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RESEARCH ARTICLE

Three Previously Undescribed Compounds Isolated From the Leaves of *Syzygium antisepticum* With Their α-Glucosidase and Nitric Oxide Inhibitory Activity

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ABSTRACT

Three previously undescribed compounds, 2α,3β,20α,23-tetrahydroxy-nor-30-urs-12-en-28-oic acid 28-*O*-β-D-glucopyranoside (**1**), 2α,3β,6β,23-tetrahydroxyoleana-11,13(18)-dien-28-oic acid (**2**), and 4,6-dihydroxy-3-methyl-2-*O*-β-D-glucopyranosylbenzophenone (**3**), together with 11 known compounds (**4**–**14**) are isolated from the leaves of *Syzygium antisepticum*. The isolated compounds are characterized via HR–ESI–MS and NMR spectra. Compounds **1**, **2**, **6**, and **7** exhibited significant inhibition of NO production in lipopolysaccharide (LPS)-activated murine macrophage RAW264.7 cells with IC_{50} values of 16.3, 14.9, 25.5, and 24.7 μM, respectively. In addition, compounds **9**–**12** displayed the most potential α-glucosidase with IC_{50} values ranging from 23.6 to 162.0 μM.

1 | Introduction

The plant *Syzygium antisepticum* (Blume) Merr. & L.M.Perry belongs to Myrtaceae family, which is found in the mountains and forests of the central of Vietnam, such as Quang Tri, Thua Thien Hue, Quang Nam provinces. In folk medicine, the leaves are used to treat stomachache, diarrhea, dysentery, and aid digestion. The seeds are ground into powder and taken to treat diabetes. The bark is used to treat tuberculosis and asthma [1, 2]. In the screening program to search for active ingredients with anti α-glucosidase and NO production inhibitory activities from Vietnamese medicinal plants, the methanol extract of *S. antisepticum* leaves showed significant effects in both anti α-glucosidase (IC_{50} 143.0 μg/mL) and NO inhibition (IC_{50} 67.5 μg/mL). Up to now, there have been very few publications on the biological activity of some extracts of the plant [3–5], but there have been no publications on the chemical composition of this plant. The above reasons have motivated us to continue further research. The main objective of this study is to clarify the composition of the active ingredients as well as to search for compounds with anti α-glucosidase and inhibition of NO production activities. Herein, this paper reports on the isolation, structure determination of 3 new (**1**–**3**) and 11 known (**4**–**14**) compounds from the leaves of *S. antisepticum* and their NO production and α-glucosidase inhibitory activities.

2 | Results and Discussion

Phytochemical study on the methanol extract of the leaves of *S. antisepticum* led to the isolation of three previously undescribed (**1**–**3**) and eleven known compounds (**4**–**14**) (Figure 1).

