Supplementary Materials for paper:

A Multi-View Learning-Based Rule Extraction Algorithm For Accurate Hepatotoxicity Prediction

I. ADDITIONAL RESULTS

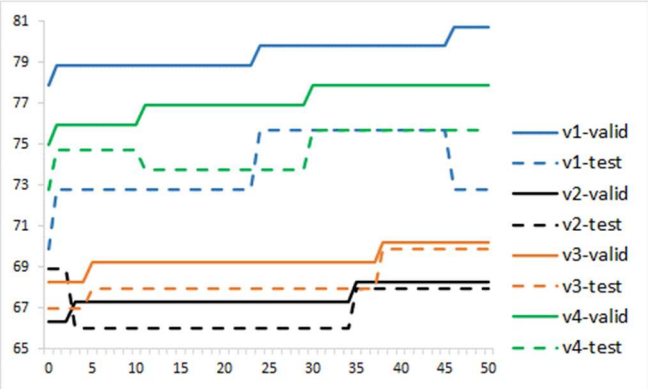

Fig. S1. The evolution curves of MVR-GA

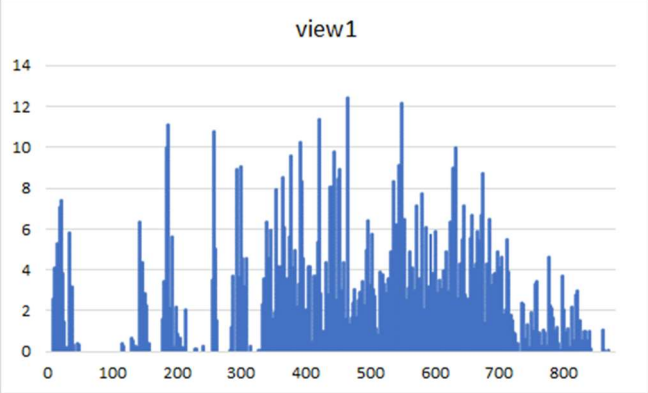

Fig. S2. The selection frequency of each feature on view1

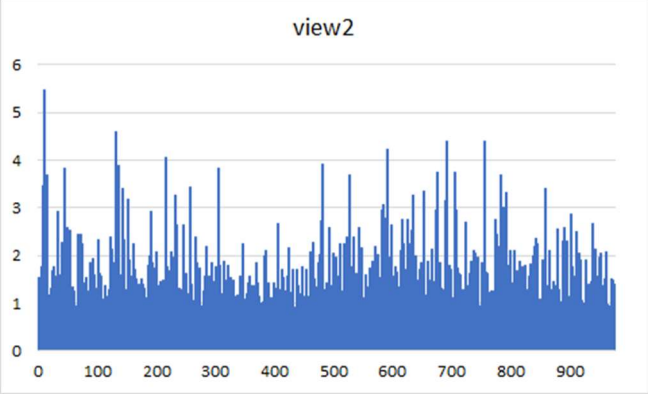

Fig. S3. The selection frequency of each feature on view2

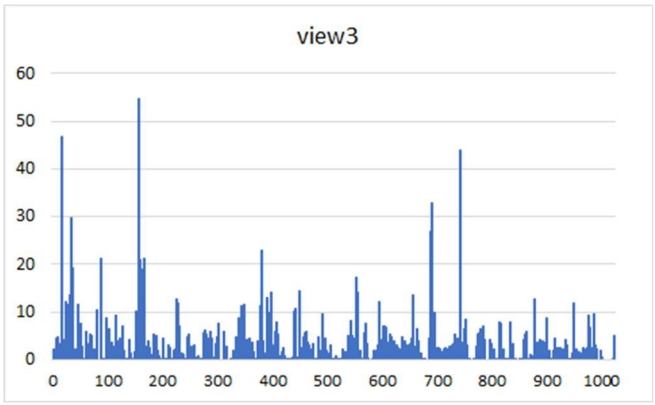

Fig. S4. The selection frequency of each feature on view3

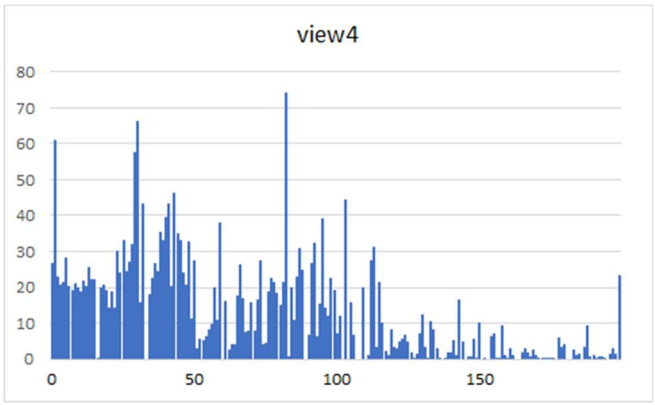

