Bioactive Constituents from the Aerial Parts of *Lippia triphylla*

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Abstract: Five new compounds, lippianosides A (**1**), B (**2**), C (**3**), D (**4**), and E (**5**), along with 26 (**6–31**) known ones were obtained from the 95% EtOH extract of *Lippia triphylla* (*L. triphylla*) aerial parts collected from Rwanda, Africa. Among the known compounds, **11** and **17–30** were isolated from the *Lippia* genus for the first time. In addition, **12**, **13**, and **16** were firstly obtained from this species. The structures of them were elucidated by chemical and spectroscopic methods. The antioxidant and triglyceride accumulation inhibition effects of the 31 compounds were examined in L6 cells and HepG2 cells, respectively.

Keywords: *Lippia triphylla*; lippianoside; structure elucidation; antioxidant; triglyceride accumulation inhibition; L6 cells; HepG2 cells

1. Introduction

The genus *Lippia* (*L.*) has a great economic value as a condiment and traditional medicine. *Lippia* leaves, flowers, and aerial parts were used in folk medicine for the treatment of respiratory and digestive system diseases [1]. Polyphenols from *L. citriodora* decreased triglyceride (TG) accumulation, the generation of reactive oxygen species (ROS) and restored mitochondrial membrane potential in adipocytes via ROS-mediated down-regulation of nuclear factor κB transcription factor, peroxisome proliferator-activated receptor γ-dependent transcription, upregulation of adiponectin and activation of AMP-activated protein kinase (AMPK) [2]. Essential oils from *L. thymoides* leaves had antimicrobial selectivity to Gram-positive bacteria *Staphylococcus aureus* and *Micrococcus luteus* [3]. Methanolic extract of *L. nodiflora* leaves showed reduced effect on ROS production against LPS induced toxicity in HepG2 cells [4]. *L. sidoides* displayed immunomodulatory effects through the inhibition of cyclic nucleotide-dependent phosphodiesterase activity and activation of p38 MAPK pathway [5]. *L. graveolens* extract and its constituents, cirsimaritin, hispidulin, and naringenin, could inhibit dipeptidyl peptidase IV and protein tyrosine phosphatase, which indicated that *L. graveolens* was useful for type 2 diabetes management [6]. Oral administration of γ-sitosterol isolated from *L. nodiflora* once daily for 21 days in STZ-induced diabetic rats resulted in a significant decrease in blood glucose and glycosylated hemoglobin with a significant increase in plasma insulin level, and, subsequently, increased insulin secretion in response to glucose [7].

L. triphylla (L'HER.) O. Kuntze (syn. *L. citrodora* (ORT.) HBK) is a perennial, bushy plant of *Verbenaceae* family, commonly named lemon verbena. It grows spontaneously in many countries in South America, such as Brazil, Chile, Argentina, and Peru, had been introduced into Europe by the end of the 17th century, and has since been cultivated in North Africa and Southern Europe [8]. It contains special lemon-like fragrance, and is used against vertigo, nausea, and headaches in Greece [9].

During the course of our studies, we identified five new compounds, lippianosides A–E (**1**–**5**), along with 26 known ones (**6**–**31**) from the 95% EtOH extract of *L. triphylla* aerial parts collected from Rwanda. Their structures were elucidated by chemical and spectroscopic methods. Based on previous *Lippia* genus activity reports evidence, the antioxidant and TG accumulation inhibitory effects of the isolates were examined.

2. Results and Discussion

The 95% EtOH extract of *L. triphylla* was subjected to solvent partition, chromatographic isolation, and chemical and spectral analyses. As a result, five new compounds, lippianosides A–E (**1**–**5**) (Figure 1), together with 26 known ones (Figure 2), jionoside C(**6**) [10], *trans*-acteoside (**7**) [11], isoverbascoside (**8**) [12], *cis*-acteoside (**9**) [13], martynoside (**10**) [14], isomartynoside (**11**) [14], β-hydroxyacteoside (**12**) [15], campneoside I (**13**) [16], cistanoside F (**14**) [17], jaceosidin (**15**) [18], nepetin (**16**) [19], nepitrin (**17**) [20], dehydrodiconiferyl glucoside D (**18**) [21], dehydrodiconiferyl glucoside E (**19**) [21], (+)-lariciresinol-9-*O*-β-D-glucopyranoside (**20**) [22], (+)-pinoresinol 4-*O*-β-D-glucoside (**21**) [23,24], dihydrovomifoliol-*O*-β-D-glucopyranoside (**22**) [25,26], turpinionoside D (**23**) [27], 9-hydroxymegastigm-5-en-4-one (**24**) [28], (−)-loliolide (**25**) [29,30], eudesm-4(15)-ene-1β,6α-diol (**26**) [31], (6S)-3,7-dimethyl-7-hydroxy-2(Z)-octen-6-olide (**27**) [32], ursolic acid (**28**) [33], avicennone A (**29**) [34], benzyl alcohol *O*-β-D-glucopyranoside (**30**) [35], and icariside H$_1$ (**31**) [36] were yielded and identified. Among the known ones, **11** and **17**–**30** were isolated from the *Lippia* genus for the first time, and **12**, **13**, and **16** were obtained from this species for the first time.