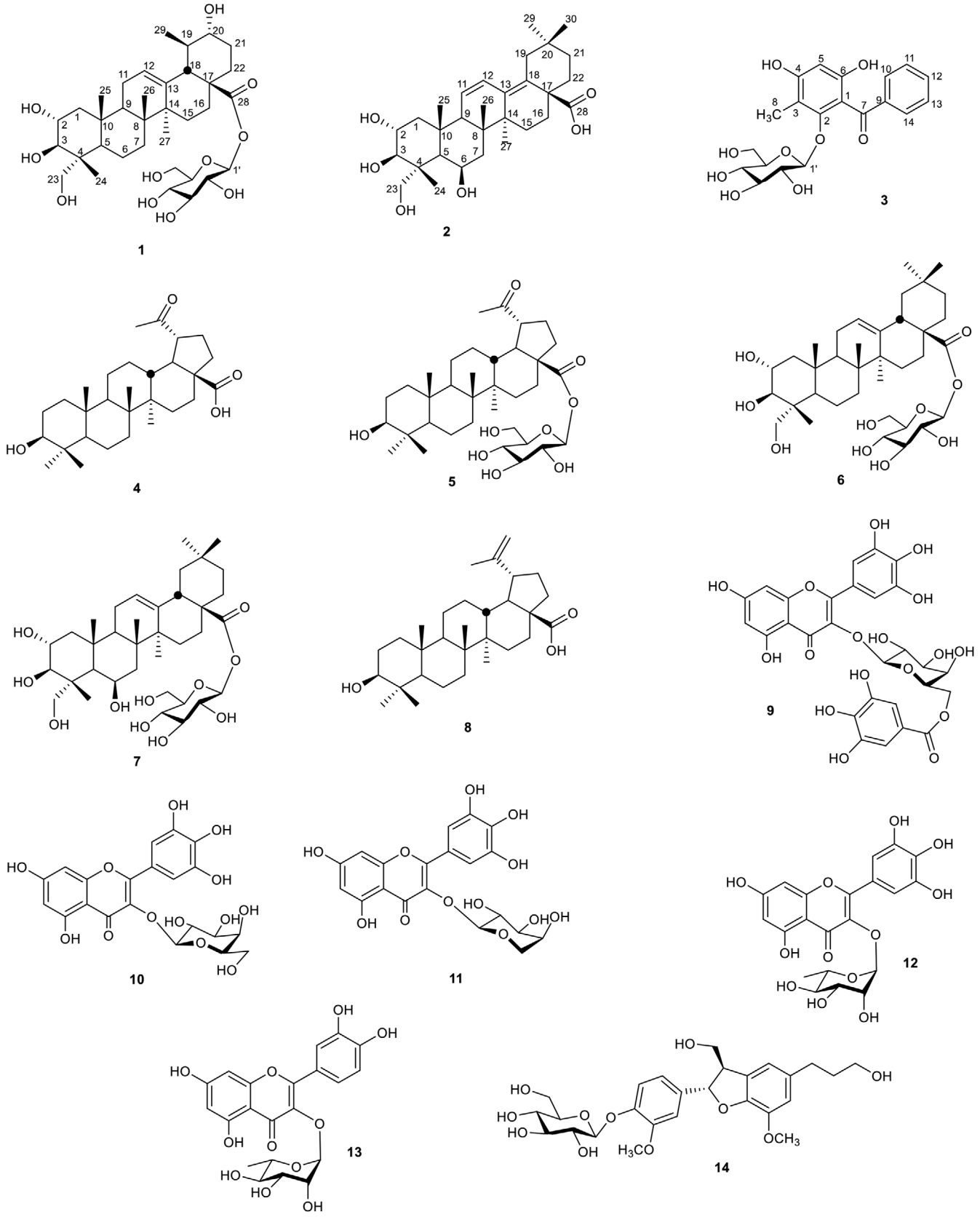

FIGURE 1 | Chemical structures of compounds **1**–**14**.

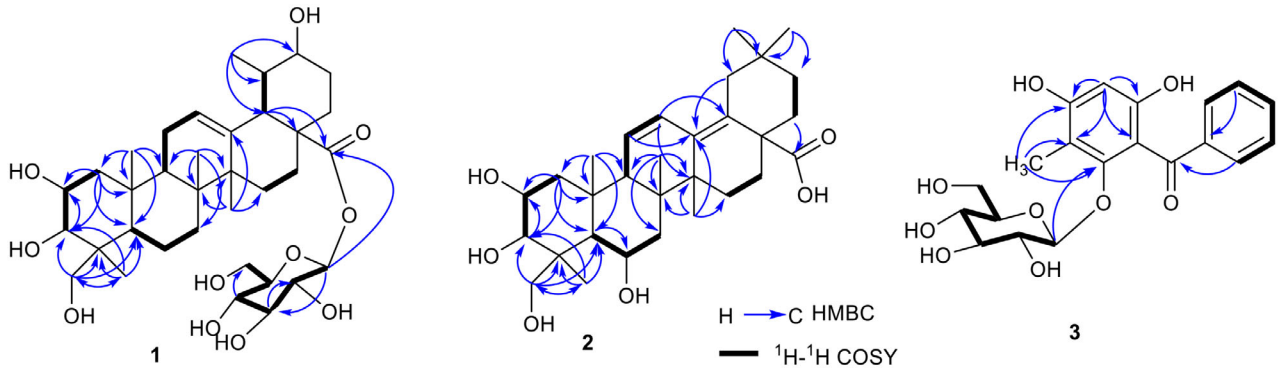

FIGURE 2 | The key heteronuclear multiple bond correlation (HMBC) and ^{1}H–^{1}H correlated spectroscopy (COSY) correlations of compounds **1**–**3**.

