Metabolomic Data Analysis with MetaboAnalyst 6.0

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1 Background

The Pathway Analysis module combines results from powerful pathway enrichment analysis with pathway topology analysis to help researchers identify the most relevant pathways involved in the conditions under study.

There are many commercial pathway analysis software tools such as Pathway Studio, MetaCore, or Ingenuity Pathway Analysis (IPA), etc. Compared to these commercial tools, the pathway analysis module was specifically developed for metabolomics studies. It uses high-quality KEGG metabolic pathways as the backend knowledgebase. This module integrates many well-established (i.e. univariate analysis, over-representation analysis) methods, as well as novel algorithms and concepts (i.e. Global Test, GlobalAncova, network topology analysis) into pathway analysis. Another feature is a Google-Map style interactive visualization system to deliver the analysis results in an intuitive manner.

2 Data Input

The Pathway Analysis module accepts either a list of compound labels (common names, HMDB IDs or KEGG IDs) with one compound per row, or a compound concentration table with samples in rows and compounds in columns. The second column must be phenotype labels (binary, multi-group, or continuous). The table is uploaded as comma separated values (.csv).

3 Compound Name Matching

The first step is to standardize the compound labels used in user uploaded data. This is a necessary step since these compounds will be subsequently compared with compounds contained in the pathway library. There are three outcomes from the step - exact match, approximate match (for common names only), and no match. Users should click the textbfView button from the approximate matched results to manually select the correct one. Compounds without match will be excluded from the subsequently pathway analysis.

Table 1 shows the conversion results. Note: *1* indicates exact match, *2* indicates approximate match, and *0* indicates no match. A text file contain the result can be found the downloaded file *name_ map.csv*

	Query	Match	HMDB	PubChem
1	HMDB0031532	1-Methyl-1,3-cyclohexadiene	HMDB0031532	121731
2	HMDB0032395	2-Methyl-1,3-cyclohexadiene	HMDB0032395	73885
3	HMDB0061889	NA	NA	NA
4	C00183	NA	NA	NA
5	C00431	NA	NA	NA
6	C00719	NA	NA	NA
7	C01799	NA	NA	NA
8	C01826	NA	NA	NA
9	C03571	NA	NA	NA

10	C06417	NA	NA	NA
11	C07457	NA	NA	NA
12	C15987	NA	NA	NA
13	C16436	NA	NA	NA
14	HMDB0000043	Betaine	HMDB0000043	247
15	HMDB0000883	L-Valine	HMDB0000883	6287
16	HMDB0001382	Vaporole	HMDB0001382	8053
17	HMDB0002141	N-Methyl-a-aminoisobutyric acid	HMDB0002141	6951124
18	HMDB0003355	5-Aminopentanoic acid	HMDB0003355	138
19	HMDB0013716	Norvaline	HMDB0013716	439575
20	HMDB0015550	Amyl Nitrite	HMDB0015550	10026
21	HMDB0034366	NA	NA	NA
22	CHEBI:15887	NA	NA	NA
23	CHEBI:16414	NA	NA	NA
24	CHEBI:17750	NA	NA	NA
25	CHEBI:18314	NA	NA	NA
26	CHEBI:19475	NA	NA	NA
27	CHEBI:2691	NA	NA	NA
28	CHEBI:27266	NA	NA	NA
29	CHEBI:27477	NA	NA	NA
30	CHEBI:28804	NA	NA	NA
31	CHEBI:356010	NA	NA	NA
32	CHEBI:37755	NA	NA	NA
33	CHEBI:42955	NA	NA	NA
34	CHEBI:52093	NA	NA	NA
35	CHEBI:55344	NA	NA	NA
36	CHEBI:57762	NA	NA	NA
37	CHEBI:58441	NA	NA	NA
38	CHEBI:66882	NA	NA	NA
39	CHEBI:74338	NA	NA	NA
40	CHEBI:77042	NA	NA	NA
41	CHEBI:87977	NA	NA	NA
42	C00503	NA	NA	NA
43	C16884	NA	NA	NA
44	HMDB0002994	Erythritol	HMDB0002994	222285
45	HMDB0004136	D-Threitol	HMDB0004136	169019
46	HMDB0094689	NA	NA	NA
47	CHEBI:17113	NA	NA	NA
48	CHEBI:42090	NA	NA	NA
49	CHEBI:48299	NA	NA	NA
50	CHEBI:48300	NA	NA	NA
51	C00850	NA	NA	NA
52	C02180	NA	NA	NA
53	C12849	NA	NA	NA
54	HMDB0060015	Phenol sulphate	HMDB0060015	74426
55	CHEBI:27905	NA	NA	NA
56	CHEBI:32354	NA	NA	NA
57	CHEBI:71047	NA	NA	NA
58	CHEBI:71049	NA	NA	NA
59	C00493	NA	NA	NA
60	C04236	NA	NA	NA
61	C16588	NA	NA	NA
62	C18307	NA	NA	NA
63	C18312	NA	NA	NA
64	HMDB0003070	Shikimic acid	HMDB0003070	8742
65	HMDB0012149	2-Isopropyl-3-oxosuccinate	HMDB0012149	5462259
66	HMDB0061388	NA	NA	NA
67	HMDB0062194	NA	NA	NA
68	HMDB0062377	NA	NA	NA
69	HMDB0130150	NA	NA	NA
70	CHEBI:1178	NA	NA	NA
71	CHEBI:1467	NA	NA	NA
72	CHEBI:15592	NA	NA	NA
73	CHEBI:15594	NA	NA	NA
74	CHEBI:16119	NA	NA	NA
75	CHEBI:28107	NA	NA	NA
76	CHEBI:35121	NA	NA	NA
77	CHEBI:37259	NA	NA	NA
78	CHEBI:72700	NA	NA	NA
79	C08278	NA	NA	NA
80	C14570	NA	NA	NA
81	C16658	NA	NA	NA
82	C19402	NA	NA	NA
83	HMDB0000837	NA	NA	NA
84	HMDB0000893	Suberic acid	HMDB0000893	10457
85	HMDB0002023	Ethyladipic acid	HMDB0002023	152459
86	HMDB0033838	Diethyl succinate	HMDB0033838	31249
87	HMDB0041606	Dimethyl adipate	HMDB0041606	12329
88	HMDB0059727	2,4-Dimethyladipic acid	HMDB0059727	549851
89	HMDB0059757	3-Methylpimelic acid	HMDB0059757	21510350
90	HMDB0060684	2-Propylglutaric acid	HMDB0060684	134970
91	CHEBI:80644	NA	NA	NA
92	CHEBI:87267	NA	NA	NA
93	CHEBI:87345	NA	NA	NA
94	CHEBI:89933	NA	NA	NA
95	CHEBI:9300	NA	NA	NA
96	C07473	NA	NA	NA

