

Supplementary Information

Table S1. The herb ingredients and their drug-likenesses.

CID	Drug Likeness	Herb Source
181271	0.86	Rhizoma Dioscoreae
6288	0.349	Rhizoma Dioscoreae
79025	0.305	Rhizoma Dioscoreae
33032	0.383	Rhizoma Dioscoreae
6508	0.317	Rhizoma Dioscoreae
6287	0.427	Rhizoma Dioscoreae
145742	0.387	Rhizoma Dioscoreae
5997	0.489	Rhizoma Dioscoreae
5318516	0.49	Rhizoma Dioscoreae
6306	0.472	Rhizoma Dioscoreae
442834	0.733	Rhizoma Dioscoreae
5283638	0.347	Rhizoma Dioscoreae
18950	0.305	Rhizoma Dioscoreae
5281326	0.36	Rhizoma Dioscoreae
119	0.398	Rhizoma Dioscoreae
5950	0.356	Rhizoma Dioscoreae
6137	0.451	Rhizoma Dioscoreae
176097	0.778	Rhizoma Dioscoreae
67678	0.317	Rhizoma Dioscoreae
5962	0.38	Rhizoma Dioscoreae

53297366	0.377	Rhizoma Dioscoreae
10466989	0.86	Rhizoma Dioscoreae
33005	0.269	Rhizoma Dioscoreae
5960	0.367	Rhizoma Dioscoreae
6665	0.513	Rhizoma Dioscoreae
173183	0.47	Rhizoma Dioscoreae
5951	0.334	Rhizoma Dioscoreae
3037102	0.458	Rhizoma Dioscoreae
971	0.428	Rhizoma Dioscoreae
65728	0.489	Rhizoma Dioscoreae
750	0.338	Rhizoma Dioscoreae
6274	0.418	Rhizoma Dioscoreae
6140	0.566	Rhizoma Dioscoreae
442711	0.881	Rhizoma Dioscoreae
6057	0.511	Rhizoma Dioscoreae
122544	0.363	Rhizoma Dioscoreae
172746	0.182	Rhizoma Dioscoreae
442694	0.749	Rhizoma Dioscoreae
6443896	0.59	Rhizoma Dioscoreae
890	0.024	Rhizoma Dioscoreae
5280896	0.605	Rhizoma Dioscoreae
99474	0.587	Rhizoma Dioscoreae
5320621	0.663	Rhizoma Dioscoreae

122159	0.733	Rhizoma Dioscoreae
681	0.55	Rhizoma Dioscoreae
204	0.339	Rhizoma Dioscoreae
6106	0.469	Rhizoma Dioscoreae
100199	0.789	Rhizoma Dioscoreae
15558616	0.437	Rhizoma Alismatis
11850	0.27	Rhizoma Alismatis
936	0.555	Rhizoma Alismatis
1252264	0.437	Rhizoma Alismatis
9996020	0.751	Rhizoma Alismatis
10458876	0.427	Rhizoma Alismatis
336892	0.758	Rhizoma Alismatis
6436630	0.191	Rhizoma Alismatis
10470100	0.605	Rhizoma Alismatis
5316550	0.48	Rhizoma Alismatis
10245341	0.542	Rhizoma Alismatis
44584326	0.818	Rhizoma Alismatis
305	0.419	Rhizoma Alismatis
21128	0.841	Rhizoma Alismatis
46829428	0.294	Rhizoma Alismatis
5317294	0.421	Rhizoma Alismatis
441434	0.077	Rhizoma Alismatis
3084460	0.301	Rhizoma Alismatis

12620	0.236	Rhizoma Alismatis
11105942	0.319	Rhizoma Alismatis
5284473	0.586	Rhizoma Alismatis
15558620	0.456	Rhizoma Alismatis
637282	0.745	Rhizoma Alismatis
14057170	0.435	Rhizoma Alismatis
5318916	0.529	Rhizoma Alismatis
44592456	0.035	Rhizoma Alismatis
3220	0.683	Rhizoma Alismatis
10005131	0.48	Rhizoma Alismatis
442420	0.496	Radix Rehmanniae Preparata
5281771	0.583~0.63	Radix Rehmanniae Preparata
5988	0.241	Radix Rehmanniae Preparata
13849	0.434	Radix Rehmanniae Preparata
59084578	0.531	Radix Rehmanniae Preparata
6325884	0.095	Radix Rehmanniae Preparata
6325881	0.141	Radix Rehmanniae Preparata
6325883	0.164	Radix Rehmanniae Preparata
6251	0.27	Radix Rehmanniae Preparata
46228750	0.045	Radix Rehmanniae Preparata
158144	0.319	Radix Rehmanniae Preparata
91458	0.47	Radix Rehmanniae Preparata
5318708	0.479	Radix Rehmanniae Preparata

179611	0.346	Radix Rehmanniae Preparata
5280666	0.788	Radix Rehmanniae Preparata
439242	0.147	Radix Rehmanniae Preparata
11953944	0.583~0.63	Radix Rehmanniae Preparata
66021	0.43	Radix Rehmanniae Preparata
8215	0.24	Radix Rehmanniae Preparata
5318707	0.657	Radix Rehmanniae Preparata
46173850	0.534	Radix Rehmanniae Preparata
237332	0.585	Radix Rehmanniae Preparata
91520	0.454	Radix Rehmanniae Preparata
5280335	0.38	Radix Rehmanniae Preparata
5320914	0.477	Radix Rehmanniae Preparata
439531	0.097	Radix Rehmanniae Preparata
7405	0.489	Radix Rehmanniae Preparata
59869172	0.433	Radix Rehmanniae Preparata
11968648	0.164	Radix Rehmanniae Preparata
6452750	0.341	Radix Rehmanniae Preparata
643801	0.278	Radix Rehmanniae Preparata
6452294	0.316	Radix Rehmanniae Preparata
1110	0.53	Radix Rehmanniae Preparata
445858	0.718	Radix Rehmanniae Preparata
177143	0.56	Radix Rehmanniae Preparata
11968737	0.393	Radix Rehmanniae Preparata

