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Original Article

Assessment of effect of Zhu-tan Tong-luo decoction on CYP450 isoforms activity of rats

Yongxi Jin[1*], Lingjiu Shao[2*], Gaowen Li[3*], Mengmeng Shao[4], Yinghao Zhi[1], Wenzong Zhu[1]

[1]Department of Rehabilitation, Wenzhou Chinese Medicine Hospital, Wenzhou 325005, China; [2]Department of Nephrology, Wenzhou Central Hospital, Wenzhou 325000, China; [3]Department of Pharmacology, Ningbo College of Health & Science, Ningbo 315100, China; [4]Department of Rehabilitation, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, China. [*]Equal contributors.

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Abstract: In order to investigate the effects of Zhu-tan Tong-luo decoction on the metabolic capacity of cytochrome P450 (CYP) enzymes, a cocktail method was employed to evaluate the activities of CYP2B6, CYP2C19, CYP1A2, CYP3A4, CYP2C9, CYP2D6. The rats were randomly divided into acute Zhu-Tan Tong-Luo decoction group (Low, High), chronic Zhu-Tan Tong-Luo decoction group (Low, High) and control group. The acute group rats were given 0.6, 1.2 g/kg (Low, High) Zhu-tan Tong-luo decoction by intragastric administration for 1 day, and the chronic group for 14 days. Six probe drugs bupropion, omeprazole, phenacetin, testosterone, tolbutamide, and metroprolol were given to rats through intragastric administration, and the plasma concentrations were determined by UPLC-MS/MS. There statistical pharmacokinetics differences for omeprazole, phenacetin, testosterone, tolbutamide, and metroprolol in rats were observed by comparing acute Zhu-tan Tong-luo decoction group with control group; and statistical pharmacokinetics differences for bupropion, omeprazole, phenacetin, testosterone, tolbutamide, and metroprolol were observed by comparing chronic Zhu-Tan Tong-Luo decoction group with control group. After intragastric administration of Zhu-Tan Tong-Luo decoction may slightly induce the activities of CYP2B6, CYP2C19, CYP1A2, CYP3A4, CYP2C9, CYP2D6 of rats. Induction of drug metabolizing enzyme by Zhu-Tan Tong-Luo decoction would reduce the efficacy of other drug. Additional, there no statistical difference for biochemical results after 1 or 14 intragastric administration of Zhu-Tan Tong-Luo decoction.

Keywords: CYP450, zhu-tan tong-luo decoction, cocktail, UPLC-MS/MS, rat

Introduction

Zhu-Tan Tong-Luo contains a series of Chinese herbs, such as *Rhubarb*, *Turmeric*, *Arisaema Cum Bile*, *Concretio Silicea Bambusae*, *Acorus Tatarinowii*, *Lumbricus*, *Scorpio* and *Rhizoma Gastrodiae*. It has a function of blood circulation to dissipate blood stasis. Cytochrome P450 (CYP) enzymes are responsible for most biotransformation steps of xenobiotics and endogenous molecules [1]. CYP1, CYP2, and CYP3 are three kinds of isoenzymes mainly involved in the metabolism of many drugs in both humans and other animals such as rats [2]. Variations of their activity by inhibition or induction can influence the pharmacokinetics and thereby the effect of drugs. Enzyme inhibition by co-administered drugs and/or genetic variations of their expression can increase the risk of adverse reactions [3] or reduce the desired effect [4]. Such drug-drug interactions were described as a major reason for hospitalization or even death [5]. Probe drug is a kind of compound specially catalyzed by CYP isoforms, and the metabolic rate of probe drug can be used to assess the activities of CYP isoforms.

So far, no study on the effects of Zhu-Tan Tong-Luo decoction on the metabolic capacity of CYP enzyme was reported. Therefore, in this study, six probe drugs were employed to evaluate effect of Zhu-Tan Tong-Luo decoction on the metabolic capacity of CYP2B6, CYP2C19, CYP1A2, CYP3A4, CYP2C9, CYP2D6. The effects of Zhu-Tan Tong-Luo decoction on rat CYP enzyme activity will be evaluated according to the pharmacokinetic parameters changes of six specific probe drugs (bupropion, omeprazole, phenacetin, testosterone, tolbutamide and metroprolol).

