Electronic Supplementary Material (ESI) for Food & Function.

Supplementary information

Memory enhancement effect of saponins from *Eleutherococcus senticosus* leaves and blood-brain barrier-permeated saponins profiling using a pseudotargeted monitoring strategy

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Experimental

Hematological and enzyme assays. After the last administration, blood sample of behavioral tests' rats were collected from abdominal aorta into heparinized tubes at 1 h, and then centrifuged at 4000 rpm for 15 min (4 °C) to obtain plasma. The supernatant was collected as plasma and stored at −80 °C before analysis. The determination of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) activities were conducted through enzymatic methods using the Chemray 800 Automatic Biochemical Analyzer (Rayto Life and Analytical Sciences Co., Ltd., China).

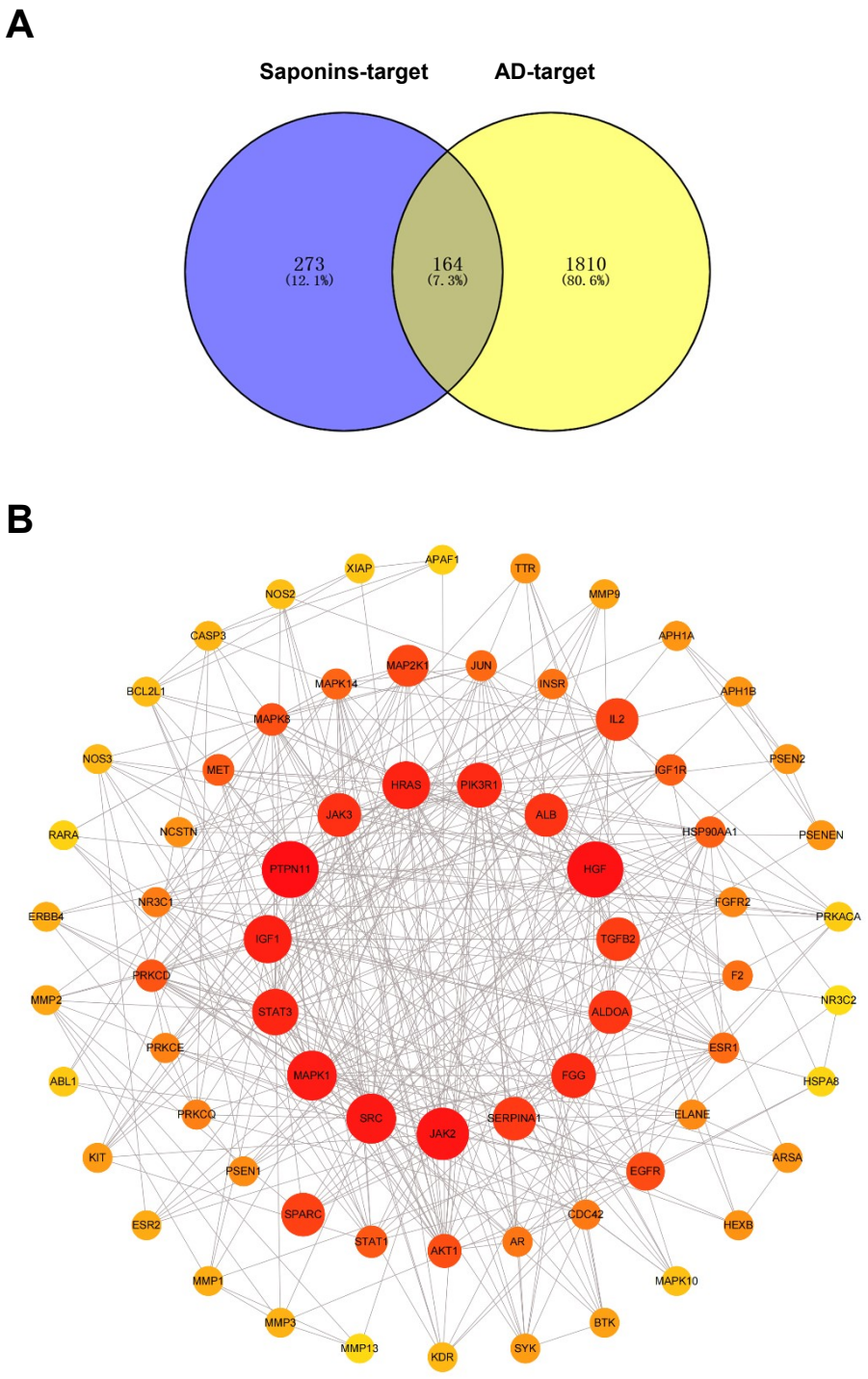

Fig. S1 Network pharmacology Diagram of bioactive saponins. (A) Intersection of component targets and AD-related targets; (B) Key targets in protein-protein interaction (PPI) network.

