Vietnam Journal of Science and Technology ***60*** *(5) (2022) 966-973*

doi:10.15625/2525-2518/16656

CHEMICAL CONSTITUENTS FROM THE STEM BARKS OF *POLYSCIAS SERRATA* BALF.

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Received: 21 October 2021; Accepted for publication: 25 December 2021

Abstract. Plants of the genus *Polyscias* (the family Araliaceae) are represented as perennial shrubs and are commonly cultivated in southeastern Asia and the Pacific regions. Pharmacological studies revealed that *Polyscias* crude extracts and their isolated compounds exhibited a variety of biological activity, such as antibacterial, antifungal, cytotoxic, immuno-stimulant, wound healing and anti-asthmatic activities. For the first time, phytochemical study on the methanol (MeOH) extract of the stem barks of Vietnamese species *Polyscias serrata* Balf. (locally named Dinh lang rang) resulted in the isolation and NMR (Nuclear Magnetic Resonance)-determination of six compounds 1-6. They include one nucleobase uracil (1), two nucleosides uridine (2) and adenosine (3), one alkaloid indole-3-carboxylic acid (4), one mono-phenol glucoside koaburside (5), and one saponin randianin (6). The chemical structures of these phytochemicals were elucidated by physicochemical, the 1D-NMR [1H, 13C-NMR, and DEPT (Distortionless Enhancement by Polarization Transfer)], the 2D-NMR [HSQC (heteronuclear single quantum coherence), HMBC (Heteronuclear Multiple Bond Correlation), and COSY (correlation spectroscopy)] spectral, and ESI-MS (Electron Spray Ionization-Mass Spectrum) data. This is the first time that compounds 2-6 have been obtained from the genus Polyscias. In agreement with various reports, the nitrogenous compounds and triterpene saponins can be seen as characteristic metabolites of genus *Polyscias*.

Keywords: Polyscias serrata, stem barks, phytochemistry.

Classification numbers: 1.1.1, 1.3.1, 1.5.2.

1. INTRODUCTION

The genus *Polyscias* (family Araliaceae) is a genus of 116 species. *Polyscias* plants are perennial shrubs and widely distributed in Southeastern Asia [1]. They have induced potential values for both traditional uses and pharmacological purposes. *P. scutellaria* leaves are used for ulcer treatment, *P. fulva* barks are consumed as a tonic medicine against obesity [1]. There have been numerous notable findings from phytochemical studies on this genus, and around 100 chemical compounds have been isolated to date [1]. Various phytochemical classes of isolated compounds, such as lignans, cerebrosides, mono-phenols, and fatty acids, have been successfully isolated, but saponin derivatives were characteristic of *Polyscias* plants [2-8]. *Polycias serrata* Balf., often known as Dinh lang rang in Viet Nam, is now available [9]. In traditional use, this species was used for diuretic and sedative treatments [10]. To date, there have been very few phytochemical studies on this species to date. Saponins, ceramides, and glucoside derivatives were the main chemical classes detected in the ethanol extract of *P. serrata* leaves [10]. Our current paper, for the first time, reports the phytochemical investigation and structural determination of 6 compounds **1-6** from the stem barks of this plant.

2. MATERIALS AND METHODS

2.1. General experimental procedures

Bruker Avance 500 MHz was used to measure 1D NMR and 2D NMR, including ^{1}H and ^{13}C NMR, HSQC and HMBC with TMS as an internal reference. Mass spectral data were measured on a JEOL MStation JMS-700. Silica gel (230 - 400 µm mesh, Japan), sephadex LH-20 (40 - 63 µm, UK), and RP-18 (25 - 100 µm, Sweden) were used for CC (column chromatography). TLC examination was carried out on plates covered with silica gel 60 F_{254} (Merck, Germany). TLC spots were visualized using a UV lamp with wavelengths of 254 and 365 nm, as well as spraying with indicators (10 % H_2SO_4 and vanillin).

