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Phytochemical analysis for ten Peruvian *Mentheae* (*Lamiaceae*) by liquid chromatography associated with high resolution mass spectrometry

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The profile of secondary metabolites in ten members of tribe *Mentheae* (*Nepetoideae*, *Lamiaceae*) from Peru by liquid chromatography associated with high resolution mass spectrometry, is presented. Salvianolic acids and their precursors were found, particularly rosmarinic acid, caffeic acid ester derivatives, as well as a diversity of free and glycosylated flavonoids as main substances. At all, 111 structures were tentatively identified.

The tropical Andes are considered one of the most diverse areas on the planet in terms of vascular plants. The flora of Perú is extremely rich, and its territory is home to some 25,000 species, almost 10% of all plants in the world. However, the percentage of them scientifically studied is quite low[1]. Phytochemical research on Peruvian biodiversity proved to be fundamental in the development of modern medicine, e.g. the isolation of cocaine from *Erythroxylum coca* was a milestone in the development of local anesthetics[2], similarly the isolation of the first antimalarial agent, quinine from *Cinchona ledgeriana* cortex initiated "the alkaloids golden age"[3]. Most of those phytochemical investigations were conducted overseas, a fact that reflects the absence or the restricted access of resources and infrastructure for developing classical phytochemical research in Peru. Today, modern platforms maybe applied for the metabolic characterization of Peruvian flora, a task that can be achieved by a liquid chromatography associated with high resolution mass spectrometry (LC-HRMS) method since it is less time consuming compared to classic methods of isolation and structure identification. Some recent investigations that exemplify the use of LC-HRMS for describing the phytochemical profile of Peruvian flora include the metabolic profile on medicinal plants of the genus *Chuquiraga* (*Asteraceae*)[4] and that related to *Capsicum* (*Solanaceae*) fruits[5].

Perú has several traditional medicine systems, that of the northern Andes[6,7], that of the southern Andes[8] and that of the Amazonian forest[9], each one of them with its main and minor plants and particular practices. With the passage of time, those traditional medicines are getting combined a fact that is especially noticeable in Lima city, the capital of Peru[10]. One aspect that is worth to highlight is that, especially in Andean medicines, but not in Amazonian ones, there is an important contribution of plants belonging to the *Lamiaceae* family to the traditional medicine systems.

The large family *Lamiaceae* has twelve subfamilies. The *Nepetoideae* subfamily, with 3400 species and 105 genera, has three tribes[11]: *Elsholtzieae*, *Ocimeae* and *Mentheae*, the latter with 65 genera. The *Mentheae* tribe is chemically characterized by having volatile terpenoids and a phenolic acid called rosmarinic acid that makes these plants aromatic and with medicinal properties[12,13] *Mentheae* can also be classified into 3 subtribes: *Menthinae* (43 genera), *Salviinae* (10 genera) and *Nepetiinae* (12 genera)[14,15]. In Peru (Herbario Nacional Universidad de San Marcos-Perú, October 2017), the main genera of *Mentheae* were *Clinopodium* (29 species), *Hedeoma* (1 specie), *Lepechinia* (11 species), *Minthostachys* (7 species) and *Salvia* (60 species). *Clinopodium*, *Hedeoma*, and *Minthostachys* belong to the *Menthinae* subtribe, while *Lepechinia* and *Salvia* belong to the *Salviinae* subtribe. Investigations on the non-volatile components in Peruvian *Mentheae* are relatively scarce compared to the works

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related to essential oils[16] . In a previous work[17] the contents of rosmarinic acid, triterpenic acids, oleanolic and ursolic were quantified in thirteen Peruvian *Mentheae*. The highest content of rosmarinic acid was observed in *Lepechina meyenii* (Walp.) Epling and the highest content of triterpenic acids in *Clinopodium revolutum* (Ruiz & Pavón) Govaerts. Subsequently[18], the non-volatile compounds were unambiguously or reasonably identified in two *Lepechinia* species: *L. meyenii* and *L. floribunda* (Benth.) Epling, by LC-HRMS, where the presence of salvianolic acids and diterpenoids were notable.

LC-HRMS methods have been used to comprehensively analyze the phenolic components of plants, this implies procedures for the systematic manually identification of mass spectra[19,20] and also the use of suitable software[21,22], in both cases the procedure involves recording of diagnostic ions for classification and then the identification of characteristic ionic products and neutral losses for confirmation. In the present communication, the profile of secondary metabolites by LC-HRMS is reported for ten Peruvian *Mentheae*: *Clinopodium* (4 species), *Salvia* (4 species), *Hedeoma* (1 species) and *Minthostachys* (1 species).