Lippianoside A (**1**), $[\alpha]_D^{25}$ +7.9° (in MeOH), white powder. Its molecular formula, C$_{27}$H$_{36}$O$_{12}$, was determined from the molecular ion peak at *m/z* 575.2113 [M + Na]$^+$ by HR-Q-TOF-ESI-MS measurement. Acid hydrolysis of **1** with 1 M HCl yielded D-glucose, which was identified on the basis of retention time (HPLC) and optical rotation [37,38]. ^{1}H- and ^{13}C-NMR (DMSO-d_6, Table 1) spectra suggested the following moieties presented in **1**: a β-D-glucopyranosyl (δ 3.98 (1H, d, *J* = 8.0 Hz, H-1″)), two ABX-type aromatic rings (δ 6.64 (1H, dd, *J* = 2.0, 8.0 Hz, H-6′), 6.71 (2H, *J* = 8.0 Hz, H-5 and 5′), 6.76 (1H, d, *J* = 2.0 Hz, H-2′), 6.77 (1H, dd, *J* = 2.0, 8.0 Hz, H-6), 6.88 (1H, d, *J* = 2.0 Hz, H-2)), three methoxy groups (δ 3.07, 3.73, 3.76 (3H each, all s, 7′, 3′, 3-OCH$_3$)). In addition, the ^{1}H and ^{13}C-NMR spectra exhibited signals attributable to two methylenes bearing oxygen (δ 3.11 (1H, dd, *J* = 9.0, 9.0 Hz, H-9′a), 3.46 (1H, dd, *J* = 4.0, 9.0 Hz, H-9′b), 3.75 (1H, m, overlapped, H-9a), 4.05 (1H, dd, *J* = 4.5, 9.0 Hz, H-9b), two methines bearing oxygen (δ 3.97 (1H, d, *J* = 7.5 Hz, H-7′), 4.56 (1H, d, *J* = 7.5 Hz, H-7)), along with two aliphatic methines at δ 1.75 (1H, m, H-8) and 2.40 (1H, m, H-8′), respectively. According to the long-range correlations (Figure 3) observed from HMBC spectrum, the planar structure of **1** was determined. The coupling constant of H-7′ (*J* = 7.5 Hz) in **1** suggested an antiperiplanar orientation of H-7′ and H-8′. On the other hand, the CD spectrum of **1** (Δε: −121.7 (201 nm), −5.9 (228 nm)) was very similar to that of (7R,8S,7′S,8′R)-4,9,4′,7′-tetrahydroxy-3,3′-dimethoxy-7,9′-epoxylignan 9-*O*-β-D-glucopyranoside (Δε: −12.9 (205 nm), −2.5 (234 nm)) [39], which indicated the absolute configuration of **1** was 7R,8S,7′S,8′R. Furthermore, the NOE correlations between δ$_H$ 4.56 (H-7) and δ$_H$ 2.40 (H-8′) and 3.75 (H-9a); δ$_H$ 1.75 (H-8) and δ$_H$ 3.97 (H-7′); and δ$_H$ 2.40 (H-8′) and δ$_H$ 3.75 (H-9a), 6.64 (H-6′) and 6.76 (H-2′) observed in the NOESY spectrum confirmed the accuracy of configuration analysis. Finally, the structure of **1** was determined as (7R,8S,7′S,8′R)-4,9,4′-trihydroxy-3,3′,7′-trimethoxy-7,9′-epoxylignan 9-*O*-β-D-glucopyranoside.
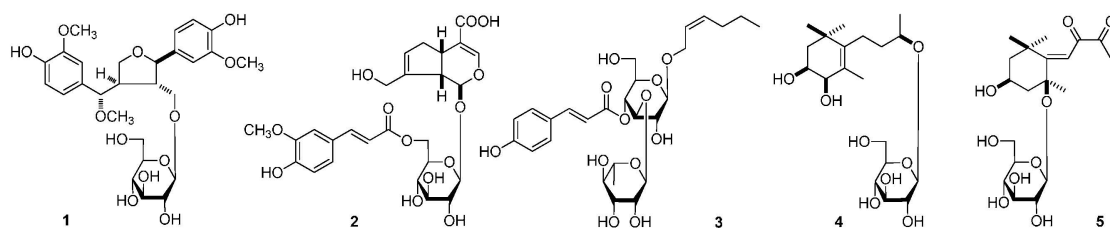
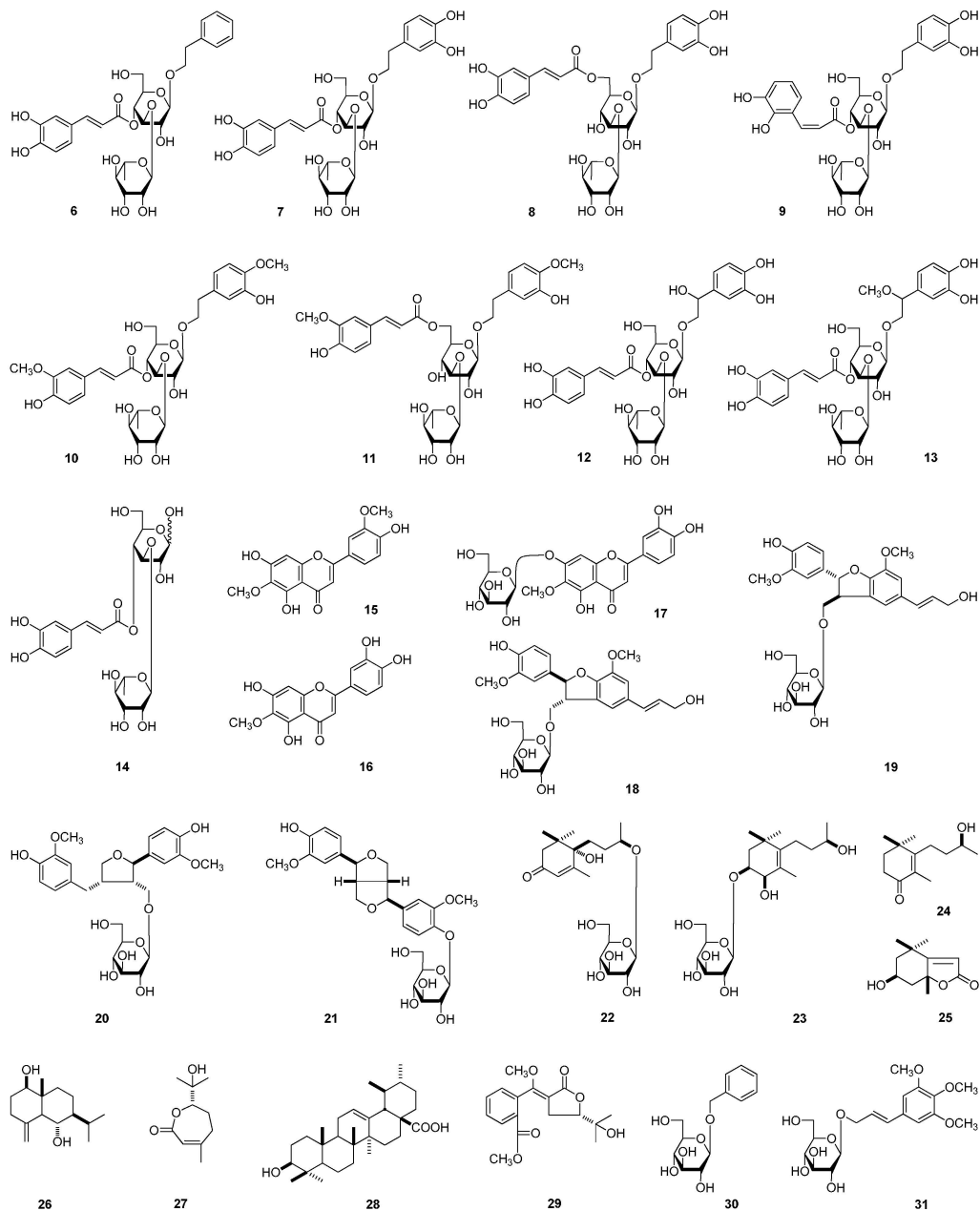**Figure 1.** The new compounds (**1–5**) obtained from *L. triphylla.*

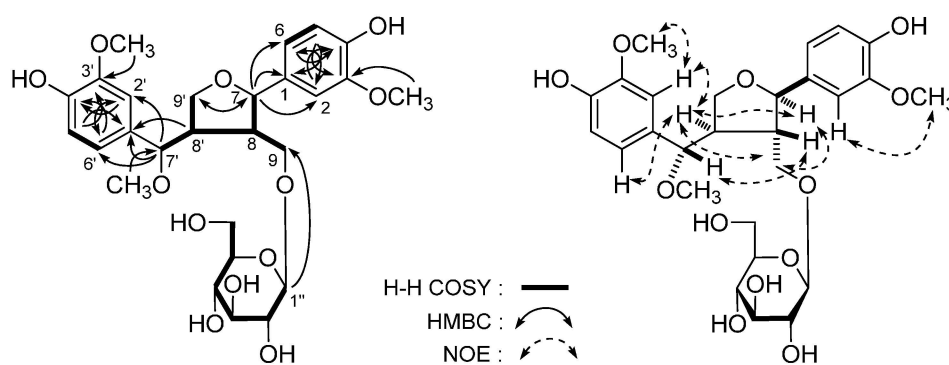**Figure 2.** The known compounds (**6–31**) obtained from *L. triphylla.*

Figure 3. The main ^{1}H-^{1}H COSY, HMBC, and NOE correlations of **1**.