2.2. Plant materials

Polycias serrata stem barks were harvested in Me Linh, Ha Noi, Viet Nam in January 2020. The sample was taxonomically identified by Nguyen Quoc Binh (Vietnam National Museum of Nature, VAST). A specimen labeled PS-1188 was kept at the Institute of Chemistry, VAST.

2.3. Extraction and isolation

Polycias serrata dried stem barks (5.5 kg) were extracted three times with MeOH (40 L) at reflux for 5.5 hours. The crude MeOH extract (150.0 g) was obtained by evaporating the mixed extract at reduced pressure. This extract was diluted with *n*-hexane (2.0 L) and MeOH (2.5 L) to obtain soluble fractions (fr.s) *n*-hexane (55.5 g), and MeOH (56.7 g), as well as MeOH solid residue.

The MeOH-soluble fr. (56.7 g) was eluted step by step with CH_2Cl_2/MeOH (100:0 → 75:25 → 50:50 → 25:75 → 0:100, v/v) on a silica gel CC, to afford 15 fr.s (M1-M15). Fr. M5 (10.2 g) was subjected to sephadex LH-20 CC [CH_2Cl_2/MeOH (1:9, v/v)] to yield 7 fr.s (M51-M57). Repeating sephadex LH-20 CC [CH_2Cl_2/MeOH (1:9, v/v)] for fr. M55 (0.9 g), compound **4** (3.0 mg) was obtained. Fr. M9 (10.0 g) was separated by sephadex LH-20 CC [MeOH (100 %)] to afford 9 fr.s (M91-M99). Compound **1** (5.5 mg) was purified from fr. M94 (1.3 g) using preparative TLC [CH_2Cl_2/EtOAc (6:1, v/v)]. The same model sephadex LH-20 CC

[CH_2Cl_2/MeOH (1:9, v/v)] for fr.s M10 (7.1 g) and M11 (10.2 g) was utilized to produce 5 fr.s (M101-M105) and 8 fr.s (M111-M118), respectively. Compound **5** (5.0 mg) was obtained from fr. M104 (1.5 g) using silica gel CC [CH_2Cl_2/CH_3COCH_3 (3:1, v/v)].

Fr. M114 (1.3 g) was subjected to sephadex LH-20 CC [CH_2Cl_2/MeOH (1:9, v/v)] to yield compounds **2** (4.1 mg) and **3** (4.4 mg), and 4 fr.s (M1141-M1144). Fr. M1142 (0.5 g) was separated by RP-18 CC [MeOH/H_2O (1:2, v/v)] to obtain compound **6** (6.5 mg).

Uracil (**1**): White amorphous powder; ESI-MS: *m/z* 113 $[M+H]^+$ (calcd for $C_4H_5N_2O_2$, 113); ^{1}H-NMR (CD_3OD, 500 MHz, δ_H ppm): 7.41 (1H, d, 7.5 Hz, H-6), 5.63 (1H, d, 7.5 Hz, H-5); ^{13}C-NMR (CD_3OD, 125 MHz, δ_C ppm): 167.4 (C-4), 151.5 (C-2), 143.5 (C-6), 101.8 (C-5).

Uridine (**2**): White amorphous powder; ESI-MS: *m/z* 245 $[M+H]^+$ (calcd for $C_9H_{13}N_2O_6$, 245); ^{1}H-NMR (CD_3OD, 500 MHz, δ_H ppm): 8.01 (1H, d, 8.0 Hz, H-6), 5.92 (1H, d, 4.5 Hz, H-1'), 5.71 (1H, d, 8.0 Hz, H-5), 4.20 (1H, t, 5.5 Hz, H-2'), 4.17 (1H, t, 4.5 Hz, H-3'), 4.03 (1H, m, H-4'), 3.85 (1H, dd, 12.5, 3.0 Hz, H-5'a), 3.75 (1H, dd, 3.0 12.0 Hz, H-5'b); ^{13}C-NMR (CD_3OD, 125 MHz,δ_C ppm): 163.5 (C-4), 152.5 (C-2), 142.7 (C-6), 102.7 (C-5), 90.8 (C-1'), 86.4 (C-4'), 75.7 (C-2'), 71.3 (C-3'), 62.3 (C-5').