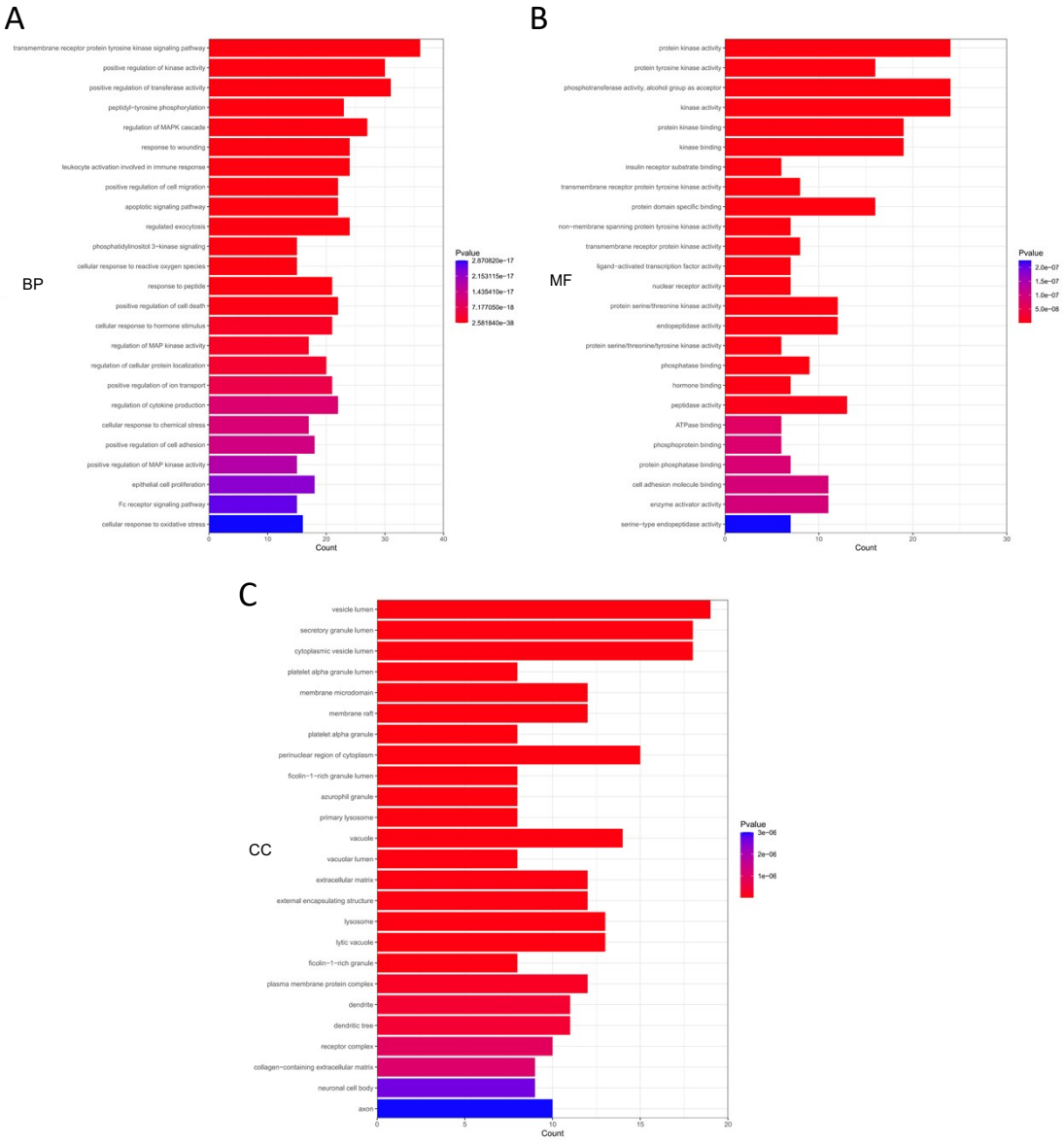

Fig. S2 GO enrichment analysis for 70 key targets. (A) Biological process (BP); (B) Molecular function (MF); (C) Cellular component (CC).

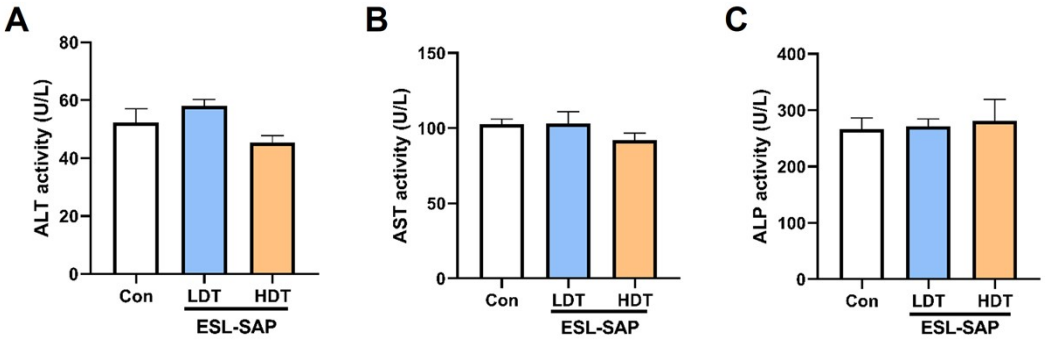

Fig. S3 ALT, AST and ALP activities in plasma of rats. (A) ALT activity. (B) AST activity. (C) ALP activity. Data were presented as mean ± SEM, with significance different from control (n=4) *P<0.05.