Table 1. The ^{1}H- and ^{13}C-NMR data of **1**.

No.	1 [a]		1 [b]	
	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)
1	133.2	-	134.8	-
2	110.4	6.88 (d, 2.0)	111.6	6.97 (d, 1.5)
3	147.2	-	149.0	-
4	145.5	-	147.2	-
5	115.0	6.71 (d, 8.0)	116.1	6.77 (d, 8.0)
6	118.5	6.77 (dd, 2.0, 8.0)	120.3	6.86 (dd, 1.5, 8.0)
7	82.7	4.56 (d, 7.5)	85.3	4.76 (d, 7.0)
8	49.7	1.75 (m)	51.6	1.96 (m)
9	69.5	3.75 (m, overlapped)	70.4	3.17 (dd, 4.0, 10.0)
		4.05 (dd, 4.5, 9.0)		3.55 (dd, 6.5, 10.0)
3-OCH$_3$	55.5	3.76 (s)	56.7	3.86 (s)
1′	130.7	-	132.7	-
2′	110.9	6.76 (d, 2.0)	112.1	6.79 (d, 1.5)
3′	147.5	-	149.3	-
4′	145.9	-	147.6	-
5′	115.0	6.71 (d, 8.0)	116.2	6.76 (d, 8.5)
6′	120.2	6.64 (dd, 2.0, 8.0)	121.8	6.70 (dd, 1.5, 8.0)
7′	84.5	3.97 (d, 7.5)	87.1	4.01 (d, 9.0)
8′	48.5	2.40 (m)	50.3	2.52 (m)
9′	68.7	3.11 (dd, 9.0, 9.0)	71.8	3.97 (dd, 9.0, 9.0)
		3.46 (dd, 4.0, 9.0)		4.18 (dd, 4.0, 9.0)
3′-OCH$_3$	55.7	3.73 (s)	56.6	3.82 (s)
7′-OCH$_3$	55.4	3.07 (s)	56.7	3.16 (s)
1′′	102.8	3.98 (d, 7.5)	104.5	4.02 (d, 8.0)
2′′	73.4	2.91 (dd, 7.5, 9.0)	75.2	3.11 (dd, 8.0, 9.0)
3′′	76.6	3.11 (dd, 9.0, 9.0)	78.2	3.29 (dd, 9.0, 9.0)
4′′	69.8	3.03 (dd, 9.0, 9.0)	71.7	3.28 (dd, 9.0, 9.0)
5′′	76.7	3.01 (m)	77.9	3.16 (m)
6′′	60.9	3.45 (dd, 5.5, 12.5)	62.8	3.66 (dd, 5.5, 12.0)
		3.61 (dd, 2.5, 12.5)		3.82 (dd, 2.5, 12.0)

[a]: determined in DMSO-d_6; [b]: determined in CD$_3$OD.

Lippianoside B (**2**) was obtained with negative optical rotation ($[\alpha]_D^{25}$ −8.9° in MeOH). The molecular formula of **2** was revealed as $C_{26}H_{30}O_{13}$ by HR-Q-TOF-ESI-MS (*m/z* 549.1604 [M − H], calcd for $C_{26}H_{29}O_{13}$, 549.1614). Treatment of **2** with 1 M HCl gave D-glucose, which was identified by HPLC analysis [37,38]. ^{1}H-, ^{13}C-NMR (CD$_3$OD, Table 2) and various 2D NMR spectra (Figure 4), indicated the presence of an iridoid moiety, a *trans*-feruloyl, and a β-D-glucopyranosyl in **2**. In the HMBC experiment (Figure 4), the long-range correlations between the following proton and carbon

pairs were observed: δ_H 4.98 (H-1) and δ_C 145.0 (C-8), 152.9 (C-3); δ_H 3.13 (H-5) and δ_C 145.0 (C-8), 171.0 (C-11); δ_H 2.69 (H-9) and δ_C 113.3 (C-4), 128.9 (C-7); δ_H 4.19, 4.25 (H$_2$-10) and δ_C 46.7 (C-9), 128.9 (C-7), 145.0 (C-8); δ_H 4.73 (H-1′) and δ_C 98.9 (C-1); δ_H 4.40, 4.44 (H$_2$-6′) and δ_C 169.1 (C-9″). Finally, in the NOESY spectrum, the NOE correlations between δ_H 4.98 (H-1) and δ_H 1.96 (Hα-6); δ_H 3.13 (H-5) and δ_H 2.69 (H-9) and 2.75 (Hβ-6); and δ_H 2.75 (Hβ-6) and δ_H 2.69 (H-9) suggested the relative configuration of **2** was 1α,5β,9β. On the other hand, the ^{1}H and ^{13}C-NMR spectra of **2** were superimposable on those of 6′-*O-trans-p*-coumaroyl geniposidic acid [40], except for the signals due to *trans*-feruloyl group at 6′-position. Consequently, the structure of lippianoside B was elucidated to be 6′-*O-trans*-feruloyl geniposidic acid (**2**).
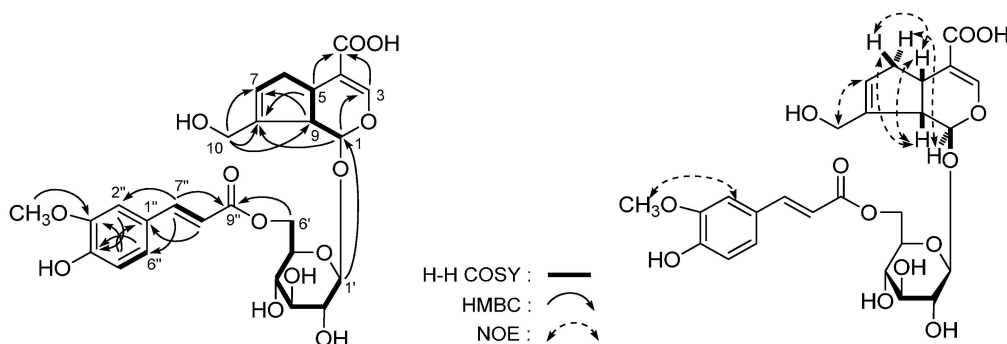

Figure 4. The main ^{1}H-^{1}H COSY, HMBC and NOE correlations of **2**.

Table 2. The ^{1}H- and ^{13}C-NMR data of **2** in CD$_3$OD.