Fig. S5. The selection frequency of each feature on view4

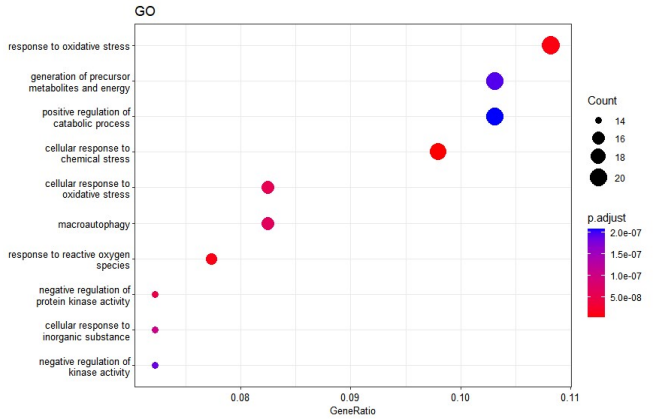

Fig. S6. The top 10 GOBP pathways enriched with important feature of L1000 expression profile

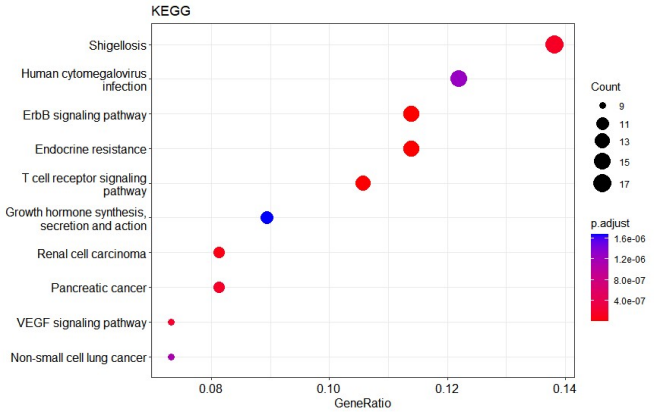

Fig. S7. The top 10 KEGG pathways enriched with important feature of L1000 expression profile

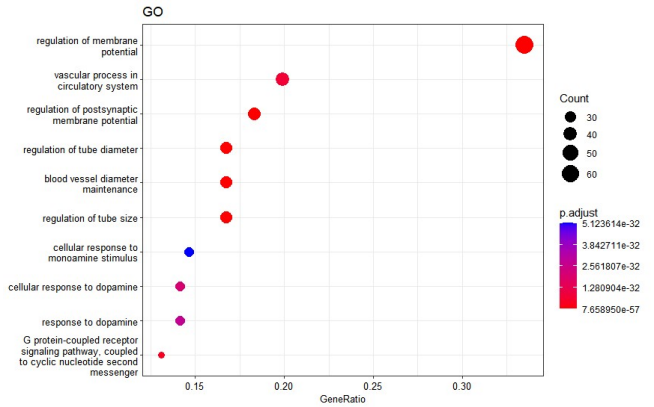

Fig. S8. The top 10 GOBP terms enriched with important feature of DrugBank compound-related target genes

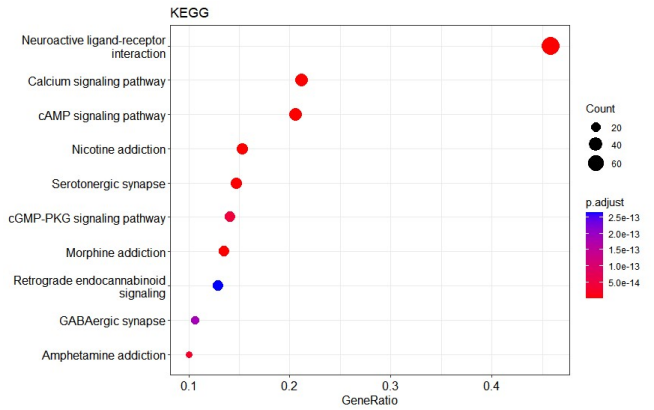

Fig. S9. The top 10 KEGG pathways enriched with important feature of DrugBank compound-related target genes

