

Supporting information

**Toxicity assessment of *Arisaematis Rhizoma* in rats by ^1H
NMR-based metabolomics approach**

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Figures in supporting information:

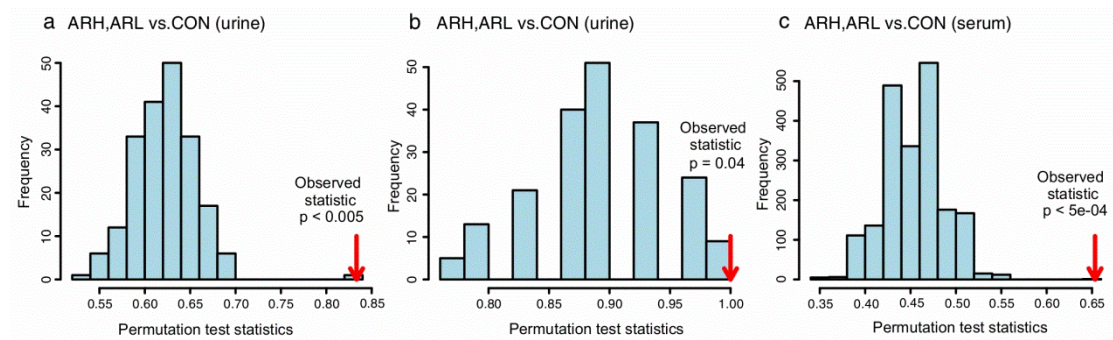


Figure S1 Histograms for permutation test scores of OSC-PLS-DA models for urine (a, b) and serum (c) of CON, ARL and ARH groups at all-time point (a, c) and on day 29 (b) after AR treatment on the basis of 200 permutations: the red arrows indicate the performance based on the original labels, significant for a p-value less than 0.05.