10467	0.277	Radix Rehmanniae Preparata
6443015	0.227	Radix Rehmanniae Preparata
10430488	0.353	Radix Rehmanniae Preparata
33934	0.306	Radix Rehmanniae Preparata
20393	0.683	Radix Rehmanniae Preparata
44424830	0.198	Poria cocos
16757534	0.256	Poria cocos
12314445	0.309	Poria cocos
59707781	0.161	Poria cocos
379	0.622	Poria cocos
247705	0.511	Poria cocos
3086648	0.289	Poria cocos
44152250	0.466	Poria cocos
985	0.391	Poria cocos
5318130	0.294	Poria cocos
237891	0.315	Poria cocos
74112	0.338	Poria cocos
345510	0.307	Poria cocos
6744	0.435	Poria cocos
56841132	0.344	Poria cocos
3893	0.561	Poria cocos
11062697	0.433	Poria cocos
5484385	0.212	Poria cocos

5471851	0.254	Poria cocos
8180	0.588	Poria cocos
15391340	0.46	Poria cocos
519298	0.427	Poria cocos
5742590	0.458	Poria cocos
73659	0.442	Fructus Corn
10296	0.699	Fructus Corn
73467	0.392	Fructus Corn
9855795	0.427	Fructus Corn
7222	0.544	Fructus Corn
12391	0.32	Fructus Corn
9161	0.544	Fructus Corn
3083834	0.578	Fructus Corn
69423	0.288	Fructus Corn
12523	0.317	Fructus Corn
323	0.522	Fructus Corn
92094	0.377	Fructus Corn
5274585	0.536	Fructus Corn
7055	0.529	Fructus Corn
995	0.461	Fructus Corn
994	0.566	Fructus Corn
5144	0.622	Fructus Corn
11228693	0.312	Fructus Corn

7967	0.446	Fructus Corn
138812	0.209	Fructus Corn
557445	0.439	Fructus Corn
7127	0.66	Fructus Corn
94321	0.292	Fructus Corn
12389	0.344	Fructus Corn
12388	0.373	Fructus Corn
6560	0.488	Fructus Corn
92729	0.367	Fructus Corn
16132398	0.409~0.489	Fructus Corn
11287	0.545	Fructus Corn
5282184	0.174	Fructus Corn
102611	0.515	Fructus Corn
445638	0.412	Fructus Corn
595	0.317	Fructus Corn
6853	0.562	Fructus Corn
6988	0.488	Fructus Corn
10329	0.508	Fructus Corn
31404	0.753	Fructus Corn
5281855	0.572	Fructus Corn
6386	0.445	Fructus Corn
637563	0.626	Fructus Corn
6782	0.534	Fructus Corn

12398	0.287	Fructus Corn
3026	0.475	Fructus Corn
31256	0.553	Fructus Corn
525	0.459	Fructus Corn
24721416	0.322	Fructus Corn
10398656	0.669	Fructus Corn
7996	0.555	Fructus Corn
521556	0.282	Fructus Corn
8203	0.192	Fructus Corn
16131156	0.007	Fructus Corn
11635	0.274	Fructus Corn
9316	0.165	Fructus Corn
289985	0.475	Fructus Corn
442360	0.578	Fructus Corn
11005	0.48	Fructus Corn
39150	0.221	Fructus Corn
5280794	0.363	Fructus Corn
445354	0.412	Fructus Corn
92139	0.578	Fructus Corn
24360	0.794	Fructus Corn
15266	0.306	Fructus Corn
5280450	0.294	Fructus Corn
19775	0.331	Fructus Corn

65340	0.612	Fructus Corn
73170	0.401	Fructus Corn
12401	0.262	Fructus Corn
8217	0.258	Fructus Corn
161036	0.353	Fructus Corn
73219	0.798	Fructus Corn
857	0.469	Fructus Corn
7269	0.506	Fructus Corn
442355	0.562	Fructus Corn
471122	0.356~0.489	Fructus Corn
10248	0.696	Fructus Corn
165007	0.221	Fructus Corn
25201832	0.443~0.624	Fructus Corn
73178	0.489	Fructus Corn
568	0.488	Fructus Corn
4276	0.689	Fructus Corn
123409	0.322	Fructus Corn
74138	0.208	Fructus Corn
85785	0.35	Fructus Corn
608115	0.731	Fructus Corn
7002	0.529	Fructus Corn
5365371	0.238	Fructus Corn
30398	0.292	Fructus Corn

3036237	0.222	Fructus Corn
7274	0.326	Fructus Corn
158193	0.356~0.489	Fructus Corn
93065	0.278	Fructus Corn
8181	0.313	Fructus Corn
1183	0.65	Fructus Corn
7765	0.508	Fructus Corn
16129730	0.409~0.489	Fructus Corn
6054	0.631	Fructus Corn
427877	0.631	Fructus Corn
17100	0.575	Fructus Corn
8221	0.31	Fructus Corn
15267	0.324	Fructus Corn
15265	0.292	Fructus Corn
5641	0.523	Fructus Corn
11006	0.302	Fructus Corn
124024	0.489	Fructus Corn
18936	0.233	Fructus Corn
219219	0.565	Fructus Corn
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875	0.382	Fructus Corn
29075	0.245	Fructus Corn
107905	0.32	Fructus Corn

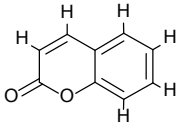
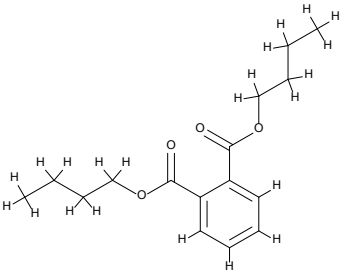
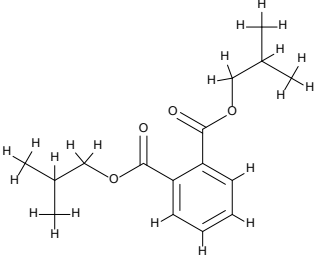
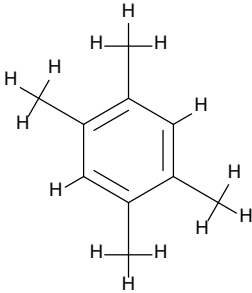
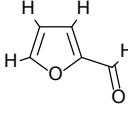
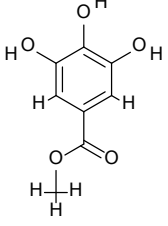
8679	0.678	Fructus Corn
294705	0.227	Fructus Corn
15979	0.334	Fructus Corn
7501	0.513	Fructus Corn
31260	0.538	Fructus Corn
73179	0.009	Fructus Corn
16132407	0.409~0.489	Fructus Corn
611	0.383	Fructus Corn
8418	0.461	Fructus Corn
72	0.527	Fructus Corn
6371716	0.148	Fructus Corn
87691	0.336	Fructus Corn
5363269	0.206	Fructus Corn
12366	0.286	Fructus Corn
131348	0.172	Fructus Corn
14896	0.449	Fructus Corn
262	0.47	Fructus Corn
13629	0.548	Fructus Corn
853433	0.727	Fructus Corn
636822	0.761	Fructus Corn
12302243	0.611	Fructus Corn
7428	0.362	Fructus Corn
8857	0.456	Fructus Corn