Table 1. Pharmacokinetic parameters of bupropion and omeprazole from control group and acute Zhu-Tan Tong-Luo decoction group rats (mean ± SD, n=8)

Parameters ng/mL *h		$AUC_{(0-t)}$ ng/mL *h	$AUC_{(0-\infty)}$ h	$t_{1/2}$ L/h/kg	CL L/kg	V ng/mL	C_{max}
Bupropion (CYP2B6)	Control	210.9±122.2	253.8±178.2	1.2±0.5	60.9±44.5	85.6±42.0	123.5±67.6
	Low	150.8±74.0	171.0±78.2	1.2±0.6	78.0±52.4	123.9 ±80.1	90.0±68.8
	High	100.7±56.5	105.3±57.5	0.8±0.4	134.2±89.8	144.2±100.3	94.0±74.2
Omeprazole (CYP2C19)	Control	771.4±302.6	818.5±350.6	1.8±1.7	15.3±9.3	33.4±24.3	790.3±339.8
	Low	400.6±128.7**	419.3±122.0*	1.5±1.2	26.0±8.7*	63.5±73.3	403.5 ±191.8*
	High	361.1±164.4**	370.5±162.3*	1.1±0.7	31.4±12.6*	50.3±34.6	320.9±143.1**

Acute Zhu-Tan Tong-Luo decoction group was compared with the control group, *P<0.05, **P<0.01.

Table 2. Pharmacokinetic parameters of phenacetin and testosterone in control group and acute Zhu-tan Tong-luo decoction group rats (mean ± SD, n=8)

Parameters ng/mL *h		$AUC_{(0-t)}$ ng/mL *h	$AUC_{(0-\infty)}$ h	$t_{1/2}$ L/h/kg	CL L/kg	V ng/mL	C_{max}
Phenacetin (CYP1A2)	Control	5374.0±2103.2	5378.2±2106.9	0.6±0.3	2.3±1.2	1.6±0.8	4402.2±1736.7
	Low	3046.5±1440.3*	3064.5±1446.9*	0.5±0.2	4.1±2.2	2.9±1.3*	2582.0±1171.3*
	High	2279.8±810.8**	2281.2±810.3**	0.4±0.1	4.8±1.6**	3.0±1.1*	2331.2±755.6*
Testosterone (CYP3A4)	Control	214.8±63.2	243.9±79.0	4.0±1.7	45.9±19.1	271.1±202.5	62.5±10.7
	Low	135.5±50.0*	162.9±53.7*	4.7±2.6	67.4±22.0	471.3±349.8	85.9±58.1
	High	84.3±24.2**	105.5±37.0**	4.3±2.2	108.5±48.6*	588.9 ±216.4*	43.7±13.1**

Acute Zhu-Tan Tong-Luo decoction group was compared with the control group, *P<0.05, **P<0.01.

Table 3. Pharmacokinetic parameters of tolbutamide and metroprolol in control group and acute Zhu-Tan Tong-Luo decoction group rats (mean ± SD, n=8)

Parameters ng/mL *h		$AUC_{(0-t)}$ ng/mL *h	$AUC_{(0-\infty)}$ h	$t_{1/2}$ L/h/kg	CL L/kg	V ng/mL	C_{max}
Tolbutamide (CYP2C9)	Control	18652.3±5270.4	23164.4±9383.1	9.1±4.0	0.005±0.001	0.057±0.013	1400.2±241.9
	Low	12337.0±2266.2*	15432.6±3662.8	9.9±3.2*	0.007 ±0.001	0.093±0.021**	1034.8±160.3**
	High	12057.4±1333.4**	14292.7±1229.7*	8.6±2.6	0.007±0.001**	0.087±0.025*	1035.8±217.0*
Metroprolol (CYP2D6)	Control	409.1±140.0	426.0±144.0	1.2±0.3	25.9±8.6	44.4±18.6	167.7±60.7
	Low	262.3±57.1*	275.9±55.6*	1.2±0.6	37.7±8.2*	64.2±39.0	113.6±42.3
	High	194.7±78.1**	199.7±77.8**	1.1±0.3	55.9±18.0**	90.1±44.5*	90.0±30.5*

Acute Zhu-Tan Tong-Luo decoction group was compared with the control group, *P<0.05, **P<0.01.

