Supplementary Information

Metabolomics-Based Discovery of Biomarkers with Cytotoxic Potential in Extracts of *Myracrodruon urundeuva*

***Caio B. Castro,[a] Licia R. Luz,[b,c] Jhonyson A. C. Guedes,[c] Diogo D. Porto,[d] Maria Francilene S. Silva,[e] Gisele S. Silva,[c] Paulo R. V. Ribeiro,[c] Kirley M. Canuto,[c] Edy S. Brito,[c] Dávila S. Zampieri,[f] Claúdia Ó Pessoa[e] and Guilherme J. Zocolo*[*,c]**

[a]*Departamento de Química, Universidade Federal de São Carlos, 13565-905 São Carlos-SP, Brazil*

[b]*Departamento de Química Analítica e Físico-Química, Universidade Federal do Ceará, Av. Humberto Monte, s/n, Pici, 60455-760 Fortaleza-CE, Brazil*

[c]*Embrapa Agroindústria Tropical, Rua Dra. Sara Mesquita, 2270, Pici, 60020-181 Fortaleza-CE, Brazil*

[d]*Embrapa Semiárido, Rodovia BR-428, km 152, Zona Rural, 56302-970 Petrolina-PE, Brazil*

[e]*Núcleo de Pesquisa e Desenvolvimento de Medicamentos (NPDM), Universidade Federal do Ceará, Rua Coronel Nunes de Mello, 1000, 60420-275 Fortaleza-CE, Brazil*

[f]*Departamento de Química Orgânica e Inorgânica, Universidade Federal do Ceará, Av. Humberto Monte, s/n, Pici, 60455-760 Fortaleza-CE, Brazil*

*e-mail: guilherme.zocolo@embrapa.br

Table S1. Tentative identification of the secondary metabolites present in the ethanolic extracts of leaf, bark, and branches of *M. urundeuva*

Peak	t_R[a] / min	MS[b] $[M-H]^-$	MS/MS	Error / ppm	Molecular formula	Tentative identification	*M. urundeuva*			Reference
							Leaves	Branch	Bark	
1	0.87	191.0546	173.0456; 127.0416; 93.0355	−5.2	$C_7H_{12}O_6$	quinic acid	+		+	1
2	0.92	191.0489	87.0094; 85.0300	−4.2	$C_{14}H_8O$	n.i[c]	+			–
3	0.98	133.0129	115.0042	−6.0	$C_4H_6O_5$	malic acid			+	1
4	0.98	377.0799	209.0308; 191.0462; 133.0132; 115.0336; 85.0308	8.3	$C_{12}H_{18}O_{11}$	n.i[c]	+			–
5	0.98	191.0192	111.0079	−2.1	$C_6H_8O_7$	citric acid		+		2
6	0.98	343.0654	191.0497; 169.0123; 125.0247	−3.2	$C_{14}H_{16}O_{10}$	galloyl quinic acid isomer	+			1, 3
7	1.56	331.0666	169.0135; 89.0265	0.3	$C_{13}H_{16}O_{10}$	glucose galloyl			+	4
8	1.75	343.0689	191.0537; 169.0145; 125.0258	7.0	$C_{14}H_{16}O_{10}$	galloyl quinic acid isomer			+	1, 3

Table S1. Tentative identification of the secondary metabolites present in the ethanolic extracts of leaf, bark, and branches of *M. urundeuva* (cont.)

Peak	t_R[a] / min	MS[b] $[M - H]^-$	MS/MS	Error / ppm	Molecular formula	Tentative identification	*M. urundeuva*			Reference
							Leaves	Branch	Bark	
9	2.24	305.0653	125.0232	−2.6	$C_{15}H_{14}O_7$	gallocatechin / epigallocatechin			+	5, 6
10	2.76	483.0813	331.0816; 169.0153	7.9	$C_{20}H_{20}O_{14}$	digalloyl hexoside			+	1
11	2.95	321.0259	169.0126; 125.0230	3.7	$C_{14}H_{10}O_9$	digallic acid	+			1
12	3.00	353.0896	191.0493; 127.0390	6.5	$C_{16}H_{18}O_9$	chlorogenic acid		+	+	analytical standard
13	3.25	951.0764	933.0729; 300.9977	2.5	$C_{41}H_{28}O_{27}$	geraniin	+			7
14	3.30	633.0744	463.0564; 300.9948	2.5	$C_{27}H_{22}O_{18}$	corilagin	+	+		7 analytical standard
15	3.48	457.0768	305.0664; 169.0125; 125.0248	0.0	$C_{22}H_{18}O_{11}$	epigallocatechin-3-*O*-gallate			+	6
16	3.50	337.0910	191.0525; 163.0423; 93.0346	−3.9	$C_{16}H_{18}O_8$	5-*p*-courmaroil quinic acid		+		8

Table S1. Tentative identification of the secondary metabolites present in the ethanolic extracts of leaf, bark, and branches of *M. urundeuva* (cont.)