Results

Phytochemical profile. The LC-HRMS metabolite profile of the ethanolic extracts of the ten peruvian *Mentheae* was obtained in the negative mode (ESI (−)) and the detected compounds appear in Table 1. Assignments were made based on the literature[21–37]. Isomers of quinic acid (*m/z* 191.0556), danshensu (*m/z* 197.0450), protocatechuic aldehyde (*m/z* 137.0239), and caffeic acid (*m/z* 179.0350) occur in most plants. Equally abundant are the monocaffeoylquinic acids present in seven species. *Minthostachys mollis* contains four different monocaffeoylquinic acids. Several derivatives of ferulic acid and *p*-coumaric acid could also be identified. The 4 (para) substitution or the 3,4 substitution with respect to C_3 cannot be determined by MS, however this is the substitution reported in *Mentheae*[19,20,23,38–49]. Caffeic acid, protocatechuic aldehyde and protocatechuic acid share the same substitution pattern. Furthermore, a diversity of flavonoids (flavonols, flavones, flavanones, flavanonols) was found in all the samples, both free and glycosylated. *Minthostachys mollis*, *Clinopodium sericeum* and *Clinopodium pulchellum* are the most diverse with respect to their flavonoids. The most frequent flavonoid aglycones were luteolin (*m/z* 285.0404), quercetin (*m/z* 301.0354), kaempferol (*m/z* 285.0404) and apigenin (*m/z* 269.0455). Eupatorin is present in five of the species studied[50]. In *Clinopodium revolutum,* apigenin and luteolin C- hexosides were detected. In all the samples the presence of rosmarinic acid (*m/z* 359.0772) was detected. In *Clinopodium revolutum*, salvianic acid C (*m/z* 377.0881), which is the result of hydrating the double bond of rosmarinic acid, has been detected, and, in *Salvia sagitatta*, teucrol (*m/z* 315.0880)[51], a decarboxylated rosmarinic acid was observed. Isorinic acid (*m/z* 343.0827) a rosmarinic acid molecule without the 3-OH was present in *Clinopodium brevicalyx*, *Salvia sagitatta*, *Salvia cuspidata* and *Hedeoma mandoniana*. Methyl (*m/z* 373.0931) and ethyl (*m/z* 387.1088) esters of rosmarinic acid were present in *Salvia cuspidata* and *Clinopodium brevicalyx*. In *Salvia cuspidata* and *Clinopodium revolutum*, the dimer of rosmarinic acid, sagerinic acid (*m/z* 719.1598), which is a molecule with a stabilized cyclobutane ring, was found. *Clinopodium pulchellum* displayed the presence of salvianolic acid A (*m/z* 493.1143) and salvianolic acid F (*m/z* 313.0722). In *Clinopodium brevicalyx, Clinopodium sericeum* and *Hedeoma mandoniana*, the presence of salvianolic acid B (*m/z* 717.1443) was observed, a particularly important substance due to its effect on neurodegenerative diseases[52]. However, the plant with the greatest diversity of salvianolic acids was *Clinopodium sericeum*, "romero de jalca", in addition to salvianolic acid B, lithospermic acid (*m/z* 537.1038), two isomers of salvianolic acid A and two isomers of salvianolic acid F. This type of substances is very important due to its effect on cell fibrosis (scar formation) in direct relation to cancer[53]. Among the other substances found, it should be noted that the *Rosmarinus* type diterpenoids, common in *Lepechinia*[18,54] are scarce in this work; only *Salvia sagitatta* and *Salvia cuspidata* show the presence of carnosol (*m/z* 329.1761) and the phenolic diterpenoid, rosmadial (*m/z* 343.1552) in the last one[28]. *Salvia haenkei* contains the ent-(*5R,9R*)-15,16-epoxy-*10S*-hydroxycleroda-3,7,13(16),14-tetraene-17,12S; 18,19 diolide (*m/z* 355.1190)[26], while *Salvia cuspidata* had a lignan, isolariciresinol (*m/z* 359.1502) previously reported in *Linum* seeds[31,55], and 5-epi-icetexone (*m/z* 341.1396) described as an anti- *Trypanosoma cruzii* molecule[56]. Oleanolic and ursolic triterpenic acids, quantified in a previous report by Serrano et al.[17], do not appear in this analysis due to the elution program used, which does not reach 100% acetonitrile[57]. Figure 1 shows the typical ESI (−) chromatogram of *Salvia sagitatta* and Fig. 2 shows the chromatogram of *Clinopodium sericeum*. The chemical structures of the main metabolites detected are displayed in Fig. 3.

Discussion

This is the first time that the phytochemical profile has been obtained for the ten Peruvian *Mentheae* (*Lamiaceae*) here reported. The botanical genera studied were *Salvia* (*Salviinae*), *Clinopodium*, *Hedeoma* and *Minthostachys* (*Menthinae*). While *Salvia* and *Clinopodium* are genera of worldwide distribution, *Hedeoma* and *Minthostachys* are American and South American genera, respectively. All *Salvia* species in this work belong to the *Salvia* subgenus *Calosphace* Benth. (Epling)[63]. Assignments were based on the search for diagnostic ions, characteristic product ions and neutral losses[19,20,25,40,41]. The fragmentation patterns shown in said references are particularly useful for this work since they are specifically directed to *Lamiaceae/Mentheae*. The phytochemical profiles of those *Mentheae* here surveyed are quite similar to their European and Asian relatives. All the species analyzed show the presence of rosmarinic acid, while, quinic acid, 3,4-dihydroxyphenyl-lactic acid "danshensu", protocatechuic aldehyde and caffeic acid are present in most of the samples. Monocaffeoylquinic acids, also called chlorogenic acids, are also frequent but better expressed in *Minthostachys*. Dicaffeoylquinic acid was detected only in *Clinopodium revolutum*. All samples contained flavonoids with more diversity in *Minthostachys* and *Clinopodium*. Flavonoid-free aglycones predominate in several plants: In *Salvia sagitatta*, cirsimaritin is abundant[64], while eupatorin predominates in *Clinopodium revolutum*[50], genkwanin in *Salvia haenkei*[36] and hesperetin in *Clinopodium pulchellum*[27]. In several plants, rosmarinic acid is the main peak: *Clinopodium brevicalyx*, *Salvia*