TABLE SI. DATASETS OF DRUG INDUCED HEPATOTOXICITY AND BINARIZATION RULES OF LABELS

ID	Source	Type of Data	No. of Compound (Positive/Negative)	DILI Categories
1	Greene et al.,2010	Literature reviews and medical monographs	487(331/156)	HE, WE represented positives and NE represented negatives
2	Xu et al.,2015	Medical monographs and FDA-approved drug labeling	475(236/239)	Authors definition
3	Mulliner et al,2017	Clinical data and drug labeling	1370(932/438)	Authors definition

4	DILIrank	Drug labeling and clinical data	504(192/312)	Most concern as 1; no concern as 0
5	Livertox[1][1]	Scientific literature and public database	343(119/224)	Categories A and B were combined into positives, and Category E was considered as negatives
6	LTKB	FDA-approved drug labeling	195(113/82)	Most concern as 1;no concern as 0

TABLE SII. FEATURES OF HEPATOTOXICITY DATASET

Feature	View	Dimensionality	Type
finger print (fp)	V1	881	Boolean type
expression	V2	978	Continuity type
target	V3	1023	Boolean type
phychem	V4	200	Continuity type

TABLE SIII. ACCURACY AND COVERAGE OF OUTSTANDING RULES

No.	Accuracy	Coverage
Rule 536	71.43	74.04
Rule 561	72.00	72.00
Rule 690	70.00	67.31
Rule 805	67.94	75.00
Rule 815	75.71	67.31

TABLE SIV. MODEL COMPARISON

View	MVR-GA			Random Forest		
	Rule Num	Rule Length	Feature Num	Rule Num	Rule Length	Feature Num
V_1	249.18	5.29	355.04	10,469.32	10.89	536.76
V_2	349.42	3.64	484.94	4,521.26	8.55	964.44
V_3	246.06	8.93	320.96	15,513.64	54.55	633.24
V_4	410.32	6.22	149.58	5,742.06	8.41	169.56
V_1+V_2	598.60	4.33	839.98	4,722.38	8.49	1,165.72
V_1+V_3	495.24	7.10	676.00	10,927.86	12.18	963.34
V_1+V_4	659.50	5.87	504.62	6,665.82	8.85	623.54
V_2+V_3	595.48	5.83	805.90	4,759.88	8.77	1,057.54
V_2+V_4	759.74	5.03	634.52	4,370.24	8.12	1,078.68
V_3+V_4	656.38	7.23	470.54	7,236.40	9.67	487.50
$V_1+V_2+V_3$	844.66	5.67	1160.94	4,892.38	8.65	1,251.74
$V_1+V_2+V_4$	1008.92	5.10	989.56	4,531.16	8.17	1,252.22
$V_1+V_3+V_4$	905.56	6.70	825.58	7,184.32	9.43	865.44
$V_2+V_3+V_4$	1005.80	5.99	955.48	4,588.86	8.35	1,166.92
$V_1+V_2+V_3+V_4$	1254.98	5.85	1310.52	4,679.52	8.34	1,329.38

TABLE SV. IMPORTANT FEATURES

View	Feature_index
V_1	464, 549, 420, 186, 257, 392, 633, 185, 443, 376, 545, 299, 628, 451, 293, 391, 673, 365, 449, 393

V_2	11, 131, 755, 692, 591, 216, 480, 135, 304, 45, 706, 675, 527, 784, 14, 7, 257, 142, 859, 653
V_3	156, 16, 741, 689, 157, 34, 688, 379, 165, 87, 158, 159, 166, 35, 164, 552, 33, 32, 162, 449
V_4	82, 30, 1, 29, 43, 103, 41, 32, 40, 95, 59, 38, 44, 39, 45, 25, 48, 92, 28, 113