Peak	t_R[a] / min	MS[b] $[M-H]^-$	MS/MS	Error / ppm	Molecular formula	Tentative identification	*M. urundeuva*			Reference
							Leaves	Branch	Bark	
17	3.67	739.1738	561.1341; 449.0960; 305.0672; 289.0721; 191.0554; 169.0134	2.2	$C_{32}H_{36}O_{20}$	n.i[c]		+		–
18	3.77	367.1048	191.0548	5.2	$C_{17}H_{20}O_9$	5-*O*-feruloyl quinic acid		+		8
19	3.78	953.0887	300.9953; 169.0121	−0.9	$C_{41}H_{30}O_{27}$	geraniinic acid	+			9
20	3.86	785.0815	300.9965; 169.0135	−2.8	$C_{34}H_{26}O_{22}$	n.i[c]	+			–
21	3.94	787.1043	635.0976; 483.0720; 169.0121	6.2	$C_{34}H_{28}O_{22}$	tetra-*O*-galloyl hexoside	+			1
22	4.03	357.0596	231.0304; 217.0113; 177.0165; 125.0250	−3.9	$C_{18}H_{14}O_8$	n.i[c]			+	–
23	4.04	609.1486	300.9949	4.9	$C_{27}H_{30}O_{16}$	rutin	+			1
24	4.08	497.1338	301.0029	8.6	$C_{22}H_{26}O_{13}$	n.i[c]		+		–

Table S1. Tentative identification of the secondary metabolites present in the ethanolic extracts of leaf, bark, and branches of *M. urundeuva* (cont.)

Peak	t_R[a] / min	MS[b] $[M - H]^-$	MS/MS	Error / ppm	Molecular formula	Tentative identification	*M. urundeuva*			Reference
							Leaves	Branch	Bark	
25	4.10	497.1295	313.0569; 217.0141; 169.0131	−2.2	$C_{22}H_{25}O_{13}$	n.i[c]			+	–
26	4.20	463.0867	301.0127	−2.2	$C_{21}H_{20}O_{12}$	quercetin 3-*O*-galactoside	+			3
27	4.22	477.0648	301.0137; 151.0047	−4.4	$C_{21}H_{18}O_{13}$	quercetin 3-*O*-glucuronide	+			3
28	4.23	463.0881	301.0102	0.9	$C_{21}H_{20}O_{12}$	quercetin 3-*O*-glucoside	+			3
29	4.24	467.0902	357.0596; 217.0108	−3.6	$C_{31}H_{16}O_5$	gallic acid derivative I			+	10
30	4.28	939.1104	769.0933; 617.0834; 169.0125	0.0	$C_{41}H_{32}O_{26}$	pentagalloyl hexoside	+			3
31	4.28	939.1196	769.0943; 467.1019; 357.0903	3.6	$C_{34}H_{36}O_{31}$	n.i[c]		+		–
32	4.42	433.0777	301.0091; 300. 0276	1.4	$C_{20}H_{18}O_{11}$	quercetin 3-*O*-xyloside	+			11
33	4.50	433.0779	301.0098	1.8	$C_{20}H_{18}O_{11}$	quercetin 3-*O*-arabinopyranoside	+			11
34	4.56	433.0769	301.0157; 300.0251	−0.5	$C_{20}H_{18}O_{11}$	quercetin 3-*O*-arabinofuranoside	+			11

Table S1. Tentative identification of the secondary metabolites present in the ethanolic extracts of leaf, bark, and branches of *M. urundeuva* (cont.)