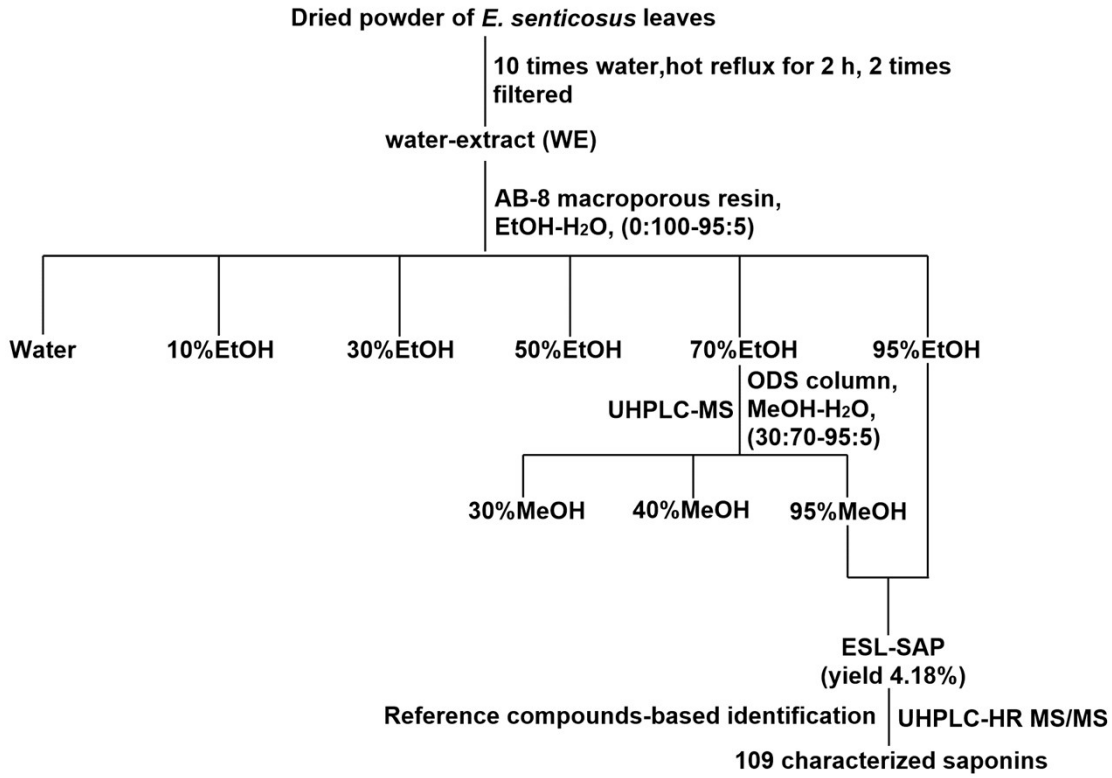

Fig. S4 The workflow of the preparation of ESL-SAP.

Table S1 Characterization of 109 triterpene saponins in ESL-SAP

No.	t_R (min)	Precursor Ion (*m/z*)	Characterization[a]			
			aglycone	α-chain	β-chain	formula
1	55.96	763.4276	I	-	-A-R	$C_{40}H_{62}O_{11}$
2	54.57	779.4224	I	-	-A-G	$C_{40}H_{62}O_{12}$
3	43.76	1087.5324	I	-G-G-R	-A	$C_{52}H_{82}O_{21}$
4	45.32	1129.5440	I	-G-G(Ac)-R	-A	$C_{54}H_{84}O_{22}$
5*	46.54	1129.5431	I	-G-G(Ac)-R	-A	$C_{54}H_{84}O_{22}$
6	52.04	1187.5845	I	-G(R)-G	-A-R	$C_{58}H_{92}O_{25}$
7	52.55	1187.5870	I	-G(R)-G	-A-R	$C_{58}H_{92}O_{25}$
8	52.59	1229.5957	I	-G(R)-G(Ac)	-A-R	$C_{60}H_{94}O_{26}$
9*	42.43	1233.5903	I	-G-G-R	-A-R	$C_{58}H_{92}O_{25}$
10	40.89	1249.5866	I	-G-G-R	-A-G	$C_{58}H_{92}O_{26}$
11	41.19	1249.5857	I	-G-G-R	-A-G	$C_{58}H_{92}O_{26}$
12*	44.55	1275.6002	I	-G-G(Ac)-R	-A-R	$C_{60}H_{94}O_{26}$
13	45.21	1275.6017	I	-G-G(Ac)-R	-A-R	$C_{60}H_{94}O_{26}$
14*	42.73	1291.5963	I	-G-G(Ac)-R	-A-G	$C_{60}H_{94}O_{27}$
15	41.70	1291.5967	I	-G-G(Ac)-R	-A-G	$C_{60}H_{94}O_{27}$
16	43.82	1317.6104	I	-G-G(Ac)-R(Ac)	-A-R	$C_{62}H_{96}O_{27}$
17	41.06	1453.6467	I	-G-G(Ac)-R	-A-G-G	$C_{66}H_{104}O_{32}$
18	59.95	633.4020	II	-	-A	$C_{35}H_{56}O_{7}$
19	57.28	663.4116	II	-G	-	$C_{36}H_{58}O_{8}$
20	57.85	779.4586	II	-	-A-R	$C_{41}H_{66}O_{11}$
21	48.94	793.4383	II	-G	-Gu	$C_{42}H_{66}O_{14}$
22	56.25	795.4539	II	-G	-A	$C_{41}H_{66}O_{12}$
23	56.42	795.4542	II	-	-A-G	$C_{41}H_{66}O_{12}$
24	55.46	825.4657	II	-	-G-G	$C_{42}H_{68}O_{13}$
25	43.23	955.4908	II	-G-G	-Gu	$C_{48}H_{76}O_{19}$
26	46.22	957.5082	II	-G-G	-A	$C_{47}H_{76}O_{17}$
27	48.70	957.5075	II	-G	-A-G	$C_{47}H_{76}O_{17}$
28	53.48	971.5226	II	-G-G-R	-	$C_{48}H_{78}O_{17}$
29	52.49	981.5064	II	-G (Ma)	-A-R	$C_{50}H_{78}O_{19}$
30	51.37	997.5006	II	-G(Ma)	-A-G	$C_{50}H_{78}O_{20}$
31	44.80	1103.5635	II	-G-G-R	-A	$C_{53}H_{86}O_{21}$
32	45.45	1103.5648	II	-G-G-R	-A	$C_{53}H_{86}O_{21}$
33	45.76	1103.5656	II	-G-G	-A-R	$C_{53}H_{86}O_{21}$
34*	46.76	1103.5641	II	-G-G-R	-A	$C_{53}H_{86}O_{21}$
35	41.81	1119.5603	II	-G-G	-A-G	$C_{53}H_{86}O_{22}$
36	43.54	1119.5585	II	-G-G	-A-G	$C_{53}H_{86}O_{22}$
37	44.48	1143.5544	II	-G-G(Ac)-R	-Gu	$C_{56}H_{88}O_{24}$
38	46.71	1145.5701	II	-G-G(Ac)-R	-A	$C_{55}H_{88}O_{22}$
39	47.17	1145.5721	II	-G-G(Ac)-R	-A	$C_{55}H_{88}O_{22}$
40	49.29	1145.5752	II	-G-G(Ac)-R	-A	$C_{55}H_{88}O_{22}$
41	49.46	1145.5764	II	-G-G(Ac)-R	-A	$C_{55}H_{88}O_{22}$
42	43.31	1203.6158	II	-G(R)-G	-A-R	$C_{59}H_{96}O_{25}$
43	53.76	1203.6168	II	-G(R)-G	-A-R	$C_{59}H_{96}O_{25}$
44	54.29	1245.6274	II	-G(R)-G(Ac)	-A-R	$C_{61}H_{98}O_{26}$
45*	44.72	1249.6215	II	-G-G-R	-A-R	$C_{59}H_{96}O_{25}$
46	42.82	1265.6167	II	-G-G-R	-A-G	$C_{59}H_{96}O_{26}$
47*	47.81	1291.6322	II	-G-G(Ac)-R	-A-R	$C_{61}H_{98}O_{26}$
48	40.95	1295.6274	II	-G-G-R	-G-G	$C_{60}H_{98}O_{27}$
49*	44.97	1307.6267	II	-G-G(Ac)-R	-A-G	$C_{61}H_{98}O_{27}$
50	45.49	1307.6279	II	-G-G(Ac)-R	-A-G	$C_{61}H_{98}O_{27}$
51	42.19	1469.6808	II	-G-G(Ac)-R	-A-G-G	$C_{67}H_{108}O_{32}$
52	53.95	647.3814	III	-	-A	$C_{35}H_{54}O_{8}$