Material and methods

Chemicals

Bupropion, omeprazole, phenacetin, testosterone, tolbutamide, metroprolol (all >98%) and the internal standard diazepam (IS) were obtained from Sigma-Aldrich Company (St. Louis, USA). Ultra-pure water was prepared by Millipore Milli-Q purification system (Bedford, USA). Methanol and acetonitrile (HPLC grade) were obtained from Merck Company (Darmstadt, Germany).

Animals

Sprague-Dawley rats (male, 220±20 g) purchased from Shanghai SLAC Laboratory Animal Co., Ltd. Animals were housed under a natural light-dark cycle conditions with controlled temperature (22°C). All forty-eight rats were housed at Laboratory Animal Research Center of Wenzhou Medical University. All experimental procedures were approved ethically by the Wenzhou Medical University Administration Committee of Experimental animals.

Zhu-Tan Tong-Luo decoction

Zhu-Tan Tong-Luo contains a series of Chinese herbs, such as *Rhubarb* (6 g), *Turmeric* (12 g), *Arisaema Cum Bile* (6 g), *Concretio Silicea Bambusae* (6 g), *Acorus Tatarinowii* (6 g), *Lumbricus* (15 g), *Scorpio* (15 g) and *Rhizoma Gastrodiae* (10 g). These raw materials were obtained from the Wenzhou Municipal Hospital of Traditional Chinese Medicine, China, and stored in an environment of normal atmospheric pressure and decoction at 100°C for 30 minutes, and then the residues were discarded, the final decoction concentration was fixed at 1.2 g/mL. The decoction was stored at 4°C.

Table 4. Pharmacokinetic parameters of bupropion and omeprazole from control group and chronic Zhu-Tan Tong-Luo decoction group rats (mean ± SD, n=8)

Parameters ng/mL *h		$AUC_{(0-t)}$ ng/mL *h	$AUC_{(0-\infty)}$ h	$t_{1/2}$ L/h/kg	CL L/kg	V ng/mL	C_{max}
Bupropion (CYP2B6)	Control	545.1±137.5	772.6±301.6	8.3±3.4	15.3±7.7	158.9±45.8	326.9±105.7
	Low	196.7±106.3**	224.9±126.4**	1.1±0.4**	59.6±33.9*	80.0 ±25.6**	103.5±46.5**
	High	79.4±36.0**	86.2±38.4**	0.9±0.4**	145.9±91.0**	212.9±221.4	49.4±25.3**
Omeprazole (CYP2C19)	Control	626.2±253.6	693.4±311.3	2.7±1.5	16.5±5.9	60.1±33.3	546.0±242.4
	Low	434.8±162.4	554.6±206.0	5.2±3.5	20.8±9.7	132.2±61.6	379.7±231.4
	High	355.6±94.5*	383.6±103.8*	1.7±0.6	27.5±6.6*	68.4±33.1	297.1±68.4*

Chronic Zhu-Tan Tong-Luo decoction group was compared with the control group, *P<0.05, **P<0.01.

Table 5. Pharmacokinetic parameters of phenacetin and testosterone in control group and chronic Zhu-Tan Tong-Luo decoction group rats (mean ± SD, n=8)