TABLE SVI. MVR-GA IMPORTANT FEATURES TOP 200

Index	V1 (fingerprint)		V2 (expression)		V3 (target)		V4 (phychem)	
	feature name	*frequency*	*feature name*	*frequency*	*feature name*	*frequency*	*feature name*	*frequency*
1	464	12.4	3108	5.48	CHRM1	54.74	82	74.2
2	549	12.14	5058	4.6	ACHE	46.76	30	66.1
3	420	11.38	29978	4.4	SCN10A	44.04	1	61
4	186	11.14	10318	4.4	PTGS2	32.82	29	57.4
5	257	10.78	55011	4.22	CHRM2	32.2	43	46.18
6	392	10.24	5440	4.06	ADRB2	29.76	103	44.28
7	633	10	3482	3.92	PTGS1	26.88	41	43.1
8	185	9.98	5223	3.88	HRH1	22.96	32	43.04
9	443	9.8	7168	3.84	CHRNA7	21.16	40	39.48
10	376	9.6	695	3.82	BCHE	21.12	95	39.02
11	545	9.1	9924	3.76	CHRM3	20.84	59	37.86
12	299	9.06	54807	3.74	CHRM4	20.24	38	35.24
13	628	9	9961	3.7	CHRNB2	20.22	44	34.9
14	451	8.96	4846	3.68	ADRB3	19.28	39	33.16
15	293	8.94	1633	3.68	CHRNA4	19.06	45	32.98
16	391	8.76	5898	3.46	NR1I2	17.32	25	32.9
17	673	8.72	27032	3.44	ADRB1	17.16	48	32.8
18	365	8.56	652	3.42	ADRA2C	16.18	92	32.08
19	449	8.44	5982	3.4	CHRNA2	15.24	28	31.86
20	393	8.36	10245	3.34	KCNJ8	14.54	113	31.1
21	535	8.36	23223	3.32	HTR2C	14.24	87	30.6
22	437	8.06	7849	3.28	NR3C1	14.06	23	30.18
23	439	8.06	1452	3.26	ADRA2A	13.54	5	27.96
24	353	7.92	9128	3.26	PPARG	13.46	50	27.54
25	579	7.76	6464	3.18	ADRA2B	13.14	112	27.5
26	377	7.54	23131	3.16	HTR1A	13.08	73	27.32
27	20	7.44	5438	3.06	TOP2A	12.82	27	26.86
28	571	7.16	55604	3.02	DRD1	12.8	0	26.64
29	645	7.12	5255	2.98	ADORA2A	12.26	91	26.6
30	19	7.06	89910	2.96	PCNA	12.12	36	26.58
31	657	6.7	2778	2.96	DRD2	11.96	66	26.2
32	672	6.7	5480	2.96	gyrA	11.94	13	25.32
33	553	6.5	5290	2.94	GRIN3A	11.72	88	24.86
34	684	6.46	1029	2.94	PPARA	11.56	26	24.32
35	495	6.44	960	2.86	AKR1C1	11.5	37	24.2
36	143	6.38	9124	2.82	ADRA1A	11.48	24	23.94

Index	V1 (fingerprint)		V2 (expression)		V3 (target)		V4 (phychem)	
	feature name	*frequency*	*feature name*	*frequency*	*feature name*	*frequency*	*feature name*	*frequency*
37	624	6.36	55111	2.8	HPGDS	11.4	46	23.84
38	339	6.34	22841	2.76	GRIN1	11.24	199	23.28
39	540	6.22	10270	2.76	KCNH7	10.74	86	22.88
40	366	6.08	5747	2.76	GRIN2D	10.62	2	22.72
41	585	6.08	1994	2.72	TOP1	10.52	77	22.58
42	345	5.94	7866	2.7	ATP6V1A	10.4	35	22.42
43	665	5.9	5827	2.68	ADRA1B	10.34	98	22.28
44	600	5.86	5427	2.68	KCNH2	10.18	14	21.96
45	33	5.84	8480	2.66	CDIPT	10.06	15	21.92
46	502	5.78	4836	2.64	KCNH6	9.96	11	21.82
47	346	5.76	64746	2.64	NR1I3	9.96	4	21.48
48	580	5.76	22827	2.64	PTPRS	9.94	115	21.26
49	671	5.72	1956	2.6	HTR2A	9.82	78	21.18
50	593	5.7	226	2.58	MAOA	9.58	81	21.16
51	192	5.64	1429	2.58	plcA	9.54	8	20.88
52	375	5.64	8204	2.58	CACNA1C	9.36	47	20.74
53	442	5.56	5287	2.56	parC	9.28	3	20.6
54	654	5.54	1050	2.52	ADRA1D	8.96	18	20.56
55	643	5.52	1738	2.52	CA1	8.76	12	20.34
56	712	5.48	23597	2.5	GRIA2	8.74	42	20.34
57	546	5.46	30849	2.46	TYR	8.66	6	20.26
58	667	5.46	4791	2.46	SCN5A	8.54	84	19.98
59	418	5.36	22905	2.46	NOS2	8.32	9	19.86
60	15	5.3	1870	2.4	SLC6A2	8.06	109	19.76
61	259	5.06	9813	2.4	HTR7	8.02	17	19.72
62	383	4.96	22823	2.4	SOD1	7.86	57	19.7
63	493	4.96	11007	2.38	MAOB	7.84	19	19.22
64	531	4.92	4651	2.38	OPRM1	7.78	99	19.02
65	697	4.9	7511	2.36	ALB	7.64	7	18.9
66	560	4.88	3486	2.34	SLC6A4	7.54	21	18.86
67	617	4.88	7099	2.34	GBA	7.5	76	18.68
68	532	4.78	27244	2.32	ADORA1	7.48	10	18.54
69	776	4.66	998	2.3	PDE4C	7.1	79	18.32
70	704	4.62	93594	2.3	PDE4A	7.08	34	17.92
71	308	4.6	51569	2.3	CHRNB4	7.06	65	17.46
72	395	4.58	3091	2.28	SLC15A1	7.04	67	16.82
73	301	4.56	8974	2.28	CACNB2	7.02	143	16.3
74	341	4.54	5715	2.26	CACNA1D	6.96	72	16.28
75	342	4.4	51422	2.26	DRD5	6.94	61	16.08
76	146	4.38	8900	2.26	PDE4D	6.92	31	15.74
77	459	4.38	6284	2.26	pbp3	6.82	105	15.68
78	432	4.36	2356	2.26	DRD3	6.76	70	15.62
79	681	4.34	3725	2.24	SCN4A	6.62	94	15.24