Peak	t_R[a] / min	MS[b] $[M-H]^-$	MS/MS	Error / ppm	Molecular formula	Tentative identification	*M. urundeuva*			Reference
							Leaves	Branch	Bark	
35	4.57	1091.1266	939.1158; 769.0972	4.9	$C_{48}H_{36}O_{30}$	hexagalloyl hexoside	+			3
36	4.71	341.0647	217.0136; 189.0191; 169.0123	−4.1	$C_{18}H_{14}O_7$	n.i[c]		+		–
37	4.76	451.1027	341.0663; 315.0154; 299.9924	−0.4	$C_{24}H_{20}O_9$	n.i[c]		+		–
38	4.79	461.0719	315.0167; 299.9943; 169.0120	−0.2	$C_{21}H_{18}O_{12}$	isorhamnetin-*O*-rhamnoside	+			10
39	4.94	615.0977	469,0454; 317.0319; 169.0127	−1.5	$C_{28}H_{24}O_{16}$	myricitrin 2''-*O*-gallate	+			1
40	5.03	545.0521	469.0479; 393.0441; 169.0124	−8.4	$C_{24}H_{18}O_{15}$	dihydroxybenzoic acetate-digallate	+			1
41	5.08	619.1078	467.0990; 449.0925; 357.0618	−1.6	$C_{31}H_{24}O_{14}$	gallic acid derivative II			+	10

Table S1. Tentative identification of the secondary metabolites present in the ethanolic extracts of leaf, bark, and branches of *M. urundeuva* (cont.)

Peak	t_R[a] / min	MS[b] $[M-H]^-$	MS/MS	Error / ppm	Molecular formula	Tentative identification	*M. urundeuva*			Reference
							Leaves	Branch	Bark	
42	5.18	629.1295	519.0919; 467.1021; 169.0126	−1.3	$C_{33}H_{26}O_{13}$	n.i[c]			+	–
43	5.12	621.0590	469.5466; 393.0484; 169.0135	2.4	$C_{22}H_{22}O_{21}$	valoneic acid-galloyl lactone	+			1
44	5.26	585.0914	301.0345	5.8	$C_{27}H_{22}O_{15}$	quercetin galloyl pentoside	+			3
45	5.34	603.1172	341.0698; 323.0532; 169.0111	5.5	$C_{31}H_{24}O_{13}$	n.i[c]		+		–
46	5.44	599.0995	301.0322	−7.0	$C_{28}H_{24}O_{15}$	quercitrin 2” *O*-gallate isomer I	+			1
47	5.44	603.1172	341.0678; 297.0623; 217.0160	6.8	$C_{31}H_{24}O_{13}$	n.i[c]		+		–
48	5.45	349.0540	198.0496; 197.0422; 169.0128; 124.0163	−5.7	$C_{16}H_{14}O_9$	ethyl 2,4-dihydroxy-3-(3,4,5-trihydroxybenzoyl) oxybenzoate	+			4
49	5.51	599.1052	301.0328	2.5	$C_{28}H_{24}O_{15}$	quercitrina 2” *O*- gallate isomer II	+			1

Table S1. Tentative identification of the secondary metabolites present in the ethanolic extracts of leaf, bark, and branches of *M. urundeuva* (cont.)

Peak	t_R[a] / min	MS[b] $[M - H]^-$	MS/MS	Error / ppm	Molecular formula	Tentative identification	*M. urundeuva*			Reference
							Leaves	Branch	Bark	
50	5.59	447.0757	295.0283; 169.0137	9.2	$C_{24}H_{16}O_9$	n.i[c]		+		–
51	5.78	193.0869	178.0597; 163.0395	2.1	$C_{11}H_{14}O_3$	n.i[c]		+		–
52	5.93	501.0681	349.0569; 197.0431	2.4	$C_{23}H_{18}O_{13}$	ethyl β-trigallate	+			4
53	5.97	523.1057	467.0979; 387.0932; 357.0617; 251.0755; 169.0178	5.4	$C_{30}H_{20}O_9$	urundeuvine B isomer I			+	12
54	6.12	525.1203	447.0691; 389.1017; 371.0922; 135.0076	3.2	$C_{30}H_{22}O_9$	urundeuvine A isomer I		+	+	12
55	6.24	525.1195	507.1172; 389.1032; 371.0961; 135.0076	1.7	$C_{30}H_{22}O_9$	urundeuvine A isomer II		+	+	12

Table S1. Tentative identification of the secondary metabolites present in the ethanolic extracts of leaf, bark, and branches of *M. urundeuva* (cont.)