97	HMDB0013223	Butyrylcholine	HMDB0013223	17233
98	HMDB0029936	(2S,4R,5S)-Muscarine	HMDB0029936	5079496
99	CHEBI:327449	NA	NA	NA
100	CHEBI:522933	NA	NA	NA
101	HMDB0030083	(±)-Hydroxycitronellol	HMDB0030083	249494
102	HMDB0037639	xi-1-Ethoxy-1-hexyloxyethane	HMDB0037639	108244
103	HMDB0040267	1,1-Dimethoxyoctane	HMDB0040267	61431
104	HMDB0061936	Isooctanedioldibutyrate	HMDB0061936	95379
105	CHEBI:88828	NA	NA	NA
106	C02123	NA	NA	NA
107	C02504	NA	NA	NA
108	C03328	NA	NA	NA
109	C04411	NA	NA	NA
110	HMDB0000402	2-Isopropylmalic acid	HMDB0000402	5280523
111	HMDB0002025	2,3-Dimethyl-3-hydroxyglutaric acid	HMDB0002025	21252268
112	HMDB0012156	3-Isopropylmalic acid	HMDB0012156	5462261
113	HMDB0029169	3-Hydroxy-2-methylglutaric acid	HMDB0029169	20070700
114	HMDB0031712	(±)-Glycerol 1,2-diacetate	HMDB0031712	66021
115	CHEBI:27567	NA	NA	NA
116	CHEBI:28635	NA	NA	NA
117	CHEBI:28652	NA	NA	NA
118	CHEBI:30850	NA	NA	NA
119	CHEBI:35114	NA	NA	NA
120	CHEBI:35128	NA	NA	NA
121	CHEBI:43468	NA	NA	NA
122	CHEBI:88156	NA	NA	NA
123	C03672	NA	NA	NA
124	C03964	NA	NA	NA
125	C04044	NA	NA	NA
126	C05582	NA	NA	NA
127	C05583	NA	NA	NA
128	C10447	NA	NA	NA
129	C10680	NA	NA	NA
130	C12622	NA	NA	NA
131	HMDB0000118	Homovanillic acid	HMDB0000118	1738
132	HMDB0000333	Isohomovanillic acid	HMDB0000333	160562
133	HMDB0000423	3,4-Dihydroxyhydrocinnamic acid	HMDB0000423	348154
134	HMDB0000755	Hydroxyphenyllactic acid	HMDB0000755	9378
135	HMDB0002643	HPHPA	HMDB0002643	102959
136	HMDB0004061	3-Methoxy-4-hydroxyphenylglycolaldehyde	HMDB0004061	440729
137	HMDB0004285	NA	NA	NA
138	HMDB0006776	NA	NA	NA
139	HMDB0029232	3-Hydroxyphenyllactate	HMDB0029232	265740
140	HMDB0029273	2,6-Dimethoxybenzoic acid	HMDB0029273	15109
141	HMDB0029646	2',6'-Dihydroxy-4'-methoxyacetophenone	HMDB0029646	24135
142	HMDB0033624	(±)-2-Hydroxy-3-(2-hydroxyphenyl)propanoic acid	HMDB0033624	3083977
143	HMDB0037274	Maltol propionate	HMDB0037274	110543
144	HMDB0041270	2',4'-Dihydroxy-6'-methoxyacetophenone	HMDB0041270	10965145
145	HMDB0059763	NA	NA	NA
146	HMDB0062595	Meta-hydroxyphenylhydracrylic Acid	HMDB0062595	22600106
147	HMDB0124923	NA	NA	NA
148	HMDB0125533	NA	NA	NA
149	HMDB0125591	NA	NA	NA
150	HMDB0125595	NA	NA	NA
151	HMDB0126386	NA	NA	NA
152	HMDB0127495	NA	NA	NA
153	HMDB0129348	NA	NA	NA
154	HMDB0131428	NA	NA	NA
155	HMDB0133494	NA	NA	NA
156	HMDB0133788	NA	NA	NA
157	HMDB0134042	NA	NA	NA
158	HMDB0134043	NA	NA	NA
159	HMDB0140294	NA	NA	NA
160	HMDB0140892	NA	NA	NA
161	HMDB0240266	NA	NA	NA
162	CHEBI:16003	NA	NA	NA
163	CHEBI:17385	NA	NA	NA
164	CHEBI:18136	NA	NA	NA
165	CHEBI:27906	NA	NA	NA
166	CHEBI:296881	NA	NA	NA
167	CHEBI:46477	NA	NA	NA
168	CHEBI:48400	NA	NA	NA
169	CHEBI:49070	NA	NA	NA
170	CHEBI:49071	NA	NA	NA
171	CHEBI:545935	NA	NA	NA
172	CHEBI:545959	NA	NA	NA
173	CHEBI:562351	NA	NA	NA
174	CHEBI:61462	NA	NA	NA
175	CHEBI:62195	NA	NA	NA
176	CHEBI:64939	NA	NA	NA
177	CHEBI:64942	NA	NA	NA
178	CHEBI:67380	NA	NA	NA
179	CHEBI:70818	NA	NA	NA
180	CHEBI:78336	NA	NA	NA
181	CHEBI:85344	NA	NA	NA
182	CHEBI:85357	NA	NA	NA
183	CHEBI:86369	NA	NA	NA