Index	V1 (fingerprint)		V2 (expression)		V3 (target)		V4 (phychem)	
	feature name	*frequency*	*feature name*	*frequency*	*feature name*	*frequency*	*feature name*	*frequency*
80	663	4.32	10007	2.24	PRKAA1	6.6	80	14.8
81	638	4.3	51001	2.24	GRIN3B	6.54	20	14.34
82	538	4.22	54512	2.24	SLC12A3	6.5	96	14.08
83	358	4.18	1829	2.24	ADORA2B	6.48	22	14
84	374	4.18	3028	2.2	CA2	6.42	130	12.1
85	403	4.18	6253	2.2	HTR1B	6.4	101	12.06
86	362	4.16	51021	2.2	CHRNA3	6.38	97	11.96
87	406	4.16	2887	2.2	GABRA3	6.34	49	11.32
88	11	4.14	8444	2.18	SLC6A3	6.08	85	10.82
89	379	4.14	5873	2.16	ALOX5	6	58	10.58
90	380	4.14	813	2.16	GABRA4	5.96	133	10.36
91	699	4.14	4775	2.14	KCNN3	5.94	116	9.86
92	566	4.12	11011	2.14	GABRG2	5.92	150	9.84
93	659	4.06	11031	2.14	HTR6	5.86	56	9.62
94	613	4	10892	2.12	GLRA1	5.82	188	9.28
95	340	3.98	2353	2.12	THRB	5.82	158	9.06
96	453	3.94	55129	2.1	CHRM5	5.76	119	8.18
97	514	3.94	10150	2.1	KCNMB3	5.66	134	8.12
98	550	3.92	9710	2.1	KCNN1	5.64	55	7.94
99	713	3.9	11000	2.1	SLC12A1	5.62	69	7.82
100	23	3.86	4482	2.1	GABRA2	5.58	71	7.58
101	692	3.86	11182	2.08	OPRD1	5.52	68	7.3
102	623	3.84	23378	2.08	RXRA	5.5	100	7.08
103	596	3.82	25874	2.08	THRA	5.5	129	7.08
104	10	3.78	23325	2.08	CRYZ	5.44	155	6.84
105	519	3.76	11142	2.08	HTR2B	5.42	124	6.74
106	691	3.76	3930	2.04	ESR1	5.4	106	6.5
107	414	3.74	9112	2.04	IKBKB	5.4	90	6.46
108	797	3.74	57178	2.04	AGTR1	5.38	93	6.34
109	412	3.72	9842	2.04	SIGMAR1	5.38	154	6.26
110	287	3.68	23670	2.02	GABRA6	5.34	54	6.18
111	405	3.66	7158	2.02	PDK1	5.34	178	6.04
112	294	3.62	9270	2.02	GRIN2A	5.28	123	5.44
113	334	3.6	51160	2.02	AR	5.24	148	5.4
114	364	3.58	23013	2.02	GABRA1	5.24	52	5.3
115	370	3.58	2264	2	yedY	5.18	141	5.24
116	440	3.56	55746	2	HTR3A	5.08	53	5.02
117	528	3.56	51375	2	ARG1	5.06	125	4.7
118	576	3.56	57192	2	CTNNB1	5.04	144	4.64
119	256	3.52	55012	2	NPY	5.02	122	4.56
120	714	3.52	664	1.98	HRH2	4.98	75	4.44
121	607	3.5	10813	1.98	NOLC1	4.98	64	3.98
122	145	3.48	51170	1.98	KCNN2	4.92	63	3.96