Adenosine (**3**): White amorphous powder; ESI-MS: *m/z* 268 $[M+H]^+$ (calcd for $C_{10}H_{14}N_5O_4$, 268); ^{1}H-NMR (CD_3OD, 500 MHz, δ_H ppm): 8.32 (1H, s, H-8), 8.20 (1H, s, H-2), 5.98 (1H, d, 6.5 Hz, H-1'), 4.76 (1H, dd, 5.0, 6.5 Hz, H-2'), 4.34 (1H, dd, 3.0, 5.0 Hz, H-3'), 4.19 (1H, dd, 2.5, 3.0 Hz, H-4'), 3.90 (1H, dd, 2.5, 10.5 Hz, H-5'a), 3.76 (1H, dd, 2.5, 10.5 Hz, H-5'b); ^{13}C-NMR (CD_3OD, 125 MHz, δ_C ppm): 157.6 (C-4), 153.5 (C-2), 150.0 (C-6), 142.0 (C-8), 121.0 (C-5), 91.3 (C-1'), 88.2 (C-4'), 75.5 (C-2'), 72.7 (C-3'), 63.5 (C-5').

Indole-3-carboxylic acid (**4**): White amorphous powder; ESI-MS: *m/z* 162 $[M+H]^+$ (calcd for $C_9H_8NO_2$, 162); ^{1}H-NMR (CD_3OD, 500 MHz, δ_H ppm): 8.15 (1H, dd, 1.5, 6.5 Hz, H-4), 7.87 (1H, s, H-2), 7.40 (1H, d, 1.5, 6.5 Hz, H-7), 7.15 (2H, m, H-5, H-6); ^{13}C-NMR (CD_3OD, 125 MHz, δ_C ppm): 163.5 (3-COOH), 138.2 (C-7a), 132.2 (C-2), 128.0 (C-3a), 123.0 (C-6), 122.3 (C-4), 121.7 (C-5), 112.5 (C-7), 110.3 (C-3).

Koaburside (**5**): White amorphous powder; ESI-MS: *m/z* 369 $[M+Na]^+$ (calcd for $C_{15}H_{22}O_9Na$, 369); ^{1}H-NMR (CD_3OD, 500 MHz, δ_H ppm): 6.51 (2H, s, H-2, H-6), 4.83 (1H, d, 7.5 Hz, H-1'), 3.93 (1H, dd, 2.0, 12.0 Hz, H-6'a), 3.83 (6H, s, 3-OCH_3, 5-OCH_3), 3.72 (3H, s, 4-OCH_3), 3.68 (1H, dd, 6.5, 12.0 Hz, H-6'b), 3.46 (3H, m, H-2', H-3', H-5'), 3.35 (1H, m, H-4'); ^{13}C-NMR (CD_3OD, 125 MHz, δ_C ppm): 156.0 (C-1), 154.8 (C-3, C-5), 134.5 (C-4), 103.2 (C-1'), 96.2 (C-2, C-6), 78.4 (C-5'), 78.1 (C-3'), 75.0 (C-2'), 71.7 (C-4'), 62.7 (C-6'), 61.2 (4-OCH_3), 56.6 (3-OCH_3, 5-OCH_3).