No.	δ_C	δ_H (*J* in Hz)	No.	δ_C	δ_H (*J* in Hz)
1	98.9	4.98 (d, 8.0)	3′	77.8	3.43 (dd, 8.5, 9.0)
3	152.9	7.49 (s)	4′	71.9	3.37 (dd, 9.0, 9.0)
4	113.3	-	5′	75.7	3.56 (m)
5	37.1	3.13 (q like, 8.0, 8.0)	6′	64.4	4.40 (dd, 6.0, 12.0)
6	39.9	1.96 (br. dd, *ca.* 8, 16)			4.44 (dd, 2.5, 12.0)
		2.75 (br. dd, *ca.* 8, 16)	1″	127.7	-
7	128.9	5.76 (br. s)	2″	111.6	7.17 (br. s)
8	145.0	-	3″	149.4	-
9	46.7	2.69 (dd, 8.0, 8.0)	4″	150.7	-
10	61.6	4.19 (d, 14.0)	5″	116.5	6.81 (d, 8.0)
		4.25 (d, 14.0)	6″	124.3	7.05 (br. d, *ca.* 8)
11	171.0	-	7″	147.1	7.59 (d, 16.0)
1′	100.7	4.73 (d, 7.5)	8″	115.3	6.35 (d, 16.0)
2′	74.8	3.27 (dd, 7.5, 8.5)	9″	169.1	-
			3″-OCH$_3$	56.5	3.88 (s)

Lippianoside C (**3**), $[\alpha]_D^{25}$ −61.4° (in MeOH), was isolated as a white powder. Its molecular formula, C$_{27}$H$_{38}$O$_{12}$, was established by HR-Q-TOF-ESI-MS with *m/z* 557.2267 [M + Na]$^+$ (calcd for C$_{27}$H$_{38}$O$_{12}$Na, 557.2255). Its IR spectrum showed absorption bands due to hydroxyl (3384 cm^{-1}), α,β-unsaturated carbonyl (1701 cm^{-1}), aromatic ring (1603, 1514 cm^{-1}), and ether function (1064 cm^{-1}). Acid hydrolysis of **3** with 1 M HCl gave D-glucose and L-rhamnose [37,38]. The ^{1}H-, ^{13}C-NMR (CD$_3$OD, Table 3) and various kinds of 2D NMR (Figure 5) including ^{1}H-^{1}H COSY, HMQC, and HMBC showed signals assignable to 2-hexene-1-alcohol, *trans-p*-coumaroyl, β-D-glucopyranosyl, and α-L-rhamnopyranosyl. In the HMBC experiment, the long-range correlations were observed between δ_H 4.36 (H-1′) and δ_C 70.7 (C-1); δ_H 5.19 (H-1″) and δ_C 81.7 (C-3′); and δ_H 4.92 (H-4′) and δ_C 168.4 (C-9‴), and the connectivities of the above-mentioned moieties were elucidated. Finally, in the NOESY experiment, the NOE correlations observed between δ_H 2.39 (H$_2$-4) and δ_H 3.56, 3.87 (H$_2$-1)

as well as δ_H 5.47 (H-2) and δ_H 5.38 (H-3) indicated the double bond configuration of 2-position in **3** was *Z*.

Lippianoside D (**4**) was a white powder with negative optical rotation ($[\alpha]_D^{25}$ −62.1° in MeOH). Its elemental composition was determined to be $C_{19}H_{34}O_8$ by HR-Q-TOF-ESI-MS observed at *m/z* 413.2158 [M + Na]$^+$. The ^{1}H and ^{13}C-NMR (CD$_3$OD, Table 4) showed signals due to four methyl (δ 1.05, 1.07, 1.78 (3H each, all s, H$_3$-11, 12, 13), 1.20 (3H, d, *J* = 6.0 Hz, H$_3$-10)), three methylene (δ (1.38 (1H, dd, *J* = 5.0, 13.0 Hz), 1.74 (1H, ddd, *J* = 13.0, 13.0 Hz), H$_2$-2), 1.57, 1.66 (1H each, both m, H$_2$-8), (1.99 (1H, ddd, *J* = 5.0, 13.0, 13.0 Hz), 2.27 (1H, ddd, *J* = 5.0, 13.0, 13.0 Hz), H$_2$-7)), three methine bearing an oxygen function (δ 3.71 (1H, ddd, *J* = 4.0, 5.0, 13.0 Hz, H-3), 3.73 (1H, br. d, *ca.* *J* = 4 Hz, H-4), 3.90 (1H, m, H-9)), together with a β-D-glucopyranosyl (δ 4.35 (1H, d, *J* = 7.5 Hz, H-1′)). The ^{1}H-^{1}H COSY experiment indicated the presence of partial structure written in bold lines (Figure 6). According to the long-range correlations (Figure 6) observed from HMBC spectrum, the planar structure of **4** was determined. Finally, treatment of **4** with 1 M HCl liberated D-glucose [37,38]. Enzymatic hydrolysis of it with β-glucosidase gave (3*S*,4*R*,9*R*)-3,4,9-trihydroxymegastigman-5-ene [27] as aglycon. Then, the structure lippianoside D was determined to be (3*S*,4*R*,9*R*)-3,4,6-trihydroxymegastigman-5-ene 9-*O*-β-D-glucopyranoside (**4**).
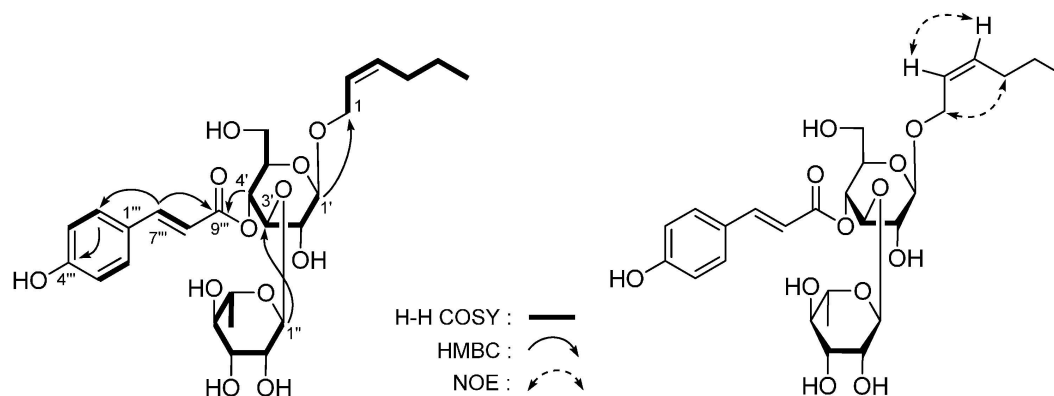

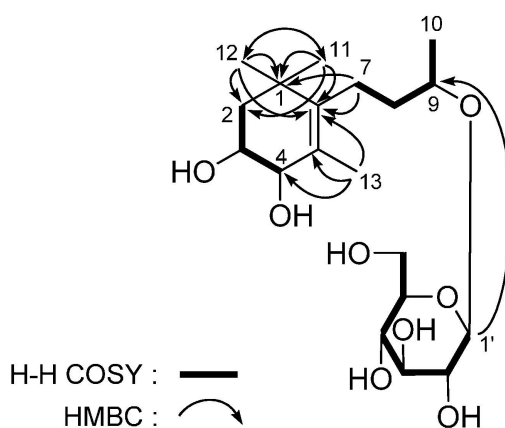**Figure 5.** The main ^{1}H-^{1}H COSY, HMBC and NOE correlations of **3**.