Index	V1 (fingerprint)		V2 (expression)		V3 (target)		V4 (phychem)	
	feature name	*frequency*	*feature name*	*frequency*	*feature name*	*frequency*	*feature name*	*frequency*
123	335	3.46	9467	1.96	KCNMB2	4.86	180	3.9
124	487	3.44	10776	1.96	ABCC8	4.84	74	3.84
125	758	3.44	2542	1.96	GAST	4.82	179	3.36
126	180	3.42	1019	1.94	KCNMB1	4.82	187	3.12
127	450	3.42	3162	1.94	ERG1	4.8	120	3.1
128	598	3.4	1398	1.94	PDXK	4.8	114	3.08
129	614	3.4	1454	1.92	GPR55	4.76	131	3.08
130	656	3.4	2770	1.92	LPA	4.74	135	3
131	601	3.38	1153	1.92	PLAT	4.7	121	2.94
132	674	3.34	22934	1.92	PTGER1	4.66	166	2.9
133	521	3.32	10557	1.92	bla	4.66	161	2.88
134	389	3.3	7852	1.9	NQO1	4.64	197	2.84
135	755	3.3	6657	1.88	HBA1	4.6	51	2.7
136	597	3.28	55556	1.88	POMC	4.58	183	2.6
137	337	3.26	57147	1.88	OPRK1	4.54	62	2.54
138	689	3.24	50813	1.88	GABRA5	4.5	169	2.32
139	390	3.22	50810	1.88	GABRB2	4.5	117	2
140	501	3.22	8996	1.88	MAPK1	4.5	167	1.86
141	655	3.22	2064	1.88	CYP2A6	4.48	140	1.84
142	37	3.2	8727	1.88	KCNMB4	4.48	165	1.82
143	591	3.2	4893	1.86	CACNA1S	4.46	126	1.76
144	698	3.2	5696	1.86	RYR1	4.46	139	1.64
145	396	3.18	55847	1.86	GABRQ	4.44	198	1.46
146	548	3.18	8985	1.86	S100P	4.42	185	1.44
147	305	3.16	9143	1.86	ABCC2	4.4	196	1.32
148	639	3.16	847	1.86	TRPV3	4.36	128	1.22
149	572	3.14	10190	1.86	fabI	4.36	111	1.08
150	357	3.12	1385	1.86	CALM1	4.32	162	1.08
151	452	3.1	23224	1.86	SLC18A2	4.3	190	1
152	558	3.1	56924	1.84	SLC15A2	4.28	142	0.9
153	577	3.1	2109	1.84	ANXA1	4.24	118	0.88
154	615	3.1	94239	1.84	GPT2	4.24	184	0.88
155	476	3.06	54915	1.84	PDE3A	4.22	159	0.84
156	611	3.06	80758	1.84	GSTZ1	4.2	170	0.8
157	181	3.02	831	1.84	DRD4	4.18	168	0.7
158	504	3.02	1534	1.82	TGM2	4.18	146	0.66
159	454	2.98	5321	1.8	GSS	4.14	189	0.58
160	696	2.98	5347	1.8	ACY1	4.12	147	0.54
161	255	2.96	2523	1.8	GABRG1	4.1	193	0.46
162	569	2.96	392	1.8	GRIN2C	4.1	192	0.44
163	821	2.96	79170	1.8	GRIN2B	4.06	83	0.42
164	621	2.94	1052	1.8	PPARD	4.06	132	0.34
165	144	2.92	102	1.8	TOP1MT	4.06	157	0.32