No peak	Assignment	Rt	[M–H]⁻	Experimental mass	Δ (ppm)	Fragments	Detected in*	References
1	Quinic acid	1.33	$C_7H_{11}O_6$	191.0559	1.57	127.0394	*Cb, So, Mm, Sc, Cr, Cs, Cp*	23
2	Malic acid	1.36	$C_4H_5O_5$	133.0139	1.5		*Ss, Sc,*	23
3	Quinic acid isomer	1.44	$C_7H_{11}O_6$	191.0560	2.09	127.8695	*Cb, Mm, Cr, Cs, Cp*	23
4	Citric acid	1.77	$C_6H_7O_7$	191.0196	2.09	111.0081	*So*	23
5	Pyroglutamic acid	1.87	$C_5H_6O_3N$	128.0348	0.00		*Sh*	23
6	Succinic acid	1.98	$C_4H_5O_4$	117.0187	0.85		*So, Mm, Ss, Sc, Cr, Cs, Sh, Hm*	23
7	Monoacetylglycerol	2.09	$C_5H_9O_4$	133.0502	0.75		*Ss*	
8	Mesaconic acid	2.96	$C_5H_5O_4$	129.0190	1.55		*Cp*	
9	3,4-dihydroxyphenyl lactic acid "danshensu"	4.05	$C_9H_9O_5$	197.0454	2.02	123.0445, 135.0446, 179.0346	*So, Cb, So, Mm, Sc, Cr, Cs, Hm, Sh*	24,25
10	Protocatechuic acid	4.64	$C_7H_5O_4$	153.0190	1.31	109.0289, 135.0448	*So, Sc, Hm, Cp*	24
11	1-*O*-Caffeoylquinic acid	6.39	$C_{16}H_{17}O_9$	353.0883	2.83	135.0447, 179.0347, 191.0559	*Mm*	58,59,58–60
12	Protocatechuic aldehyde	7.73	$C_7H_5O_3$	137.0239	0.00	109.0289	*Cb, So, Mm, Ss, Cr, Cs, Sh, Hm, Cp*	24
13	Hydroxyheptandioic acid	8.78	$C_7H_{11}O_5$	175.0611	2.28		*So, Ss*	
14	*p*-Coumaroyl quinic acid	8.83	$C_{16}H_{17}O_8$	337.0934	2.96	119.0496, 163.0398, 173.0453, 191.0559	*Mm*	58,59,58–60
15	3-*O*-Caffeoylquinic acid	8.99	$C_{16}H_{17}O_9$	353.0883	2.83	173.0453, 179.0559, 191.056	*Mm, Cr*	58,59,58–60
16	Caffeic acid *O*-hexoside	9.02	$C_{15}H_{17}O_9$	341.0883	2.93	179.0347, 233.0458, 251.0564, 281.0670	*So, Ss, Sc*	60,41
17	*p*-Coumaric acid	9.28	$C_9H_7O_3$	163.0399	2.45	119.0497	*Ss*	38
18	5-*O*-Caffeoylquinic acid	9.41	$C_{16}H_{17}O_9$	353.0883	2.83	135.0446, 179.0346, 191.055	*Cb, So, Mm, Cr, Hm, Cp*	58,59,58–60
19	Eucomic acid	9.54	$C_{11}H_{11}O_6$	239.0561	2.09	195.0660, 178.0586	*Cb*	
20	Caffeic acid	9.64	$C_9H_7O_4$	179.0348	1.67	135.0446, 161.0446	*So, Mm, Ss, Sc, Cr, Cs, Sh,*	38,39,41
21	Caffeic acid *O*-hexoside	9.77	$C_{15}H_{17}O_9$	341.088	2.05	179.0345, 235.0453, 251.0561, 281.0667	*Sc*	60,41
22	Tuberonic acid hexoside	9.86	$C_{18}H_{27}O_9$	387.1665	2.58	101.5668, 163.0033, 206.9725	*So, Ss, Cr, Sh*	23
23	*p*-Coumaroylquinic acid isomer	10.1	$C_{16}H_{17}O_8$	337.0934	2.97	163.0397, 173.0454	*So, Mm*	58,59,61,27
24	Salvianic acid C	10.21	$C_{18}H_{17}O_9$	377.0882	2.39	161.0240, 179.0347, 359.0776	*Cr*	41
25	*p*-Coumaroyl hexoside	10.38	$C_{15}H_{17}O_8$	325.0930	1.85	119.0496, 163.0396	*Sc*	60
26	Feruloylquinic acid	10.38	$C_{17}H_{19}O_9$	367.1040	3.0	149.0240, 191.0560, 193.0504, 173.0453	*Mm*	20,27
27	Quercetin 3,7-di-*O*-hexoside	10.43	$C_{27}H_{29}O_{17}$	625.1407	0.32	121.0288, 179.0346, 273.0980, 301.0354, 303.1084, 463.0882,	*Cs, Cp*	62,29,30
28	4-*O*-Caffeoylquinic acid	10.45	$C_{16}H_{17}O_9$	353.0880	1.12	135.0445, 179.0345, 191.0557	*Sc*	58,59,58–60
29	*p*-Coumaroyl hexoside	10.59	$C_{15}H_{17}O_8$	325.0930	1.85	119.0496, 163.0396	*Sc*	60
30	Salvianic acid C isomer	10.67	$C_{18}H_{17}O_9$	377.0881	2.12	197.0453, 347.1708, 359.0775	*Cr*	41
31	Tuberonic acid	10.67	$C_{12}H_{17}O_4$	225.1132	2.22	134.8648, 146.9382, 168.8359, 187.9417, 213.0961	*Mm, Sh,*	23
32	Quercetin *O*-rutinoside	10.78	$C_{27}H_{29}O_{16}$	609.1458	0.33	121.0289, 179.0345, 301.0356, 273.0881	*Mm, Cp*	60,29,30,35
33	Eriodictyol *O*-rutinosise	10.89	$C_{27}H_{31}O_{15}$	595.1661	0.34	151.0397, 287.0562	*Cs, Sh, Hm*	42,29,30
34	Luteolin *O*-rutinoside	11.00	$C_{27}H_{29}O_{15}$	593.1504	0.51	285.0403, 447.0928	*Cb, Sc, Cr, Cp*	16,63,26
35	Apigenin *O*-rutinoside	11.01	$C_{27}H_{29}O_{14}$	577.1556	0.35	269.1030	*Sc, Cr*	16,38,63,26
36	Kaempferol *O*-hexoside	11.02	$C_{21}H_{19}O_{11}$	447.0936	1.78	151.0031, 285.0406,	*Cb, Ss, Cs*	20,29,30
37	Quercetin *O*-hexoside	11.02	$C_{21}H_{19}O_{12}$	463.0886	1.94	301.0358	*So, Mm, Ss, Sc, Cp*	60,44,29,30
38	Quercetin *O*-glucuronide	11.09	$C_{21}H_{17}O_{13}$	477.0679	2.1	301.0356	*So, Ss*	44,29,30
39	Feruloyl hexoside	11.12	$C_{16}H_{19}O_9$	355.1036	1.97	149.0240, 193.0502	*Sc*	60
40	Pentahydroxy-methoxyflavone hexoside	11.12	$C_{22}H_{21}O_{13}$	493.0989	1.42	162.8387, 163.0397, 331.0827, 315.1089	*Cs*	29,30
41	Isorhamnetin *O*-hexoside	11.23	$C_{22}H_{21}O_{12}$	477.1046	2.72	315.0824, 357.0352, 462.0768	*Ss*	43,29,30
42	Naringenin *O*- rutinoside	11.33	$C_{27}H_{31}O_{14}$	579.1714	0.00	151.0030, 271.0612	*Mm, Cb, Cs, Hm, Cp*	29,30
43	Eriodictyol *O*- rutinoside	11.4	$C_{27}H_{31}O_{15}$	595.1665	0.34	151.0033, 287.0564	*Cs*	29,30
44	Luteolin *O*-glucuronide	11.56	$C_{21}H_{17}O_{12}$	461.0729	1.95	133.0290, 151.0395, 285.0407,	*So, Ss, Cr, Sh*	44,29,30
45	Luteolin *O*-hexoside	11.57	$C_{21}H_{19}O_{11}$	447.0937	2.01	151.0398, 241.1084, 285.0407	*Mm, Cr*	60,29,30
46	Dihydrobaicalin	11.57	$C_{21}H_{19}O_{11}$	447.0936	1.79	271.0250, 403.1613	*Sc*	62
47	Sagerinic acid	11.58	$C_{36}H_{31}O_{16}$	719.1600	1.67	161.0239, 179.0348, 359.0715, 539.1186	*Sc, Cr*	38,39,45–47
48	Hesperetin 7-*O*-rutinoside	11.64	$C_{28}H_{33}O_{15}$	609.1819	0.16	151.0397, 179.0347, 301.0718, 257.1035	*Mm, Cb, Hm, Cp*	29,30,64
Continued								

