Supporting Information

***Rec. Nat. Prod*. 17:5 (2023) 878-895**

Comparative Anti-dengue Activities of Ethanolic and Supercritical Extracts of *Lippia origanoides* Kunth: *in-vitro* and *in-silico* analyses

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Table S1: Exact mass characteristic positive ions of compounds identified in the ethanolic extract of *Lippia origanoides*

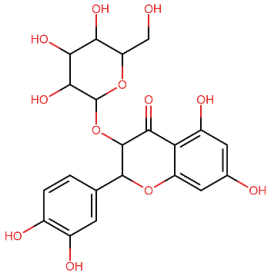
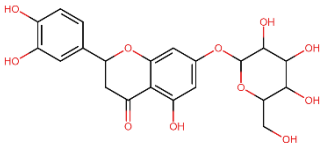
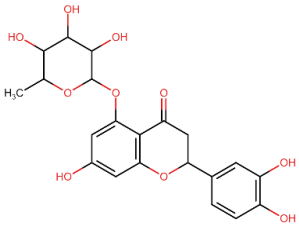
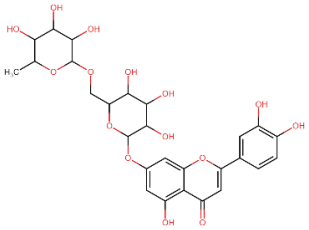
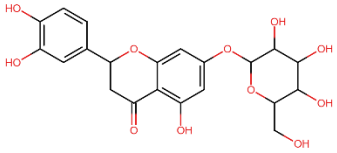
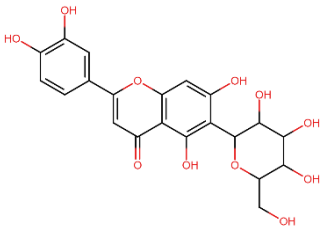
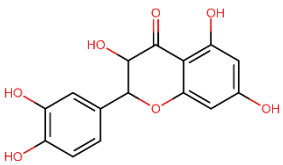
Name	Fragment type	Fragment formula	*m/z* (%)	
Taxifolin glucoside	$[(M+H)-C_6H_{10}O_5]^+$	$C_{15}H_{13}O_7$	305.06561 (44)	a, b, c
	$[(M+H)-C_6H_{10}O_5-H_2O]^+$	$C_{15}H_{11}O_6$	287.05496 (8)	
	$[(M+H)-C_6H_{10}O_5-C_8H_8O_3]^+$	$C_7H_5O_4$	153.01832 (72)	
Quercetin glucoside	$[(M+H)-C_6H_{10}O_5]^+$	$C_{15}H_{11}O_7$	303.04971 (100)	a, b, c
	$[(M+H)-C_6H_{10}O_5-H_2O]^+$	$C_{15}H_9O_6$	285.03970 (1)	
	$[(M+H)-C_6H_{10}O_5-C_8H_6O_3]^+$	$C_7H_5O_4$	153.01811 (1)	
Eriodictyol rhamnoside	$[(M+H)-C_6H_{10}O_4]^+$	$C_{15}H_{13}O_6$	289.07086 (23)	a, b, c
	$[(M+H)-C_6H_{10}O_4-H_2O]^+$	$C_{15}H_{11}O_5$	271.05937 (1)	
	$[(M+H)-C_6H_{10}O_4-H_2O-C_6H_4O_2]^+$	$C_9H_7O_3$	163.03883 (7)	
	$[(M+H)-C_6H_{10}O_4-C_8H_8O_2]^+$	$C_7H_5O_4$	153.01846 (15)	
Luteolin rutinoside	$[(M+H)-C_6H_{10}O_4]^+$	$C_{21}H_{21}O_{11}$	449.10864 (6)	a, b, c
	$[(M+H)-C_6H_{10}O_4-C_6H_{10}O_5]^+$	$C_{15}H_{11}O_6$	287.05530 (30)	
	$[(M+H)-C_6H_{10}O_4-C_6H_{10}O_5-C_8H_6O_2]^+$	$C_7H_5O_4$	153.01832 (1)	
Eriodictyol glucoside	$[(M+H)-C_6H_{10}O_5]^+$	$C_{15}H_{13}O_6$	289.07062 (100)	a, b, c
	$[(M+H)-C_6H_{10}O_5-H_2O]^+$	$C_{15}H_{11}O_5$	271.05969 (1)	
	$[(M+H)-C_6H_{10}O_5-C_8H_8O_2]^+$	$C_7H_5O_4$	153.01810 (7)	
Luteolin glucoside	$[(M+H)-C_6H_{10}O_5]^+$	$C_{15}H_{11}O_6$	287.05515 (100)	a, b, c
	$[(M+H)-C_6H_{10}O_5-C_2H_2O]^+$	$C_{13}H_9O_5$	245.04386 (1)	
	$[(M+H)-C_6H_{10}O_5-C_6H_4O_2]^+$	$C_9H_7O_4$	179.03411 (1)	
	$[(M+H)-C_6H_{10}O_5-C_8H_6O_2]^+$	$C_7H_5O_4$	153.01846 (6)	
Taxifolin	$[(M+H)-H_2O]^+$	$C_{15}H_{11}O_6$	287.05487 (37)	a, b, c
	$[(M+H)-H_2O-CO]^+$	$C_{14}H_{11}O_5$	259.06003 (1)	
	$[(M+H)-H_2O-2CO]^+$	$C_{13}H_{11}O_4$	231.06512 (41)	
	$[(M+H)-2H_2O-2CO]^+$	$C_{13}H_9O_3$	213.05463 (14)	
	$[(M+H)-C_8H_8O_3]^+$	$C_7H_5O_4$	153.01826 (72)	
Galangin glucoside	$[(M+H)-C_6H_{10}O_5]^+$	$C_{15}H_{11}O_5$	271.06012 (70)	a, b, c
	$[(M+H)-C_6H_{10}O_5-C_2H_2O]^+$	$C_{13}H_9O_4$	229.04935 (7)	
	$[(M+H)- C_6H_{10}O_5-$	$C_9H_7O_3$	163.03894 (3)	