Table S1 *Continued*

No.	t_R (min)	Precursor Ion (*m/z*)	Characterization[a]			
			aglycone	α-chain	β-chain	formula
53	52.35	793.4384	III	-	-A-R	$C_{41}H_{64}O_{12}$
54	48.96	809.4332	III	-	-A-G	$C_{41}H_{64}O_{13}$
55	39.23	1117.5435	III	-G-G-R	-A	$C_{53}H_{84}O_{22}$
56	40.74	1117.5433	III	-G-G-R	-A	$C_{53}H_{84}O_{22}$
57	41.34	1159.5551	III	-G-G(Ac)-R	-A	$C_{55}H_{86}O_{23}$
58	38.41	1263.6007	III	-G-G-R	-A-R	$C_{59}H_{94}O_{26}$
59	37.00	1279.5957	III	-G-G-R	-A-G	$C_{59}H_{94}O_{27}$
60*	40.37	1305.6119	III	-G-G(Ac)-R	-A-R	$C_{61}H_{96}O_{27}$
61	38.94	1321.6018	III	-G-G(Ac)-R	-A-G	$C_{61}H_{96}O_{28}$
62*	40.25	1265.6167	IV	-G-G-R	-A-R	$C_{59}H_{96}O_{26}$
63	39.18	1281.6126	IV	-G-G-R	-A-G	$C_{59}H_{96}O_{27}$
64	42.83	1307.6273	IV	-G-G(Ac)-R	-A-R	$C_{61}H_{98}O_{27}$
65	55.42	603.3906	V	-	-A	$C_{35}H_{56}O_{8}$
66	47.73	649.3955	V	-	-A	$C_{35}H_{56}O_{8}$
67	45.42	795.4539	V	-	-A-R	$C_{41}H_{66}O_{12}$
68	53.79	795.4545	V	-	-A-R	$C_{41}H_{66}O_{12}$
69	42.58	811.4489	V	-	-A-G	$C_{41}H_{66}O_{13}$
70	43.38	811.4499	V	-	-A-G	$C_{41}H_{66}O_{13}$
71	52.85	811.4457	V	-G	-A	$C_{41}H_{66}O_{13}$
72	36.19	973.5015	V	-G-G	-A	$C_{47}H_{76}O_{18}$
73	36.52	973.5013	V	-G	-A-G	$C_{47}H_{76}O_{18}$
74	40.58	973.5009	V	-	-A-G-G	$C_{47}H_{76}O_{18}$
75	35.77	1119.5587	V	-G-G	-A-R	$C_{53}H_{86}O_{22}$
76	40.94	1119.5574	V	-G-G-R	-A	$C_{53}H_{86}O_{22}$
77	41.81	1119.5598	V	-G-G-R	-A	$C_{53}H_{86}O_{22}$
78	34.23	1135.5542	V	-G-G	-A-G	$C_{53}H_{86}O_{23}$
79	34.87	1135.5571	V	-G-G	-A-G	$C_{53}H_{86}O_{23}$
80	43.34	1159.5548	V	-G-G(Ac)-R	-A(Ma)	$C_{56}H_{88}O_{25}$
81	37.75	1161.5692	V	-G-G(Ac)-R	-A	$C_{55}H_{88}O_{23}$
82	43.12	1161.5691	V	-G-G(Ac)-R	-A	$C_{55}H_{88}O_{23}$
83	44.00	1161.5701	V	-G-G(Ac)-R	-A	$C_{55}H_{88}O_{23}$
84	35.24	1265.6160	V	-G-G-R	-A-R	$C_{59}H_{96}O_{26}$
85	33.55	1281.6113	V	-G-G-R	-A-G	$C_{59}H_{96}O_{27}$
86*	37.17	1307.6266	V	-G-G(Ac)-R	-A-R	$C_{61}H_{98}O_{27}$
87	35.78	1323.6219	V	-G-G(Ac)-R	-A-G	$C_{61}H_{98}O_{28}$
88	41.56	1323.6204	V	-G-G(Ac)-R	-A-G	$C_{61}H_{98}O_{28}$
89	34.07	1485.6771	V	-G-G(Ac)-R	-A-G-G	$C_{67}H_{108}O_{33}$
90	40.02	1485.6774	V	-G-G(Ac)-R	-A-G-G	$C_{67}H_{108}O_{33}$
91	41.57	999.4805	VI	-G-G-R	-	$C_{48}H_{74}O_{19}$
92	45.57	617.3699	VII	-	-A	$C_{35}H_{54}O_{9}$
93	44.07	763.4278	VII	-	-A-R	$C_{41}H_{64}O_{13}$
94	41.30	779.4232	VII	-G	-A	$C_{41}H_{64}O_{14}$
95	42.14	779.4232	VII	-G	-A	$C_{41}H_{64}O_{14}$
96	34.59	1087.5328	VII	-G-G-R	-A	$C_{53}H_{84}O_{23}$
97	36.74	1129.5432	VII	-G-G(Ac)-R	-A	$C_{55}H_{86}O_{24}$
98	36.89	1129.5431	VII	-G-G(Ac)-R	-A	$C_{55}H_{86}O_{24}$
99	34.42	1233.5908	VII	-G-G-R	-A-R	$C_{59}H_{94}O_{27}$
100	39.02	1233.5906	VII	-G(R)-G-R	-A	$C_{59}H_{93}O_{27}$
101	32.52	1249.5857	VII	-G-G-R	-A-G	$C_{59}H_{94}O_{28}$
102	32.82	1249.5855	VII	-G-G-R	-A-G	$C_{59}H_{94}O_{28}$
103*	36.56	1275.6008	VII	-G-G(Ac)-R	-A-R	$C_{61}H_{96}O_{28}$
104	35.12	1291.5964	VII	-G-G(Ac)-R	-A-G	$C_{61}H_{96}O_{29}$