Compound **1** was isolated as a colorless amorphous powder. The molecular formula of **1** was determined to be $C_{35}H_{56}O_{11}$ from its high-resolution electrospray ionization mass spectrometry (HR–ESI–MS) data (found *m/z* 675.3731 $[M+Na]^+$, calcd for $[C_{35}H_{56}O_{11}Na]^+$ 675.3731, Δ = +2.4 ppm; *m/z* 670.4182 $[M+NH_4]^+$ caldc for $[C_{35}H_{60}NO_{11}]^+$ 670.4161 Δ = −3.1 ppm, and *m/z* 635.3811 $[M\text{-}H_2O+H]^+$, calcd for $[C_{35}H_{55}O_{10}]^+$ 635.3790, Δ = +3.3 ppm), indicating 8 degrees of unsaturation. The ^{1}H NMR spectrum of **1** revealed the presence four methyl singlets [δ_H 0.72 (H-24), 1.07 (H-25), 0.86 (H-26), and 1.17 (H-27), one secondary methyl doublet (δ_H 1.01, d, *J* = 6.6 Hz, H-29), one olefinic proton (δ_H 5.30, t, *J* = 3.6 Hz, H-12), three oxygenated methine groups [δ_H 3.71 (ddd, *J* = 12.0, 9.6, 4.8 Hz, H-2), 3.37 (d, *J* = 9.6 Hz, H-3), and 3.03 (ddd, *J* = 10.8, 10.8, 3.6 Hz, H-20)], one oxygenated methylene group [δ_H 3.52 (d, *J* = 10.8 Hz, H-23) and 3.28 (d, *J* = 10.8 Hz, H-23)], which were assigned to a triterpene aglycone [6, 7]. In addition, a glucose moiety was identified by signals of an anomeric proton [δ_H (5.37 (d, *J* = 7.8 Hz, H-1′)], one oxymethylene group [δ_H 3.82 (dd, *J* = 12.0, 2.4 Hz, H_a-6′) and 3.69 (dd, *J* = 12.0, 4.8 Hz, H_b-6′)]. The ^{13}C NMR and HSQC spectra of **1** indicated 35 carbons, including 6 of the glucose moiety [δ_C 95.7, 73.9, 78.3, 71.2, 78.6 (5CH), and 62.5 (CH_2)], and 29 of a nor-30 ursane triterpene skeleton. Of these, one carboxylate (δ_C 177.4, C-28), one double bond [(δ_C 126.9 (C-12) and 138.6 (C-13)], three oxymethine carbons [δ_C 69.7 (C-2), 78.3 (C-3), 75.6 (C-20)], and oxymethylene group (δ_C 66.4, C-23) were identified [6, 7]. These observations were further confirmed by HSQC, ^{1}H–^{1}H COSY, and HMBC spectra (Figure 2). The NMR data of **1** were similar to those of quadranoside IV [7] except the 30-CH_3 group was replaced by a hydoxy group in **1**. This substitution has been clearly demonstrated by ^{1}H–^{1}H correlations of H-18/H-19/H-20 and H_3-29/H-19 (Figure 2), by HSQC correlations of H-18/C-18, H-19/C-19, H-20/C-20, and H_3-29/C-29, and by HMBC correlations from H_3-29 (δ_H 1.01) to C-18 (δ_C 52.9)/C-19 (δ_C 41.3)/C-20 (δ_C 75.6), as well as by the above HR–ESI–MS results. The location of the other three hydroxy groups at C-2, C-3, and C-23 were indicated by the observation of ^{1}H–^{1}H cross peaks of H-1/H-2/H-3, by HSQC correlations of H-2/C-2, H-3/C-3, H-23/C-23, H-24/C-24, and by HMBC correlations from H_3-24 (δ_H 0.72) to C-3 (δ_C 78.3)/C-4 (δ_C 44.1)/C-5 (δ_C 48.2)/C-23 (δ_C 66.4), in comparison with the corresponding data of quadranoside II–IV [7]. The glucose moiety linked to C-28 by an ester linkage as suggested by the upfield-shifted anomeric carbon (δ_C 95.7, C-1′) and downfield-shifted of anomeric proton at δ_H 5.37 [5–7], and further determined by HMBC correlation from H-1′ δ_H 5.37 to C-28 (δ_C 177.4). The relative configuration of **1** were revealed by interaction constant (*J*) between protons and confirmed by NOESY spectrum (Figure 3). The large $^{3}J_{2,3}$ value of H-3 proton (9.6 Hz) suggested both H-2 and H-3 were *axial* orientation. In the NOESY spectrum, the NOEs cross peaks of H_3-25 (δ_H 1.07)/H-2 (δ_H 3.71), H-2/H-24 (δ_H 0.72), H-25 (δ_H 1.07)/H-26 (δ_H 0.86), H-3 (δ_H 3.37)/H-5 (δ_H 1.30) were observed further indicating that Me-25, H-2, Me-24 groups were in *β*/*axial* orientation and H-3 and H-5 were in *α*/*axial* orientation. In addition, H-18 (δ_H 2.31) showed NOEs correlation with 29-Me (δ_H 1.01) and H-20 (δ_H 3.03) confirming *β*/*axial* orientation of H-18 and H-20, and *β*/*equatorial* orientation of Me-19 group. The large $^{3}J_{1',2'}$ value (7.8 Hz) of the anomeric proton at δ_H 5.37 suggested *β*-form of the glycosidic linkage. Acid hydrolysis of **1** yielded D-glucose, identified by TLC and optical rotation in comparison with authentic samples [9, 10]. Thus, compound **1** was determined to be (2*α*,3*β*,20*α*,23-tetrahydroxy-nor-30-urs-12-en-28-oic acid 28-*O*-*β*-D-glucopyranoside, a novel triterpene glycoside.