184	CHEBI:86541	NA	NA	NA
185	C03843	NA	NA	NA
186	C04718	NA	NA	NA
187	C06066	NA	NA	NA
188	C11405	NA	NA	NA
189	C11419	NA	NA	NA
190	C19079	NA	NA	NA
191	C19084	NA	NA	NA
192	C20324	NA	NA	NA
193	HMDB0036117	(1'R)-Nepetalic acid	HMDB0036117	12313272
194	HMDB0036998	(S)-Oleuropeic acid	HMDB0036998	12313716
195	HMDB0039052	(4S,8R)-8,9-Dihydroxy-p-menth-1(6)-en-2-one	HMDB0039052	73120805
196	HMDB0039710	1-Acetylcyclohexyl acetate	HMDB0039710	62017
197	HMDB0040883	(E)-10-Oxo-8-decenoic acid	HMDB0040883	12431569
198	CHEBI:29064	NA	NA	NA
199	CHEBI:37287	NA	NA	NA
200	CHEBI:37291	NA	NA	NA
201	CHEBI:37379	NA	NA	NA
202	CHEBI:64264	NA	NA	NA
203	CHEBI:64274	NA	NA	NA
204	CHEBI:64899	NA	NA	NA
205	CHEBI:70741	NA	NA	NA
206	CHEBI:87777	NA	NA	NA
207	HMDB0036451	(S)-gamma-Calacorene	HMDB0036451	5315609
208	HMDB0036453	3,4-Dihydrocadalene	HMDB0036453	528708
209	HMDB0038204	alpha-Corocalene	HMDB0038204	5316074
210	HMDB0059829	Isolongifolene, 4,5,9,10-dehydro-	HMDB0059829	588771
211	HMDB0059858	beta-Calacorene	HMDB0059858	529621
212	CHEBI:89675	NA	NA	NA
213	HMDB0029835	Tetrahydroharmol	HMDB0029835	368982
214	HMDB0032756	N-Methyl-1H-indole-3-propanamide	HMDB0032756	7661699
215	CHEBI:114202	NA	NA	NA
216	CHEBI:55515	NA	NA	NA
217	C08277	NA	NA	NA
218	C14566	NA	NA	NA
219	C17803	NA	NA	NA
220	HMDB0000792	Sebacic acid	HMDB0000792	5192
221	HMDB0031510	R-2-Hydroxy-3-methylbutanoic acid 3-Methylbutanoyl	HMDB0031510	22922043
222	HMDB0040196	Oxalic acid dibutyl ester	HMDB0040196	16306
223	HMDB0059708	2-Ethylsuberic acid	HMDB0059708	19872
224	HMDB0059719	Heptylmalonic acid	HMDB0059719	136574
225	HMDB0059754	3-Methylazelaic acid	HMDB0059754	22450170
226	HMDB0062180	NA	NA	NA
227	CHEBI:41865	NA	NA	NA
228	CHEBI:68453	NA	NA	NA
229	CHEBI:70747	NA	NA	NA
230	CHEBI:89889	NA	NA	NA
231	HMDB0028690	Alanylisoleucine	HMDB0028690	7408078
232	HMDB0028691	Alanylleucine	HMDB0028691	96801
233	HMDB0028900	Isoleucyl-Alanine	HMDB0028900	5246009
234	HMDB0028922	Leucylalanine	HMDB0028922	81721
235	HMDB0094713	NA	NA	NA
236	CHEBI:61061	NA	NA	NA
237	CHEBI:64859	NA	NA	NA
238	CHEBI:73527	NA	NA	NA
239	CHEBI:73770	NA	NA	NA
240	CHEBI:73805	NA	NA	NA
241	CHEBI:73838	NA	NA	NA
242	CHEBI:74062	NA	NA	NA
243	CHEBI:74389	NA	NA	NA
244	CHEBI:74527	NA	NA	NA
245	HMDB0032443	3-Hydroxynonyl acetate	HMDB0032443	234237
246	HMDB0059736	2-Hydroxyundecanoate	HMDB0059736	5282899
247	HMDB0061654	NA	NA	NA
248	CHEBI:71005	NA	NA	NA
249	CHEBI:77419	NA	NA	NA
250	CHEBI:78956	NA	NA	NA
251	CHEBI:79126	NA	NA	NA
252	C09649	NA	NA	NA
253	HMDB0035707	(6alpha,7alpha,10alpha)-1(5),3-Aromadendradiene	HMDB0035707	13892028
254	HMDB0036416	beta-Spathulene	HMDB0036416	15923778
255	HMDB0036796	(1alpha,6alpha,7alphaH)-2,4(15)-Copadiene	HMDB0036796	5316058
256	HMDB0038125	1,4,9-Cadinatriene	HMDB0038125	14083575
257	HMDB0059676	beta-Vatirenene	HMDB0059676	608753
258	HMDB0059857	beta-Vetivenene	HMDB0059857	14475467
259	HMDB0059878	alpha-Curcumene	HMDB0059878	92139
260	HMDB0059910	(E)-Calamene	HMDB0059910	10224
261	HMDB0061837	Calamenene	HMDB0061837	11298625
262	HMDB0061838	(-)-alpha-Curcumene	HMDB0061838	442360
263	CHEBI:10225	NA	NA	NA
264	CHEBI:62757	NA	NA	NA
265	CHEBI:88614	NA	NA	NA
266	CHEBI:89456	NA	NA	NA
267	HMDB0038256	Geranyl acetoacetate	HMDB0038256	54611954
268	HMDB0112083	3,4-Dimethyl-5-pentyl-2-furanpropanoic acid	HMDB0112083	23425504
269	CHEBI:85255	NA	NA	NA
270	HMDB0031772	1-Methoxy-1-(2,4,5-trimethoxyphenyl)-2-propanol	HMDB0031772	131751190