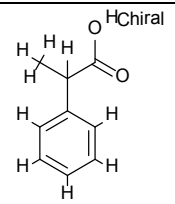
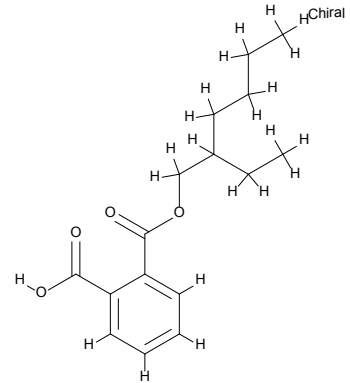
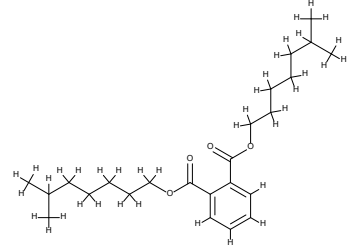
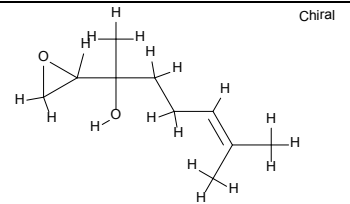
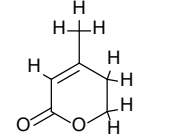
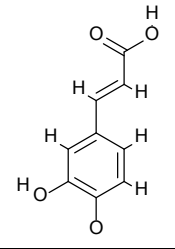
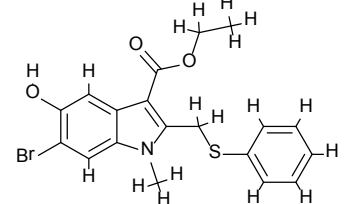
7362	0.479	Fructus Corn
64945	0.443	Fructus Corn
442534	0.822	Cortex Moutan
689043	0.475	Cortex Moutan
135	0.613	Cortex Moutan
157139	0.497	Cortex Moutan
9064	0.514	Cortex Moutan
64971	0.463	Cortex Moutan
2214	0.674	Cortex Moutan
222284	0.435	Cortex Moutan
370	0.368	Cortex Moutan
46882884	0.68	Cortex Moutan
133475	0.832	Cortex Moutan
6781	0.547	Cortex Moutan
10258205	0.489~0.704	Cortex Moutan
65238	0.489	Cortex Moutan
22116985	0.177	Cortex Moutan
46882880	0.599~0.712	Cortex Moutan
3314	0.696	Cortex Moutan
8892	0.608	Cortex Moutan
445639	0.333	Cortex Moutan
12820	0.53	Cortex Moutan
243	0.612	Cortex Moutan

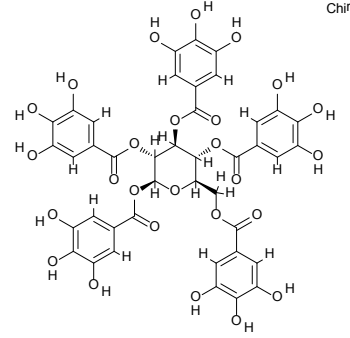
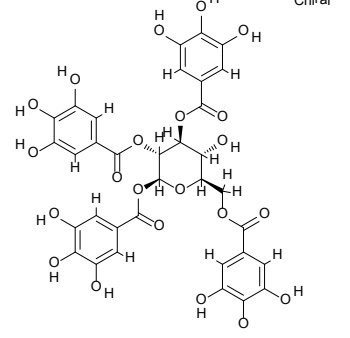
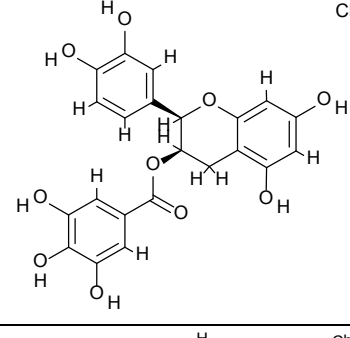
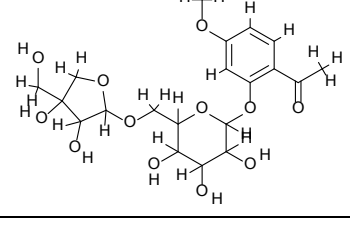
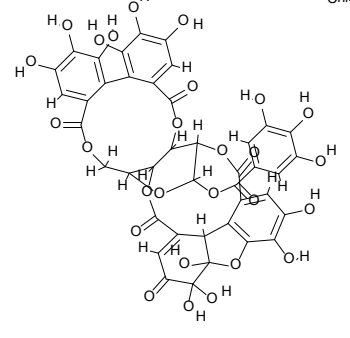
11092	0.674	Cortex Moutan
3036133	0.489~0.544	Cortex Moutan
7361	0.542	Cortex Moutan
442923	0.704	Cortex Moutan
388792	0.523	Cortex Moutan
10258206	0.489~0.704	Cortex Moutan
10494	0.446	Cortex Moutan
72326	0.492	Cortex Moutan
5280343	0.506	Cortex Moutan
99650	0.712	Cortex Moutan
95693	0.674	Cortex Moutan
99477	0.59	Cortex Moutan
53384347	0.527	Cortex Moutan
127509	0.704	Cortex Moutan
5321547	0.489~0.704	Cortex Moutan