The molecular formula of **2** was determined as $C_{30}H_{46}O_6$ by the HR–ESI–MS (found *m/z* 525.3192 $[M+Na]^+$, calcd for $[C_{30}H_{46}O_6Na]^+$ 525.3187, Δ = +1.0 ppm) together with the results of NMR spectrum analysis, indicating 8 degrees of unsaturation. The ^{1}H NMR spectrum of **2** showed six methyl singlets [δ_H 1.08 (H-24), 1.36 (H-25), 1.15 (H-26), 0.98 (H-27), 0.96 (H-29), and 0.83 (H-30)], three oxymethine protons [δ_H 3.83 (ddd, *J* = 11.4, 9.6, 4.8 Hz, H-2), 3.36 (d, *J* = 9.6 Hz, H-3), 4.42 (d, *J* = 2.4 Hz, H-6), an oxygenated methylene group [δ_H 3.62 (d, *J* = 10.8 Hz, H_a-23) and 3.50 (d, *J* = 10.8 Hz, H_b-23)] and two olefinic protons at δ_H 6.52 (dd, *J* = 10.8, 2.4 Hz, H-11) and 5.70 (br d, *J* = 10.8 Hz, H-12). The ^{13}C NMR spectrum of **2** suggested 30 carbons, including one carboxyl group at δ_C 183.4 (C-28), two double bonds at δ_C 126.5 (C-11), 126.9 (C-12), 136.5 (C-13), and 135.6 (C-18), three oxymethine groups at δ_C 69.8 (C-2), 78.4 (C-3), 68.9 (C-6), and one oxymethylene group at δ_C 66.0. The NMR data of **2** were closely resembling those of harproside except for the disappearance of glucose signals [11], as well as similar to the corresponding data of 2*α*,3*β*,23-trihydroxyoleana-11,13(18)-dien-28-oic acid except for the additional signal due to the hydroxy group at C-6 in **2** [12]. The NMR data of **2** indicated combined analysis of HSQC, ^{1}H–^{1}H COSY, and HMBC spectra as shown in Figure 2. The matching of NMR data of the C, D, E rings of **2** with those of harproside [11] and 2*α*,3*β*,23-trihydroxyoleana-11,13(18)-dien-28-oic acid [12] suggested two double bonds were at C-11/C-12 and C-13/C-18. Which were further confirmed by HMBC correlations from H_3-27 (δ_H 0.98) to C-13 (δ_C 136.5), from H-11 (δ_H 6.52) to C-13 (δ_C 136.5), and from H-12 (δ_H 5.70) to C-18 (δ_C 135.6). Three hydroxy groups were at C-2, C-3, C-23 as indicated by

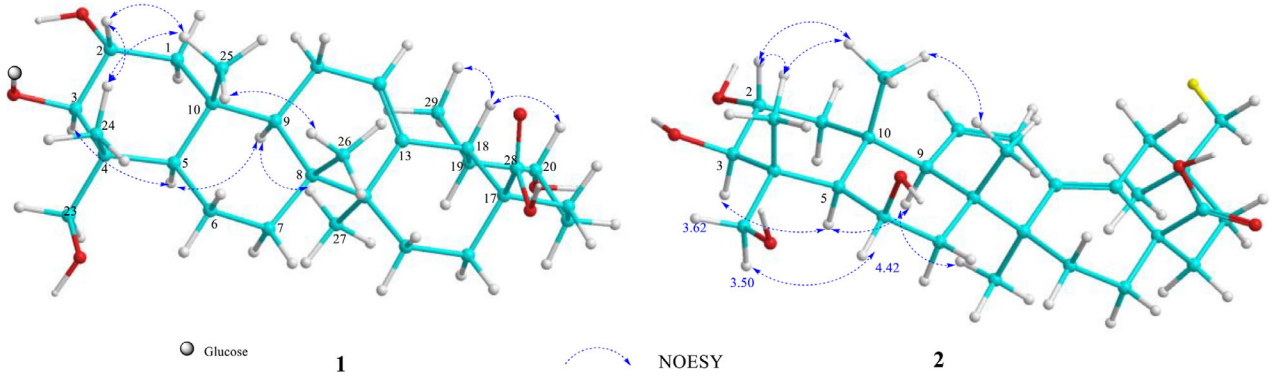

FIGURE 3 | The key nuclear Overhauser effect spectroscopy (NOESY) correlations and electronic circular dichroism (ECD) spectra of compounds **1** and **2**.

^{1}H–^{1}H COSY cross peak of H-2/H-3, and by HMBC correlations from H_3-24 (δ_H 1.08) to C-3 (δ_C 78.4)/C-4 (δ_C 44.8)/C-5 (δ_C 49.2), and from H_2-23 (δ_H 3.62/3.50) to C-3 (δ_C 78.4)/C-4 (δ_C 44.8)/C-5 (δ_C 49.2)/C-24 (δ_C 14.7) (Figure 2). The last hydroxy group was located at C-6 as confirmed by ^{1}H–^{1}H COSY cross peak of H-5 (δ_H 1.30)/H-6 (δ_H 4.42) and by HMBC correlation from H-5 (δ_H 1.30) to C-6 (δ_C 68.9). The relative configuration of **2** was suggested by interaction constant (*J*) between protons and confirmed by NOESY spectrum (Figure 3). The large $^{3}J_{2,3}$ (9.6 Hz) indicated *axial* configuration of both H-2 and H-3. Whereas the small $^{3}J_{5,6}$ (2.4 Hz) confirmed *α*/*equatorial* configuration of H-6. These were further revealed by NOEs cross peaks as shown in Figure 3. Therefore, compound **2** was determined to be 2*α*,3*β*,6*β*,23-tetrahydroxyoleana-11,13(18)-dien-28-oic acid, an previously undescribed compound.