Index	V1 (fingerprint)		V2 (expression)		V3 (target)		V4 (phychem)	
	feature name	*frequency*	*feature name*	*frequency*	*feature name*	*frequency*	*feature name*	*frequency*
166	484	2.92	4690	1.78	HTR1F	4.04	191	0.32
167	680	2.92	9533	1.78	PRKAB1	4.04	16	0.3
168	573	2.9	7398	1.78	NQO2	3.98	194	0.28
169	423	2.88	4016	1.78	CNR1	3.96	127	0.24
170	150	2.86	5529	1.78	ACE	3.94	136	0.16
171	604	2.86	7088	1.78	CACNA1H	3.92	171	0.16
172	523	2.84	51719	1.78	CACNA2D1	3.92	160	0.12
173	641	2.84	3553	1.76	GABRP	3.92	172	0.12
174	381	2.82	5289	1.76	HRH4	3.92	173	0.08
175	483	2.82	5359	1.76	TK	3.9	176	0.06
176	818	2.82	572	1.76	PGR	3.88	149	0.04
177	373	2.8	54442	1.76	HLCS	3.86	152	0.04
178	435	2.8	10921	1.76	PLG	3.86	138	0.02
179	338	2.78	9702	1.76	PTPRE	3.86	156	0.02
180	646	2.78	868	1.74	RYR2	3.86	174	0.02
181	457	2.74	9517	1.74	TUBB	3.86	175	0.02
182	594	2.74	93487	1.74	GABRE	3.84	33	0
183	622	2.74	57149	1.74	PTPN4	3.82	60	0
184	503	2.7	6909	1.74	PGD	3.78	89	0
185	507	2.7	56889	1.74	CA6	3.76	102	0
186	527	2.7	10320	1.72	ABCC1	3.74	104	0
187	574	2.7	6622	1.72	PDE7B	3.74	107	0
188	619	2.7	6919	1.72	HTR1D	3.72	108	0
189	711	2.7	10058	1.72	KCNMA1	3.7	110	0
190	590	2.68	9688	1.72	TUBG1	3.7	137	0
191	382	2.66	8678	1.72	HDAC2	3.68	145	0
192	421	2.64	64422	1.72	TUBE1	3.66	151	0
193	438	2.64	128	1.72	GABRB1	3.64	153	0
194	682	2.64	5867	1.72	KCNN4	3.64	163	0
195	637	2.62	375346	1.72	TPK1	3.64	164	0
196	651	2.62	9805	1.7	CACNB1	3.62	177	0
197	695	2.62	57048	1.7	CHRNA10	3.62	181	0
198	626	2.6	63933	1.7	GRIK2	3.62	182	0
199	9	2.58	3315	1.68	GABRD	3.6	186	0
200	536	2.58	207	1.68	GABRB3	3.56	195	0

Rule 536

```
1. if X['1626'] > -0.6336418986320496:
2.     if X['889'] > -0.29730215668678284:
3.         if X['1676'] <= 0.7438333928585052:
4.             if X['1587'] > -0.34194841980934143:
5.                 return 1
```

Rule 561

```
if X['1721'] > -0.7491983473300934:
    if X['1445'] <= 0.18207036703824997:
        if X['1692'] > -0.6236386001110077:
            if X['1558'] > -0.5988142788410187:
                return 1
```

Rule 690

```
if X['1225'] <= 0.06973003223538399:
    if X['941'] > -0.18589357286691666:
        if X['1430'] > -0.5958110690116882:
            if X['1479'] > -0.4400264173746109:
                return 1
```

Rule 805

```
if X['1828'] <= 0.6469834744930267:
    if X['1154'] <= 0.4267232120037079:
        if X['1044'] > -0.36726604402065277:
            if X['927'] <= 0.5427587032318115:
                return 1
```

Rule 815

```
if X['892'] > -0.23688504099845886:
    if X['942'] <= 0.2453337162733078:
        if X['1573'] <= 0.7088802456855774:
            if X['1853'] > -0.1360762044787407:
                return 1
```

II. FURTHER ANALYSIS ON THE RESULTS

According to the feature selection frequency in the optimal rule set, the important features of the first 200 dimensions are shown in Table SVI. For the important features of v2 (expression),we use the L1000 expression profile to conduct GO biological process(GOBP) term and KEGG pathway enrichment analysis (P<0.05) with Rstudio, as shown in Fig. S6 and Fig. S7.