Randianin (**6**): White amorphous powder; ESI-MS: *m/z* 782 $[M+H]^+$ (calcd for $C_{42}H_{69}O_{13}$, 782); ^{1}H-NMR (CD_3OD, 500 MHz, δ_H ppm): 5.26 (1H, t, 3.5 Hz, H-12), 4.62 (1H, d, 8.0 Hz, H-1''), 4.44 (1H, d, 8.0 Hz, H-1'), 3.21-3.90 (12H, m, sugar), 3.19 (1H, m, H-3), 1.18 (3H, s, H-27), 1.06 (3H, s, H-24), 0.98 (3H, s, H-25), 0.97 (3H, s, H-29), 0.91 (3H, s, H-30), 0.85 (3H, s, H-23), 0.82 (3H, s, H-26);^{13}C-NMR (CD_3OD, 125 MHz, δ_C ppm): 181.8 (C-28), 145.1 (C-13), 123.7 (C-12), 106.5 (C-1'), 105.0 (C-1''), 91.0 (C-3), 86.6 (C-3'), 78.2 (C-5''), 77.8 (C-5'), 75.5 (C-3''), 75.0 (C-2''), 74.9 (C-2'), 71.5 (C-4''), 71.2 (C-4'), 62.6 (C-6', C-6''), 57.0 (C-5), 48.8 (C-9), 47.6 (C-17), 47.2 (C-19), 42.9 (C-14), 42.7 (C-18), 40.6 (C-8), 40.1 (C-4), 39.7 (C-1), 37.9 (C-10), 34.9 (C-21), 34.0 (C-7), 33.8 (C-22), 33.6 (C-30), 31.5 (C-20), 28.8 (C-15), 28.5 (C-24), 26.9 (C-2), 26.4 (C-27), 24.5 (C-11), 24.1 (C-16), 24.0 (C-29), 19.3 (C-6), 17.7 (C-26), 17.0 (C-23), 15.9 (C-25).

3. RESULTS AND DISCUSSION

Compound **1** was separated as a white amorphous powders. Its ^{1}H-NMR data only showed two proton signals at δ_H 5.63 (d, 7.5 Hz, H-5) and δ_H 7.41 (d, 7.5 Hz, H-6). The ^{13}C-NMR data of **1** included two olefinic carbons at δ_C 101.8 (C-5) and δ_C 143.5 (C-6), and two carbonyl carbons at δ_C 151.5 (C-2) and δ_C 167.4 (C-4) (Fig. 1). The structure of **1** was further affirmed by 2D-NMR data. Olefinic proton H-6 induced HMBC correlations to carbons C-2 and C-4, while H-5 has HMBC cross-peaks to C-4 and C-6 (Fig. 2). Moreover, the molecular formula of **1** was to be $C_4H_4N_2O_2$ due to the observation of ion peak at *m/z* 113 $[M+H]^+$ in the positive ESI-MS spectrum. Therefore, compound **1** was elucidated as a nucleobase, namely uracil (**1**) [11]. Compound **1** can be found in various plants, such as *P. guilfoylei* [11], but it is detected in *P. serrata* for the first time.

