

Supplementary Materials: Study on the Mechanism of Mesaconitine-Induced Hepatotoxicity in Rats Based on Metabonomics and Toxicology Network

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Table S1 Trends of differential metabolites involved in metabolic pathways

Metabolic pathway	Metabolite	Trend (MA vs NS)
Phenylalanine, tyrosine and tryptophan biosynthesis	L-Phenylalanine	↑
Histidine metabolism	Methylimidazoleacetic acid	↑
Aminoacyl-tRNA biosynthesis	L-Phenylalanine	↑
Aminoacyl-tRNA biosynthesis	L-Proline	↓
Phenylalanine metabolism	L-Phenylalanine	↑
Retinol metabolism	Retinyl ester	↑
Steroid hormone biosynthesis	Dehydroepiandrosterone	↑
Steroid hormone biosynthesis	Aldosterone	↑
Pentose and glucuronate interconversions	beta-D-Glucuronoside	↑
Biosynthesis of unsaturated fatty acids	(4Z,7Z,10Z,13Z,16Z,19Z)-Docosaehaenoic acid	↑
Arginine and proline metabolism	L-Proline	↓
Tryptophan metabolism	5-Hydroxyindoleacetaldehyde	↑
Primary bile acid biosynthesis	Glycocholic acid	↑

Table S2 Results of hepatotoxicity targets on online database

No	Keywords	Targets in CTD	Targets with "marker/mechanism"	Targets in GeneCards	Targets of "score> 40"
1	Chemically-Induced Liver Toxicity	83368	410	685	0
2	Chemically Induced Liver Toxicity	83368	410	4897	30
3	Chemically-Induced Liver Toxicities	83368	410	685	0
4	Liver Toxicities,Chemically-Induced	83368	410	685	0
5	Liver Toxicity, Chemically-Induced	83368	410	685	0
6	Toxicities,Chemically-Induced Liver	83368	410	685	0
7	Toxicity, Chemically-Induced Liver	83368	410	685	0
8	Drug-Induced Acute Liver Injury	83368	410	1724	17
9	Drug Induced Acute Liver Injury	83368	410	5020	100
10	Liver Injury, Drug-Induced, Acute	83368	410	1724	17
11	Acute Liver Injury, Drug-Induced	83368	410	1724	17
12	Acute Liver Injury, Drug Induced	83368	410	5020	100
13	Hepatitis, Toxic	83368	410	4722	6
14	Toxic Hepatitis	83368	410	4722	6
15	Hepatitides, Toxic	83368	410	19	0
16	Toxic Hepatitides	83368	410	19	0
17	Drug-Induced Liver Disease	83368	410	2272	22
18	Disease, Drug-Induced Liver	83368	410	2272	22
19	Diseases, Drug-Induced Liver	83368	410	2272	22
20	Drug Induced Liver Disease	83368	410	11663	170
21	Drug-Induced Liver Diseases	83368	410	2272	22
22	Liver Disease, Drug-Induced	83368	410	2272	22
23	Liver Diseases, Drug-Induced	83368	410	2272	22
24	Drug-Induced Liver Injury	/	/	1939	6
25	Drug Induced Liver Injury	/	/	5989	62
26	Drug-Induced Liver Injuries	/	/	1939	6
27	Injuries, Drug-Induced Liver	/	/	1939	6
28	Injury, Drug-Induced Liver	/	/	1939	6
29	Liver Injuries, Drug-Induced	/	/	1939	6
30	Liver Injury, Drug-Induced	/	/	1939	6
31	Liver Injury, Drug Induced	/	/	5989	62
32	Hepatitis, Drug-Induced	/	/	1918	1
33	Drug-Induced Hepatitides	83368	410	17	0
34	Drug-Induced Hepatitis	/	/	1918	1
35	Hepatitides, Drug-Induced	83368	410	17	0
36	Hepatitis, Drug Induced	/	/	7396	45