Parameters ng/mL *h		$AUC_{(0-t)}$ ng/mL *h	$AUC_{(0-\infty)}$ h	$t_{1/2}$ L/h/kg	CL L/kg	V ng/mL	C_{max}
Phenacetin (CYP1A2)	Control	4273.1±1021.8	4295.4±1012.3	1.2±0.9	2.4±0.5	4.5±3.3	3274.1±726.0
	Low	2833.3±2161.5	2844.0±2152.8	0.9±0.8	7.5±8.4	11.7±13.9	2482.4 ±1781.0
	High	1455.8±993.5**	1499.0±961.1**	1.6±1.3	8.9±4.9**	24.9±27.5	1279.8±728.9**
Testosterone (CYP3A4)	Control	549.2±128.7	776.8±294.5	8.3±3.4	14.9±7.0	156.3±41.6	330.2±99.0
	Low	404.0±50.6*	547.4±110.5	7.3±5.2	18.8±3.4	181.4±91.4	177.8±49.6**
	High	333.7±25.8**	603.7±235.6	13.4±11.3	19.1±8.4	268.8±173.5	93.8±35.5**

Chronic Zhu-Tan Tong-Luo decoction group was compared with the control group, *P<0.05, **P<0.01.

Table 6. Pharmacokinetic parameters of tolbutamide and metroprolol in control group and chronic Zhu-Tan Tong-Luo decoction group rats (mean ± SD, n=8)

Parameters ng/mL *h		$AUC_{(0-t)}$ ng/mL *h	$AUC_{(0-\infty)}$ h	$t_{1/2}$ L/h/kg	CL L/kg	V ng/mL	C_{max}
Tolbutamide (CYP2C9)	Control	16977.2±4308.6	19651.3±5102.8	8.0±2.0	0.005±0.001	0.061±0.014	1416.9±301.1
	Low	12986.4±1527.3	16007.2±3507.3	9.5±3.8	0.007±0.001	0.084±0.026	1092.0±202.3
	High	12108.1±1350.7*	14234.3±1054.0*	8.5±1.8	0.007*	0.088±0.023	1018.6±351.0
Metroprolol (CYP2D6)	Control	317.3±175.6	349.3±184.6	1.4±0.8	37.9±22.2	71.9±45.2	139.5±60.3
	Low	256.3±135.1	286.0±128.4	2.0±0.9	41.4±19.1	134.1±118.7	121.2±74.4
	High	127.5±63.7*	130.3±64.0*	1.1±0.3	119.8±116.6	178.3±152.1	67.0±44.6*

Chronic Zhu-Tan Tong-Luo decoction group was compared with the control group, *P<0.05, **P<0.01.

Pharmacokinetics

Forty rats (220±20 g) were randomly divided into acute Zhu-tan Tong-luo decoction groups (Low-group, High-group and control group with 8 rats in each group), chronic Zhu-Tan Tong-Luo decoction groups (Low-group, High-group and control group with 8 rats in each group). The different Zhu-Tan Tong-Luo decoction group (Low-group, High-group) were respectively give Zhu-Tan Tong-Luo decoction 0.6, 1.2 g/kg one time by intragastric administration at every morning, and acute Zhu-Tan Tong-Luo group last for 1 day, chronic Zhu-Tan Tong-Luo group last for 14 days. Control group were give saline by same administration method. At 2 days morning for acute Zhu-Tan Tong-Luo group, and at 15 days morning for chronic Zhu-Tan Tong-Luo group, six probe drugs bupropion, omeprazole, phenacetin, testosterone, tolbutamide and metroprolol were mixtured in corn oil and given to the rats of acute and chronic Zhu-Tan Tong-Luo decoction groups, and control group by intragastric administration at a single dosage 10 mg/kg for bupropion, omeprazole, phenacetin, testosterone, metroprolol, 0.1 mg/kg for tolbutamide.

Blood (0.3 mL) samples were collected into heparinized 1.5 mL polythene tubes from the tail vein at 0.0833, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 h after intragastric administration of six probe drugs. Plasma (100 μL) was obtained from blood sample after centrifugation at 4000 *g* for 10 min. In a 1.5 mL centrifuge tube, 200 μL of acetonitrile (containing 50 ng/mL IS) was added into 100 μL of collected plasma sample. After vortex-mixing for 1.0 min, the sample was centrifuged at 13000 *g* for 15 min. Then supernatant (2 μL) was injected into the UPLC-MS/MS system for analysis.