Compound **3** was obtained as a colorless powder, which showed a quasi-molecular ion peak at *m*/*z* 429.1139 $[M+Na]^+$ (calcd $[C_{20}H_{22}O_9Na]^+$ 429.1157, $\Delta = -4.2$ ppm) on the HR–ESI–MS, indicating the molecular formula of $C_{20}H_{22}O_9$ with 10 degrees of unsaturation. The ^{1}H NMR of **3** clearly indicated a mono-substituted benzene ring (five protons at δ_H 7.70–7.52) and a 1,2,3,4,6-substituted benzene ring (one singlet at δ_H 6.31). The methyl singlet at δ_H 2.13 suggested this group directly attached to the benzene ring. In addition, one glucose moiety was identified by the anomeric proton at δ_H 4.36 (d, $J = 7.8$ Hz) [13]. The ^{13}C NMR and HSQC spectra of **3** indicated 20 carbons, including 12 of two benzene rings, one ketone (δ_C 200.9, C-7), one methyl group (δ_C 8.8, C-8), and 6 of one glucose sugar (δ_C 105.0, 75.2, 77.5, 71.7, 77.8, and 63.2). The NMR data of **3** were closely resembling those of guavinoside D [13], except for the difference carbon chemical shifts of the 1,2,3,4,6-substituted benzene ring (Table 1), suggesting the positions of the substituents have changed. The singlet proton at δ_H 6.31 was assigned to H-5 since this showed HMBC correlation to C-1 (δ_C 114.3)/C-6 (δ_C 158.4)/C-3 (δ_C 111.4)/C-4 (δ_C 162.2) but not to C-7 (δ_C 200.9). The strong downfiled-shifted carbons at δ_C 155.4 (C-2), 162.2 (C-4), and 158.4 (C-6) suggested these carbons linked to oxygen atom. In addition, the methyl proton at δ_H 2.13 showed HMBC correlations with C-2/C-3/C-4. These observations indicated the position of substituted groups in this benzene ring. The glucose linked to C-2 as confirmed by HMBC correlation from an anomeric proton at δ_H 4.36 to C-2 (Figure 2). The large $^{3}J_{1',2'}$ value (7.8 Hz) of the anomeric proton at δ_H 4.36 suggested *β*-form of the glycosidic linkage. Acid hydrolysis of **3** yielded D-glucose, identified by TLC and optical rotation in comparison with authentic samples [9, 10]. Thus, compound **3** was determined as 4,6-dihydroxy-3-methyl-2-*O*-*β*-D-glucopyranosylbenzophenone an previously undescribed compound.

The known compounds were identified to be platanic acid (**4**) [14], platanic acid 28-*O*-*β*-D-glucopyranosyl ester (**5**) [15], arjunolic acid (**6**) [16], terminolic acid (**7**) [17], betulinic acid (**8**) [18], myricetin 3-*O*-(6″-galloyl)-*β*-D-galactopyranoside (**9**) [19], myricetin 3-*O*-*β*-D-galactopyranoside (**10**) [20], myricetin-3-*O*-*α*-L-arabinopyranoside (**11**) [19], myricitrin (**12**) [21], quercitrin (**13**) [22], and scorzonoside (**14**) [23]. The identification of these compounds was revealed by detailed spectroscopic analysis and comparison with literature data. Of these compounds, platanic acid (**4**) and betulinic acid (**8**) had been isolated from the *Syzygium claviflorum* leaves and exhibits anti-HIV activity [24], platanic acid 28-*O*-*β*-D-glucopyranosyl ester (**5**) had been isolated from *Eugenia moraviana* O. Berg (Myrtaceae) as a xanthine oxidase inhibitor [15]. Arjunolic acid (**6**) was found in some kingdom plants and well known for various biological functions, including anti-fungal [25], anticholinesterase [26], antidiabetic [27], anti-bacterial [28], and anti-asthmatic [29].

Compounds **1**–**14** were screened for anti *α*-glucosidase activities at the concentration of 200 μM. Acarbose was used as a positive control in both tests. Compounds **1**–**3**, **9**–**14** inhibited *α*-glucosidase with inhibitory percentages over 50%. Therefore, further evaluation for *α*-glucosidase inhibition of these compounds were assayed to obtain the IC_{50} values. As the results (Table 2), compound **9** showed strongest effect with IC_{50} value of 23.6 μM and **10**–**13** showed weak effect with IC_{50} values ranging from 148.0 to 164.4 μM.

The isolated compounds also were screened for their NO production inhibition. Compounds **1**–**3**, **6**, **7**, **14** did not show significant cytotoxic activity at a concentration of 100 μM in the MTT assay and were further screened for their NO production effects in lipopolysaccharide (LPS) stimulated RAW264.7 cells. As shown in Table 3, compounds **1**, **2**, **6**, and **7** showed significantly inhibition effects with IC_{50} values of 16.3, 14.9, 25.5, and 24.7, respectively, compared to that of the positive control compound, dexamethasone, which showed IC_{50} value of 13.6 μM. These results suggested that the compounds with three hydroxy groups

TABLE 1 | Nuclear magnetic resonance (NMR) spectral data for compounds **1–3** in CD_3OD.