Table S3 Potential direct targets of hepatotoxicity induced by MA

No	Gene	Targets	Type	Dgree
1	ALB	Serum albumin	direct targets	25
2	AKT1	RAC-alpha serine/threonine-protein kinase	direct targets	16
3	IGF1	Insulin-like growth factor IA	direct targets	15
4	ESR1	Estrogen receptor	direct targets	15
5	CASP3	Caspase-3	direct targets	13
6	MMP2	72 kDa type IV collagenase	direct targets	11
7	IL2	Interleukin-2	direct targets	11
8	MAPK1	Mitogen-activated protein kinase 1	direct targets	10
9	HMOX1	Heme oxygenase 1	direct targets	10
10	JAK2	Tyrosine-protein kinase JAK2	direct targets	10
11	PTPN11	Tyrosine-protein phosphatase non-receptor type 11	direct targets	9
12	KIT	Mast/stem cell growth factor receptor	direct targets	8
13	INSR	Insulin receptor	direct targets	8
14	F2	Prothrombin	direct targets	8
15	CYP2C9	Cytochrome P450 2C9	direct targets	8
16	NR1H4	Bile acid receptor	direct targets	6
17	ELANE	Leukocyte elastase	direct targets	6
18	VDR	Vitamin D3 receptor	direct targets	5
19	GSTM2	Glutathione S-transferase Mu 2	direct targets	5
20	GSTM1	Glutathione S-transferase Mu 1	direct targets	5
21	LCN2	Neutrophil gelatinase-associated lipocalin	direct targets	5
22	NR1I2	Nuclear receptor subfamily 1 group I member 2	direct targets	4
23	SLC6A4	Transporter	direct targets	4
24	TGFBR1	TGF-beta receptor type-1	direct targets	4
25	HTR2A	Serotonin receptor 2A	direct targets	3
26	SULT1E1	Estrogen sulfotransferase	direct targets	3
27	DHFR	Dihydrofolate reductase	direct targets	2
28	SORD	Sorbitol dehydrogenase	direct targets	1
29	BLVRB	Flavin reductase	direct targets	1
30	SULT2B1	Sulfotransferase family cytosolic 2B member 1	direct targets	1
31	CHRM3	Muscarinic acetylcholine receptor M3	direct targets	0

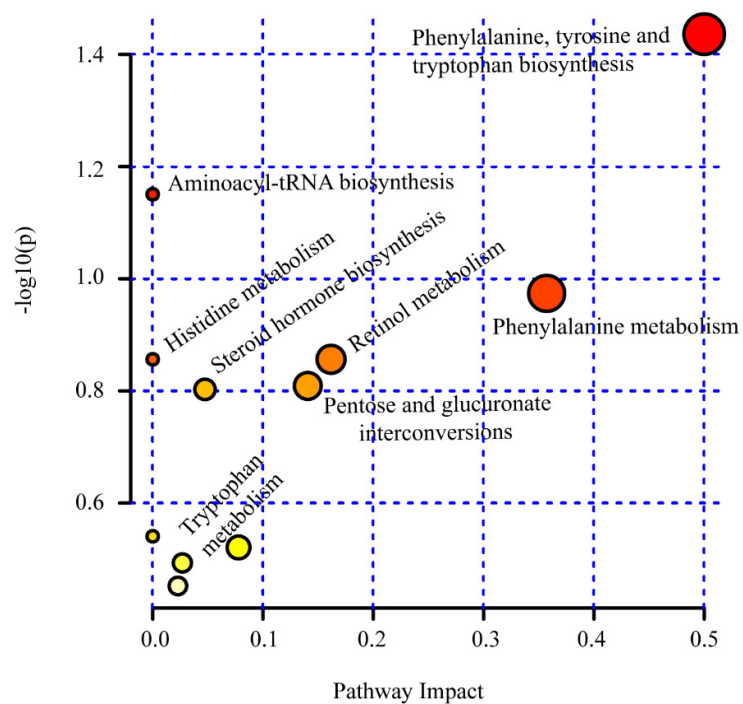


Figure S1. The summarized metabolic pathways in the low dose and high dose rats