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Influence of Zuojin Pill on the metabolism of venlafaxine in vitro and in rats and associated herb-drug interaction

Yue Li, Juan Li, Dongmin Yan, Qian Wang, Jingyi Jin, Bo Tan, Furong Qiu

Supplementary Table 1. The contents of four alkaloids in Zuojin Pill

Batch	Berberine	Coptisine	Evodiamine	Rutaecarpine
1	24.1	3.12	0.352	0.479
2	25.7	3.22	0.339	0.492
3	25.6	3.07	0.311	0.472
4	25.5	3.06	0.290	0.444
5	25.4	3.08	0.276	0.484
6	26.7	3.08	0.269	0.514
Mean (mg/g)	25.5	3.11	0.306	0.481
Standard derivation (mg/g)	0.83	0.06	0.034	0.023
CV (%)	3.26	1.93	11.08	4.81

Supplementary Table 2. Mass spectrometry parameters for measuring four major alkaloids of ZJP (berberine, coptisine, evodiamine, and rutaecarpine)

Analyte	Transition (*m/z*)	Spray voltage (V)	Temperature (°C)	DP (V)	CE (V)	CXP (V)	EP (V)
berberine	336.1>292.0	4500	600	77	35	13	10
coptisine	320.3>262.2	4500	600	84	48	18	10
evodiamine	304.1>134.1	4500	600	109	55	15	10
rutaecarpine	288.2>115.1	4500	600	120	52	12	10
Diphenhydramine (IS)	256.0>167.1	4500	600	46	25	12	10

Supplementary Table 3. Intra- and inter-batch precision and accuracy of coptisine, berberine, evodiamine, and rutaecarpine in rat livers (Mean ± S.D., n = 5)

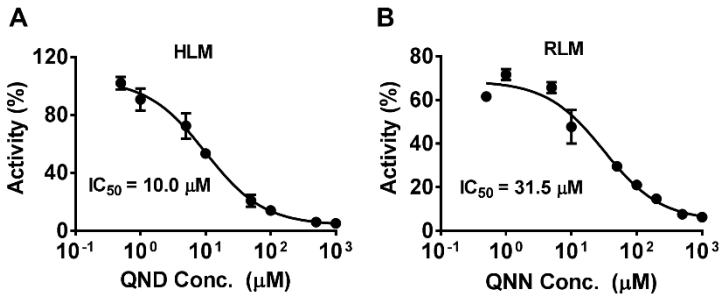
Analytes	Nominal conc.(ng/mL)	Observed Conc.(ng/mL)	Precision (%)		Accuracy (%)
			Intra-batch	Inter-batch	
Coptisine	10	10.8±0.4	4.0	5.7	107.8
	30	31.8±1.4	4.4	3.4	105.9
	160	162.0±4.6	2.8	4.3	101.3
	1600	1565.0±52.4	3.4	3.8	97.8
Berberine	10	8.8±0.8	8.9	14.5	88.1
	30	29.5±2.0	6.9	6.7	98.4
	160	160.7±6.7	4.2	4.2	100.4
	1600	1557.0±58.2	3.7	3.2	97.3
Evodiamine	10	8.4±1.0	12.1	12.3	84.4
	30	28.3±1.0	3.6	10.1	94.2
	160	153.2±6.2	4.1	5.7	95.7
	1600	1437.0±57.9	4.0	6.4	89.8
Rutaecarpine	10	8.8±0.9	9.7	9.1	88.3
	30	25.5±1.1	4.4	13.3	84.9
	160	167.2±9.1	5.4	6.5	104.5
	1600	1485.0±115.4	7.8	7.0	92.8

Supplementary Table 4. Stability of coptisine, berberine, evodiamine, and rutaecarpine in rat livers (Mean ± S.D., n = 3)

Analyte	Nominal Conc.(ng/mL)	Samples at 25°C for 6 h		Processed samples at autosampler for 36 h		Three freeze-thaw cycles	
		Observed Conc.(ng/mL)	Stability (%)	Observed Conc.(ng/mL)	Stability (%)	Observed Conc.(ng/mL)	Stability (%)
Coptisine	30	32.6±2.5	108.7	29.6±0.6	98.5	30.3±0.8	100.9
	1600	1505.0±45.1	94.1	1380.0±8.9	86.3	1496.7±19.7	93.5
Berberine	30	33.2±2.2	110.7	29.2±0.4	97.3	28.4±0.6	94.7
	1600	1495.0±30.8	93.4	1415.0±18.7	88.4	1506.7±16.3	94.2
Evodiamine	30	33.1±3.9	110.3	29.2±0.8	97.3	31.8±1.6	105.9
	1600	1570.0±20	98.1	1415.0±18.7	88.4	1551.7±30.6	97.0
Rutaecarpine	30	32.5±5.0	108.3	27.2±1.4	90.7	30.3±2.5	100.9
	1600	1510.0±29.7	94.4	1433.3±30.8	89.6	1561.7±27.1	97.6

Supplementary Table 5. Intra-batch precision and accuracy of VEN, ODV, NDV, and NODV in rat livers (Mean ± S.D., n = 5)

Analyte	Nominal conc.(ng/mL)	Observed Conc.(ng/mL)	Precision (%)	Accuracy (%)
VEN	0.2	0.188±0.010	5.1	93.8
	0.4	0.386±0.041	10.7	96.5
	10	9.65±0.99	10.2	96.5
	90	83.8±5.3	6.3	93.2
ODV	0.2	0.219±0.007	3.1	110
	0.4	0.436±0.012	2.7	109
	10	11.0±0.4	4.1	110
	90	99.8±5.5	5.5	111
NDV	0.2	0.217±0.008	3.6	109
	0.4	0.426±0.024	5.6	106
	10	11.1±0.4	3.4	111
	90	98.2±5.5	2.5	109
NODV	0.2	0.207±0.005	3.6	104
	0.4	0.412±0.018	4.4	103
	10	10.6±0.3	2.8	106
	90	95.4±4.2	4.4	106



Supplementary Figure 1. Inhibitory effects (IC50) of quinidine (A) and quinine (B) on ODV formation in HLM and RLM, respectively. Data were presented as mean ± S.D. in triplicates. The curve represented the fitting of the observed ODV formation rate (% control) (y) versus the inhibitor concentration (x).