271	HMDB0040352	2-[4-(3-Hydroxypropyl)-2-methoxyphenoxy]-1,3-propanediol	HMDB0040352	10264377
272	HMDB0011170	gamma-Glutamylisoleucine	HMDB0011170	22885096
273	HMDB0011171	gamma-Glutamylleucine	HMDB0011171	151023
274	HMDB0028822	Glutamylisoleucine	HMDB0028822	9813855
275	HMDB0028823	Glutamylleucine	HMDB0028823	9856500
276	HMDB0028906	Isoleucyl-Glutamate	HMDB0028906	18218218
277	HMDB0028928	Leucyl-Glutamate	HMDB0028928	5259589
278	HMDB0029152	NA	NA	NA
279	HMDB0029153	NA	NA	NA
280	CHEBI:68433	NA	NA	NA
281	CHEBI:68434	NA	NA	NA
282	CHEBI:73506	NA	NA	NA
283	CHEBI:74531	NA	NA	NA
284	C10029	NA	NA	NA
285	C10244	NA	NA	NA
286	C15052	NA	NA	NA
287	HMDB0030698	5,7-Dimethoxyisoflavone	HMDB0030698	6710704
288	HMDB0030719	5,6-Dimethoxyflavone	HMDB0030719	14349486
289	HMDB0036620	5,7-Dimethoxyflavone	HMDB0036620	88881
290	HMDB0037255	5-Hydroxy-7-methoxy-6-methylflavone	HMDB0037255	369599
291	HMDB0130371	NA	NA	NA
292	HMDB0140467	NA	NA	NA
293	CHEBI:205093	NA	NA	NA
294	CHEBI:3684	NA	NA	NA
295	CHEBI:70164	NA	NA	NA
296	CHEBI:75934	NA	NA	NA
297	CHEBI:79572	NA	NA	NA
298	C05174	NA	NA	NA
299	C09333	NA	NA	NA
300	C09334	NA	NA	NA
301	C09367	NA	NA	NA
302	C09389	NA	NA	NA
303	C19980	NA	NA	NA
304	HMDB0030245	Nornantenine	HMDB0030245	3084228
305	HMDB0032143	Palaudine	HMDB0032143	167736
306	HMDB0033354	Cassythicine	HMDB0033354	4440434
307	HMDB0033360	Isodomesticine	HMDB0033360	69523059
308	HMDB0036987	Romucosine A	HMDB0036987	131752126
309	HMDB0038145	Junosine	HMDB0038145	15286413
310	CHEBI:16233	NA	NA	NA
311	CHEBI:3211	NA	NA	NA
312	CHEBI:804420	NA	NA	NA
313	HMDB0032383	N1-(2-Methoxy-4-methylbenzyl)-n2-(2-(pyridin-2-yl) ethyl)oxalamide	HMDB0032383	11221120
314	HMDB0035218	Cinereain	HMDB0035218	51340308
315	C08687	NA	NA	NA
316	C12580	NA	NA	NA
317	C18769	NA	NA	NA
318	HMDB0015240	Trilostane	HMDB0015240	656583
319	HMDB0033448	Retrofractamide C	HMDB0033448	25255091
320	HMDB0038646	(8E)-Piperamide-C9:1	HMDB0038646	131752412
321	HMDB0039808	Pipertipine	HMDB0039808	11110295
322	HMDB0061042	N-desethyloxybutynin	HMDB0061042	133577
323	CHEBI:32260	NA	NA	NA
324	CHEBI:64080	NA	NA	NA
325	CHEBI:69685	NA	NA	NA
326	HMDB0002277	2,3-Dinor-6-keto-prostaglandin F1 a	HMDB0002277	53477747
327	HMDB0002904	2,3-Dinor-TXB2	HMDB0002904	5283138
328	HMDB0038940	(-)-11-Hydroxy-9,15,16-trioxooctadecanoic acid	HMDB0038940	131752496
329	HMDB0061154	Monic acid	HMDB0061154	131770055
330	HMDB0062618	2,3-dinor-6-oxoprostaglandin F1alpha	HMDB0062618	5283084
331	CHEBI:73944	NA	NA	NA
332	CHEBI:89991	NA	NA	NA
333	HMDB0033222	(1R,3S,4S,6R)-6,9-Dihydroxyfenchone 6-O-b-D-glucoside	HMDB0033222	85160606
334	HMDB0033223	(1S,3R,4R)-8,10-Dihydroxyfenchone 10-O-b-D-glucoside	HMDB0033223	85241696
335	HMDB0035822	Glucosyl 6-hydroxy-2,6-dimethyl-2E,7-octadienoate	HMDB0035822	131751869
336	HMDB0038149	Nepetaside	HMDB0038149	14020067
337	C00639	NA	NA	NA
338	C02314	NA	NA	NA
339	C04741	NA	NA	NA
340	C04843	NA	NA	NA
341	C05959	NA	NA	NA
342	C06438	NA	NA	NA
343	C12786	NA	NA	NA
344	C13809	NA	NA	NA
345	C14782	NA	NA	NA
346	C14809	NA	NA	NA
347	C14811	NA	NA	NA
348	C14814	NA	NA	NA
349	HMDB0001139	Prostaglandin F2a	HMDB0001139	5283078
350	HMDB0001442	Prostaglandin E1	HMDB0001442	5280723
351	HMDB0001483	Prostaglandin F2b	HMDB0001483	5280506
352	HMDB0001965	Troxilin B3	HMDB0001965	5283210
353	HMDB0001977	Trioxilin A3	HMDB0001977	5283208
354	HMDB0002115	8-isoprostaglandin PGF2b	HMDB0002115	5283216
355	HMDB0004684	11,12,15-THETA	HMDB0004684	11954043
356	HMDB0004685	13,14-Dihydro-15-keto PGF2a	HMDB0004685	5283039
357	HMDB0004686	8-Isoprostaglandin E1	HMDB0004686	5283212