	1		2			3	
No.	δ_C[a]	δ_H[b] (*J* in Hz)	δ_C[a]	δ_H[b] (*J* in Hz)	**No.**	δ_C[a]	δ_H[b] (*J* in Hz)
1	48.1	0.92 (dd, 12.0, 12.0) 1.97 (dd, 12.0, 4.8)	49.5	0.95 (dd, 12.6, 11.4) 2.21 (dd, 12.6, 4.8)	1	114.3	—
2	69.7	3.71 (ddd, 12.0, 9.6, 4.8)	69.8	3.83 (ddd, 11.4, 9.6, 4.8)	2	155.4	—
3	78.3	3.37 (d, 9.6)	78.4	3.36 (d, 9.6)	3	111.4	—
4	44.1	—	44.8	—	4	162.2	—
5	48.2	1.30 (br d, 11.4)	49.2	1.30[c]	5	100.5	6.31 (s)
6	19.1	1.39–1.43 (m)/1.46–1.50 (m)	68.9	4.42 (d, 2.4)	6	158.4	—
7	33.6	1.30–1.34 (m)/1.64–1.68 (m)	40.7	1.57–1.62 (m)	7	200.9	—
8	41.1	—	43.7	—	8	8.8	2.13 (s)
9	48.8	1.59–1.62 (m)	56.2	2.12 (br s)	9	142.0	—
10	39.0	—	38.2	—	10	130.7	7.70 (d, 7.8)
11	24.5	1.97–2.02 (m)	126.5	6.52 (dd, 10.8, 2.4)	11	128.8	7.41 (t, 7.8)
12	126.9	5.30 (t, 3.6)	126.9	5.70 (br d, 10.8)	12	128.8	7.52 (t, 7.8)
13	138.6	—	136.5	—	13	128.8	7.41 (t, 7.8)
14	43.3	—	40.8	—	14	130.7	7.70 (d, 7.8)
15	29.1	1.14 (br d, 13.8)/1.93–1.98 (m)	26.3	1.04–1.06 (m)/1.79–1.81 (m)	2-*O*-glucopyranose		
16	25.1	1.80/2.13	37.3	1.34–1.37 (m)/2.26 (br d, 13.2)	1″	105.0	4.36 (d, 7.8)
17	49.0	—	48.5	—	2″	75.2	2.72 (dd, 9.0, 7.8)
18	52.9	2.31 (d, 11.4)	135.6	—	3″	77.5	3.24 (t, 9.0)
19	41.3	1.70–1.74 (m)	41.5	1.88 (d, 15.6)/2.54 (d, 15.6)	4″	71.7	3.09 (t, 9.0)
20	75.6	3.03 (ddd, 10.8, 10.8, 3.6)	33.5	—	5″	77.8	3.04 (ddd, 9.0, 5.4, 2.4)
21	35.6	1.66–1.69 (m)/1.80–1.84 (m)	38.3	1.24–1.26 (m)/1.43–1.46 (m)	6″	63.2	3.59 (dd, 12.0, 5.4) 3.71 (dd, 12.0, 2.4)
22	31.4	1.58–1.62 (m)/1.80–1.84 (m)	34.2	1.63–1.66 (m)/1.99–2.01 (m)			
23	66.4	3.28 (d, 10.8)/3.52 (d, 10.8)	66.0	3.62 (d, 10.8)/3.50 (d, 10.8)			
24	13.9	0.72 (s)	14.7	1.08 (s)			
25	17.7	1.07 (s)	21.5	1.36 (s)			
26	17.9	0.86 (s)	17.7	1.15 (s)			
27	24.1	1.17 (s)	20.2	0.98 (s)			
28	177.4	—	183.4	—			
29	16.5	1.01 (d, 6.6)	32.9	0.96 (s)			
30	—	—	24.7	0.83 (s)			
28-*O*-glucopyranose							
1′	95.7	5.37 (d, 7.8)					
2′	73.9	3.33[c]					
3′	78.3	3.42 (t, 9.0)					
4′	71.2	3.37[c]					
5′	78.6	3.34[c]					
6′	62.5	3.82 (dd, 12.0, 2.4) 3.69 (dd, 12.0, 4.8)					

[a]Recorded in 150 MHz.
[b]Recorded in 600 MHz.
[c]Overlapped signals.

TABLE 2 | α-Glucosidase inhibitory effects of the isolated compounds.

Compounds	Inhibition (IC_{50}, μM)
1	> 200
2	> 200
3	> 200
9	23.6 ± 1.8
10	148.0 ± 3.5
11	164.4 ± 2.9
12	137.7 ± 2.4
13	160.1 ± 3.1
14	> 200
Acarbose[a]	47.1 ± 1.4

[a]Acarbose was used as a positive control.

TABLE 3 | NO inhibitory effects in LPS-activated RAW264.7 cells of the isolated compounds.