Figure 6. The main ^{1}H-^{1}H COSY and HMBC correlations of **4**.

Table 3. The ^{1}H- and ^{13}C-NMR data of **3** in CD$_3$OD.

No.	δ_C	δ_H (*J* in Hz)	No.	δ_C	δ_H (*J* in Hz)
1	70.7	3.56 (m) 3.87 (m)	2″	72.4	3.91 (dd, 1.0, 3.0)
2	134.6	5.47 (m)	3″	72.1	3.57 (dd, 3.0, 9.5)
3	125.9	5.38 (m)	4″	73.8	3.27 (dd, 9.5, 9.5)
4	28.8	2.39 (q like, *ca.* 7)	5″	70.4	3.58 (m)
5	21.6	2.08 (m)	6″	18.5	1.08 (d, 6.5)
6	14.7	0.97 (t, 7.5)	1‴	127.1	-
1′	104.2	4.36 (d, 8.0)	2‴	131.4	7.46 (d, 8.5)
2′	76.2	3.38 (dd, 8.0, 8.5)	3‴	117.0	6.80 (d, 8.5)
3′	81.7	3.82 (dd, 8.5, 9.0)	4‴	161.6	-
4′	70.7	4.92 (dd, 9.0, 9.0)	5‴	117.0	6.80 (d, 8.5)
5′	76.1	3.54 (m)	6‴	131.4	7.46 (d, 8.5)
6′	62.4	3.52 (dd, 6.0, 12.0)	7‴	147.7	7.66 (d, 16.0)
		3.62 (br. d, *ca.* 12)	8‴	114.8	6.34 (d, 16.0)
1″	103.1	5.19 (d, 1.0)	9‴	168.4	-

Table 4. The ^{1}H- and ^{13}C-NMR data of **4**.

No.	**4** [a]		**4** [b]	
	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)
1	38.8	-	37.9	-
2	42.0	1.38 (dd, 5.0, 13.0)	42.4	1.72 (dd, 3.0, 12.5)
		1.74 (dd, 13.0, 13.0)		2.20 (dd, 12.5, 12.5)
3	68.1	3.71 (ddd, 4.0, 5.0, 13.0)	67.1	4.12 (ddd, 4.0, 5.5, 12.5)
4	73.1	3.73 (br. d, *ca.* 4)	72.3	4.19 (br. d, *ca.* 4)
5	128.1	-	128.4	-
6	143.7	-	141.6	-
7	25.6	1.99 (ddd, 5.0, 13.0, 13.0)	25.0	2.11 (ddd, 4.5, 13.0, 13.0)
		2.27 (ddd, 5.0, 13.0, 13.0)		2.48 (ddd, 4.5, 13.0, 13.0)
8	38.3	1.57 (m), 1.66 (m)	37.9	1.65 (m), 1.85 (m)
9	76.1	3.90 (m)	74.8	4.14 (m)
10	19.8	1.20 (d, 6.0)	19.9	1.31 (d, 6.5)
11	27.7	1.05 (s)	27.4	1.03 (s)
12	30.0	1.07 (s)	29.6	1.04 (s)
13	18.5	1.78 (s)	18.5	1.97 (s)
1′	102.3	4.35 (d, 7.5)	102.4	4.93 (d, 7.5)
2′	75.2	3.16 (dd, 7.5, 8.5)	75.2	4.04 (dd, 7.5, 8.5)
3′	78.2	3.36 (dd, 8.5, 9.0)	78.6	4.29 (dd, 8.5, 9.0)
4′	71.9	3.30 (dd, 9.0, 9.0)	71.9	4.23 (dd, 9.0, 9.0)
5′	77.9	3.26 (m)	78.3	3.97 (m)
6′	63.0	3.67 (dd, 5.5, 12.0)	63.0	4.36 (dd, 5.0, 11.5)
		3.85 (dd, 2.0, 12.0)		4.55 (dd, 2.0, 11.5)

[a] measured in CD$_3$OD; [b] measured in C$_5$D$_5$N.

Lippianoside E (**5**) was obtained as a white powder. Its molecular formula, C$_{19}$H$_{30}$O$_9$, was determined from the positive HR-Q-TOF-ESI-MS. The ^{1}H- and ^{13}C-NMR (CD$_3$OD, Table 5) spectra showed signals assignable to four methyls (δ 1.15, 1.37, 1.47, 2.19 (3H each, all s, H$_3$-12, 11, 13, 10)), two methylenes (δ (1.33 (1H, dd, *J* = 12.0, 12.0 Hz), 1.92 (1H, ddd, *J* = 2.5, 5.0, 12.0 Hz), H$_2$-2), (1.37 (1H, dd, *J* = 12.0, 12.0 Hz), 2.48 (1H, ddd, *J* = 2.5, 4.5, 12.0 Hz), H$_2$-4)), a methine bearing an oxygen function (δ 4.32 (1H, m, H-3)), a three-substituted double bond (δ 5.89 (1H, s, H-7)), two carboxyl groups (δ$_C$ 200.7 (C-9), 213.0 (C-8)), and a β-D-glucopyranosyl (δ 4.52 (1H, d, *J* = 7.5 Hz, H-1′)). Selected long-range correlations observed in the HMBC experiment were shown in Figure 7. Treatment of **5** with 1 M HCl yielded D-glucose [37,38]. In the NOESY experiment, NOE correlations were observed between the following proton pairs: δ$_H$ 1.92 (H*eq*-2) and δ$_H$ 1.37 (H$_3$-11) and 4.32 (H-3); δ$_H$ 4.32 (H-3)

and δ_H 1.37 (H$_3$-11) and 1.47 (H$_3$-13); and δ_H 5.89 (H-7) and δ_H 1.37 (H$_3$-11), 1.47 (H$_3$-13), and 2.19 (H$_3$-10), which suggested the configuration of **5** was 3*S**5*S**6*E*.
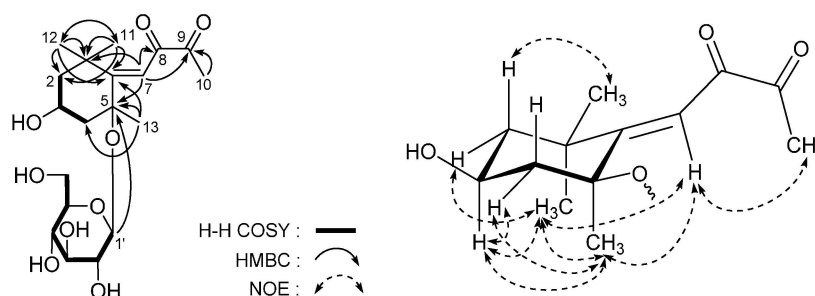

Figure 7. The main ^{1}H-^{1}H COSY, HMBC, and NOE correlations of **5**.

Table 5. The ^{1}H- and ^{13}C-NMR data of **5**.