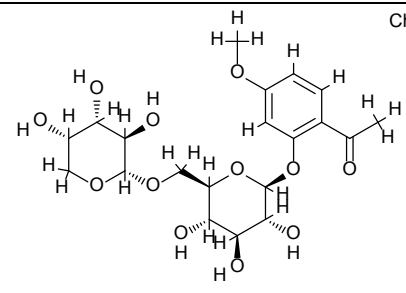
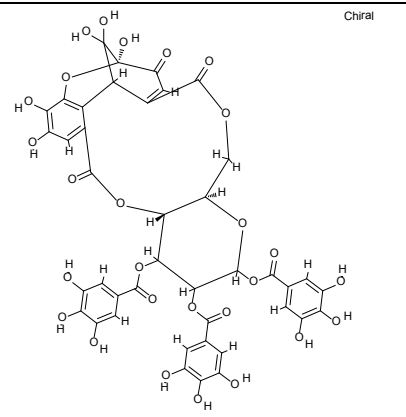
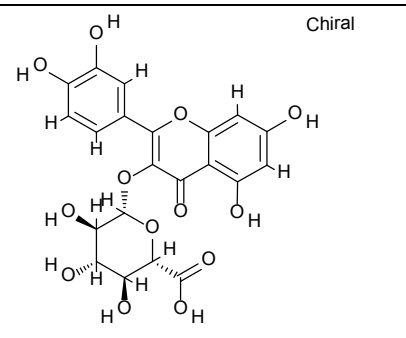
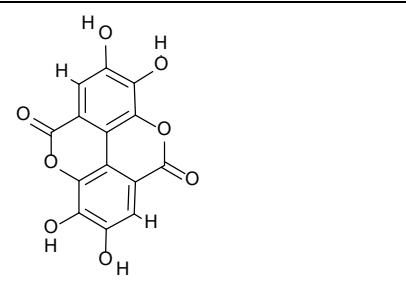
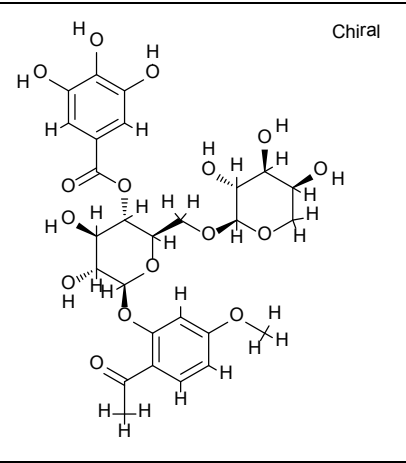
* For hydrolysable tannins and glycosides, the drug-likenesses were calculated after deglycosylation; the range of the drug-likenesses of compound fragments is given if there were more than one fragments after removing glycan.

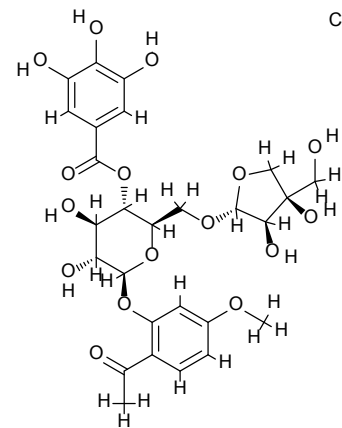
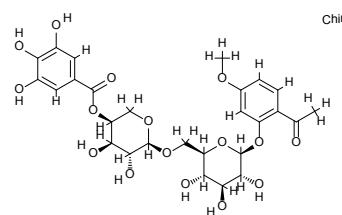
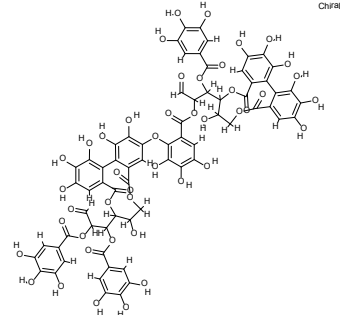
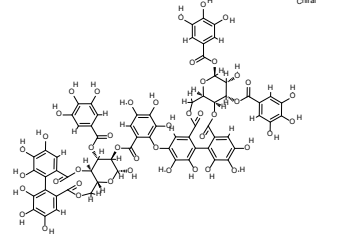
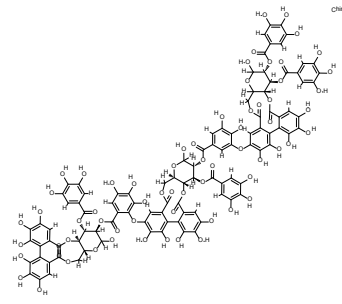
Table S1. Top 25% ranked compounds in LWDH.

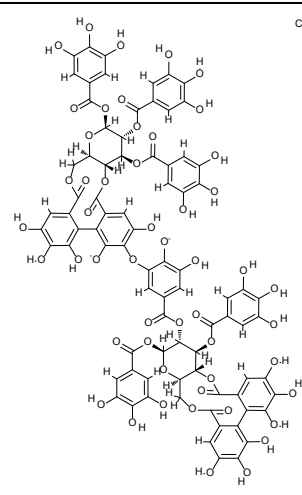
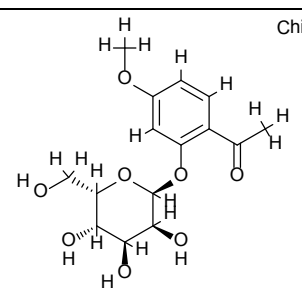
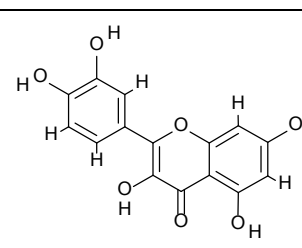
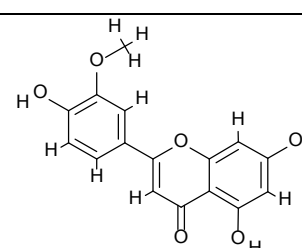
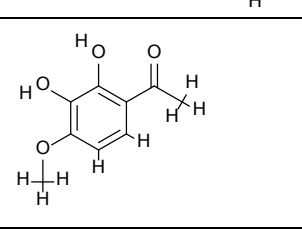
Chemical Name	Herb source	CID	Efficacy scores	Group	Structure
Coumarin	Fructus Corn	323	0.62	A	
Dibutyl phthalate	Fructus Corn	3026	0.56	A	
Diisobutyl phthalate	Fructus Corn	6782	0.57	A	
1,2,4,5-tetramethylbenzene	Fructus Corn	7269	0.46	A	
Furfural	Fructus Corn	7362	0.51	A	
Methyl gallate	Fructus Corn	7428	0.47	A	