Compounds	NO inhibition (IC_{50}, μM)
1	16.3 ± 1.5
2	14.9 ± 2.8
3	74.6 ± 3.8
6	25.5 ± 2.6
7	24.7 ± 2.3
14	86.2 ± 2.1
Dexamethasone[a]	13.6 ± 1.1

[a]Positive control compound. IC50 values of the remaining compounds were over 100 μM.

located at C-2, C-3, and C-23 have strongest NO production inhibitory effects, and the flavonoids with galloyl groups in its structure significantly inhibited α-glucosidase. The above results are quite consistent with some previous publications on the anti-inflammatory activity of pentacyclic triterpenes with similar structures [30, 31]. In particular, arjunolic acid (**6**) affects the metabolism of arachidonic acid by cyclooxygenase, thereby exerting anti-inflammatory and analgesic effects [32]. In addition, the other flavonoids bearing galloyl groups have been reported to enhance α-glucosidase inhibitory activity by increasing polyphenol-enzyme binding interactions [33]. Interestingly, myricetin 3-*O*-(6″-galloyl)-β-D-galactopyranoside (**9**) is the main component in the leaves of this plant. Therefore, this may predict that the galloyl groups present in the flavonoids of this plant play an important role in the α-glucosidase inhibitory activity.

3 | Conclusions

Phytochemical study on the methanol extract of the leaves of *S. antisepticum* led to the isolation of three previously undescribed compounds, 2α,3β,20α,23-tetrahydroxy-nor-30-urs-12-en-28-oic acid 28-O-β-D-glucopyranoside (**1**), 2α,3β,6β,23-tetrahydroxyoleana-11,13(18)-dien-28-oic acid (**2**), and 4,6-dihydroxy-3-methyl-2-*O*-β-D-glucopyranosylbenzophenone (**3**), together with eleven known compounds (**4**–**14**). Compounds **1**, **2**, **6**, and **7** showed significantly NO production inhibitory activity in LPS-activated murine macrophage RAW264.7 cells with IC_{50} values of 16.3, 14.9, 25.5, and 24.7 μM, respectively. Compounds **9**–**12** displayed the most potential α-glucosidase with IC_{50} values ranging from 23.6 to 162.0 μM.

4 | Experimental Section

4.1 | General

The optical rotations were measured on a Jasco P2000 polarimeter. The HR–ESI–MS was acquired on an Agilent 6530 Accurate Mass Q-TOF LC/MS. The NMR spectra were recorded on a Bruker 600 MHz spectrometer. Semi-preparative high-performance liquid chromatography (HPLC) were run on an Agilent 1260 system including binary pump, autosampler, DAD detector, and semi-preparative HPLC column YMC J'sphere ODS-H80 (4 μm, 20 × 250 mm). Isocratic mobile phase with a flow rate of 2.5 mL/min was used in Semi-prep-HPLC. The compound was monitored at wavelengths of 205, 230, 254, and 280 nm. Flash column chromatography was performed using silica gel, reversed phase C-18, and diaion HP-20 resins as stationary phase. Thin layer chromatography was carried out on pre-coated silica gel 60 F_{254} and RP-18 F_{254S} plates. The spots were detected by spraying with aqueous solution of H_2SO_4 5% followed by heating with a heat gun.

4.2 | Plant Material

The leaves of *S. antisepticum* (Blume) Merr. & L.M.Perry were collected in Quang Tri, Vietnam, in April 2024 and identified by Dr. Le Tuan Anh, Vietnam National Museum of Nature. A voucher specimen (NCCT-P162) was deposited at the Institute of Chemistry, VAST.

4.3 | Extraction and Isolation

The dried leaves of *S. antisepticum* (4.3 kg) was minced and ultrasonic extracted with MeOH to obtain the residue (235 g) after removal the solvent. This extract was suspended in water and then partitioned in turn with *n*-hexane, CH_2Cl_2, and EtOAc to give the corresponding extracts, SA1 (58.2 g), SA2 (16.5 g), SA3 (39.4 g), and water layer. Fraction SA2 was chromatographed on a silica gel column (SC) eluting with *n*-hexane/acetone (50/1, 20/1, 5/1, 1/1) to get four fractions, SA2A–SA2D. Fraction SA2B was isolated on a SC eluting with *n*-hexane/EtOAc (7/1) to get three fractions, SA2B1–SA2B3. Fraction SA2B2 was isolated by a semi-preparative HPLC eluting with 38% acetonitrile (ACN) in water to yield compounds **4** (12.5 mg, t_R = 52.8 min), and **5** (14.8 mg, t_R = 58.1 min). Fraction SA3 was chromatographed on a SC eluting with CH_2Cl_2/MeOH (50/1, 5/1, 1/1, 2/1) to get four fractions, SA3A–SA3D. Fraction SA3B was isolated an YMC RP18 column eluting with MeOH/H_2O (2/1) to get four fractions, SA3B1–SA3B4. Fraction SA3B2 was isolated on the semi-preparative HPLC eluting with 25% ACN in water to get **12** (11.5 mg, t_R = 48.5 min) and **14** (14.8 mg, t_R = 55.1 min). Fraction