Table S1 *Continued*

No.	t_R (min)	Precursor Ion (*m/z*)	Characterization[a]			
			aglycone	α-chain	β-chain	formula
105	41.79	781.4390	VIII	-	-A-R	$C_{40}H_{64}O_{12}$
106	39.10	797.4329	VIII	-G	-A	$C_{40}H_{64}O_{13}$
107	52.42	989.4950	VIII	-G	-G-	$C_{47}H_{76}O_{19}$
108	35.01	1147.5542	VIII	-G-G(Ac)-R	-A	$C_{54}H_{86}O_{23}$
109	34.93	1293.6112	VIII	-G-G(Ac)-R	-A-R	$C_{60}H_{96}O_{27}$

*, compounds identified by comparing with reference compounds. 5, ciwujianoside D2; 9, ciwujianoside B; 12, ciwujianoside C2; 14, acanthopanaoside A; 34, ciwujianoside C3; 45, eleutheroside M; 47, ciwujianoside C4; 49, acanthopanaxoside B; 60, ezoukoginoside E; 62, tauroside H1; 86, ezoukoginoside C. 103, ezoukoginoside A;

[a] I, akebonoic acid; II, oleanolic acid; III, 3-hydroxy-29-alolean-12-en-28-oic acid; IV, echinocystic acid; V, hederagenin or mesembryanthemoidigenic acid; VI, 3-oxo-11-methoxyolean-12-en-28-oic acid; VII, serratagenic acid; VIII, 3,20-dihydroxy-30-norlean-12-ene-28-oic acid; G, D-glucosyl moiety; R, L-rhamnosyl moiety; A, L-arabinosyl moiety; Ac, Acetyl group; Ma, Malonic acid moiety; Gu, Glucuronyl moiety. The linkage position between monosaccharaides was neglected.

Table S2 Precursor ions information of IVSL

No.	Mass [*m/z*]	Formula	No.	Mass [*m/z*]	Formula
1	485.3277	$C_{30}H_{46}O_5$	85	1041.5311	$C_{52}H_{82}O_{21}$
2	485.3278	$C_{29}H_{44}O_3$	86	1055.5059	$C_{52}H_{80}O_{22}$
3	499.3075	$C_{30}H_{44}O_6$	87	1073.5546	$C_{53}H_{86}O_{22}$
4	501.3221	$C_{29}H_{44}O_4$	88	1077.1370	$C_{51}H_{100}O_{20}$
5	501.3237	$C_{30}H_{46}O_6$	89	1081.5193	$C_{53}H_{80}O_{20}$
6	503.3380	$C_{29}H_{46}O_4$	90	1087.5311	$C_{53}H_{84}O_{23}$
7	517.3175	$C_{29}H_{44}O_5$	91	1087.5345	$C_{52}H_{82}O_{21}$
8	517.3182	$C_{30}H_{46}O_7$	92	1103.5239	$C_{52}H_{82}O_{22}$
9	531.3325	$C_{30}H_{46}O_5$	93	1103.5653	$C_{53}H_{86}O_{21}$
10	531.3333	$C_{30}H_{46}O_5$	94	1105.6847	$C_{57}H_{102}O_{20}$
11	533.3487	$C_{30}H_{48}O_5$	95	1115.5640	$C_{55}H_{88}O_{23}$
12	535.2236	$C_{30}H_{34}O_6$	96	1117.5443	$C_{53}H_{84}O_{22}$
13	535.3644	$C_{31}H_{52}O_7$	97	1119.5597	$C_{53}H_{86}O_{22}$
14	539.3032	$C_{31}H_{42}O_5$	98	1123.5116	$C_{59}H_{80}O_{21}$
15	545.3240	$C_{30}H_{44}O_6$	99	1123.6943	$C_{57}H_{104}O_{21}$
16	617.3709	$C_{35}H_{54}O_9$	100	1129.5441	$C_{54}H_{84}O_{22}$
17	633.3654	$C_{34}H_{52}O_8$	101	1129.5452	$C_{55}H_{86}O_{24}$
18	647.3813	$C_{35}H_{54}O_8$	102	1133.5754	$C_{54}H_{88}O_{22}$
19	649.3964	$C_{35}H_{56}O_8$	103	1135.5471	$C_{61}H_{84}O_{20}$
20	651.4121	$C_{35}H_{58}O_8$	104	1139.7245	$C_{65}H_{104}O_{16}$
21	663.3762	$C_{35}H_{54}O_9$	105	1145.5774	$C_{55}H_{88}O_{22}$
22	679.4072	$C_{36}H_{58}O_9$	106	1147.5563	$C_{54}H_{86}O_{23}$
23	741.3279	$C_{43}H_{50}O_{11}$	107	1155.5212	$C_{55}H_{82}O_{23}$
24	749.4109	$C_{39}H_{60}O_{11}$	108	1159.5557	$C_{55}H_{86}O_{23}$
25	749.4484	$C_{41}H_{66}O_{12}$	109	1161.5698	$C_{55}H_{88}O_{23}$
26	763.4282	$C_{40}H_{62}O_{11}$	110	1169.8250	$C_{57}H_{104}O_{21}$
27	763.4290	$C_{41}H_{64}O_{13}$	111	1173.5741	$C_{56}H_{88}O_{23}$
28	765.4429	$C_{41}H_{66}O_{13}$	112	1187.5471	$C_{56}H_{86}O_{24}$
29	765.4446	$C_{40}H_{64}O_{11}$	113	1187.5857	$C_{58}H_{92}O_{25}$
30	779.4225	$C_{41}H_{64}O_{14}$	114	1187.5861	$C_{58}H_{92}O_{25}$
31	779.4235	$C_{40}H_{62}O_{12}$	115	1203.5171	$C_{60}H_{84}O_{25}$
32	779.4601	$C_{41}H_{66}O_{11}$	116	1203.6188	$C_{59}H_{96}O_{25}$
33	781.4380	$C_{40}H_{64}O_{12}$	117	1205.5972	$C_{58}H_{94}O_{26}$
34	785.4095	$C_{43}H_{62}O_{13}$	118	1213.5612	$C_{58}H_{88}O_{24}$
35	785.4258	$C_{47}H_{62}O_{10}$	119	1219.5941	$C_{59}H_{96}O_{26}$
36	793.4390	$C_{41}H_{64}O_{12}$	120	1219.6117	$C_{59}H_{96}O_{26}$
37	795.4553	$C_{41}H_{66}O_{12}$	121	1219.6127	$C_{58}H_{94}O_{24}$
38	797.4341	$C_{40}H_{64}O_{13}$	122	1229.5961	$C_{60}H_{94}O_{26}$
39	809.4347	$C_{41}H_{64}O_{13}$	123	1229.5962	$C_{60}H_{94}O_{26}$
40	811.4500	$C_{41}H_{66}O_{13}$	124	1233.5917	$C_{59}H_{94}O_{27}$