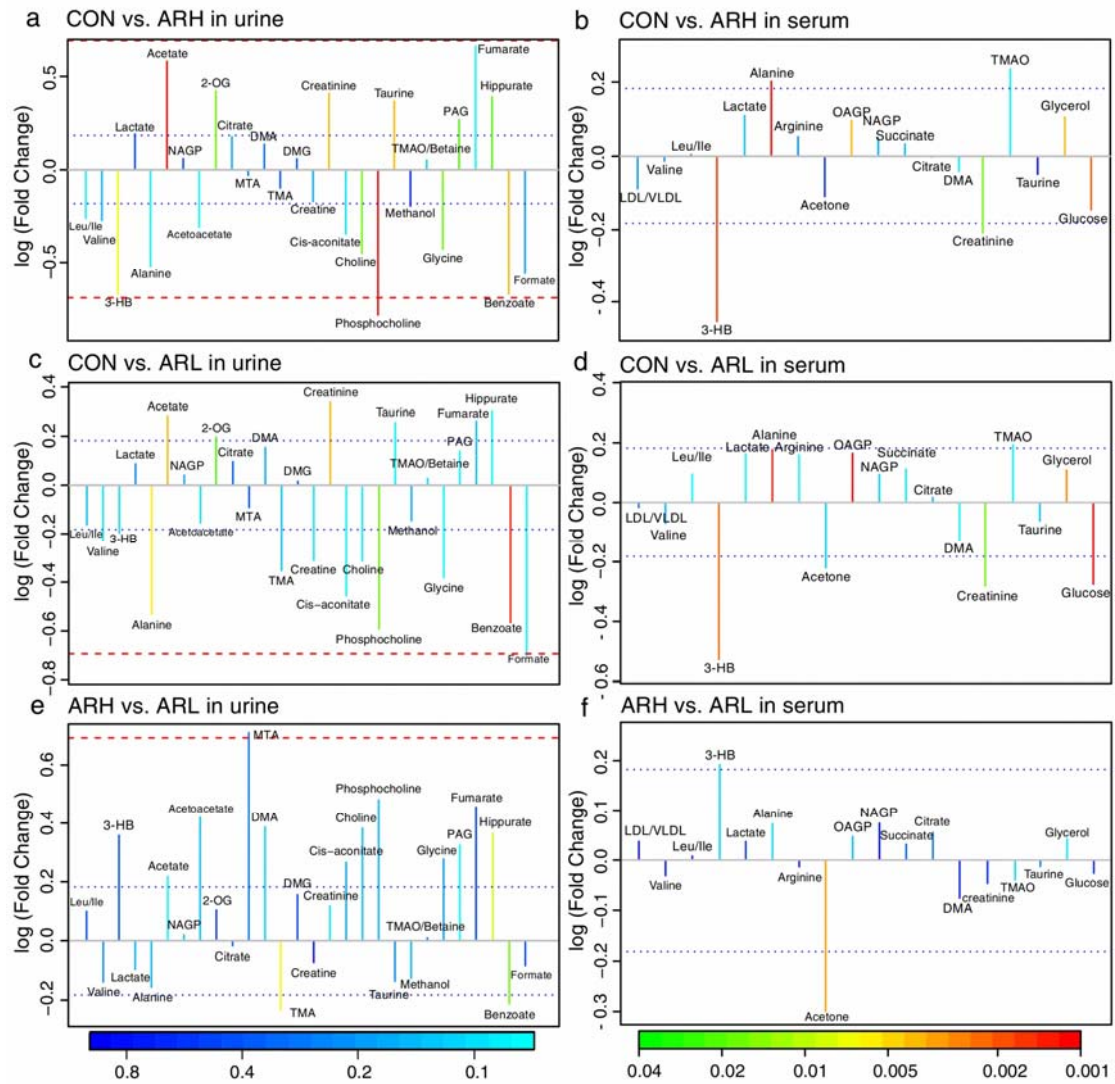


Figure S2 Fold change plots color-coded with p-values adjusted by Benjamini-Hochberg method indicating significance of altered metabolites in urine (a, c, e) and serum (b, d, f) of CON rats vs. ARH rats (a, b), CON rats vs. ARL rats (c, d) and ARH rats vs. ARL rats (e, f) on day 29 after AR treatment. The blue and red dashed lines represented variations of 20% and 100%, respectively. Metabolites abbreviation: Leu/Ile: Leucine/Isoleucine; 3-HB: 3-Hydroxybutyrate; NAGP: N-Acetyl Glycoproteins; 2-OG: 2-oxoglutarate; MTA: Methylamine; DMA: Dimethylamine; TMA: Trimethylamine; DMG: N, N-Dimethylglycine; PAG: Phenylacetyl glycine; OAGP: O-Acetyl Glycoproteins; TMAO: Trimethylamine N-oxide.

Table legend:**Table S1** Analysis of normality of urinary metabolites distribution by Shapiro-Wilk normality test in CON, ARH and ARL groups

Metabolites	CON	ARH	ARL
Isoleucine/Leucine	0.0000	0.0096	0.0039
Valine	0.0001	0.0003	0.0000
3-Hydroxybutyrate	0.0000	0.0004	0.0000
Lactate	0.0000	0.0000	0.1849
Alanine	0.0000	0.0009	0.0001
Acetate	0.0000	0.0004	0.0000
N-Acetyl Glycoproteins	0.0110	0.0012	0.3651
Succinate	0.0000	0.0000	0.0000
2-oxoglutarate	0.2950	0.5156	0.0506
Citrate	0.3397	0.5694	0.4014
Methylamine	0.0191	0.0000	0.0000
Dimethylamine	0.0000	0.0000	0.0000
Trimethylamine	0.0000	0.0000	0.0000
N,N-Dimethylglycine	0.0000	0.0000	0.0000
Creatine	0.0773	0.0000	0.0236
Creatinine	0.0000	0.0000	0.0002
Cis-aconitate	0.0000	0.0050	0.0915
Choline	0.0000	0.0072	0.0005
Phosphocholine	0.0000	0.0000	0.0000
Taurine	0.3838	0.0044	0.3421
Methanol	0.0000	0.0003	0.0000
TMAO/Betaine	0.1471	0.0886	0.0067
Glycine	0.0001	0.0007	0.0000
Phenylacetyl glycine	0.0002	0.0068	0.2225
Fumarate	0.0000	0.0005	0.0000
Hippurate	0.0028	0.0166	0.0000
Benzoate	0.0000	0.0051	0.0236
Formate	0.0001	0.0139	0.0742

Table S2 Analysis of normality of serum metabolites distribution by Shapiro-Wilk normality test in CON, ARH and ARL groups