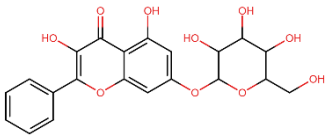
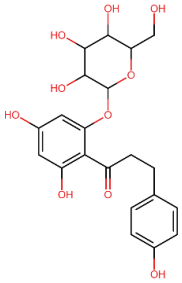
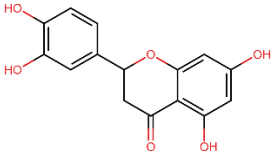
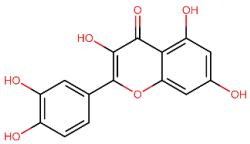
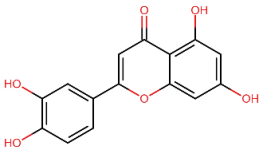
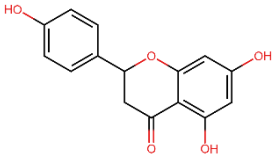
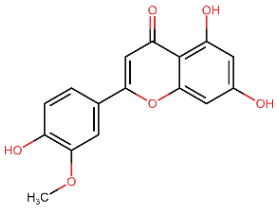
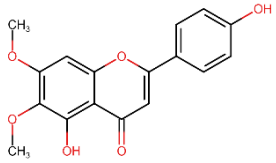
	$C_6H_4O_2]^+$			
	$[(M+H)-C_6H_{10}O_5-C_8H_6O]^+$	$C_7H_5O_4$	153.01825 (8)	
Phloridzin	$[(M+H)-C_6H_{10}O_5]^+$	$C_{15}H_{15}O_5$	275.09131 (18)	a, b, c
	$[(M+H)-C_6H_{10}O_5-H_2O]^+$	$C_{15}H_{13}O_4$	257.08081 (5)	
	$[(M+H)-C_6H_{10}O_5-C_7H_6O]^+$	$C_8H_9O_4$	169.04961 (6)	
Eriodictyol	$[(M+H)-H_2O]^+$	$C_{15}H_{11}O_5$	271.05969 (4)	b, c, d
	$[(M+H)-H_2O-CO]^+$	$C_{14}H_{11}O_4$	243.05995 (0.3)	
	$[(M+H)-C_6H_6O_2]^+$	$C_9H_7O_4$	179.03374 (9)	
	$[(M+H)-H_2O-C_6H_4O_2]^+$	$C_9H_7O_3$	163.03882 (79)	
	$[(M+H)-C_8H_8O_2]^+$	$C_7H_5O_4$	153.01810 (100)	
Quercetin	$[(M+H)-H_2O]^+$	$C_{15}H_9O_6$	285.03787 (1)	b, c, d
	$[(M+H)-2CO]^+$	$C_{13}H_{11}O_5$	247.06012 (1)	
	$[(M+H)-H_2O-2CO]^+$	$C_{13}H_9O_4$	229.04951 (1)	
	$[(M+H)-C_8H_6O_3]^+$	$C_7H_5O_4$	153.01836 (8)	
Luteolin	$[(M+H)-C_2H_2O]^+$	$C_{13}H_9O_5$	245.04393 (0.6)	b, c, d
	$[(M+H)-C_6H_4O_2]^+$	$C_9H_7O_4$	179.03409 (1)	
	$[(M+H)-C_8H_6O_2]^+$	$C_7H_5O_4$	153.01822 (39)	
	$[(M+H)-C_7H_4O_4]^+$	$C_8H_7O_2$	135.04424 (12)	
Naringenin	$[(M+H)-H_2O]^+$	$C_{15}H_{11}O_4$	255.06464 (1)	b, c, d
	$[(M+H)-C_2H_2O]^+$	$C_{13}H_{11}O_4$	231.06487 (1)	
	$[(M+H)-C_8H_8O]^+$	$C_7H_5O_4$	153.01810 (100)	
	$[(M+H)-C_6H_6O]^+$	$C_9H_7O_4$	179.03371 (1)	
	$[(M+H)-3C_2H_2O]^+$	$C_9H_7O_2$	147.04393 (65)	
Chrysoeriol	$[(M+H)-CH_3]^+$	$C_{15}H_{10}O_6$	286.04718 (100)	
	$[(M+H)-CH_3-CO]^+$	$C_{14}H_{10}O_5$	258.05222 (1)	a, b, c
	$[(M+H)-C_9H_8O_2]^+$	$C_7H_5O_4$	153.01855 (4)	
	$[(M+H)-C_7H_4O_4]^+$	$C_9H_9O_2$	149.05977 (1)	
	$[(M+H)-C_8H_6O_5]^+$	C_8H_7O	119.04939 (1)	
Cirsimaritin	$[(M+H)-CH_3]^+$	$C_{16}H_{12}O_6$	300.06265 (19)	a, b, c
	$[(M+H)-2CH_3]^+$	$C_{15}H_9O_6$	285.03961 (1)	
	$[(M+H)-CH_3-H_2O]^+$	$C_{16}H_{10}O_5$	282.05215 (94)	
	$[(M+H)-CH_3-H_2O-CO]^+$	$C_{15}H_{10}O_4$	254.05727 (100)	
	$[(M+H)-CH_3-H_2O-2CO]^+$	$C_{14}H_{10}O_3$	226.06232 (6)	
	$[(M+H)-C_8H_6O]^+$	$C_9H_9O_5$	197.04445 (1)	
Sakuranetin	$[(M+H)-C_2H_2O]^+$	$C_{14}H_{13}O_4$	245.08090 (0.15)	a, b, c
	$[(M+H)-C_6H_6O]^+$	$C_{10}H_9O_4$	193.04971 (0.1)	
	$[(M+H)-C_8H_8O]^+$	$C_8H_7O_4$	167.03386 (50)	
	$[(M+H)-C_7H_8O_3]^+$	$C_9H_7O_2$	147.04402 (36)	
Pinocembrin	$[(M+H)-H_2O]^+$	$C_{15}H_{11}O_3$	239.06998 (1)	b, c, d
	$[(M+H)-C_2H_2O]^+$	$C_{13}H_{11}O_3$	215.07010 (3)	
	$[(M+H)-C_6H_6]^+$	$C_9H_7O_4$	179.03415 (3)	
	$[(M+H)-C_8H_8]^+$	$C_7H_5O_4$	153.01816 (100)	