358	HMDB0004694	11,14,15-THETA	HMDB0004694	11954059
359	HMDB0005083	8-Isoprostaglandin F2a	HMDB0005083	5282263
360	HMDB0005102	Prostaglandin D1	HMDB0005102	5280936
361	HMDB0006562	8-iso-13,14-dihydro-15-keto-PGF2a	HMDB0006562	5283214
362	HMDB0010170	11,12,15-TriHETRE	HMDB0010170	53480356
363	HMDB0010199	11b-PGF2a	HMDB0010199	5280886
364	HMDB0011137	11-Epi-PGF2a	HMDB0011137	53480669
365	HMDB0012563	13,14-Dihydro- lipoxin A4	HMDB0012563	53481469
366	HMDB0013041	Prostaglandin H1	HMDB0013041	50921242
367	HMDB0035380	Sterebin G	HMDB0035380	13996077
368	HMDB0060045	15-keto-PGF1alpha	HMDB0060045	5283118
369	HMDB0060107	(5Z,9E,12S,14Z)-8,11,12-Trihydroxyicosa-5,9,14-trienoate	HMDB0060107	131769825
370	HMDB0062278	11,12,15-trihydroxyeicosatrienoic acid	HMDB0062278	6439610
371	CHEBI:15544	NA	NA	NA
372	CHEBI:15553	NA	NA	NA
373	CHEBI:15630	NA	NA	NA
374	CHEBI:27595	NA	NA	NA
375	CHEBI:27696	NA	NA	NA
376	CHEBI:28922	NA	NA	NA
377	CHEBI:34128	NA	NA	NA
378	CHEBI:34131	NA	NA	NA
379	CHEBI:34505	NA	NA	NA
380	CHEBI:35032	NA	NA	NA
381	CHEBI:36203	NA	NA	NA
382	CHEBI:63976	NA	NA	NA
383	CHEBI:72593	NA	NA	NA
384	CHEBI:79199	NA	NA	NA
385	CHEBI:91133	NA	NA	NA
386	C09266	NA	NA	NA
387	HMDB0039774	5-Hydroxy-6-methoxycoumarin 7-glucoside	HMDB0039774	131752724
388	HMDB0041733	Ferulic acid 4-O-glucuronide	HMDB0041733	6443140
389	HMDB0041734	Feruloyl C1-glucuronide	HMDB0041734	102331585
390	HMDB0041747	Isoferulic acid 3-O-glucuronide	HMDB0041747	49844484
391	HMDB0041749	Isoferuloyl C1-glucuronide	HMDB0041749	131753197
392	HMDB0127515	NA	NA	NA
393	HMDB0127953	NA	NA	NA
394	HMDB0127954	NA	NA	NA
395	HMDB0127997	NA	NA	NA
396	HMDB0127998	NA	NA	NA
397	HMDB0133307	NA	NA	NA
398	HMDB0133308	NA	NA	NA
399	HMDB0135747	NA	NA	NA
400	HMDB0135748	NA	NA	NA
401	CHEBI:133508	NA	NA	NA
402	HMDB0029782	6-Epi-7-isocucurbic acid glucoside	HMDB0029782	131750903
403	HMDB0036893	Gibberellin A75	HMDB0036893	14583169
404	HMDB0037056	8-Oxodiacetoxyscirpenol	HMDB0037056	131752136
405	HMDB0038328	(S)-Bitalin A 12-glucoside	HMDB0038328	85391088
406	HMDB0038450	Gibberellin A86	HMDB0038450	101663489
407	HMDB0040899	Methyl helianthenoate A glucoside	HMDB0040899	131752980
408	C06475	NA	NA	NA
409	HMDB0012109	5,6-Dihydroxyprostaglandin F1a	HMDB0012109	6439819
410	C18044	NA	NA	NA
411	HMDB0000774	Pregnenolone sulfate	HMDB0000774	20845972
412	HMDB0060382	3beta-Hydroxypregn-5-en-20-one sulfate	HMDB0060382	105074
413	CHEBI:35420	NA	NA	NA
414	HMDB0015686	Pipazethate	HMDB0015686	22425
415	HMDB0032156	alpha-Acetolactate decarboxylase (enzyme preparation from bacillus subtilis recombinant)	HMDB0032156	1151802
416	HMDB0000416	17-Hydroxypregnenolone sulfate	HMDB0000416	152971
417	C14924	NA	NA	NA
418	HMDB0030157	Austalide K	HMDB0030157	13942822
419	HMDB0036340	Ethyl 7-epi-12-hydroxyjasmonate glucoside	HMDB0036340	131751966
420	HMDB0007005	NA	NA	NA
421	HMDB0007006	NA	NA	NA
422	CHEBI:1293375	NA	NA	NA
423	CHEBI:62838	NA	NA	NA
424	CHEBI:77465	NA	NA	NA
425	CHEBI:78164	NA	NA	NA
426	C03033	NA	NA	NA
427	HMDB0002430	(3a,5b,7a)-23-Carboxy-7-hydroxy-24-norcholan-3-yl-b-D-Glucopyranosiduronic acid	HMDB0002430	21252299
428	HMDB0002596	Deoxycholic acid 3-glucuronide	HMDB0002596	53477755