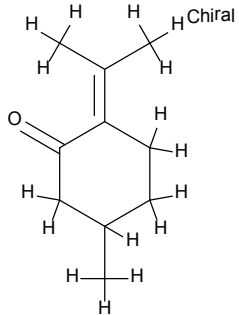
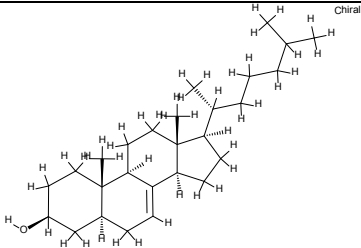
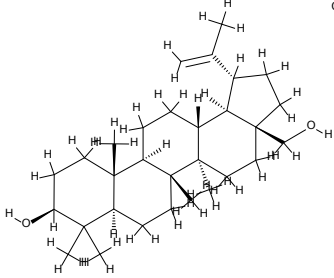
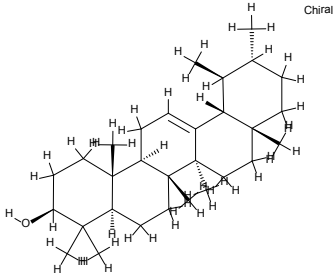
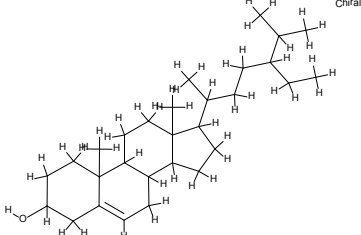
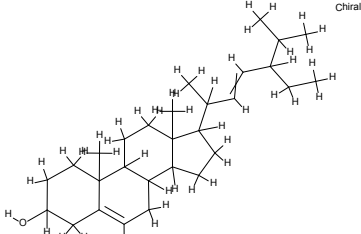
2-Phenylpropionic acid	Fructus Corn	10296	0.63	A	
Mono[2-ethylhexyl] ester	Radix Rehmanniae Preparata	20393	0.63	A	
Diisooctyl ester	Radix Rehmanniae Preparata	33934	0.61	A	
Linalool oxide	Fructus Corn	102611	0.60	A	
Dehydromevalonic lactone	Fructus Corn	557445	0.47	A	
Caffeic acid	Cortex Moutan	689043	0.58	A	
1h-indole-3-carboxylic acid	Rhizoma Alismatis	1252264	0.71	A	

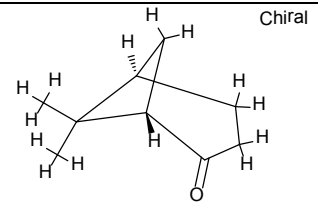
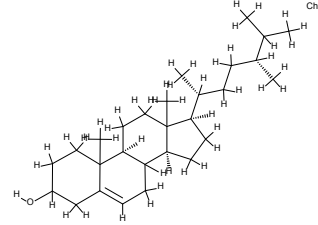
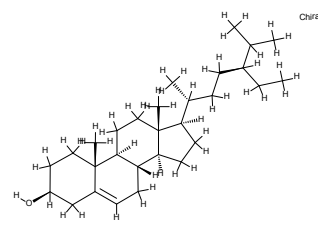
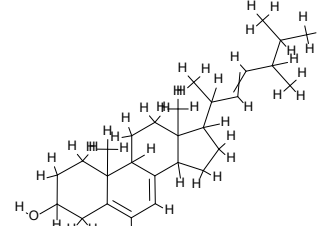
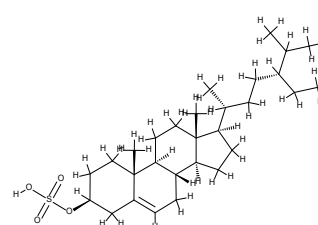
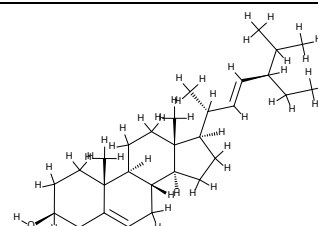
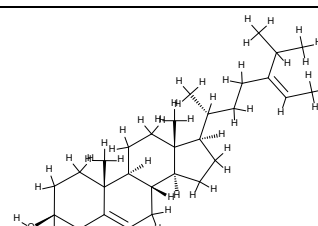
1,2,3,4,6-pentagalloylglucose	Cortex Moutan	65238	0.50	B	
1,2,3,6-tetra-O-galloyl-β-D-glucose	Fructus Corn	73178	0.51	B	
(-)-Epicatechin-3-O-gallate	Fructus Corn	107905	0.49	B	
Apiopaeonoside	Cortex Moutan	127509	0.49	B	
1-O-Galloyl-4,6-(S)-hexahydroxydiphenyl-α-D-glucose	Fructus Corn	158193	0.49	B	