No peak	Assignment	Rt	[M–H]⁻	Experimental mass	Δ (ppm)	Fragments	Detected in*	References
49	Apigenin *O*-rutinoside	11.66	$C_{27}H_{29}O_{14}$	577.1557	0.17	225.1129, 269.0453	*Cr*	[29,30]
50	Dimethylrosmarinic acid	11.67	$C_{20}H_{19}O_8$	387.1091	2.84	179.0347, 135.0447, 161.0452	*So, Sh*	
51	Isorhamnetin 3-*O*-glucuronide	11.7	$C_{22}H_{19}O_{13}$	491.0834	1.62	151.0396, 179.0346, 302.0388, 300.0602, 301.0358, 299.0565, 315.0513	*So*	[29,30]
52	Salvianolic acid A isomer	11.75	$C_{26}H_{21}O_{10}$	493.1142	1.42	179.0344, 197.0450, 269.0821, 295.1192, 313.0723, 359.0778	*Cs*	[24,25,41,49]
53	Tetrahydroxy-methoxyflavone *O*-hexoside	11.78	$C_{22}H_{21}O_{12}$	477.1041	1.68	162.8398, 163.8391, 315.1451	*Cr*	[29,30]
54	Trihydroxymethoxyflavone *O*-hexoside	11.89	$C_{22}H_{21}O_{11}$	461.1093	1.95	299.0559	*Sh,*	[29,30]
55	Salvianolic acid B isomer	11.99	$C_{36}H_{29}O_{16}$	717.1443	1.81	321.0616, 519.0945	*Cs*	[25,40,41,47,48]
56	Apigenin C-hexoside	12.01	$C_{21}H_{19}O_{10}$	431.0984	0.00	269.0452, 281.1024, 311.1130, 341.1960, 371.1002	*Cr*	[20]
57	Rosmarinic acid	12.04	$C_{18}H_{15}O_8$	359.0775	2.23	161.0240, 179.0345, 197.0452	*Cb, So, Mm, Ss, Sc, Cr, Cs, Sh, Hm, Cp*	[25,38,39,45,46,48]
58	Luteolin C-hexoside	12.07	$C_{21}H_{19}O_{11}$	447.0934	2.91	285.0404, 297.1353, 357.1921, 387.1160	*Cr*	[20]
59	Dicaffeoylquinic acid	12.17	$C_{25}H_{23}O_{12}$	515.1194	0.19	135.0444, 161.0238, 179.0345, 353.0881	*Cr*	[58,59,58–60]
60	Salvianolic acid B isomer	12.53	$C_{36}H_{29}O_{16}$	717.1443	1.81	295.0611, 321.0408, 339.0512, 493.1137, 519.0930, 537.1024	*Cb, Ss, Hm*	[25,40,41,47,48]
61	Luteolin *O*-acetylhexoside	12.71	$C_{23}H_{21}O_{12}$	489.1039	1.23	133.0289, 151.0395, 241.0537, 257.1035, 267.0667, 285.0404, 447.0935	*Cr*	[63,26]
62	Artemetin	12.8	$C_{20}H_{19}O_8$	387.1089	2.32	327.1241, 342.1067, 357.0992, 372.1184	*Sh,*	[29,30]
63	Isorinic acid	12.95	$C_{18}H_{15}O_7$	343.0827	2.62	161.0241, 327.2181	*Cb, Ss, Sc Hm*	[41,65]
64	Lithospermic acid	13.03	$C_{27}H_{21}O_{12}$	537.1038	0.93	295.0610, 493.1147	*Cs*	[24,41]
65	Isosakuranetin *O*-rutinoside	13.15	$C_{28}H_{33}O_{14}$	593.1874	0.51	285.0770, 594.1905	*Mm, Cp*	[29,30]
66	Methyl rosmarinate	13.28	$C_{19}H_{17}O_8$	373.0935	2.95	179.0347, 194.0540, 359.0778	*Sc*	[20,25,38]
67	Quercetin *O*-(*p*-coumaroyl)-hexoside	13.51	$C_{30}H_{25}O_{14}$	609.1242	0.49	301.0719, 447.0940, 462.0747, 594.1343	*Cr*	[29,30]
68	Eriodictyol	13.6	$C_{15}H_{11}O_6$	287.0563	2.44	107.0133, 135.0445, 151.0030	*Cb, Cp*	[29,30]
69	Luteolin	13.62	$C_{15}H_9O_6$	285.0408	3.16	133.0289, 151.0032, 241.1085	*Cb, Hm*	[29,30,32]
70	Dihydrophilonotisflavone	13.63	$C_{30}H_{19}O_{12}$	571.0883	1.05	133.0290, 151.0033, 285.0410, 286.0441	*So, Ss*	[29,30]
71	Ferulic acid	13.68	$C_{10}H_9O_4$	193.0504	1.55	134.0367, 149.0239, 178.0220	*Sc*	[20,25,66]
72	Salvianolic acid A isomer	13.87	$C_{26}H_{21}O_{10}$	493.1141	1.22	159.8595, 179.0345, 197.0451, 295.0612, 269.0821, 313.0719, 359.0774	*Cs, Cp*	[24,25,41,49]
73	Protocatechuic acid *O*-(hydroxybenzoyl)hexoside	13.94	$C_{20}H_{19}O_{11}$	435.0935	1.61	137.0239, 153.0191, 297.1346, 315.1452	*Cr*	
74	Trihydroxy-methoxyflavone	14.00	$C_{16}H_{11}O_6$	299.0565	3.01	151.0397, 255.0698, 285.0413	*Ss, Sh*	[29,30,32,35]
75	Hesperetin *O*-hexoside	14.27	$C_{22}H_{23}O_{11}$	463.1250	2.06	151.0395, 179.0347, 301.0720	*Cp*	[29,30,34]
76	Caffeic acid ethyl ester	14.66	$C_{11}H_{11}O_4$	207.0661	1.44	179.0347	*Cb, Sc*	
77	Quercetin	14.97	$C_{15}H_9O_7$	301.0356	2.33	273.0407, 257.8189, 179.0346, 151.0392, 121.0288	*Sc*	[67,29,30]
78	Caffeic acid dimethyl derivative	15.01	$C_{11}H_{11}O_4$	207.0661	1.45	16,931.0239, 151.940396, 147.069552	*Cs*	
79	Salvianolic acid F isomer	15.46	$C_{17}H_{13}O_6$	313.0721	2.88	269.082196, 15,979.0656	*Sc, Cs*	[41]
80	Dimethylquercetin	15.49	$C_{17}H_{13}O_7$	329.0673	3.34	314.0756, 301.0716, 179.0347, 151.0396, 121.0288	*Cb*	[29,30]
81	Trihydroxy-dimethoxyflavone	15.53	$C_{17}H_{13}O_7$	329.0672	3.04	151.0398, 201.8020, 257.8197, 283.0612, 299.0201, 313.0722, 314.0754	*Mm*	[29,30]
82	Trihydroxylinoleic acid	16.03	$C_{18}H_{31}O_5$	327.2183	2.75	269.0457	*Cb, Mm, Ss, Sc, Hm*	
83	Ethyl caffeate	16.14	$C_{11}H_{11}O_4$	207.0660	0.97	179.0346	*Ss*	
84	Apigenin	16.15	$C_{15}H_9O_5$	269.0459	3.35	151.0396, 117.0187	*Ss, Sc, Cr*	[40,67,29,30,32]
85	Naringenin	16.39	$C_{15}H_{11}O_5$	271.0616	3.32	151.0397, 177.0190	*Ss, Cp*	[68,29,30]
86	Salvianolic acid F isomer	16.87	$C_{17}H_{13}O_6$	313.0719	2.23	269.0822, 159.0658	*Sc*	[41]
87	Ethyl rosmarinate	17.23	$C_{20}H_{19}O_8$	387.1088	2.07	179.0344, 206.9724, 359.0777	*Cb*	[20,38,39]
88	Dimethylquercetin	17.59	$C_{17}H_{13}O_7$	329.0673	3.34	121.0291, 151.0397, 179.0350, 301.0715, 314.0756	*Ss, Cp*	[66,29,30]
89	Hesperetin	17.66	$C_{16}H_{13}O_6$	301.0722	3.32	151.0032, 179.0343, 286.0495	*Cp*	[29,30,34]
Continued								