4 Pathway Analysis

In this step, users are asked to select a pathway library, as well as specify the algorithms for pathway enrichment analysis and pathway topology analysis.

4.1 Pathway Library

There are 15 pathway libraries currently supported, with a total of 1173 pathways :

- Homo sapiens (human) [80]
- Mus musculus (mouse) [82]
- Rattus norvegicus (rat) [81]
- Bos taurus (cow) [81]
- Danio rerio (zebrafish) [81]
- Drosophila melanogaster (fruit fly) [79]
- Caenorhabditis elegans (nematode) [78]
- Saccharomyces cerevisiae (yeast) [65]
- Oryza sativa japonica (Japanese rice) [83]
- Arabidopsis thaliana (thale cress) [87]
- Escherichia coli K-12 MG1655 [87]
- Bacillus subtilis [80]
- Pseudomonas putida KT2440 [89]
- Staphylococcus aureus N315 (MRSA/VSSA)[73]
- Thermotoga maritima [57]

Your selected pathway library code is **hsa** (KEGG organisms abbreviation).

4.2 Over Representation Analysis

Over-representation analysis tests if a particular group of compounds is represented more than expected by chance within the user uploaded compound list. In the context of pathway analysis, we are testing if compounds involved in a particular pathway are enriched compared to random hits. MetPA offers two of the most commonly used methods for over-representation analysis:

- Fishers'Exact test
- Hypergeometric Test

Please note, MetPA uses one-tailed Fisher's exact test which will give essentially the same result as the result calculated by the hypergeometric test.

The selected over-representation analysis method is 'Hypergeometric test'.