No.	5 [a]		5 [b]	
	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)
1	37.1	-	35.4	-
2	49.9	1.33 (dd, 12.0, 12.0)	49.1	1.21 (dd, 12.5, 12.5)
		1.92 (ddd, 2.5, 5.0, 12.0)		1.79 (ddd, 3.0, 4.5, 12.0)
3	63.8	4.32 (m)	61.0	4.15 (m)
4	48.1	1.37 (dd, 12.0, 12.0)	45.9	1.19 (dd, 12.0, 12.0)
		2.48 (ddd, 2.5, 4.5, 12.0)		2.38 (ddd, 3.0, 5.0, 12.0)
5	78.7	-	76.9	-
6	141.6	-	117.4	-
6	119.1	-	117.4	-
7	101.4	5.89 (s)	99.8	5.86 (s)
8	213.0	-	210.6	-
9	200.7	-	197.5	-
10	26.7	2.19 (s)	26.2	2.12 (s)
11	30.1	1.37 (s)	29.0	1.29 (s)
12	32.5	1.15 (s)	31.7	1.05 (s)
13	26.6	1.47 (s)	26.3	1.33 (s)
1′	98.7	4.52 (d, 7.5)	96.8	4.36 (d, 7.0)
2′	75.3	3.14 (dd, 7.5, 9.0)	73.6	2.91 (dd, 7.0, 8.0)
3′	78.6	3.35 (dd, 9.0, 9.0)	77.3	3.16 (dd, 8.0, 9.0)
4′	71.7	3.25 (dd, 9.0, 9.0)	70.1	3.01 (dd, 9.0, 9.0)
5′	77.8	3.22 (m)	76.6	3.06 (m)
6′	62.9	3.61 (dd, 5.5, 12.0)	61.1	3.37 (dd, 6.0, 12.0)
		3.81 (dd, 2.0, 12.0)		3.62 (dd, 2.0, 12.0)

[a] measured in CD$_3$OD; [b] measured in DMSO-*d*$_6$.

Antimycin A, an electron transport chain inhibitor in mitochondria between cytochromes b and c, can produce ROS in cells, causing the leakage of superoxide radicals from cell mitochondria by inhibiting mitochondrial electron transport [41]. Compared with normal group, 20 µg/mL antimycin A induced significant L6 cell injury at a rate of 50%, while 10 µM resveratrol showed increased cell survival rate effects compared with the antimycin treated group. Except for **1**, **2** and **20**, all the compounds isolated from *L. triphylla* displayed significant protective effects against antimycin A-induced L6 cell injury at 30 µM, and **21** showed strongest protective activity (Figure 8).
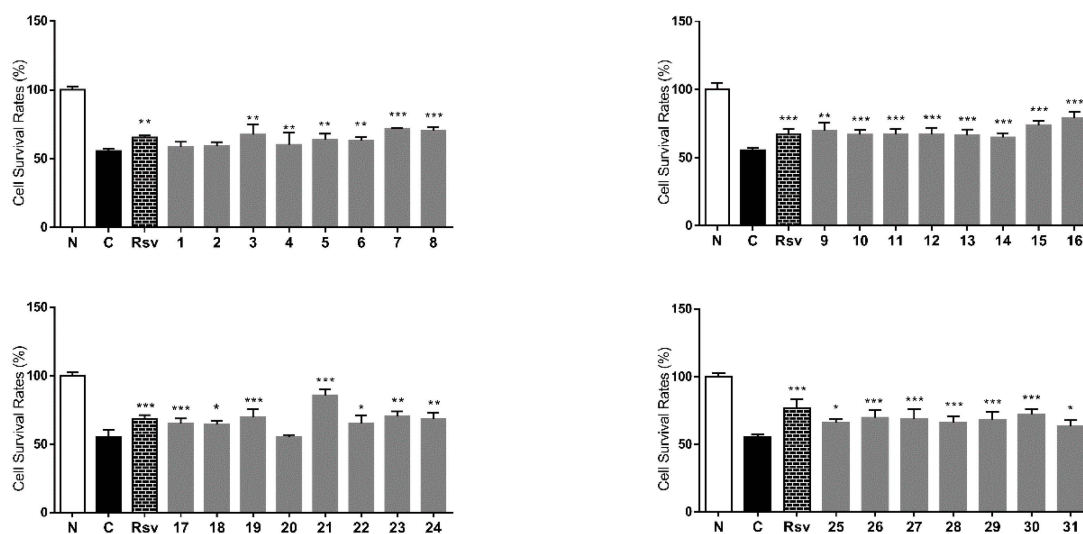
Figure 8. Cell survival rate of **1**–**31** on L6 cells treated with antimycin A. Values represent the mean ± SD of determinations (*n* = 8). * *p* < 0.05; ** *p* < 0.01; *** *p* < 0.001 *vs.* control group. Final administrated concentration of revestrol was 10 μM, and **1**–**31** was 30 μM.

Intracellular excess lipid accumulation (especially in liver and muscle) is a mediator of metabolic syndrome, which is comprised of a cluster of risk factors such as diabetes, hyperlipidemia, and hypertension. Free fatty acid (FFA) induced TG accumulation in HepG2 cells is commonly used for research on lipid metabolism regulation effects [42]. As shown in Figure 9, intracellular lipid contents were significantly increased after 0.2 mM oleic acid treatment. This accumulation effects were inhibited by orlistat at 0.5 μM. The TG accumulation inhibitory effects of the isolates were tested. Except for compounds **12**, **13** and **20**–**22**, all isolates displayed inhibitory effects on TG accumulation in FFA induced HepG2 cells.
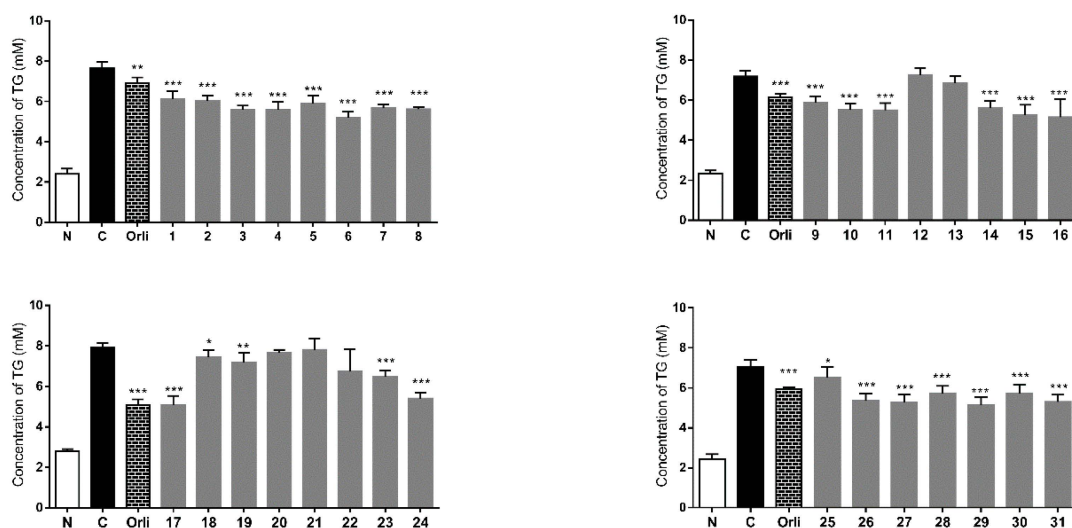

Figure 9. TG accumulation inhibitory effects of **1**–**31** in HepG2 cells. TG relative concentration: percentage of control group, which set as 100%. Values represent the mean ± SD of determinations (*n* = 8). * *p* < 0.05; ** *p* < 0.01; *** *p* < 0.001 *vs.* control group. Final administrated concentration of **1**–**31** was 10 μM, and oristat was 0.5 μM.