No peak	Assignment	Rt	[M–H]⁻	Experimental mass	Δ (ppm)	Fragments	Detected in*	References
90	Salvianolic acid F isomer	17.87	$C_{17}H_{13}O_6$	313.0721	2.87	159.0448, 269.0821	*Cs*	41
91	15,16-epoxi-10S-hidrox-icleroda-3,7,13(16),14 tetraeno-17, 12S; 18,19 diolido	17.94	$C_{20}H_{19}O_6$	355.1190	2.25	311.1291	*Sh*	55
92	Trihydroxyoleic acid	18.13	$C_{18}H_{33}O_5$	329.2336	2.43	171.0195, 224.7632, 250.1448	*Mm, Cb Cs*	37
93	Hydroxyhexadecandioic acid	18.63	$C_{16}H_{29}O_5$	301.2025	3.32		*Cs*	37
94	Trihydroxy-trimethoxyflavone	18.73	$C_{18}H_{15}O_8$	359.0766	0.28	301.6655, 314.2232, 329.0299, 344.0546	*Mm, Cb, Cp*	
95	Trihydroxy-methoxyflavanone (hesperetin isomer)	19.15	$C_{16}H_{13}O_6$	301.0721	2.87	161.0240, 139.0032	*Cp*	28,30
96	trihydroxymethoxyflavone	19.23	$C_{16}H_{11}O_6$	299.0565	3.01	151.0397, 284.0327	*So, Mm, Cr, Sh, Cp, Sd*	69,32
97	Cirsimaritin	19.34	$C_{17}H_{13}O_6$	313.0724	3.19	298.0488, 283.0249	*Ss, Cr*	70,35
98	Isolariciresinol	19.61	$C_{20}H_{23}O_6$	359.1502	1.95	345.1346, 344.1582, 313.0714	*Sc*	55,31
99	Salvianolic acid F isomer	19.77	$C_7H_{13}O_6$	313.0722	3.19	269.0459, 159.8597	*Cp*	41
100	Rosmadial	20.03	$C_{20}H_{23}O_5$	343.1552	1.75	299.1652, 315.1598	*Sc*	
101	Eupatorin	20.06	$C_{18}H_{15}O_7$	343.0829	3.21	328.0595, 313.0359, 298.0125	*Cb, Mm, Ss, Cr, Cp*	48,50
102	Teucrol	20.3	$C_{17}H_{15}O_6$	315.0880	3.5	179.0349, 135.0447, 161.0244	*Ss*	51
103	Dihydroxy-methoxyflavone	20.32	$C_{16}H_{11}O_5$	283.0617	3.53	268.0386, 151.0034, 107.0327	*Mm, Cp*	29,30
104	Dihydroxy-dimethoxyfla-vanone	20.36	$C_{16}H_{13}O_5$	285.0773	3.51	153.0190, 161.0453, 179.0349, 151.0397, 243.0668, 270.0535, 164.0012	*Mm*	29,30
105	Genkwanin	20.47	$C_{16}H_{11}O_5$	283.0616	3.18	268.0386, 239.0922, 165.0192	*Ss, Cr, Sh*	43
106	Sakuranetin	20.57	$C_{16}H_{13}O_5$	285.0771	2.81	241.1076, 165.0188, 121.0289	*Cr*	29
107	Octadecendioic acid	20.68	$C_{18}H_{31}O_4$	311.2232	2.89	310.2107	*So, Sh*	23
108	Octadihydroxyoctadecadi-enoic acid	21.15	$C_{18}H_{31}O_4$	311.2229	1.93	197.8076	*Sc*	23
109	Carnosol	22.2	$C_{20}H_{25}O_4$	329.1761	2.7	285.1861	*Ss, Sc*	38,39,54
110	5-Epi-icetexone	22.45	$C_{20}H_{21}O_5$	341.1396	0.88	297.1500, 299.1652	*Sc*	56
111	9,10-Dihydroxystearic acid	23.47	$C_{18}H_{35}O_4$	315.2547	3.47		*Ss*	23