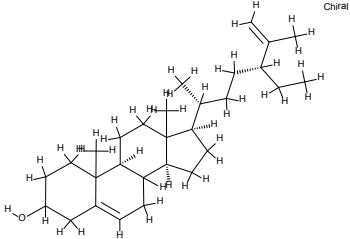
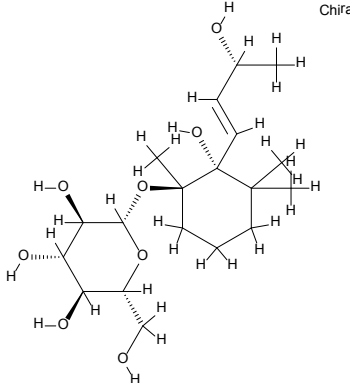
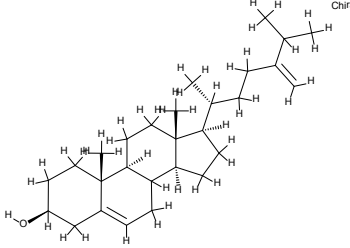
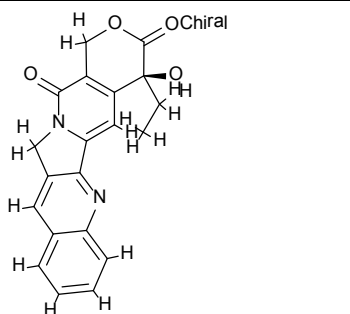
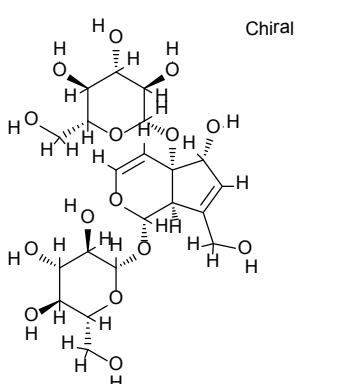
Paeonolide	Cortex Moutan	442923	0.56	B	
Isoterchebin	Fructus Corn	471122	0.54	B	
Quercetin 3-O-β-D- Glucuron ide	Fructus Corn	5274585	0.81	B	
Hexahydroxydiph enic acid	Fructus Corn	5281855	0.60	B	
Suffruticoside D	Cortex Moutan	5321547	0.61	B	

Suffruticoside B	Cortex Moutan	10258205	0.59	B	 Chiral
Suffruticoside A	Cortex Moutan	10258206	0.63	B	 Chiral
Camptothin A	Fructus Corn	16129730	0.49	B	 Chiral
Oenothin C	Fructus Corn	16132398	0.63	B	 Chiral
Cornusiin C	Fructus Corn	16132407	0.57	B	 Chiral

Cornusiin E	Fructus Corn	25201832	0.53	B	 Chiral
Paeonoside	Cortex Moutan	53384347	0.59	B	 Chiral
Quercetin	Cortex Moutan	5280343	0.68	B	
Luteolin-3'-methyl ether	Radix Rehmanniae Preparata	5280666	0.62	B	
2,3-dihydroxy-4-methoxyacetophenone	Cortex Moutan	12820	0.55	B	

Pulegone	Fructus Corn	6988	0.57	C	
Holest-7-enol	Rhizoma Dioscoreae	65728	0.60	C	
Betulin	Cortex Moutan	72326	0.69	C	
Alpha-amyrin	Fructus Corn	73170	0.66	C	
Stigmast-5-en-3-ol	Poria cocos	86821	0.63	C	
Stigmasterol	Poria cocos	122544	0.65	C	

Nopinone	Cortex Moutan	157139	0.50	C	 Chiral
Campesterol	Rhizoma Dioscoreae	173183	0.72	C	 Chiral
Beta-sitosterol	Rhizoma Alismatis	222284	0.69	C	 Chiral
Ergosterol	Rhizoma Dioscoreae	247705	0.65	C	 Chiral
Stigmast-8-en-3-beta-o; (3-beta,5-alpha,24 R)-form	Rhizoma Dioscoreae	3037102	0.90	C	 Chiral
Stigmasterol	Radix Rehmanniae Preparata	5280794	0.62	C	 Chiral
Isofucosterol	Rhizoma Dioscoreae	5281326	0.73	C	 Chiral

Clerosterol	Rhizoma Dioscoreae	5283638	0.75	C	
Rehmaionoside B (5R,6R,9R)-form	Radix Rehmanniae Preparata	10430488	0.49	C	
24-methylenecholesterol	Rhizoma Dioscoreae	53297366	0.71	C	
Camptothin A	Fructus Corn	24360	0.99	Other	
Melittoside	Radix Rehmanniae Preparata	11968737	0.59	Other	

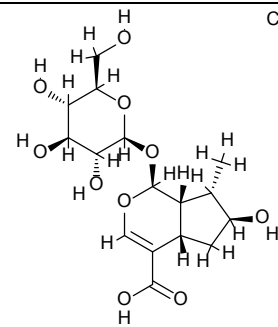
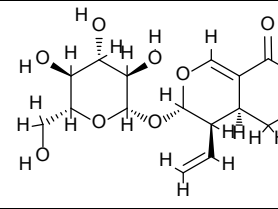
8-Epi-loganic acid	Radix Rehmanniae Preparata	158144	0.47	Other	 Chiral
Sweroside	Fructus Corn	161036	0.46	Other	 Chiral

Table S3. Compounds for Experimental validation

CID	Compounds name	Company	Test Targets
323	Coumarin	Acros Organics	RARA, ESR1, PPARG
689043	Caffeic acid	Acros Organics	
20393	Mono-(2-ethylhexyl)phthalate	Accustandard	
72326	Betulin	TOKYO CHEMICAL INDUSTRY CO., LTD.	CCR2, ESR1
73170	α -Amyrin and β -Amyrin	SIGMA	
5281326	Fucoesterol	SIGMA	

Table S4. Statistics of Chemical characters and Drug-likeness

		MW	ALogP	HBA	HBD	PSA	ROTB	AROM	Weighted QED
Herb ingredients	Mean	342.16	2.39	5.93	3.2	100.37	6.46	0.74	0.39
	SD	252.71	4.01	7.76	4.47	129.43	5.43	1.4	0.2
Approved drugs	Mean	339.53	2.39	4.51	1.65	78.59	4.84	1.44	0.67
	SD	129.77	2.1	2.68	1.38	47.19	3.36	0.99	0.18

Table S5. Top 15 connected genes in the compound-target-disease network

Entrez ID	Gene symbol	Degree	Connection number to other genes	Connection number to compounds	Connection number to diseases
2099	ESR1	80	24	38	18
8648	NCOA1	69	23	46	0
8204	NRIP1	54	18	36	0
10499	NCOA2	51	12	39	0
367	AR	47	21	19	7
2100	ESR2	37	6	22	9
6256	RXRA	34	5	29	0
190	NR0B1	34	5	27	2
7068	THRB	32	9	23	0
5467	PPARD	28	5	23	0
7067	THRA	28	5	23	0
506	ATP5B	27	2	24	1
6258	RXRG	26	12	13	1
2185	PTK2B	26	2	22	2