3. Experimental Section

3.1. General

The following instruments were used to obtain physical data: Optical rotations were determined on a Rudolph Autopol IV automatic polarimeter (Rudolph Research Analytical, Hackettstown, NJ, USA, l = 50 mm), IR and UV spectra were recorded on Varian 640-IR FT-IR (Varian Australia Pty Ltd., Mulgrave, Australia)and Varian Cary 50 UV-VIS spectrophotometer (Varian, Inc., Hubbardsdon, MA, USA), respectively. ^{1}H- and ^{13}C-NMR spectra were measured on a Bruker 500 MHz NMR spectrometer (Bruker BioSpin AG Industriestrasse 26 CH-8117, Fällanden, Switzerland) at 500 MHz for ^{1}H- and 125 MHz for ^{13}C-NMR, with tetramethylsilane (TMS) as an internal standard. Positive- and negative-ion HR-ESI-Q-TOF-MS were recorded on an Aglient 6520 Q-TOF mass spectrometer (Agilent Corp., Santa Clara, CA, USA).

The following experimental conditions were used for chromatography: A macroporous synthetic resin (D101) (Haiguang Chemical Co., Ltd., Tianjin, China), Silica gel (74–149 μm, Qingdao Haiyang Chemical Co., Ltd., Qingdao, China), and ODS (50 μm, YMC Co., Ltd., Tokyo, Japan). HPLC was performed on ODS (Cosmosil 5C18-MS-II, Tokyo, Japan; Φ = 20 mm, L = 250 mm, flow rate 9.0 mL/min), and the eluate was monitored with a UV detector (Shimadzu RID-10ª UV-vis, Shimadzu Co. Ltd., Kyoto, Japan).

3.2. Plant Material

The aerial parts of *Lippia triphylla* were collected in Rwanda, Africa, and identified by Dr. Tianxiang Li at Tianjin University of TCM as M. indica L. A voucher specimen was deposited at the Academy of Traditional Chinese Medicine of Tianjin University of TCM.

3.3. Extraction and Isolation

The dried aerial parts of *L. triphylla* (2.85 kg) were extracted with 95% EtOH under reflux. Evaporation of the solvent under reduced pressure to yield a 95% ethanol–water extract (403 g). The extract partitioned with $CHCl_3$–H_2O (1:1, *v/v*) to give $CHCl_3$ (105 g) and H_2O (258 g) layers. The H_2O layer (215 g) was subjected to D101 macroporous resin CC and eluted with H_2O and 95% EtOH, successively, to yield H_2O (131 g) and 95% EtOH (63 g) eluates, respectively.

The 95% EtOH eluate (50.0 g) was separated by SiO_2 gel CC ($CHCl_3$ → $CHCl_3$-MeOH (100:2 → 100:4 → 100:6, *v/v*) → $CHCl_3$–MeOH–H_2O (10:3:1 → 7:3:1 → 6:4:1, *v/v/v*, lower layer) → MeOH) to afford 16 fractions (Fr. 1–16). Fraction 3 (1.0 g) was isolated by SiO_2 gel and Sephadex LH-20 CC to give nepetin (**16**, 12.0 mg). Fraction 6 (1.2 g) was subjected to ODS, Sephadex LH-20 CC, and purified by PHPLC to yield benzyl alcohol *O*-β-D-glucopyranoside (**30**, 5.2 mg) and icariside H_1 (**31**, 4.3 mg). Fraction 7 (7.3 g) was separated by PHPLC and Sephadex LH-20 CC with different analysis conditions to afford lippianosides B (**2**, 19.0 mg) and C (**3**, 5.0 mg), martynoside (**10**, 7.0 mg), isomartynoside (**11**, 7.0 mg), nepitrin (**17**, 12.0 mg), dehydrodiconiferyl glucosides D (**18**, 20.0 mg) and E (**19**, 13.0 mg), (+)-lariciresinol-9-*O*-β-D-glucopyranoside (**20**, 28.0 mg), (+)-pinoresinol 4-*O*-β-D-glucoside (**21**, 6.0 mg), and dihydrovomifoliol-*O*-β-D-glucopyranoside (**22**, 40.0 mg). Fraction 8 (5.8 g) was purified by PHPLC, and as a result, lippianosides A (**1**, 14.0 mg), D (**4**, 10.1 mg), and E (**5**, 11.0 mg), jionoside C (**6**, 8.4 mg), and turpinionoside D (**23**, 7.2 mg) were given. Fraction 11 (8.6 g) was separated by PHPLC and ODS CC to yield *trans*-acteoside (**7**, 17.3 mg), isoverbascoside (**8**, 55.1 mg), *cis*-acteoside (**9**, 36.1 mg), β-hydroxyacteoside (**12**, 8.3 mg), campneoside I (**13**, 60.6 mg), and cistanoside F (**14**, 70.4 mg).

The above-mentioned $CHCl_3$ layer (85.0 g) was subjected to Silica gel CC ($CHCl_3$ → $CHCl_3$–MeOH (100:1 → 100:3 → 100:5 → 100:7, *v/v*) → MeOH) to give 13 fractions (Fr. 1'–13'). Fraction 5 (29.3 g) was purified by Sephadex LH-20 and Silica gel CC, along with PHPLC to afford jaceosidin (**15**, 11.2 mg), 9-hydroxymegastigm-5-en-4-one (**24**, 2.4 mg), (−)-loliolide (**25**,

13.1 mg), (6*S*)-3,7-dimethyl-7-hydroxy-2(*Z*)-octen-6-olide (**27**, 11.5 mg), ursolic acid (**28**, 20.9 mg), and avicennone A (**29**, 5.4 mg).

Lippianoside A (**1**): White powder; $[\alpha]_D^{25}$ +7.9° (*c* = 0.61, MeOH); CD (*c* = 0.00166 M, MeOH) $\Delta\varepsilon$ (λ nm) −121.7 (201), −5.9 (228); UV (MeOH) λ_{max} (log ε) 203 (4.89), 229 (4.07), 279 (3.70); IR (KBr) ν_{max} 3384, 2930, 1603, 1514, 1451, 1263, 1163, 1064, 1039, 833 cm^{-1}; ^{1}H- and ^{13}C-NMR (CD$_3$OD) data see Table 1; Positive-ion mode HR-Q-TOF-ESI-MS *m/z* 575.2113 (calcd for C$_{27}$H$_{36}$O$_{12}$Na [M + Na]$^+$, 575.2099).