Table 1. Compounds detected in the ethanolic extracts of then Peruvian *Mentheae* by LC-HRMS. **Clinopodium brevicalyx* (*Cb*), *Salvia oppositiflora* (*So*), *Minthostachys mollis* (*Mm*), *Salvia sagittata* (*Ss*), *Salvia cuspidate* (*Sc*), *Clinopodium revolutum* (*Cr*), *Clinopodium sericeum* (*Cs*), *Salvia haenkei* (*Sh*), *Hedeoma mandoniana* (*Hm*), *Clinopodium pulchellum* (*Cp*).

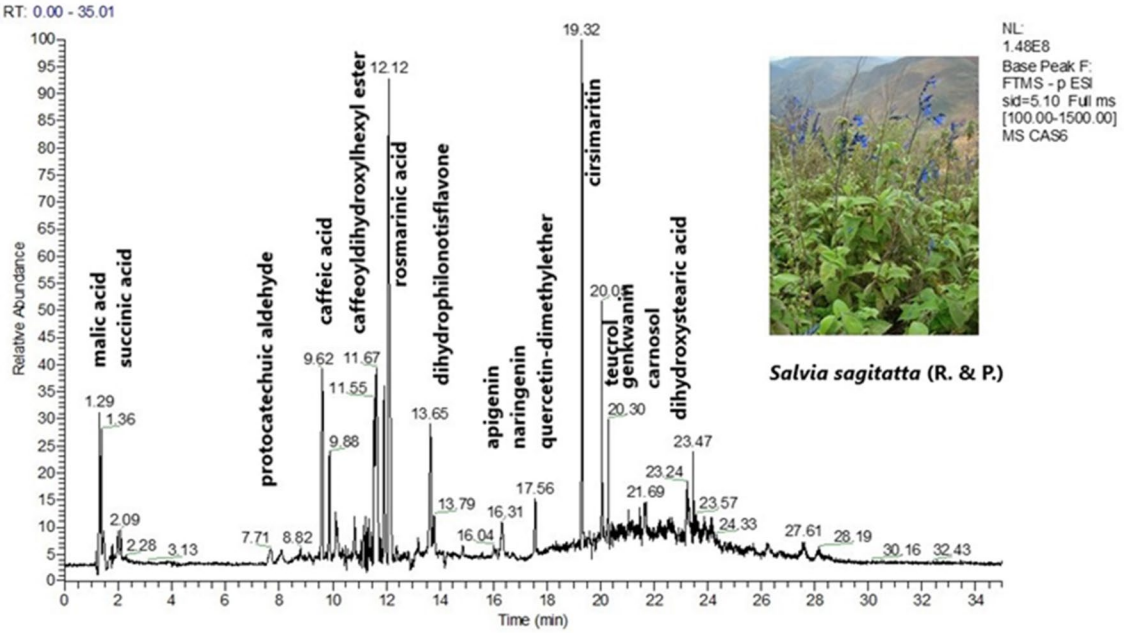

Figure 1. ESI (–) chromatogram of *Salvia sagitatta*.