Peak	t_R[a] / min	MS[b] $[M - H]^-$	MS/MS	Error / ppm	Molecular formula	Tentative identification	*M. urundeuva*			Reference
							Leaves	Branch	Bark	
56	6.63	525.1180	389.1053; 371.0939; 135.0079	−1.1	$C_{30}H_{22}O_9$	urundeuvine A isomer III		+	+	12
57	6.74	523.1036	521.0576; 387.0816; 371.0969; 251.0719; 135.0080	1.3	$C_{30}H_{20}O_9$	urundeuvine B isomer II		+	+	12
58	7.27	329.2357	229.1500; 211.1381; 135.0294	8.8	$C_{18}H_{34}O_5$	9,12,13-trihydroxyoctadecaenoic acid		+	+	10
59	7.86	931.3142	513.1505; 325.1795; 255.2356; 175.0410	2.3	$C_{34}H_{60}O_{29}$	n.i[c]		+		−
60	15.35	369.2426	325.2519; 255.2318; 183.0120; 133.0716	−1.1	$C_{24}H_{34}O_3$	anacardic acid (17:3)	+	+		−
61	15.89	345.2429	301.2523	−0.3	$C_{22}H_{34}O_3$	anacardic acid (15:1)	+	+		3
62	16.04	371.2587	327.2703	0.3	$C_{24}H_{36}O_3$	anacardic acid (17:2)		+		3

[a]Retention time; [b]mass spectrometry; [c]not identified.

Table S2. Cytotoxic activities of *M. urundeuva* extracts (at a concentration of 100 μg mL^{-1}) in tumor and non-tumoral cell lines

Selectivity index IC_{50}[a] (non-tumor cells) / IC_{50} (tumor cell)						
	SF-295 (glioblastoma)	PC3 (prostate)	HL-60 (leukemia)	RAJI (leukemia)	HCT-116 (colorectal)	SW-620 (colorectal)
Bark	> 2.6	> 1	> 5.7	> 1.5	> 3.1	> 2.5
Leaves	0.76	> 1	3.0	1.0	1.0	> 1.0

[a]Half maximal inhibitory concentration.

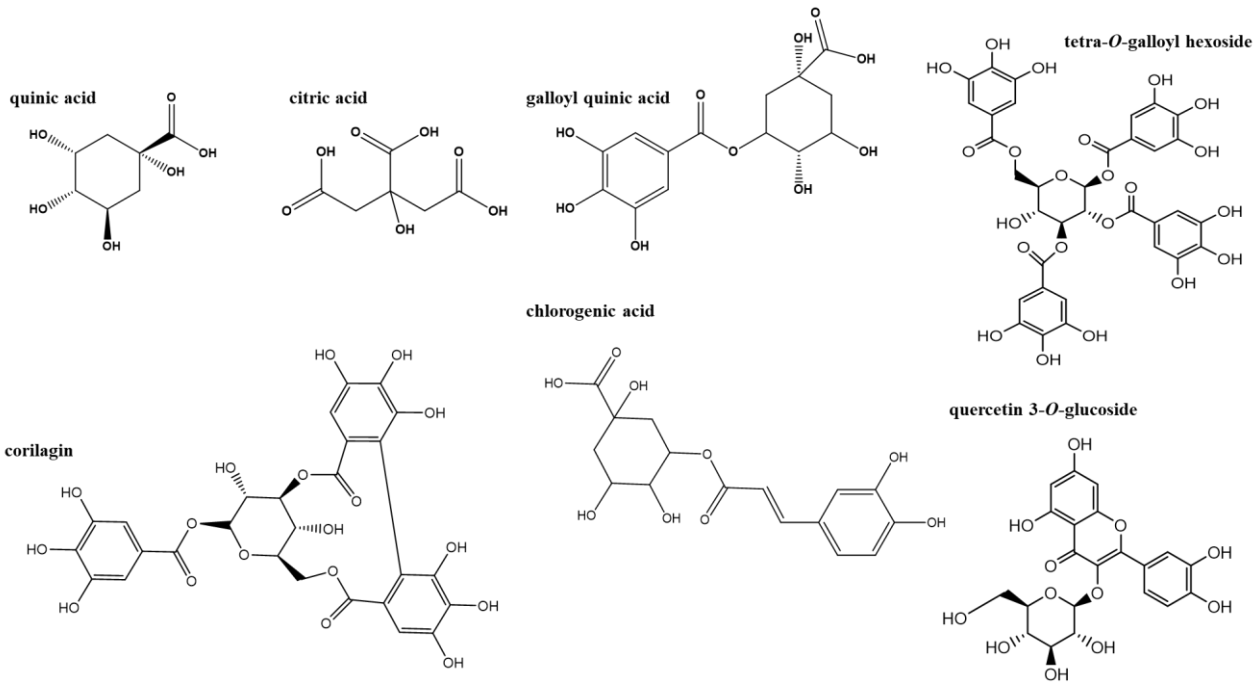

Figure S1. Chemical structures of some tentatively identified compounds.