	$[(M+H)-3C_2H_2O]^+$	C_9H_7O	131.04918 (67)	
Trimethylated tricetin	$[(M+H)-CH_3]^+$	$C_{17}H_{14}O_7$	330.07339 (12)	a, b, c
	$[(M+H)-2CH_3]^+$	$C_{16}H_{11}O_7$	315.05063 (10)	
	$[(M+H)-CH_3-H_2O]^+$	$C_{17}H_{12}O_6$	312.06262 (18)	
	$[(M+H)-CH_3-H_2O-CO]^+$	$C_{16}H_{12}O_5$	284.06769 (20)	
	$[(M+H)-C_{11}H_{12}O_3]^+$	$C_7H_5O_4$	153.01817 (44)	
Galangin	$[(M+H)-H_2O]^+$	$C_{15}H_9O_4$	253.04956 (10)	b, c, d
	$[(M+H)-C_2H_2O]^+$	$C_{13}H_9O_4$	229.04935 (8)	
	$[(M+H)-C_6H_4O_2]^+$	$C_9H_7O_3$	163.03894 (5)	
	$[(M+H)-C_8H_6O]^+$	$C_7H_5O_4$	153.01825 (26)	
	$[(M+H)-C_6H_6O_3]^+$	$C_9H_5O_2$	145.02840 (1)	
Methylated Galangin	$[(M+H)-CH_3]^+$	$C_{15}H_{10}O_5$	270.05219 (100)	
	$[(M+H)-CH_3-CO]^+$	$C_{14}H_{10}O_4$	242.05734 (23)	b, c
	$[(M+H)-CH_3-CO-HCO]^+$	$C_{13}H_9O_3$	213.05461 (7)	
	$[(M+H)-C_9H_8O]^+$	$C_7H_5O_4$	153.01830 (35)	