Metabolites	CON	ARH	ARL
LDL/VLDL	0.2807	0.0274	0.9327
Valine	0.2897	0.4497	0.0243
Leucine/Isoleucine	0.8692	0.0062	0.2010
3-Hydroxybutyrate	0.0303	0.4175	0.2832
Lactate	0.5042	0.9363	0.8558
Alanine	0.9961	0.0858	0.3661
Arginine	0.2795	0.0063	0.0175
Acetone	0.5692	0.3189	0.9527
O-Acetyl Glycoproteins	0.4818	0.0000	0.0016
N-Acetyl Glycoproteins	0.8975	0.0516	0.2138
Succinate	0.0615	0.2552	0.5289
Citrate	0.2768	0.7964	0.6103
Dimethylamine	0.0705	0.2730	0.4976
TMAO	0.1187	0.5421	0.4114
Taurine	0.8216	0.4311	0.1156
Glycerol	0.3193	0.0003	0.0111
Glucose	0.1545	0.0636	0.0092
creatinine	0.7987	0.0000	0.0056

Table S3 P-values associated with fold change of metabolites in urine (CON vs. ARH, CON vs. ARL and ARH vs. ARL) with Benjamini-Hochberg multiple testing on day 29 after AR treatment.

Metabolites	CON vs. ARH	CON vs. ARL	ARH vs. ARL
Isoleucine/Leucine	0.0873	0.2808	0.7264
Valine	0.0818	0.1303	0.5076
3-Hydroxybutyrate	0.0291	0.1294	0.7248
Lactate	0.7779	0.5340	0.3425
Alanine	0.0829	0.0259	0.3240
Acetate	0.0009	0.0438	0.0756
N-Acetyl Glycoproteins	0.7880	0.3944	0.2875
Acetoacetate	0.0907	0.1266	0.3074
2-oxoglutarate	0.0345	0.0397	0.8378
Citrate	0.7890	0.6911	0.6567
Methylamine	0.6037	0.7443	0.5932
Dimethylamine	0.6133	0.4004	0.2430
Trimethylamine	0.7533	0.2915	0.0293
N,N-Dimethylglycine	0.7276	0.1291	0.7663
Creatine	0.4103	0.1260	0.9657
Creatinine	0.0192	0.0209	0.1282
Cis-aconitate	0.1235	0.0603	0.3805
Choline	0.0414	0.0649	0.2670
Phosphocholine	0.0006	0.0438	0.3306
Taurine	0.0209	0.0622	0.5082
Methanol	0.9404	0.4083	0.3554
TMAO/Betaine	0.2311	0.1691	0.5787
Glycine	0.0837	0.0782	0.4210
Phenylacetyl glycine	0.0430	0.0744	0.7722
Fumarate	0.1041	0.3111	0.8146
Hippurate	0.0475	0.0620	0.0318
Benzoate	0.0192	0.0052	0.0468
Formate	0.4498	0.1092	0.7712

Table S4 P-values associated with fold change of metabolites in serum (CON vs. ARH, CON vs. ARL and ARH vs. ARL) with Benjamini-Hochberg multiple testing on day 29 after AR treatment.

Metabolites	CON vs. ARH	CON vs. ARL	ARH vs. ARL
LDL/VLDL	0.4797	0.6292	0.9923
Valine	0.4636	0.3252	0.9644
Leucine/Isoleucine	0.7342	0.0580	0.9381
3-Hydroxybutyrate	0.0078	0.0091	0.2190
Lactate	0.2676	0.0583	0.8341
Alanine	0.0021	0.0028	0.1730
Arginine	0.4928	0.0763	0.9141
Acetone	0.8926	0.2447	0.0167
O-Acetyl Glycoproteins	0.0202	0.0030	0.3026
N-Acetyl Glycoproteins	0.3837	0.2177	0.9808
Succinate	0.3571	0.1518	0.6656
Citrate	0.6206	0.3310	0.6054
Dimethylamine	0.1398	0.0927	0.9304
Creatinine	0.0072	0.0389	0.8979
TMAO	0.0489	0.0566	0.1978
Taurine	0.9604	0.2820	0.5665
Glycerol	0.0983	0.0143	0.1321
Glucose	0.0082	0.0005	0.8827