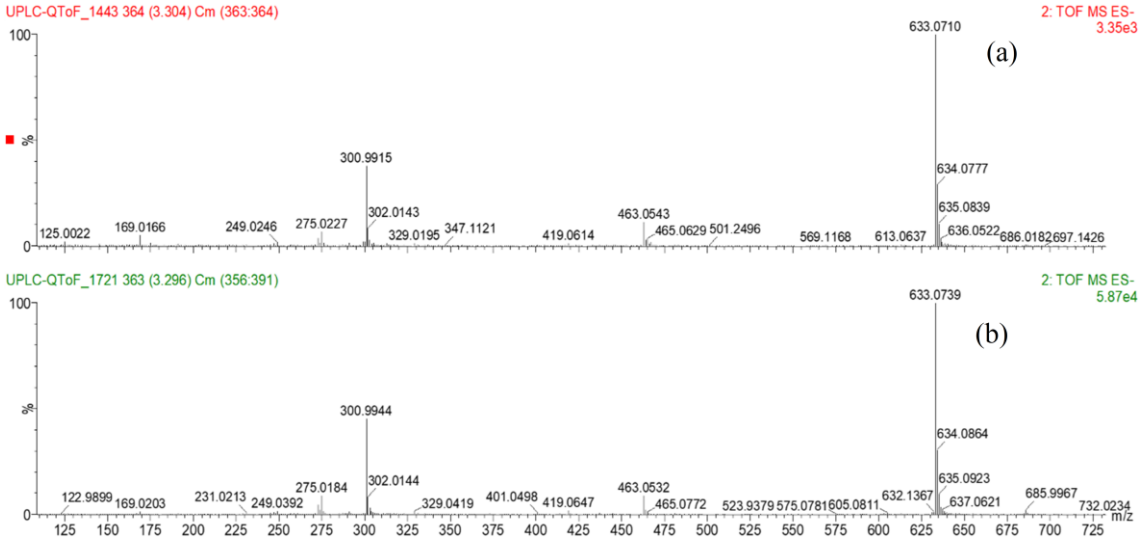

Figure S2. Spectrum in negative ion mode (ESI-MS/MS) of corilagin in the sample (a) and analytical standard (b).