[a] Amount expressed in kaempferol equivalents. [b] Tentative identification based on [M + H] +, reported in literature [1]. [c] Tentative identification based on the study of the fragmentation pattern (ESI + -HRMS) and literature [2]. [d] Confirmatory identification based on mass spectrum (ESI + -HRMS) and by comparison with the mass spectrum and tR of the certified reference substance.

Table S2: Flavonoids selected for molecular docking analyses

N°	Name	Structural formula	PubChem accession number
1	Taxifolin glucoside		14187089
2	Quercetin glucoside		5280804
3	Eriodictyol rhamnoside		42607967
4	Luteolin rutinoside		44258082
5	Eriodictyol glucoside		13254473
6	Luteolin glucoside		114776
7	Taxifolin		439533

8	Galangin glucoside		44258724
9	Phloridzin		6072
10	Eriodictyol		440735
11	Quercetin		5280343
12	Luteolin		5280445
13	Naringenin		932
14	Chrysoeriol		5280666
15	Cirsimaritin		188323

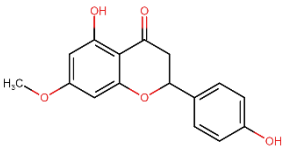
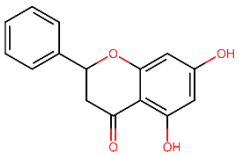
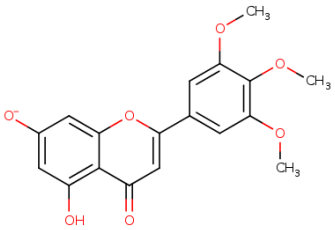
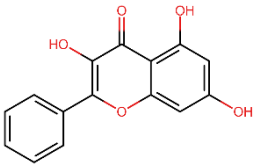
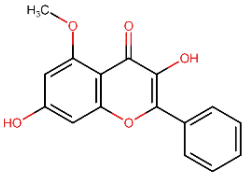
16	Sakuranetin		73571
17	Pinocembrin		68071
18	Trimethylated tricetin		46878517
19	Galangin		5281616
20	Methylaed Galangin		5488105

Table S3: Flavonoids of the extracts analyzed in this study with *in silico* anti-DENV activity reported in other studies

Flavonoid	Target protein	Kcal / mol (software)	Reference
Galangin	Envelope (E)	-8.6 (AutoDock Vina)	[7]
	Polymerase NS5, domain RdRp	-8.0 (Maestro Schrödinger)	[9]
		-8.0 (Maestro Schrödinger)	[5]
Luteolin	Protease NS3/NS2B	-8.3 (AutoDock Vina)	[3]
		-7.7 (PyRx software)	[6]
Luteolin glycoside	Protease NS3/NS2B	-8.8 (AutoDock Vina)	[3]
Naringenin	Envelope (E)	-8.1 (AutoDock Vina)	[9]
	Protease NS3/NS2B	-7.6 (AutoDock Vina)	[3]
	Polymerase NS5, domain RdRp	-5.6 (Maestro Schrödinger)	[5]
Phloridzin	Polymerase NS5, full-length	-11.1 (Glide 6.9)	[10]
Pinocembrin	Envelope (E)	-8.0 (AutoDock VinaXB)	[4]
Quercetin	Envelope (E)	-8.6 (AutoDock Vina)	[8]
	Polymerase NS5, domain RdRp	-7.8 (Glide v6.4)	[10]
		-8.0 (Maestro Schrödinger)	[5]