SA3B3 was isolated on the HPLC eluting with 28% ACN in water to get **10** (9.4 mg, t_R = 51.8 min) and **11** (7.2 mg, t_R = 56.2 min). Fraction SA3B4 was isolated on the HPLC eluting with 30% ACN in water to get **13** (11.4 mg, t_R = 42.6 min) and **9** (28.6 mg, t_R = 49.7 min). Fraction SA3C was isolated an YMC RP18 column eluting with MeOH/H_2O (3/1) to get five fractions, SA3C1-SA3C5. Fraction SA3C2 was isolated on the HPLC eluting with 33% ACN in water to get **3** (13.8 mg, t_R = 57.2 min). Fraction SA3C3 was isolated on the HPLC eluting with 30% ACN in water to get **1** (16.2 mg, t_R = 61.3 min) and **8** (12.8 mg, t_R = 65.8 min). Fraction SA3C4 was isolated on the HPLC eluting with 28% ACN in water to get **2** (13.6 mg, t_R = 58.3 min), **7** (15.8 mg, t_R = 62.0 min), and **6** (17.4 mg, t_R = 66.1 min).

4.3.1 | 2α,3β,20α,23-Tetrahydroxy-nor-30-urs-12-en-28-oic acid 28-*O*-β-D-glucopyranoside (1)

A colorless amorphous powder; $[\alpha]_D^{25}$: +35.0 (*c* 0.1, MeOH); HR–ESI–MS *m/z* 675.3731 $[M+Na]^+$, calcd for $[C_{35}H_{56}O_{11}Na]^+$ 675.3731, Δ = +2.4 ppm; *m/z* 670.4182 $[M+NH_4]^+$ caldc for $[C_{35}H_{60}NO_{11}]^+$ 670.4161 Δ = −3.1 ppm; *m/z* 635.3811 $[M-H_2O+H]^+$, calcd for $[C_{35}H_{55}O_{10}]^+$ 635.3790, Δ = +3.3 ppm. ^{1}H NMR (CD_3OD, 600 MHz) and ^{13}C NMR (CD_3OD, 150 MHz) data are shown in Table 1 (Figures S1–S9).

4.3.2 | 2α,3β,6β,23-Tetrahydroxyoleana-11,13(18)-dien-28-oic acid (2)

A colorless crystal; mp 231°C–235°C; $[\alpha]_D^{25}$: +42.5 (*c* 0.1, MeOH); HR–ESI–MS *m/z* 525.3192 $[M+Na]^+$, calcd for $[C_{30}H_{46}O_6Na]^+$, 525.3187, Δ = +1.0 ppm; *m/z* 485.3262 $[M-H_2O+H]^+$, calcd for $[C_{30}H_{45}O_5]^+$, 485.3262, Δ = 0 ppm. ^{1}H NMR (CD_3OD, 600 MHz) and ^{13}C NMR (CD_3OD, 150 MHz) data are shown in Table 1 (Figures S10–S18).

4.3.3 | 4,6-Dihydroxy-3-methyl-2-*O*-β-D-glucopyranosylbenzo-phenone (3)

A colorless amorphous powder; $[\alpha]_D^{25}$: +46.8 (*c* 0.1, MeOH); HR–ESI–MS *m/z* 429.1139 $[M+Na]^+$, calcd for $[C_{20}H_{22}O_9Na]^+$, 429.1157, Δ = −4.2 ppm. ^{1}H NMR (CD_3OD, 600 MHz) and ^{13}C NMR (CD_3OD, 150 MHz) data are shown in Table 1 (Figures S19–S25).

The ^{1}H and ^{13}C NMR data of compounds **4**–**14** were shown in Supporting information (Table S1–S11).

4.4 | Acid Hydrolysis of Compounds 1 and 3

Acid hydrolysis of compounds **1** and **3** were the same as described in previous work [9, 10] referring to Supporting Information.

4.5 | Nitric Oxide Assay

The NO assay protocol is the same as described in previous papers [34–36] referring to Supporting Information.

4.6 | α-Glucosidase Inhibitory Assay

The α-glucosidase inhibitory assay protocols are the same as described in previous papers [37, 38] referring to Supporting Information.

Author Contributions

Do Thi Trang: designed experiments, extracted, isolated compounds, elucidated chemical structures, prepared sample for bioassay, and wrote the paper. **Bui Huu Tai**: designed experiments, elucidated chemical structures and wrote the paper. **Phan Van Kiem**: designed experiments, elucidated chemical structures and wrote the paper. **Nguyen Viet Dung**: extracted and isolated compounds and prepared sample for bioassay. **Ngo Anh Bang**: extracted and isolated compounds and prepared sample for bioassay. **Vu Kim Thu**: extracted and isolated compounds and prepared sample for bioassay. **Le Thi Thuy Hang**: extracted and isolated compounds and prepared sample for bioassay. **Pham Hai Yen**: extracted and isolated compounds and prepared sample for bioassay.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Additional references cited within the Supporting Information (Ref. [9, 10, 34–38])