Table S2 *Continued*

No.	Mass [*m/z*]	Formula	No.	Mass [*m/z*]	Formula
41	811.4864	$C_{42}H_{70}O_{12}$	125	1233.5924	$C_{58}H_{92}O_{25}$
42	813.4657	$C_{41}H_{68}O_{13}$	126	1235.6090	$C_{58}H_{94}O_{25}$
43	817.4377	$C_{44}H_{66}O_{14}$	127	1249.5203	$C_{60}H_{84}O_{25}$
44	825.4290	$C_{42}H_{66}O_{16}$	128	1249.5844	$C_{58}H_{92}O_{26}$
45	825.4652	$C_{42}H_{68}O_{13}$	129	1249.5914	$C_{58}H_{92}O_{26}$
46	841.4617	$C_{43}H_{70}O_{16}$	130	1249.6243	$C_{59}H_{96}O_{25}$
47	847.3814	$C_{46}H_{58}O_{13}$	131	1251.6023	$C_{58}H_{94}O_{26}$
48	851.4438	$C_{44}H_{68}O_{16}$	132	1263.6038	$C_{59}H_{94}O_{27}$
49	855.4758	$C_{43}H_{70}O_{14}$	133	1265.6187	$C_{59}H_{96}O_{26}$
50	875.6057	$C_{47}H_{88}O_{14}$	134	1275.6021	$C_{61}H_{96}O_{28}$
51	879.4072	$C_{47}H_{62}O_{13}$	135	1275.6007	$C_{60}H_{94}O_{27}$
52	879.4771	$C_{46}H_{72}O_{16}$	136	1279.5925	$C_{59}H_{94}O_{27}$
53	895.3824	$C_{39}H_{62}O_{20}$	137	1281.6143	$C_{59}H_{96}O_{27}$
54	895.4695	$C_{45}H_{70}O_{15}$	138	1287.7640	$C_{63}H_{116}O_{26}$
55	895.5067	$C_{47}H_{76}O_{16}$	139	1291.5278	$C_{58}H_{86}O_{29}$
56	897.4868	$C_{45}H_{72}O_{15}$	140	1291.5988	$C_{60}H_{94}O_{27}$
57	911.4997	$C_{46}H_{74}O_{15}$	141	1291.6328	$C_{61}H_{98}O_{26}$
58	911.5030	$C_{47}H_{76}0_{17}$	142	1293.6133	$C_{60}H_{96}O_{27}$
59	925.4113	$C_{44}H_{64}O_{18}$	143	1295.6217	$C_{60}H_{98}O_{27}$
60	925.4796	$C_{46}H_{72}O_{16}$	144	1297.6021	$C_{60}H_{98}O_{30}$
61	927.4977	$C_{46}H_{74}O_{16}$	145	1301.5782	$C_{61}H_{92}O_{27}$
62	937.4811	$C_{48}H_{74}O_{18}$	146	1305.6130	$C_{61}H_{96}O_{27}$
63	939.4977	$C_{48}H_{76}O_{18}$	147	1307.6284	$C_{61}H_{98}O_{27}$
64	941.4739	$C_{46}H_{72}O_{17}$	148	1317.5728	$C_{61}H_{92}O_{28}$
65	941.5120	$C_{47}H_{76}O_{16}$	149	1317.6093	$C_{62}H_{96}O_{27}$
66	943.7039	$C_{53}H_{100}O_{13}$	150	1323.6232	$C_{61}H_{98}O_{28}$
67	955.4905	$C_{47}H_{74}O_{17}$	151	1343.5870	$C_{63}H_{94}O_{28}$
68	955.4921	$C_{48}H_{76}O_{19}$	152	1343.7899	$C_{66}H_{120}O_{27}$
69	957.5071	$C_{47}H_{76}O_{17}$	153	1351.6381	$C_{60}H_{104}O_{33}$
70	971.4866	$C_{48}H_{76}O_{20}$	154	1359.6226	$C_{64}H_{98}O_{28}$
71	971.5224	$C_{48}H_{78}O_{17}$	155	1365.6356	$C_{63}H_{100}O_{29}$
72	971.6624	$C_{47}H_{74}O_{18}$	156	1375.6132	$C_{65}H_{100}O_{31}$
73	973.5010	$C_{47}H_{76}O_{18}$	157	1381.6653	$C_{64}H_{104}O_{29}$
74	983.4863	$C_{48}H_{74}O_{18}$	158	1381.6656	$C_{65}H_{106}O_{31}$
75	987.5175	$C_{48}H_{78}O_{18}$	159	1395.6453	$C_{64}H_{102}O_{30}$
76	997.5002	$C_{49}H_{76}O_{18}$	160	1411.6366	$C_{64}H_{102}O_{31}$
77	997.5031	$C_{50}H_{78}O_{20}$	161	1411.6753	$C_{65}H_{106}O_{30}$
78	999.4807	$C_{48}H_{74}O_{19}$	162	1427.6703	$C_{65}H_{106}O_{31}$
79	1013.5329	$C_{50}H_{80}O_{18}$	163	1433.7686	$C_{64}H_{122}O_{34}$
80	1015.5142	$C_{49}H_{78}O_{19}$	164	1435.8531	$C_{73}H_{128}O_{27}$