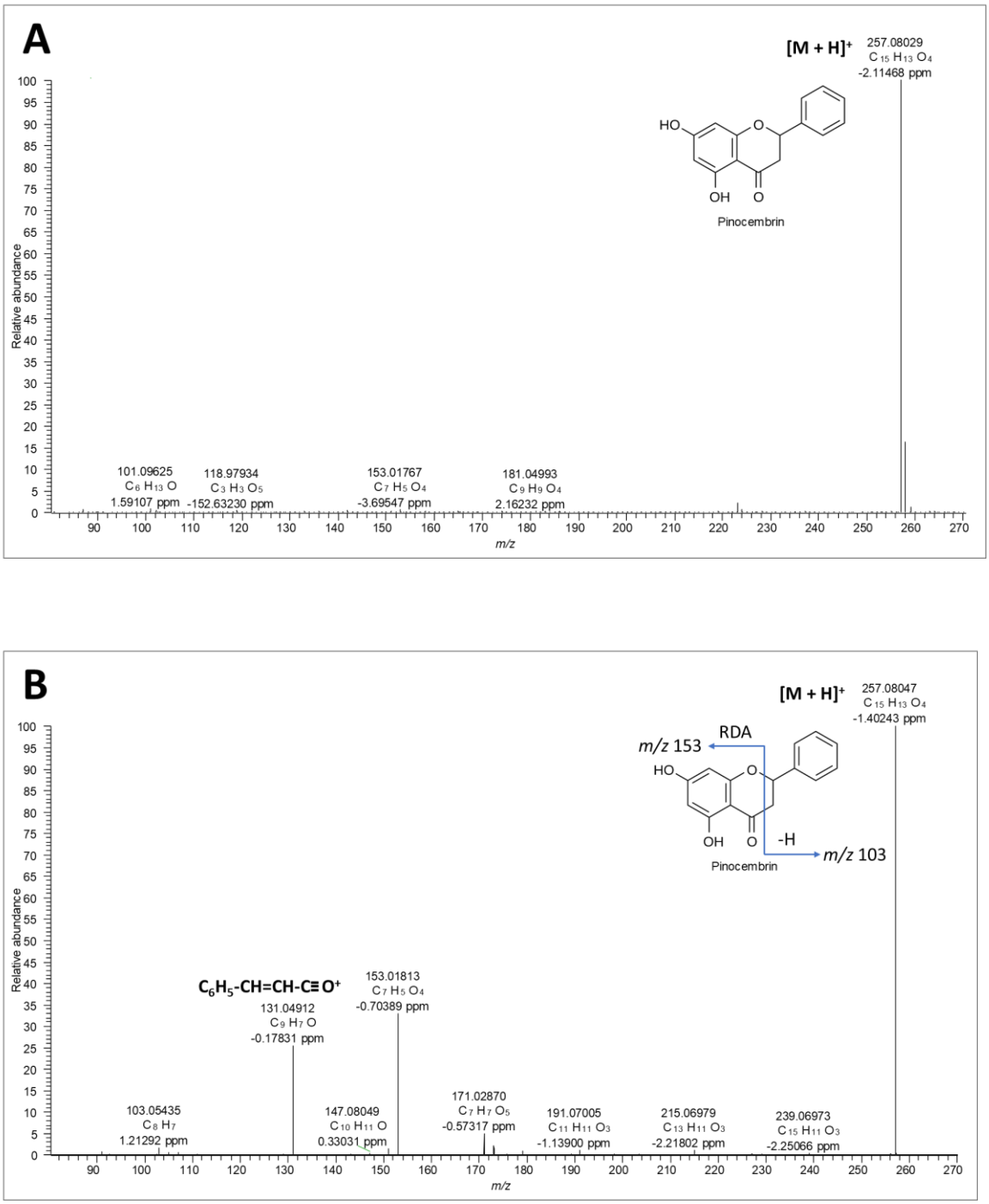


Figure S1: An example mass spectrum of pinocembrin obtained by ESI (+)-HRMS (Orbitrap). Vcap +3,5 kV; HESI (Heated-electrospray ionization interface) temperature – 350 °C. **A.** Full scan; **B.** HCD (Higher-energy collision dissociation cell), 30 eV. Collision gas – nitrogen. Pinocembrin molecule suffers retro-Diels--Alder (RDA) transposition, followed by the formation of product-ions $[(M + H) – CH_2=CH-C_6H_5]^+$ at *m/z* 153,01813 and $C_8H_7^+$ at *m/z* 103,05435, as well as a product-ion $C_6H_5CH=CHCO^+$ at *m/z* 131.

References

[1] E.E. Stashenko, J.R. Martínez, M.P. Cala, D.C. Durán and D. Caballero (2013). Chromatographic and mass spectrometric characterization of essential oils and extracts from *Lippia* (Verbenaceae) aromatic plants, *J. Sep. Sci*. **36**, 192–202.

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