4.3 Pathway Topology Analysis

The structure of biological pathways represent our knowledge about the complex relationships among molecules within a cell or a living organism. However, most pathway analysis algorithms fail to take structural information into consideration when estimating which pathways are significantly changed under conditions of study. It is well-known that changes in more important positions of a network will trigger a more severe impact on the pathway than changes occurred in marginal or relatively isolated positions.

The pathway topology analysis uses two well-established node centrality measures to estimate node importance - **degree centrality** and **betweenness centrality**. Degree centrality is defined as the number of links occurred upon a node. For a directed graph there are two types of degree: in-degree for links come from other nodes, and out-degree for links initiated from the current node. Metabolic networks are directed graph. Here we only consider the out-degree for node importance measure. It is assumed that nodes upstream will have regulatory roles for the downstream nodes, not vice versa. The betweenness centrality measures the number of shortest paths going through the node. Since the metabolic network is directed, we use the relative betweenness centrality for a metabolite as the importance measure. The degree centrality measure focuses more on local connectivities, while the betweenness centrality measure focuses more on global network topology. For more detailed discussions on various graph-based methods for analyzing biological networks, please refer to the article by Tero Aittokallio, T. et al. [1]

Please note, for comparison among different pathways, the node importance values calculated from centrality measures are further normalized by the sum of the importance of the pathway. Therefore, the total/maximum importance of each pathway is 1; the importance measure of each metabolite node is actually the percentage w.r.t the total pathway importance, and the pathway impact value is the cumulative percentage from the matched metabolite nodes.

Your selected node importance measure for topological analysis is 'relative betweenness centrality'.

5 Pathway Analysis Result

The results from pathway analysis are presented graphically as well as in a detailed table.

A Google-map style interactive visualization system was implemented to facilitate data exploration. The graphical output contains three levels of view: **metabolome view**, **pathway view**, and **compound view**. Only the metabolome view is shown below. Pathway views and compound views are generated dynamically based on your interactions with the visualization system. They are available in your downloaded files.

[1] Tero Aittokallio and Benno Schwikowski. *Graph-based methods for analyzing networks in cell biology*, Briefings in Bioinformatics 2006 7(3):243-255