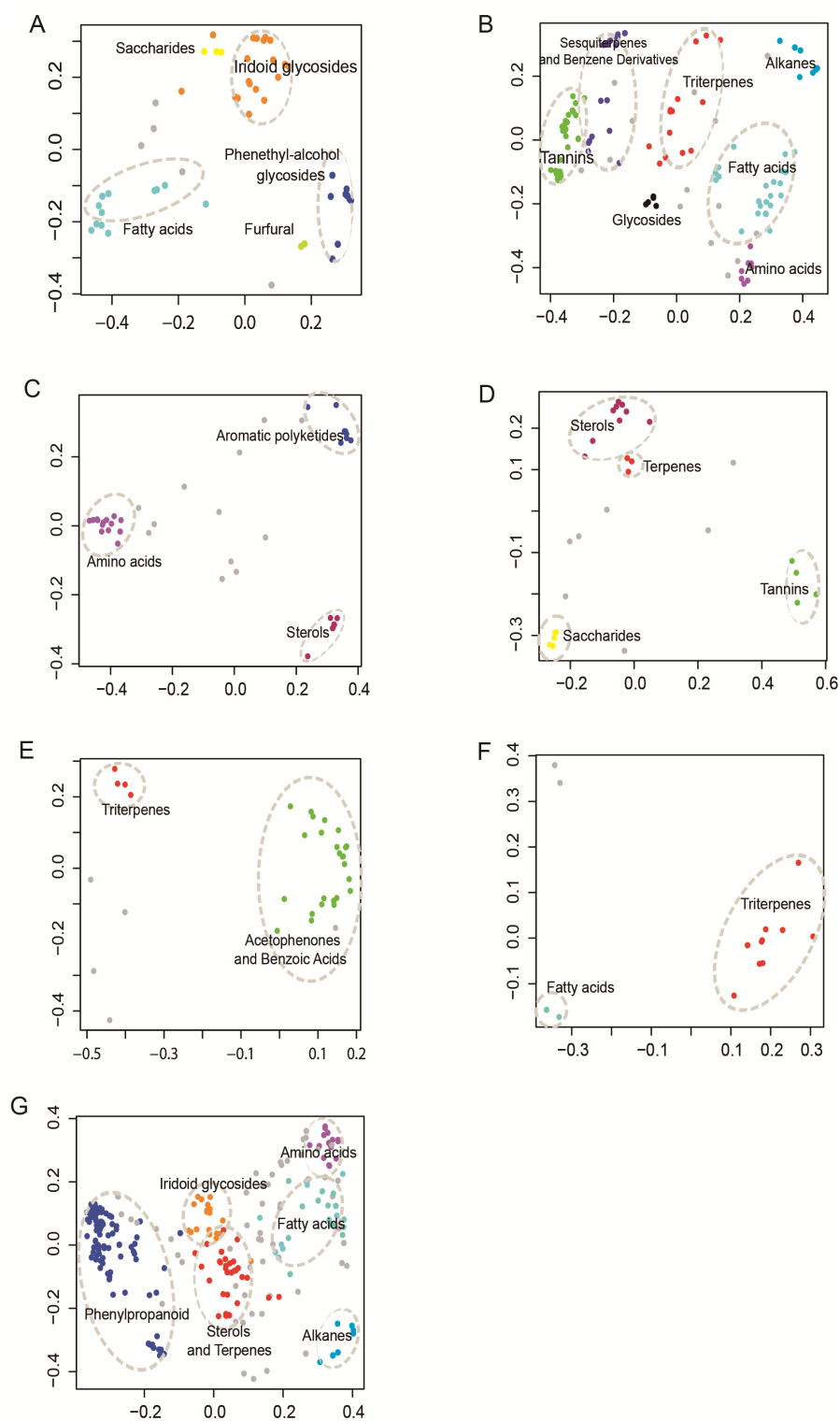
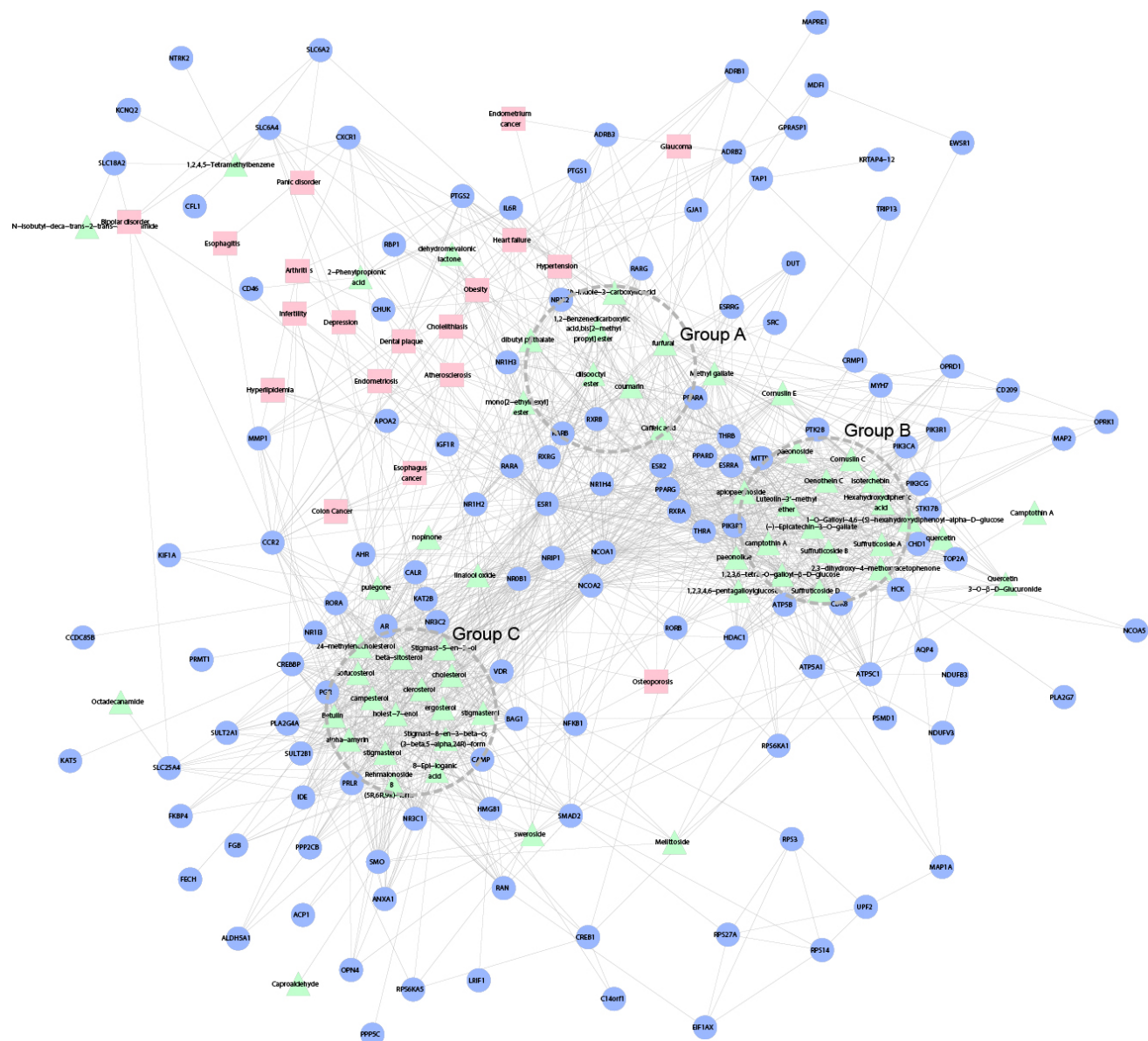
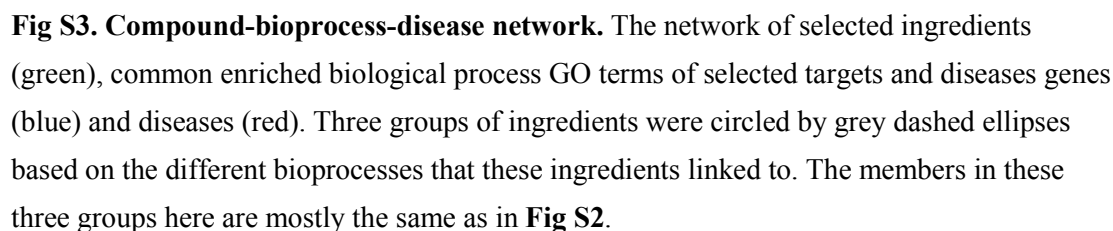


