-rhamnose, respectively. Peaks at t$_R$ (min) 14.11 and 4.50 of D-glucose and L-rhamnose were observed.

### 3.5. Cell culture

RAW 264.7 cells were cultured in Dulbecco’s Modified Eagle Medium (DMEM, Hyclone, Logan, UT, USA) supplemented with 10% fetal bovine serum (FBS, BioWest, USA) and penicillin (100 units/mL)-streptomycin (100 µg/mL) at 37°C in a humidified incubator with 5% CO$_2$. 

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**Table S1 (Supplementary material)**

| Compound | Retention Time (min) |
|----------|----------------------|
| D-glucose | 14.26                |
| L-rhamnose | 4.50                |
| D-glucose | 14.11                |
| L-rhamnose | 4.50                |
3.6. In vitro osteoclastogenic assay

The in vitro osteoclastogenic assay was performed as described previously (Tran et al. 2019). Briefly, for osteoclast differentiation, RAW 264.7 cells at a density of $5 \times 10^4$ cells/mL were seeded onto 96-well plate and stimulated with RANKL (100 ng/mL). Media were replaced every 2 days for 4 days. TRAP (tartrate-resistant acid phosphatase) staining of osteoclasts was performed using a leukocyte acid phosphatase staining kit (Sigma-Aldrich; EMD Millipore, Billerica, MA, USA). The cells were photographed under microscopy (magnification ×40). TRAP-positive multinucleated cells with more than five nuclei were quantified as mature osteoclasts.

3.7. Cell viability assay

Cell proliferation and cytotoxic effect of the extracts were assessed by using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT)-based assay. At the end of incubation, 0.5 mg/ml MTT solution was added to each well and incubated for 3 h. After removal of the culture supernatants, formazan crystals were dissolved in dimethyl sulfoxide (DMSO). Absorbance was measured at 540 nm using a microplate reader (Epoch Reader, BioTek, VT, USA).

Disclosure statement

No potential conflict of interest was reported by the authors.

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