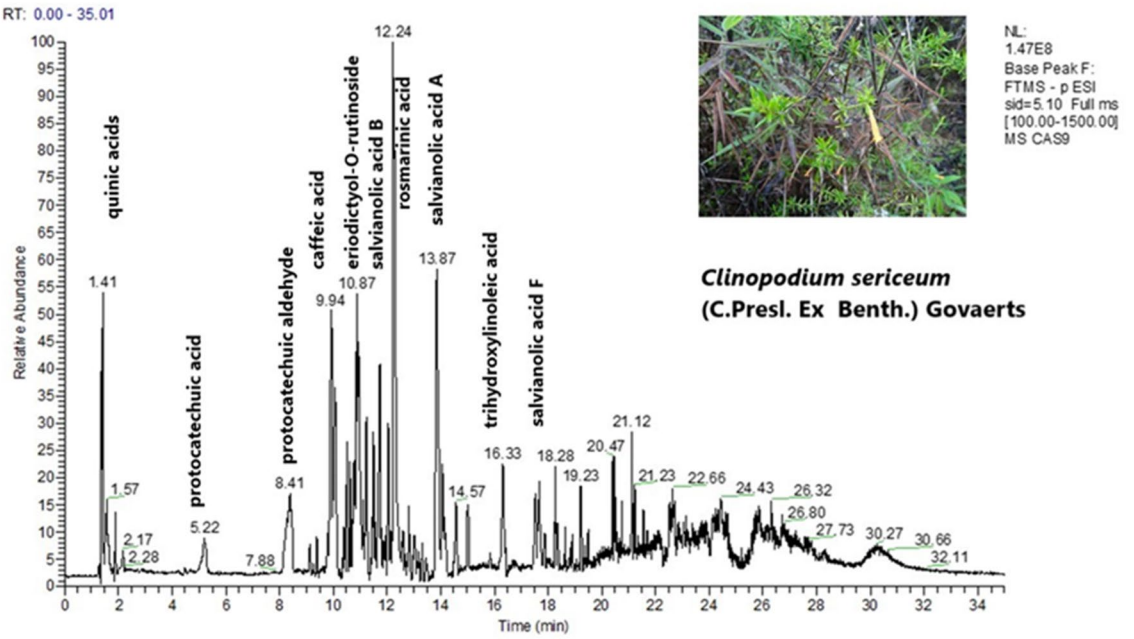

Figure 2. ESI (−) chromatogram of *Clinopodium sericeum*.

oppositiflora, *Clinopodium sericeum* and *Hedeoma mandoniana*. Some type of salvianolic acid is present in all the samples, although in some cases, they are very small modifications of the rosmarinic acid molecule. Dimers and trimers of rosmarinic acid are present in *Clinopodium brevicalyx*, *Salvia oppositiflora*, *Salvia cuspidata*, *Clinopodium sericeum*, *Hedeoma mandoniana* and *Clinopodium pulchellum*. In *Clinopodium sericeum*, not only is the diversity of salvianolic acids important but also their abundance in salvianolic acid A, which would allow the preparation of the said substance from it[71].

Conclusion

Peruvian *Mentheae* are a rich source of flavonoids, phenolic acids and terpenoids. The present study involved LC-HRMS analysis of ten species. A total of 111 compounds were detected. Most of these were identified by key ion filtering strategy and comparison with literature data. This methodology can be used to the authentication and differentiation of larger numbers of *Mentheae* species: The San Marcos Herbarium, Lima-Perú, in 2017 had 108 *Mentheae*.

Methods

Plant material. The plants used in this study are as follows: *Clinopodium brevicalyx* Epling (Harley & Granda) (*Menthinae*) (HUT 59506), *Salvia oppositiflora* (R. and P.) (*Salviinae*) (HUT 59502), *Minthostachys mollis* Griseb. (*Menthinae*) (HUT 59766), *Salvia sagittata* R. and P. (*Salviinae*) (HUT59499), *Salvia cuspidata* subsp. *cuspidata* (R. and P.) (*Salviinae*) (HUT 59505), *Clinopodium revolutum* (R. and P.) (*Menthinae*) (HUT 58329), *Clinopodium sericeum* (Briq. et Benth) Govaerts (*Menthinae*) (HUT 58,332), *Salvia haenkei* Benth. (*Salviinae*) (HUT 59500), *Hedeoma mandoniana* Wedd. (*Menthinae*) (HUT 59763), *Clinopodium pulchellum* Kunth (Govaerts) (*Salviinae*) (HUT 59765). All of them were collected in Peru (2014–2018) by the author (C.S.) according to the procedures of the Universidad San Antonio Abad and following the guidelines of the Herbarium Truxillense of the Universidad Nacional de Trujillo (HUT)—Perú https://facbio.unitru.edu.pe. Specimens were identified and deposited by the botanist Eric Frank Rodríguez (Herbarium Truxillense).

Sample preparation for metabolite profiling. Fifty milligrams of pulverized aerial parts were subjected to an ultrasonic bath for five minutes with 1 mL of ethanol for three times. The filtrates were evaporated in vacuo and stored at 4 °C until use.