Fig S1. Chemical composition of LWDH. (A)-(F): MDS plots show different chemical families of each herb in LWDH. (A) Radix Rehmanniae Praeparata, (B) Fructus Corni, (C) Rhizoma Dioscoreae, (D) Rhizoma Alismatis, (E) Cortex Moutan, (F) Poria. (G) All ingredients in LWDH. Gray dots are ingredients which do not belong to any labeled chemical families.



FigS2. Compound-target-disease network. The whole network of selected ingredients (green), selected targets (blue) and diseases (red). Ingredients were roughly clustered as three groups based on different targets that these ingredients linked to.



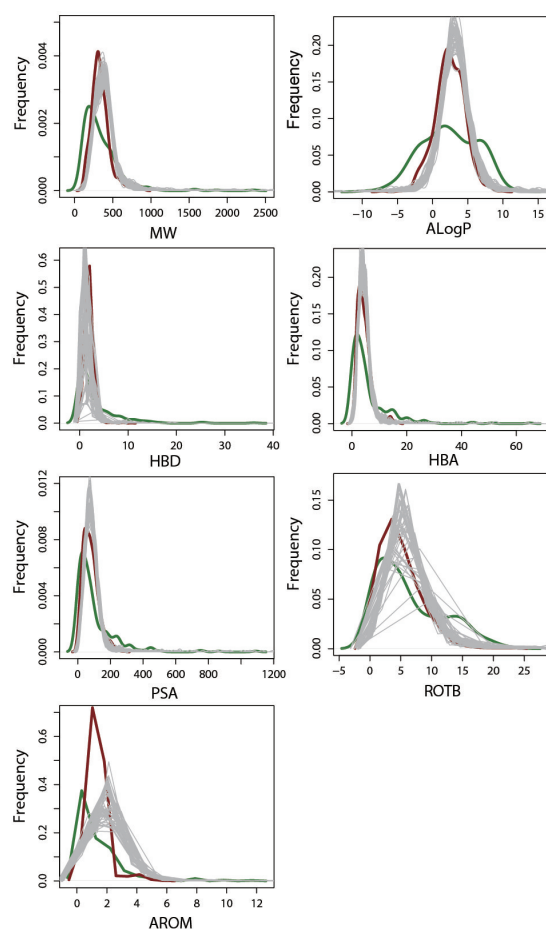


Fig S4 Comparing chemical characteristics of random compounds with ingredients of LWDH (A)-(G) are distributions of seven chemical characteristics of 30 randomly selected compound sets(gray), ingredients in LWDH(green) and approved drugs(red). MW: Molecular mass; ALogP: octanol–water partition coefficient; HBDs: number of hydrogen bond donors; HBA: number of hydrogen bond acceptors; PSA: molecular polar surface area; ROTB: number of rotatable bonds; AROM: number of aromatic rings.

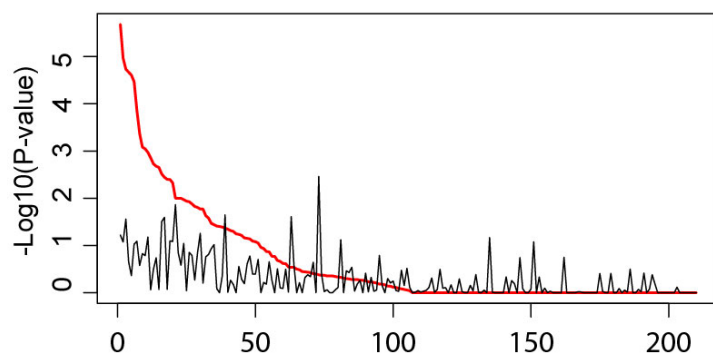


Fig S5 Comparing KEGG enrichment P-value distributions of selected targets of LWDH and targets of 30 random compound sets. X axis represents different KEGG pathways, Y axis represents the logarithms of KEGG enrichment P-values. Red line represents the KEGG enrichment P-value distribution of targets of LWDH; gray line is the average of KEGG enrichment P-value distributions of predicted targets of 30 random compound sets.