The liver plays an important role in the metabolism of drugs or exogenous poisons, protecting the body from potentially toxic chemicals [2]. The biological activation process by which parental drugs produce active metabolites and the mechanisms by which xenobiotics detoxify and excrete, most under genetic control, are critical to understanding the mechanisms of hepatotoxicity/DILI[3]. It was found that GOBP enrichment analysis based on expression profiles mainly focused on the term "response to oxidative stress" (P <0.01) as shown in Fig. S6. The hepatocyte damage may be caused by chemical reactive intermediate metabolites of metabolic activation. These metabolites and macromolecules (such as proteins, DNA) covalent bonding form new antigen protein adducts—neoantigens— that lead to the generation of oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum (ER) stress, which can eventually lead to cell death and cause drug-induced hepatotoxicity in clinical practice [4]. Moreover, reactive metabolites produced during drug metabolism are the main reason for the sharp increase of oxidative stress directly produced in mitochondria of injured hepatocytes [5]. Previous studies have demonstrated that oxidative stress is one of the major mechanisms implicated in Oxaliplatin(OXA)-induced liver injury[6]. This finding proves that our model can excavate the potential biological mechanism causing hepatotoxicity and effectively prevent the hepatotoxicity problem caused by this mechanism by inhibiting the related biological process. For example, curcumin attenuates oxaliplatin induced liver injury and oxidative stress by activating Nrf2 pathway[7]. Similarly, documented GO biological processes such as "positive regulation of catabolic process" (P <0.01) and "cellular response to chemical stress" (P <0.01) are closely related to the occurrence of hepatotoxicity [8]. At the same time, important features of gene expression profile are enriched in the ErbB signaling pathway (P <0.01), as shown in Fig. S7. ErbB pathway is one of the main pathways regulating the hepatotoxicity induced by compounds, which is highly expressed in liver and known to be involved in hepatocytes proliferation, hepatocellular carcinogenesis and liver regeneration[9]. For example, the mechanism of Schisandra chinensis against drug-induced liver injury involves the regulation of multiple targets, especially the effect on ErbB signaling pathway. The active components of Schisandra chinensis may play a role in anti-drug-induced liver injury by participating in the regulation of inflammatory factors and oxidative stress[10].

As drug-related target genes often mean the discovery of biomarkers. According to the most important features of v3 (target) in MVR-GA model, We conducted GOBP and KEGG pathway enrichment analysis for the important target genes in the first 200 dimensions, as shown in Fig. S8 and Fig. S9.

It was found a large number of genes were enriched in the GOBP term "regulation of membrane potential" ($P<0.01$). Previous studies have proved that oxidative stress is the main cause of hepatotoxicity, and mitochondrial damage driven by membrane potential is also one of the main causes of hepatotoxicity[11]. Taking acetaminophen (APAP) as an example, APAP hepatotoxicity is the leading cause of drug-induced acute liver failure in the United States[12]. The main cause of its hepatotoxicity is the loss of mitochondrial membrane potential caused by APAP, which leads to mitochondrial fission skew and eventually fragmentation, resulting in the reduction of mitochondrial function [13]. At the same time, the KEGG pathway enrichment analysis of the target gene happens to be enriched in the pathway of Amphetamine addiction ($P<0.01$), which proves that the induction of hepatotoxicity is indeed related to mitochondrial membrane potential. At the same time, it has been found that hepatotoxicity in the KEGG pathway is related to the regulation of cAMP signaling pathway ($P<0.01$). It has been documented that cAMP is a key second messenger molecule that regulates various cellular functions, including inflammation and cell injury, by affecting the expression and function of genes/proteins[14]. Dopamine receptors (DR) belong to the G protein-coupled receptor family (GPCR). Both dopamine receptor D1 (DRD1) and dopamine receptor D2 (DRD2) are expressed in hepatocytes, and their receptor agonists can increase cyclic adenosine monophosphate (cAMP) [[15]. Increased cAMP protects hepatocytes by inhibiting apoptosis induced by the JNK or PI3K/Akt pathways through key switching factors of guanine nucleotides. Stimulation of DRD1 negatively regulates NLRP3 inflammasome activation through cAMP, thereby modulating the occurrence of inflammation [16].

These results show that the data based on L1000 expression profile and drug target protein are important participants in the biological process of hepatotoxicity, and can be used to treat and inhibit the hepatotoxicity through the biological process, which is very important for the process of hepatotoxicity and drug discovery.

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