Table S2 *Continued*

No.	Mass [*m/z*]	Formula	No.	Mass [*m/z*]	Formula
81	1023.4797	$C_{50}H_{74}O_{19}$	165	1437.6547	$C_{66}H_{104}O_{31}$
82	1029.0399	$C_{52}H_{22}O_{24}$	166	1459.7366	$C_{68}H_{116}O_{33}$
83	1029.5288	$C_{50}H_{80}O_{19}$	167	1465.8455	$C_{70}H_{130}O_{31}$
84	1039.5109	$C_{51}H_{78}O_{19}$	168	1469.6805	$C_{67}H_{108}O_{32}$

Table S3 164 potential targets of 26 BBB-permeated saponins related to AD

No.	Protein Name	Gene Symbol	No.	Protein Name	Gene Symbol
1	Signal transducer and activator of transcription 3	STAT3	83	Adenosine kinase	ADK
2	Prothrombin	F2	84	Fibroblast growth factor receptor 2	FGFR2
3	Bcl-2-like protein 1	BCL2L1	85	Glycogen synthase kinase-3 beta	GSK3B
4	Transcription factor AP-1	JUN	86	RAC-beta serine/threonine-protein kinase	AKT2
5	Prostaglandin G/H synthase 2	PTGS2	87	NAD	NQO1
6	E3 ubiquitin-protein ligase Mdm2	MDM2	88	Death-associated protein kinase 1	DAPK1
7	Serine/threonine-protein phosphatase 2A activator	PTPA	89	Urokinase-type plasminogen activator	PLAU
8	Corticosteroid 11-beta-dehydrogenase isozyme 1	HSD11B1	90	Coagulation factor VII	F7
9	Sodium/potassium-transporting ATPase subunit alpha-1	ATP1A1	91	Poly	PARP1
10	Protein kinase C delta type	PRKCD	92	Alpha-1-antitrypsin	SERPINA1
11	Protein kinase C epsilon type	PRKCE	93	Tyrosine-protein kinase JAK3	JAK3
12	Protein kinase C theta type	PRKCQ	94	Fibroblast growth factor receptor 1	FGFR1
13	Presenilin-2	PSEN2	95	Catalase	CAT
14	Glycine receptor subunit alpha-1	GLRA1	96	Aldehyde dehydrogenase, mitochondrial	ALDH2
15	Glycine receptor subunit alpha-2	GLRA2	97	Retinoic acid receptor beta	RARB
16	Gamma-secretase subunit PEN-2	PSENEN	98	Receptor tyrosine-protein kinase erbB-4	ERBB4
17	Nicastrin	NCSTN	99	Glucocorticoid receptor	NR3C1
18	Gamma-secretase subunit APH-1A	APH1A	100	Peroxisome proliferator-activated receptor delta	PPARD
19	Presenilin-1	PSEN1	101	Neutrophil elastase	ELANE
20	Gamma-secretase subunit APH-1B	APH1B	102	Histamine N-methyltransferase	HNMT
21	Mitogen-activated protein kinase 1	MAPK1	103	Cytochrome P450 2C9	CYP2C9
22	Bone morphogenetic protein 2	BMP2	104	Retinoic acid receptor alpha	RARA
23	Glutathione S-transferase P	GSTP1	105	Insulin-like growth factor 1 receptor	IGF1R

Table S3 *Continued*

No.	Protein Name	Gene Symbol	No.	Protein Name	Gene Symbol
24	Mitogen-activated protein kinase 10	MAPK10	106	Phenylethanolamine N-methyltransferase	PNMT
25	Neutrophil gelatinase-associated lipocalin	LCN2	107	Interleukin-2	IL2
26	Peroxisome proliferator-activated receptor gamma	PPARG	108	Oxysterols receptor LXR-alpha	NR1H3
27	Albumin	ALB	109	Matrix metalloproteinase-9	MMP9
28	Caspase-7	CASP7	110	C-C motif chemokine 5	CCL5
29	Kinesin-like protein KIF11	KIF11	111	Tyrosine-protein kinase ZAP-70	ZAP70
30	Apolipoprotein A-II	APOA2	112	Tyrosine-protein kinase JAK2	JAK2
31	Estrogen receptor beta	ESR2	113	Tyrosine-protein kinase ABL1	ABL1
32	Aromatase	CYP19A1	114	Prosaposin	PSAP
33	Transthyretin	TTR	115	Protein S100-A9	S100A9
34	Stromelysin-1	MMP3	116	72 kDa type IV collagenase	MMP2
35	Aldo-keto reductase family 1 member B1	AKR1B1	117	Mitogen-activated protein kinase 12	MAPK12
36	Amine oxidase	MAOB	118	Hepatocyte growth factor	HGF
37	Lysosomal acid glucosylceramidase	GBA	119	Neprilysin	MME
38	Cathepsin D	CTSD	120	Cystathionine beta-synthase	CBS
39	Mitogen-activated protein kinase 8	MAPK8	121	Caspase-1	CASP1
40	Cholinesterase	BCHE	122	Hexokinase-4	GCK
41	Androgen receptor	AR	123	Phosphatidylinositol 3-kinase regulatory subunit alpha	PIK3R1
42	Caspase-3	CASP3	124	Vitamin D3 receptor	VDR
43	Coagulation factor X	F10	125	E3 ubiquitin-protein ligase XIAP	XIAP
44	Proto-oncogene tyrosine-protein kinase Src	SRC	126	Tryptophan 5-hydroxylase 1	TPH1
45	Epidermal growth factor receptor	EGFR	127	GTPase HRas	HRAS
46	Angiogenin	ANG	128	Angiopoietin-1 receptor	TEK