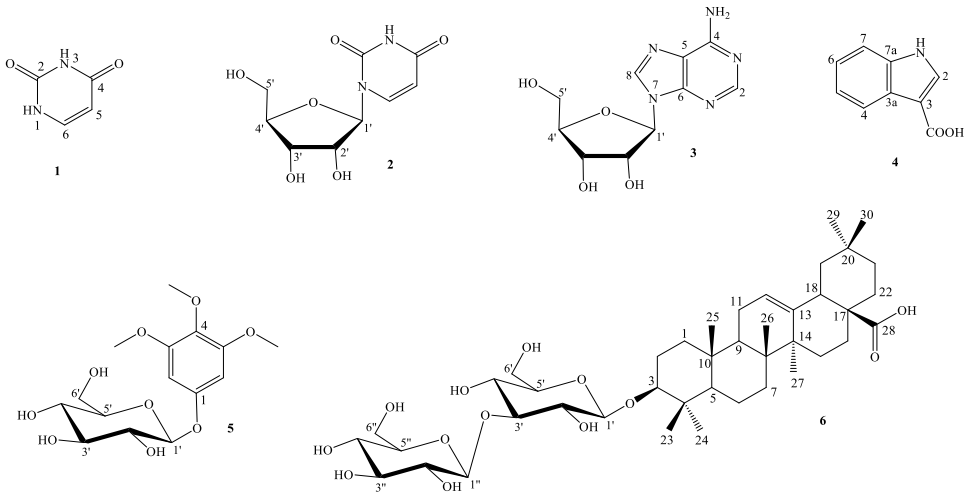

Figure 1. The chemical structures of isolated compounds **1-6.**

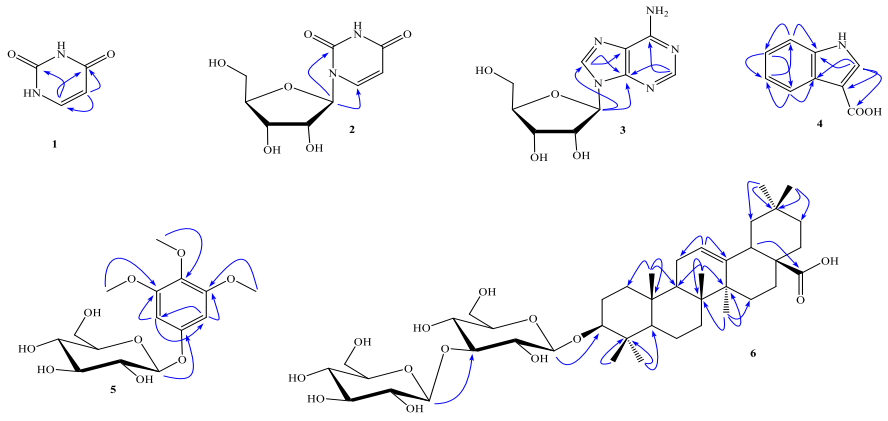

Figure 2. The HMBC key correlations of isolated compounds.

Compound **2** was obtained as a white amorphous powders. The 1D-NMR data of **2** is very similar to those of **1**, but compound **2** was superior to compound **1** by a *β*-D-ribofuranosyl unit. This sugar exhibited ^{1}H-NMR peaks at δ_H 5.92 (1H, d, 4.5 Hz, H-1'), δ_H 4.20 (1H, t, 5.5 Hz, H-

2'), δ_H 4.17 (1H, t, 4.5 Hz, H-3'), δ_H 4.03 (1H, m, H-4'), δ_H 3.85 (1H, dd, 12.5, 3.0 Hz, H-5'a), and δ_H 3.75 (1H, dd, 3.0 12.0 Hz, H-5'b). The ^{13}C-NMR data of **2** contained a signal of the anomeric carbon at δ_C 90.8 (C-1'), while the remaining sugar carbons resonated at δ_C 62.3-86.4 ppm. H-1' has HMBC correlations to C-2 and C-6, thereby sugar unit linked to N-1. The chemical structure of **2** was further confirmed by ion peak at *m/z* 245 $[M+H]^+$ (calcd for $C_9H_{13}N_2O_6$, 245) in the positive ESI-MS spectrum. Based on the findings and literature comparison, compound **2** was elucidated as a nucleoside, namely uridine (**2**) [12]. Nucleoside **2** is now common, but it is detected in the genus *Polyscias* for the first time.

Compound **3** was separated as a white amorphous powder. Its molecular formula $C_{10}H_{13}N_5O_4$ was based on ion peak at *m/z* 268 $[M+H]^+$ in the positive ESI-MS spectrum. The ^{1}H-NMR data of **3** revealed a nucleoside pattern. Two singlet proton signals peaking at δ_H 8.20 (H-2) and δ_H 8.32 (H-8) were assigned to aglycone adenine. It is similar to compound **2**, the ^{1}H-NMR data of **3** also showed peaks of a β-D-ribofuranosyl unit at δ_H 5.98 (1H, d, 6.5 Hz, H-1'), and δ_H 3.76 - 4.76 ppm. The ^{13}C-NMR/DEPT spectral data of aglycone contained two aromatic methine carbons at δ_C 153.5 (C-2) and δ_C 142.0 (C-8), three quaternary carbons at $\delta_C\delta_C$ 157.6 (C-4), 121.0 (C-5), and δ_C 150.0 (C-6), while sugar carbons resonated at δ_C91.3 (C-1'), and 63.5-88.2 ppm. The chemical structure of **3** was further elucidated by 2D-NMR data, H-2 has HMBC correlations to C-4 and C-6, while H-8 correlated to C-5 and C-6. The important HMBC cross-peaks H-1' to C-6 and C-8 determined that ribofuranosyl unit attached to adenine nucleus via *β*-N-glycosidic bond. Compared with the literature, compound **3** was adenosine [12]. Adenosine is now available in living bodies and nature, it is one of four structural subunits of DNA and RNA, which are essential for living organisms.