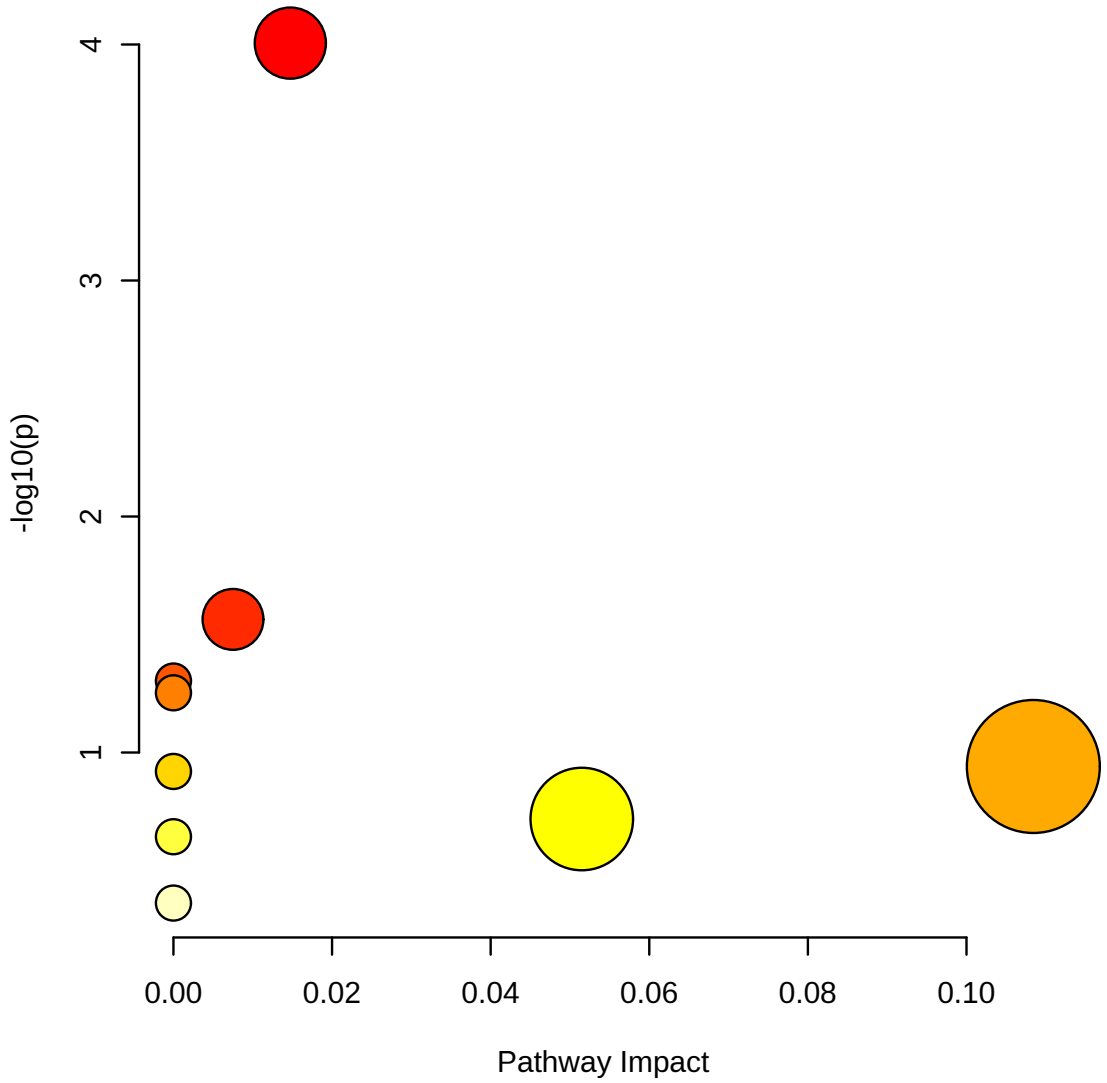

Figure 1: Summary of Pathway Analysis

The table below shows the detailed results from the pathway analysis. Since we are testing many pathways at the same time, the statistical p values from enrichment analysis are further adjusted for multiple testings. In particular, the **Total** is the total number of compounds in the pathway; the **Hits** is the actually matched number from the user uploaded data; the **Raw p** is the original p value calculated from the enrichment analysis; the **Holm p** is the p value adjusted by Holm-Bonferroni method; the **FDR p** is the p value adjusted using False Discovery Rate; the **Impact** is the pathway impact value calculated from pathway topology analysis.

Table 2: Result from Pathway Analysis

	Total	Expected	Hits	Raw p	-log10(p)	Holm adjust	FDR	Impact
Arachidonic acid metabolism	44	0.28	4	9.87E-05	4.01E+00	7.89E-03	7.89E-03	0.01
Tyrosine metabolism	42	0.27	2	2.73E-02	1.56E+00	1.00E+00	1.00E+00	0.01
Valine, leucine and isoleucine biosynthesis	8	0.05	1	4.98E-02	1.30E+00	1.00E+00	1.00E+00	0.00
Ascorbate and aldarate metabolism	9	0.06	1	5.59E-02	1.25E+00	1.00E+00	1.00E+00	0.00
Pentose and glucuronate interconversions	19	0.12	1	1.15E-01	9.41E-01	1.00E+00	1.00E+00	0.11
Pantothenate and CoA biosynthesis	20	0.13	1	1.20E-01	9.20E-01	1.00E+00	1.00E+00	0.00
Glycine, serine and threonine metabolism	33	0.21	1	1.91E-01	7.18E-01	1.00E+00	1.00E+00	0.05
Valine, leucine and isoleucine degradation	40	0.25	1	2.27E-01	6.43E-01	1.00E+00	1.00E+00	0.00
Steroid hormone biosynthesis	87	0.55	1	4.34E-01	3.62E-01	1.00E+00	1.00E+00	0.00

6 Appendix: R Command History

```
 [1] "mSet<-InitDataObjects(\"conc\", \"pathora\", FALSE)"
 [2] "cmpd.vec<-c(\"HMDB0031532\",\"HMDB0032395\",\"HMDB0061889\",\"C00183\",\"C00431\",\"C00719\",\
 [3] "mSet<-Setup.MapData(mSet, cmpd.vec);"
 [4] "mSet<-CrossReferencing(mSet, \"hmdb\");"
 [5] "mSet<-CreateMappingResultTable(mSet)"
 [6] "mSet<-SetKEGG.PathLib(mSet, \"hsa\", \"current\")"
 [7] "mSet<-SetMetabolomeFilter(mSet, F);"
 [8] "mSet<-CalculateOraScore(mSet, \"rbc\", \"hyperg\")"
 [9] "mSet<-PlotPathSummary(mSet, F, \"path_view_0_\", \"png\", 72, width=NA, NA, NA )"
[10] "mSet<-PlotKEGGPath(mSet, \"Arachidonic acid metabolism\",576, 480, \"png\", NULL)"
[11] "mSet<-RerenderMetPAGraph(mSet, \"zoom1713282930789.png\",576.0, 480.0, 100.0)"
[12] "mSet<-PlotKEGGPath(mSet, \"Arachidonic acid metabolism\",576, 480, \"png\", NULL)"
[13] "mSet<-PlotKEGGPath(mSet, \"Tyrosine metabolism\",576, 480, \"png\", NULL)"
[14] "mSet<-PlotKEGGPath(mSet, \"Glycine, serine and threonine metabolism\",576, 480, \"png\", NULL)
[15] "mSet<-PlotKEGGPath(mSet, \"Ascorbate and aldarate metabolism\",576, 480, \"png\", NULL)"
[16] "mSet<-PlotKEGGPath(mSet, \"Pentose and glucuronate interconversions\",576, 480, \"png\", NULL)
[17] "mSet<-SaveTransformedData(mSet)"
[18] "mSet<-PreparePDFReport(mSet, \"guest12962902463494310237\")\n"
```

The report was generated on Tue Apr 16 12:05:44 2024 with R version 4.3.2 (2023-10-31), OS system: Linux, version: -Ubuntu SMP Tue Mar 5 20:16:58 UTC 2024 .