Table S3 *Continued*

No.	Protein Name	Gene Symbol	No.	Protein Name	Gene Symbol
47	Nitric oxide synthase, endothelial	NOS3	129	Glycogen phosphorylase, liver form	PYGL
48	TGF-beta receptor type-1	TGFBR1	130	Mast/stem cell growth factor receptor Kit	KIT
49	Kinesin-1 heavy chain	KIF5B	131	Coagulation factor XI	F11
50	Disintegrin and metalloproteinase domain-containing protein 17	ADAM17	132	Insulin receptor	INSR
51	cAMP-dependent protein kinase catalytic subunit alpha	PRKACA	133	Heme oxygenase 1	HMOX1
52	Beta-secretase 1	BACE1	134	Angiotensin-converting enzyme	ACE
53	Vascular endothelial growth factor receptor 2	KDR	135	Transforming growth factor beta-2 proprotein	TGFB2
54	Chitotriosidase-1	CHIT1	136	Apoptotic protease-activating factor 1	APAF1
55	Collagenase 3	MMP13	137	Platelet glycoprotein Ib alpha chain	GP1BA
56	Tyrosine-protein phosphatase non-receptor type 11	PTPN11	138	Glutathione S-transferase Mu 1	GSTM1
57	Glutathione reductase, mitochondrial	GSR	139	Interstitial collagenase	MMP1
58	Estrogen receptor	ESR1	140	Cell division control protein 42 homolog	CDC42
59	Cathepsin B	CTSB	141	Signal transducer and activator of transcription 1-alpha/beta	STAT1
60	Macrophage migration inhibitory factor	MIF	142	Lithostathine-1-alpha	REG1A
61	Mineralocorticoid receptor	NR3C2	143	Glucose-6-phosphate 1-dehydrogenase	G6PD
62	Heat shock cognate 71 kDa protein	HSPA8	144	Beta-hexosaminidase subunit beta	HEXB
63	Hepatocyte growth factor receptor	MET	145	Fructose-bisphosphate aldolase A	ALDOA
64	cAMP-specific 3',5'-cyclic phosphodiesterase 4D	PDE4D	146	E-selectin	SELE
65	Macrophage metalloelastase	MMP12	147	Complement factor B	CFB
66	Mitogen-activated protein kinase 14	MAPK14	148	TGF-beta receptor type-2	TGFBR2
67	Alcohol dehydrogenase 1C	ADH1C	149	Casein kinase II subunit alpha	CSNK2A1
68	Renin	REN	150	Hexokinase-1	HK1
69	Phospholipase A2, membrane associated	PLA2G2A	151	Calmodulin-1	CALM1

Table S3 *Continued*

No.	Protein Name	Gene Symbol	No.	Protein Name	Gene Symbol
70	Phenylalanine-4-hydroxylase	PAH	152	Nitric oxide synthase, inducible	NOS2
71	3-hydroxy-3-methylglutaryl-coenzyme A reductase	HMGCR	153	P-selectin	SELP
72	Insulin-like growth factor I	IGF1	154	Arylsulfatase A	ARSA
73	Ornithine transcarbamylase, mitochondrial	OTC	155	Cyclin-dependent kinase 5 activator 1	CDK5R1
74	Retinol-binding protein 4	RBP4	156	RAC-alpha serine/threonine-protein kinase	AKT1
75	Bile acid receptor	NR1H4	157	Hypoxanthine-guanine phosphoribosyltransferase	HPRT1
76	Tyrosine--tRNA ligase, cytoplasmic	YARS1	158	Tryptophan--tRNA ligase, cytoplasmic	WARS1
77	Superoxide dismutase	SOD2	159	SPARC	SPARC
78	Cathepsin K	CTSK	160	Glutamate carboxypeptidase 2	FOLH1
79	Tyrosine-protein kinase SYK	SYK	161	A disintegrin and metalloproteinase with thrombospondin motifs 4	ADAMTS4
80	Peroxisome proliferator-activated receptor alpha	PPARA	162	Glutathione S-transferase omega-1	GSTO1
81	Heat shock protein HSP 90-alpha	HSP90AA1	163	Fibrinogen gamma chain	FGG
82	Dual specificity mitogen-activated protein kinase kinase 1	MAP2K1	164	Tyrosine-protein kinase BTK	BTK

Table S4 Molecular docking score of pivotal compounds and targets

Compound	Target	PDBID	Score
B1	MAPK1	3erk	9.2615
	MAP2K1	3w8q	6.1645
	HRAS	**6bof**	**10.1125**
	MAPK8	4hyu	7.3986
	MAPK10	4y46	6.4939
	MAPK14	5xyy	5.8726
B11	MAPK1	3erk	5.9672
	MAP2K1	5kkr	6.4056
	HRAS	**6umk**	**9.8568**
	MAPK8	4izy	7.9283
	MAPK10	4kkh	7.2712
	MAPK14	5xyy	5.7924
B12	**MAPK1**	**6opk**	**7.862**
	MAP2K1	6ate	4.4781
	HRAS	6umk	7.429
	MAPK8	4izy	7.2632
	MAPK10	4kkh	5.5554
	MAPK14	2qd9	4.7803
B22	MAPK1	6opi	10.5647
	MAP2K1	5kkr	6.2576
	HRAS	1wms	9.8913
	MAPK8	**4hyu**	**10.8325**
	MAPK10	4w4w	9.7695
	MAPK14	3oef	8.5372
B23	MAPK1	6oph	6.8208
	MAP2K1	5kkr	4.3412
	HRAS	1wms	7.1727
	MAPK8	**4izy**	**8.5017**
	MAPK10	4kkh	7.4723
	MAPK14	5xyy	3.9949
B24	MAPK1	6opi	6.0721
	MAP2K1	6ate	4.2487
	HRAS	1wms	6.8063
	MAPK8	**4izy**	**10.7487**
	MAPK10	4kkh	5.2713
	MAPK14	6m95	1.5286

The bold color means the highest score in experiments.