Compound **4** was separated as a white amorphous powder. The ^{1}H-NMR data of **4** showed signals of a 3-substituted indole, comprising of δ_H 8.15 (1H, dd, 1.5, 6.5 Hz, H-4), δ_H 7.87 (1H, s, H-2), δ_H 7.40 (1H, d, 1.5, 6.5 Hz, H-7), and δ_H 7.15 (2H, m, H-5, H-6). The ^{13}C-NMR data of **4** were associated with the appearance of five methine carbons at 112.5-132.2 ppm, three quaternary carbons at δ_C 110.3 (C-3), δ_C 128.0 (C-3a), and δ_C 138.2 (C-7a), and a carbonyl carbon at δ_C 163.5 (3-COOH). The structure of **4** was further proved by HMBC correlations. Proton H-2 had HMBC cross-peaks to C-3, C-3a, C-7a, and 3-COOH. Di-substituted phenyl unit was accompanied by the HMBC correlations H-4/C-3a and C-5, H-5/C-7, H-6/C-4 and C-5, and H-7/C-6 and C-7a. The NMR data was in agreement with MS spectrum, in which molecular formula of **4** was identified to be $C_9H_7NO_2$ because of the observation of ion peak at *m/z* 162 $[M+H]^+$ in the positive ESI-MS spectrum. From these findings, compound **4** was elucidated as indole-3-carboxylic acid [13]. This metabolite has not been observed in *P. serrata* or the genus *Polyscias* before.

Compound **5** was precipitated from the MeOH-soluble fraction as a white amorphous powder. A thorough analysis of the 1D-NMR data (^{1}H and ^{13}C), the 2D-NMR data (HSQC and HMBC) and the ESI-MS data revealed that **5** was a phenolic glycoside, namely koaburside [14]. In the ^{1}H-NMR data of the aglycone, two aromatic protons appeared at δ_H 6.51 (1H, s, H-2 and H-6), two singlet signals of three methoxy groups located at δ_H 3.83 (6H, 3-OCH_3, 5-OCH_3), and δ_H 3.72 (3H, 4-OCH_3). The^{1}H-NMR data of **5** exhibited the presence of a glycosyl unit [δ_H 4.83 (1H, H-1') and δ_H 3.35-3.93 (5H, H-2', H-3', H-4', H-5', and H-6')]. Sugar unit was determined as *β*-D-glucopyranosyl unit due to the coupling constant J = 7.5 Hz of the anomeric proton H-1' [15-17]. The^{13}C-NMR spectrum contained four signals of six aromatic carbons at δ_C 96.2-156.0 ppm, six signals of six sugar carbons at δ_C 62.7-78.4 and δ_C 103.2 (C-1'), and two signals of three methoxy carbons at δ_C 56.6 (3-OCH_3, 5-OCH_3) and δ_C 61.2 (4-OCH_3). The structure of **5** was affirmed by HMBC correlations (Fig. 2), in which phenyl nucleus was characteristic of H-

2/C-3 and C-6, and H-6/C-2 and C-5. Three methoxy groups 3-OCH_3, 4-OCH_3, and 5-OCH_3 had the key HMBC cross-peaks to C-3, C-4, and C-5, respectively. The key HMBC correlation H-1'/C-1 identified that sugar moiety bonded to the aromatic system at position C-1. Compound **5** was a phenolics compound found in several plants, such as the stems of *Viburnum erosum* [14], but it was first isolated from the genus *Polyscias*.