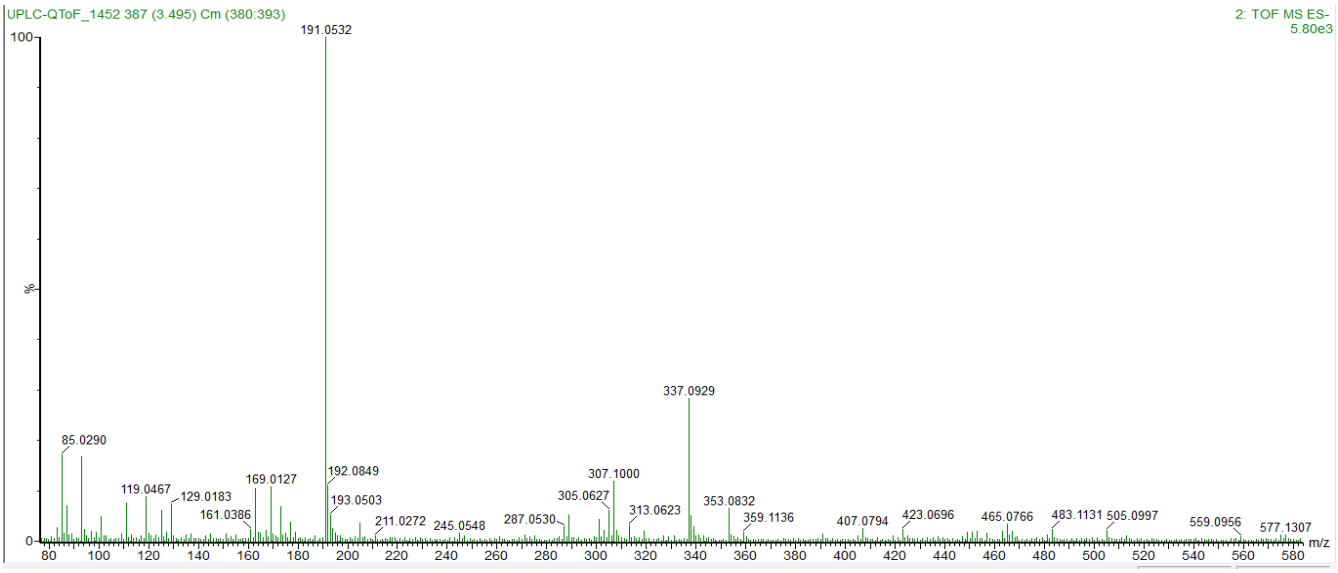

Figure S3. Spectrum in negative ion mode (ESI-MS/MS) of 5-*p*-courmaroil quinic acid.

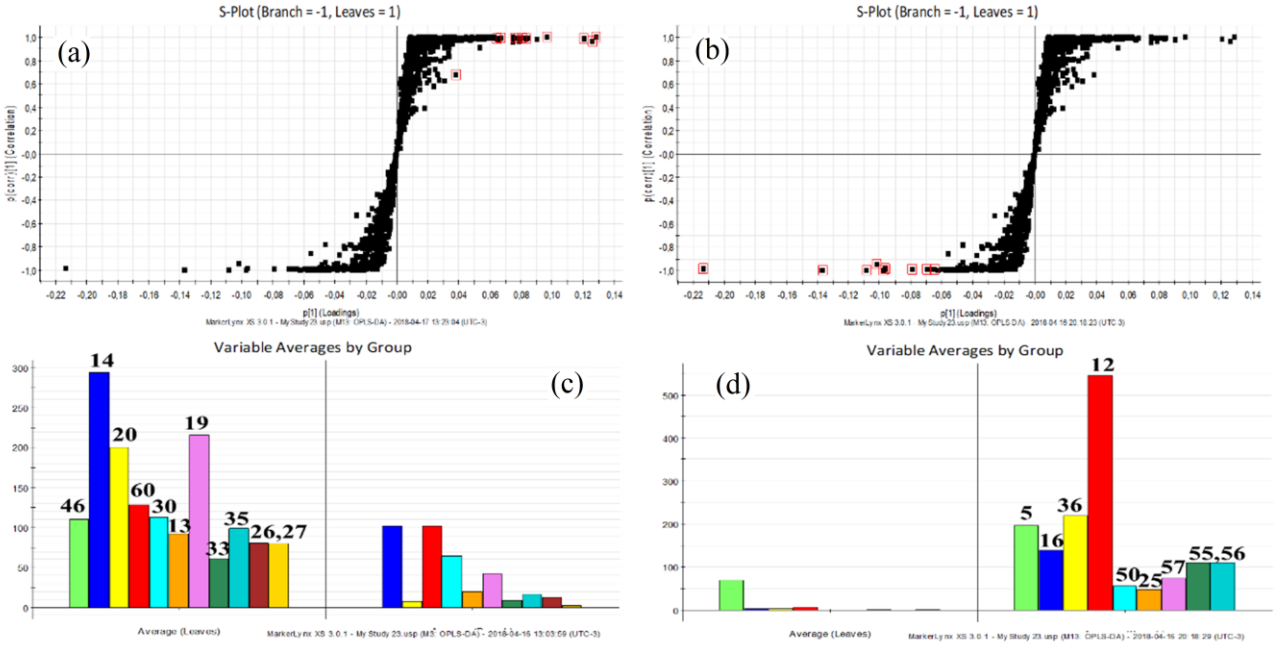

Figure S4. S-Plot of leaf samples (a), branch (b), and bar graph of leaf samples (c) and branch (d) of *M. urundeuva*.