LC-HRMS. Chromatographic separation was performed on a Thermo Scientific Dionex Ultimate 3000 UHPLC system with an Acclaim RP C_{18} 150 × 4.6 mm × 1.8 µm chromatographic column at 25 °C and a gradient of (a) 0.1% H_2CO_2 in water and (b) acetonitrile: [time, % (b)]: (0.5); (5,5); (10.30); (15.30); (20,70); (25.70); (35.5) and 12 min of equilibration before each injection. The flow rate was 1 mL min^{-1}, and the injection volume was 10 µL. The extracts were dissolved in 1.5 mL of methanol and filtered through 0.22 µm PTFE. For high resolution mass spectrometry, a Q-Exactive MS (Thermo Fisher Germany) equipped with electrospray ionization (ESI) in negative mode was used. The MS collection parameters were as follows: spray voltage 2500 V; capillary temperature, 400 °C. Sheath gas flowed at a rate of 75 units. Auxiliary gas flowed at 20 units. Scanning range of

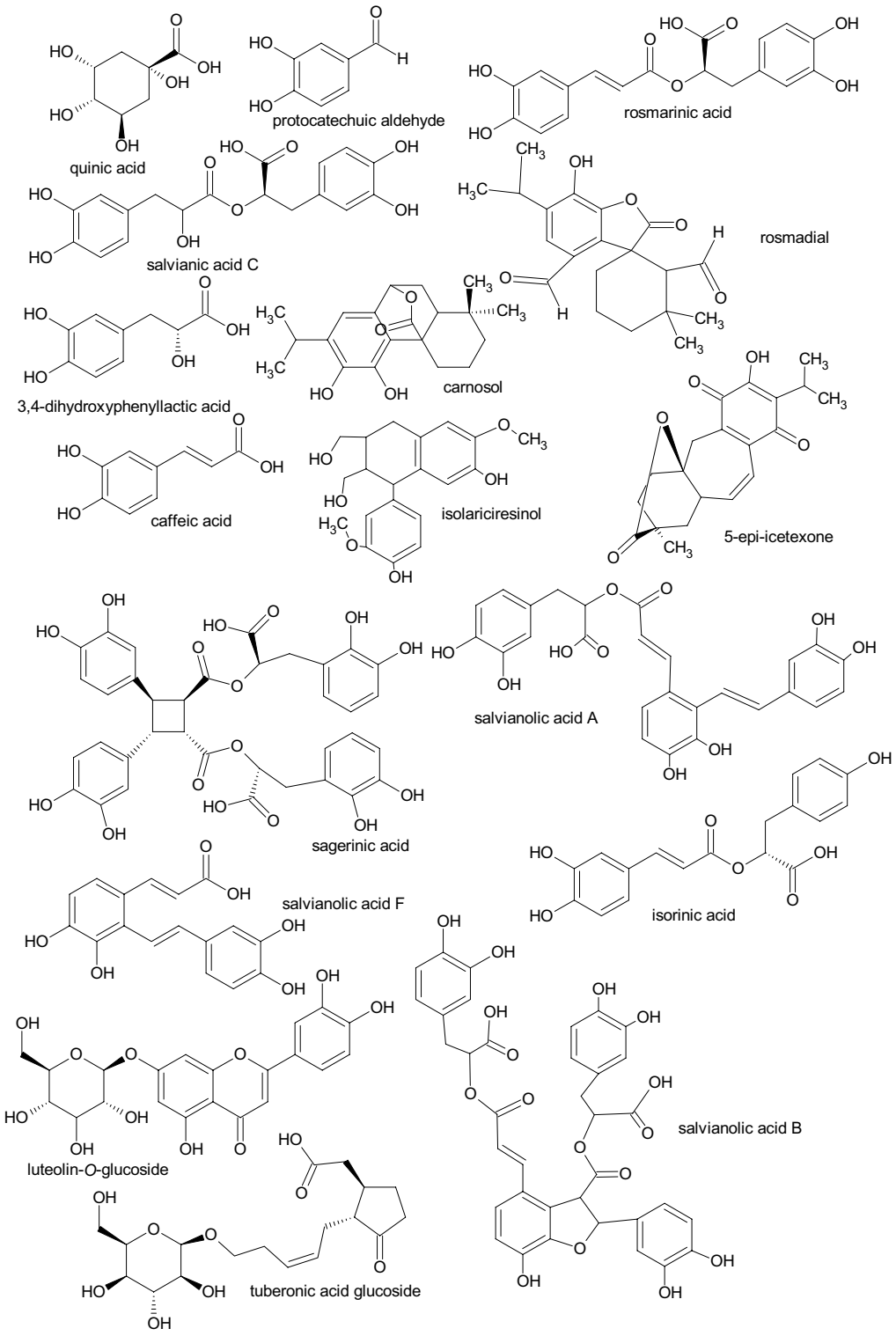

Figure 3. Chemical structures of main metabolites identified.

100–1500 *m/z*. Resolution of 35,000. The mass tolerance threshold was 5 ppm. Data acquisition and processing were performed with XCalibur 2.3 (Thermo Fisher Scientific).

Diagnostic ions for classification. Quinic acids derivatives: 337.0929 *p*-coumaroylquinic acid, 367.1035 feruloylquinic acid, 353.0878 caffeoylquinic acid, 515.1195 dicaffeoylquinic acid.

Phenylpropionic acids: 163.0401 *p*-coumaric acid, 179.0350 caffeic acid, 359.07772 rosmarinic acid.

Flavonoids: 253.0506 chrysin, 269.0455 apigenin, 285.0404 luteonin and kaemferol, 301.0354 quercetin.

Data availability

The datasets used and/or analyses during the current study are available from the corresponding author on reasonable request.

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Author contributions

C.S., G.V., G.C., M.L. conception, design of the work. C.S., G.V., G.C. wrote the main manuscript. E.R., B.C. plant material collection and taxonomical identification. C.S., G.V. and M.L. phytochemical analysis.

Competing interests
The authors declare no competing interests.

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