Lippianoside B (**2**): White powder; $[\alpha]_D^{25}$ −8.9° (*c* = 0.79, MeOH); UV (MeOH) λ_{max} (log ε) 218 (4.21), 231 (4.20), 286 (3.92, sh), 323 (4.09); IR (KBr) ν_{max} 3552, 2940, 2840, 1690, 1596, 1517, 1448, 1161, 1025, 944, 897 cm^{-1}. ^{1}H- and ^{13}C-NMR (CD$_3$OD) data see Table 2. Negative-ion mode HR-Q-TOF-ESI-MS *m/z* 549.1604 [M − H]$^-$ (calcd for C$_{26}$H$_{29}$O$_{13}$, 549.1614).

Lippianoside C (**3**): White powder; $[\alpha]_D^{25}$ −61.4° (*c* = 0.37, MeOH); UV (MeOH) λ_{max} (log ε) 312 (4.21); IR (KBr) ν_{max} 3384, 2930, 1701, 1603, 1514, 1263, 1163, 1064, 1039, 833 cm^{-1}; ^{1}H- and ^{13}C-NMR (CD$_3$OD) data see Table 3. Positive-ion mode HR-Q-TOF-ESI-MS *m/z* 557.2267 (calcd for C$_{27}$H$_{38}$O$_{12}$Na [M + Na]$^+$, 557.2255).

Lippianoside D (**4**): White powder; $[\alpha]_D^{25}$ −62.1° (*c* = 0.86, MeOH); IR (KBr) ν_{max} 3360, 2964, 2929, 1621, 1377, 1262, 1073, 1026, 875 cm^{-1}; ^{1}H- and ^{13}C-NMR (CD$_3$OD) data see Table 4; Positive-ion mode HR-Q-TOF-ESI-MS *m/z* 413.2158 (calcd for C$_{19}$H$_{34}$O$_8$Na [M + Na]$^+$, 413.2146).

Lippianoside E (**5**): White powder; $[\alpha]_D^{25}$ −87.0° (*c* = 0.20, MeOH); UV (MeOH) λ_{max} (log ε) 229 (3.62); IR (KBr) ν_{max} 3350, 2915, 2848, 1665, 1405, 1248, 1070, 1070, 1036 cm^{-1}; ^{1}H- and ^{13}C-NMR (DMSO-*d$_6$*) data see Table 5; Positive-ion mode HR-Q-TOF-ESI-MS *m/z* 425.1720 (calcd for C$_{19}$H$_{30}$O$_9$Na [M + Na]$^+$, 425.1782).

Acid Hydrolysis of **1–5**: A solution of compounds **1–5** (each 2.0 mg) in 1 M HCl (1.0 mL) was heated under reflux for 3 h. After cooling, the reaction mixture was extracted with EtOAc. The aqueous layer was subjected to HPLC analysis under the following conditions, respectively: HPLC column, Kaseisorb LC NH$_2$-60-5, 4.6 mm i.d. 250 mm (Tokyo Kasei Co., Ltd., Tokyo, Japan); detection, optical rotation (Shodex OR-2 (Showa Denko Co., Ltd., Tokyo, Japan); mobile phase, CH$_3$CN–H$_2$O (75:25, *v/v*); flow rate 0.7 mL/min. Identification of L-rhamnose (i) from **3**; and D-glucose (ii) from **1–5** present in the aqueous layer was carried out by comparison of its retention time and optical rotation with those of authentic sample, *t*$_R$: (i) 7.5 min (L-rhamnose, negative optical rotation); and (ii) 14.1 min (D-glucose, positive optical rotation).

Enzymatic hydrolysis of **4** with β-glucosidase: A solution of **4** (7.0 mg) in H$_2$O (2.5 mL) was treated with β-glucosidase (5.0 mg, Almond, Sigma-Aldrich, Co., St. Louis, MO, USA), and the solution was stirred at 37 °C for 20 h. After cooling, the reaction mixture was extracted with EtOAc. The EtOAc solvent was removed under reduced pressure to give (3*S*,4*R*,9*R*)-3,4,9-trihydroxymegastigman-5-ene.

Mitochondrial oxidative stress protective effects assay: Antimycin A was used to induce mitochondrial oxidative stress. Briefly, L6 cells (Cell Resource Center, IBMS, CAMS/PUMC, Beijing, China) were plated at a density of 5×10^4 cells/well in Dulbecco's modified Eagle's medium (DMEM, Thermo Scientific, Logan, UT, USA) supplemented with 10% calf serum (Thermo Scientific) in a 96-well plate and were incubated at 37 °C for 24 h. Cells were treated with or without 30 μM sample DMSO solution (final DMSO concentration was 0.5%). One hour later, medium was removed and 20 μg/mL antimycin A (Sigma Co. Ltd.) in 200 μL DMEM was added to each well. The MTT assay was performed 24 h later to detect the cell survival rate. Resveratrol was used as positive control.

TG accumulation inhibitory effects assay: The hepatic cell line HepG2 (IBMS, CAMS/PUMC, Beijing, China) was maintained in high glucose Minimum Essential Medium (MEM) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin–streptomycin under a humidified atmosphere of 5% CO$_2$ in air. After growth to 80% confluence, cells were seeded at 4×10^4 cells/mL on a 48-well dish. After 24 h incubation, the medium was switched to high glucose MEM and supplemented with 10% FBS and 0.2 mM oleic acid sodium salt, together with sample DMSO solution (final concentration

of DMSO was less than 0.1%). After 48 h incubation, the amount of intracellular triglycerides was determined with a Triglycerides kit (BioSino Bio-technology and Science Inc., Beijing, China) after cell lysis. Orlistat was used as positive control.

Statistical analysis: Values are expressed as mean ± SD. Analyses on the grouped data were performed using SPSS 11.0. Significant differences between means were evaluated by one-way analysis of variance (ANOVA) and Tukey's Studentized range test was used for *post hoc* evaluations. A *p* value of <0.05 was considered to indicate statistical significance.

4. Conclusions

In summary, five new, along with 26 known, compounds were identified from the 95% EtOH extract of *L. triphylla* aerial parts collected from Rwanda, Africa. Their structures were elucidated by chemical and spectroscopic methods. Among the known compounds, 11, and 17–30 were isolated from *Lippia* genus for the first time. In addition, 12, 13, and 16 were obtained from this species for the first time. All compounds were tested for their antioxidant and triglyceride accumulation inhibition effects in L6 cells and HepG2 cells, respectively. The results indicated that, except for 1, 2 and 20, all compounds isolated from *L. triphylla* displayed significant protective effects against antimycin A-induced L6 cell injury at 30 μM, and 21 showed the strongest protective activity. Meanwhile, 1–11, 14–19, and 23–26 displayed inhibitory effects on TG accumulation in FFA induced HepG2 cells. Our study provides partial scientific support for the development and utilization of *L. triphylla* aerial parts.

Author Contributions: Yi Zhang and Tao Wang designed the research and wrote the manuscript; Yue Chen, Shiyu Wang, Tingting Wang, Yongzhe Dong, and Lu Qu performed the experimental work; and Nan Li perfected the language. All authors discussed, edited and approved the final version.

Conflicts of Interest: The authors declare no conflict of interest.

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Sample Availability: Samples of all the compounds are available from the authors.