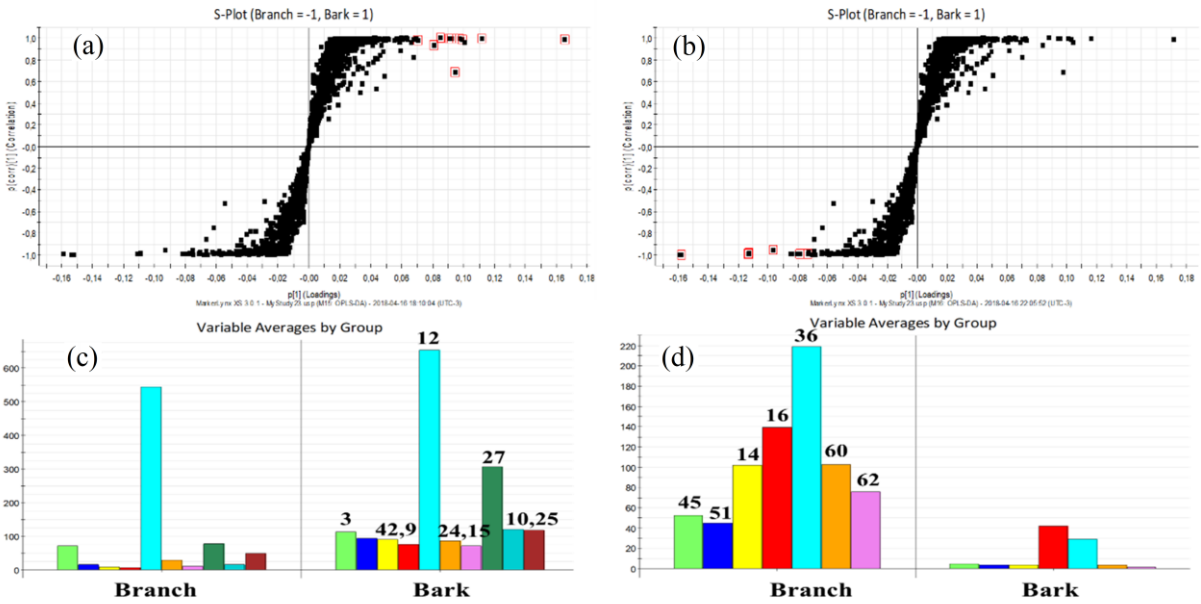

Figure S5. S-Plot of bark samples (a), branch (b), and bar graph of bark samples (c) and branch (d) of *M. urundeuva*.

References

1. Abu-Reidah, I. M.; Ali-Shtayeh, M. S.; Jamous, R. M.; Arráez-Román, D.; Segura-Carretero, A.; *Food Chem.* **2015**, *166*, 179.
2. Ojewole, J. A. O.; *J. Ethnopharmacol.* **2003**, *85*, 217.
3. Erşan, S.; Üstündağ, Ö. G.; Carle, R.; Schweiggert, R. M.; *J. Agric. Food Chem.* **2016**, *64*, 5334.
4. Dorta, E.; González, M.; Lobo, M. G.; Sánchez-Moreno, C.; de Ancos, B.; *Food Res. Int.* **2014**, *57*, 51.
5. Schulze-Kaysers, N.; Feuereisen, M. M.; Schieber, A.; *RSC Adv.* **2015**, *5*, 73301.
6. Miketova, P.; Schram, K. H.; Whitney, J.; Li, M.; Huang, R.; Kerns, E.; Valcic, S.; Timmermann, B. N.; Rourick, R.; Klohr, S.; *J. Mass Spectrom.* **2000**, *869*, 860.
7. Kumar, S.; Chandra, P.; Bajpai, V.; Singh, A.; Srivastava, M.; Mishra, D. K.; Kumar, B.; *Ind. Crops Prod.* **2015**, *69*, 143.
8. Plazonić, A.; Bucar, F.; Males, Z.; Mornar, A.; Nigović, B.; Kujundžić, N.; *Molecules* **2009**, 2466.
9. Pojchaijongdee, N.; Sotanaphun, U.; Limsirichaikul, S.; Poobrasert, O.; *Pharm. Biol.* **2010**, *48*, 740.
10. Galvão, W. R. A.; Braz Filho, R.; Canuto, K. M.; Ribeiro, P. R. V.; Campos, A. R.; Moreira, A. C. O. M.; Silva, S. O.; Mesquita Filho, F. A.; Santos, S. A. A. R.; Melo Jr., J. M. A.; Gonçalves, N. G. G.; Fonseca, S. G. C.; Bandeira, M. A. M.; *J. Ethnopharmacol.* **2018**, *222*, 177.
11. Schieber, A.; Berardini, N.; Carle, R.; *J. Agric. Food Chem.* **2003**, *51*, 5006.
12. Souza, S. M. C.; Aquino, L. C. M.; Milach Jr., A. C.; Bandeira, M. A. M.; Nobre, M. E. P.; Viana, G. S. B.; *Phytother. Res.* **2007**, *21*, 220.