Compound **6** was also purified as a white amorphous powder. The 1D-NMR data aided by the 2D-NMR data of 6 corresponded to a well-known saponin, namely randianin [18,19]. The 1D-NMR spectra indicated that aglycone triterpene of compound 6 contained signals of six methyl groups at [δ_H 0.85 (H-23), δ_C17.0 (C-23); δ_H 1.06 (H-24), δ_C 28.5 (C-24); δ_H 0.98 (H-25), δ_C 15.9 (C-25); δ_H 0.82 (H-26), δ_C 17.7 (C-26); δ_H 1.18 (H-27), δ_C 26.4 (C-27); δ_H 0.97 (H-29), δ_C24.0 (C-29), and δ_H 0.91 (H-30), δ_C 33.6 (C-30)], one methine carbinol at [3.19 (1H, m, H-3), 91.0 (C-3)], one olefinic bond at [δ_H 5.26 (1H, t, 3.5 Hz, H-12), δ_C 123.7 (C-12), and δ_C 145.1 (C-13)], one carbonyl carbon at δ_C 180.8 (C-28), and remaining aliphatic methines and methylenes. Two anomeric protons at δ_H 4.44 (H-1') and δ_H 4.62 (H-1") were in association with the same coupling constants J = 8.0 Hz, thereby indicating two β-glucopyranosyl units [15-17]. In addition, the structure 6 was proved by the HMBC spectrum. The olefinic groups located at C-12 and C-13, which were confirmed by the key HMBC cross-peaks from H-12/C-11 to C-13. The carboxyl group substituted at C-17, indicated by HMBC correlations from H-18 to C-28. The HMBC correlations H-23 and H-24/C-4 identified that two methyl groups 23-CH_3 and 24-CH_3 substituted at carbon C-4. Similarly, the HMBC correlations H-25/C-10, H-26/C-8, and H-27/C-14 revealed that three methyl groups 25-CH_3, 26-CH_3, and 27-CH_3 substituted at carbons C-10, C-8, and C-4, respectively. The correlations H-29 and H-30/C-20 in the HMBC spectrum confirmed that two methyl 29-CH_3 and 30-CH_3 substituted at carbon C-20. The key HMBC correlation H-1"/C-3' showed that the connection between two glucosyl units was 1→3 linkage, whereas the crucial HMBC correlation H-1'/C-3 revealed that sugar unit linked to aglycone at carbon carbinol C-3. The chemical structure of 6 was further supported by MS data. With the observation of ion peak at *m/z* 782 $[M+H]^+$ in the positive ESI-MS spectrum, molecular formula of 6 was $C_{42}H_{68}O_{13}$. Based on the above evidence, compound 6 was determined to be a hemolytic saponin, namely randianin (a compound was first isolated from *Randia dumetorum*) [18], but this is the first time it has been found in the genus *Polyscias*.

4. CONCLUSIONS

This is the first time one nucleobase uracil (**1**), two nucleosides uridine (**2**) and adenosine (**3**), one alkaloid indole-3-carboxylic acid (**4**), one *mono*-phenol glucoside koaburside (**5**), and one saponin randianin (**6**) have been isolated from the Vietnamese medicinal plant *P. serrata*. Significantly, compounds **2-6** were separated from the genus *Polyscias* for the first time. Saponins are now available in the genus *Polyscias*, but nucleosides are a newly discovered chemical class in the genus *Polyscias*. Extensive studies on phytochemistry and pharmacology of *P. serrata* are needed.

Acknowledgements. This study was granted by Vietnamese National Foundation for Science and Technology Development (NAFOSTED, project number: 104.01-2019.326)

CRediT authorship contribution statement. Ninh The Son: Methodology, Formal analysis, Writing and Editing. Le Thi Tu Anh, Nguyen Thi Thu Ha, Nguyen Thanh Tra, Bui Hai Ninh, and Nguyen Khac Tiep: Methodology, Investigation, Formal analysis.

Declaration of competing interest. The authors declare that they have no conflict of interest.

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