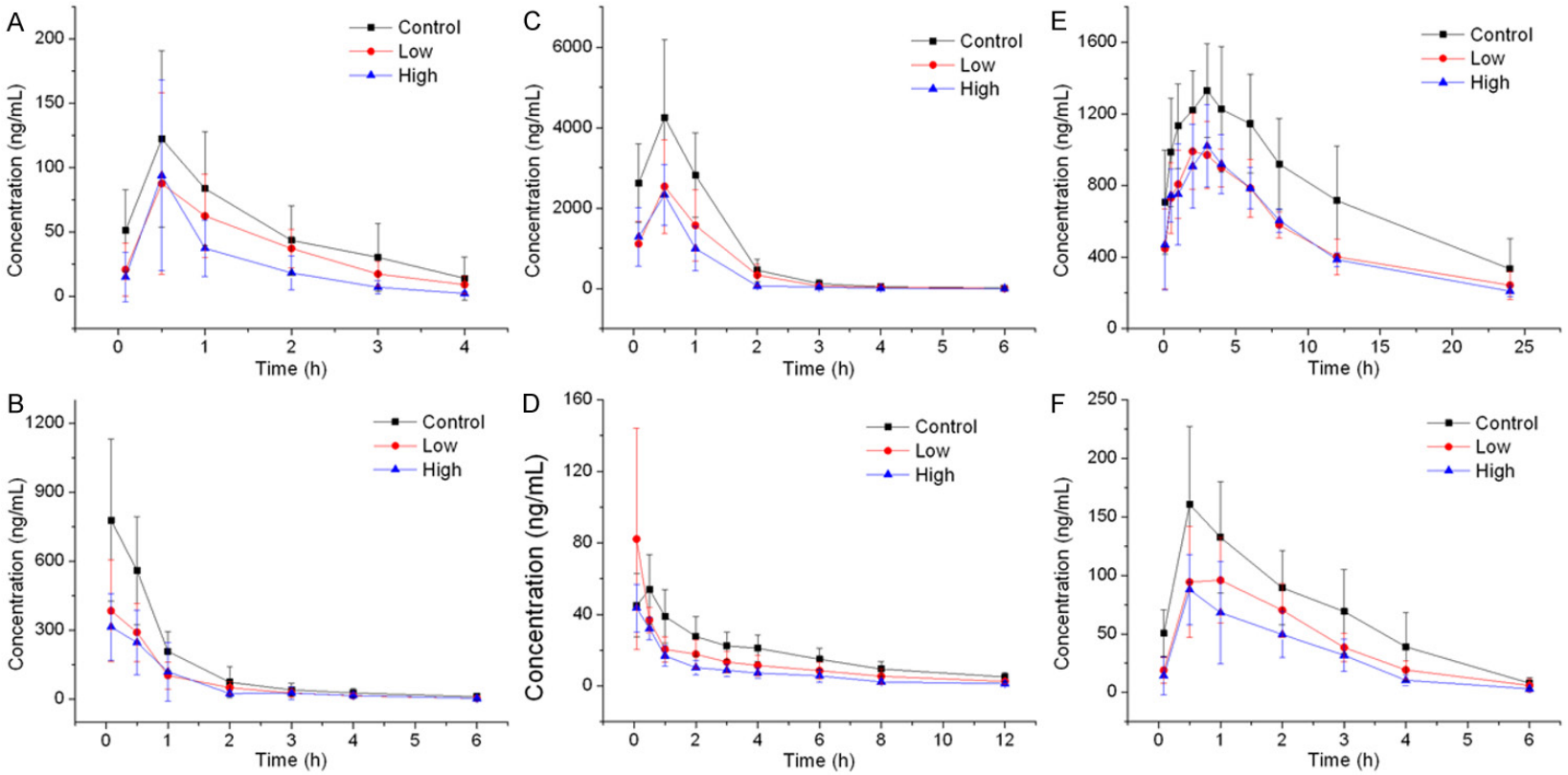

Figure 1. The pharmacokinetic profiles of bupropion (A), omeprazole (B), phenacetin (C), testosterone (D), tolbutamide (E), metroprolol (F) in control group and acute Zhu-tan Tong-luo decoction group (Low, High) rats (n=8).

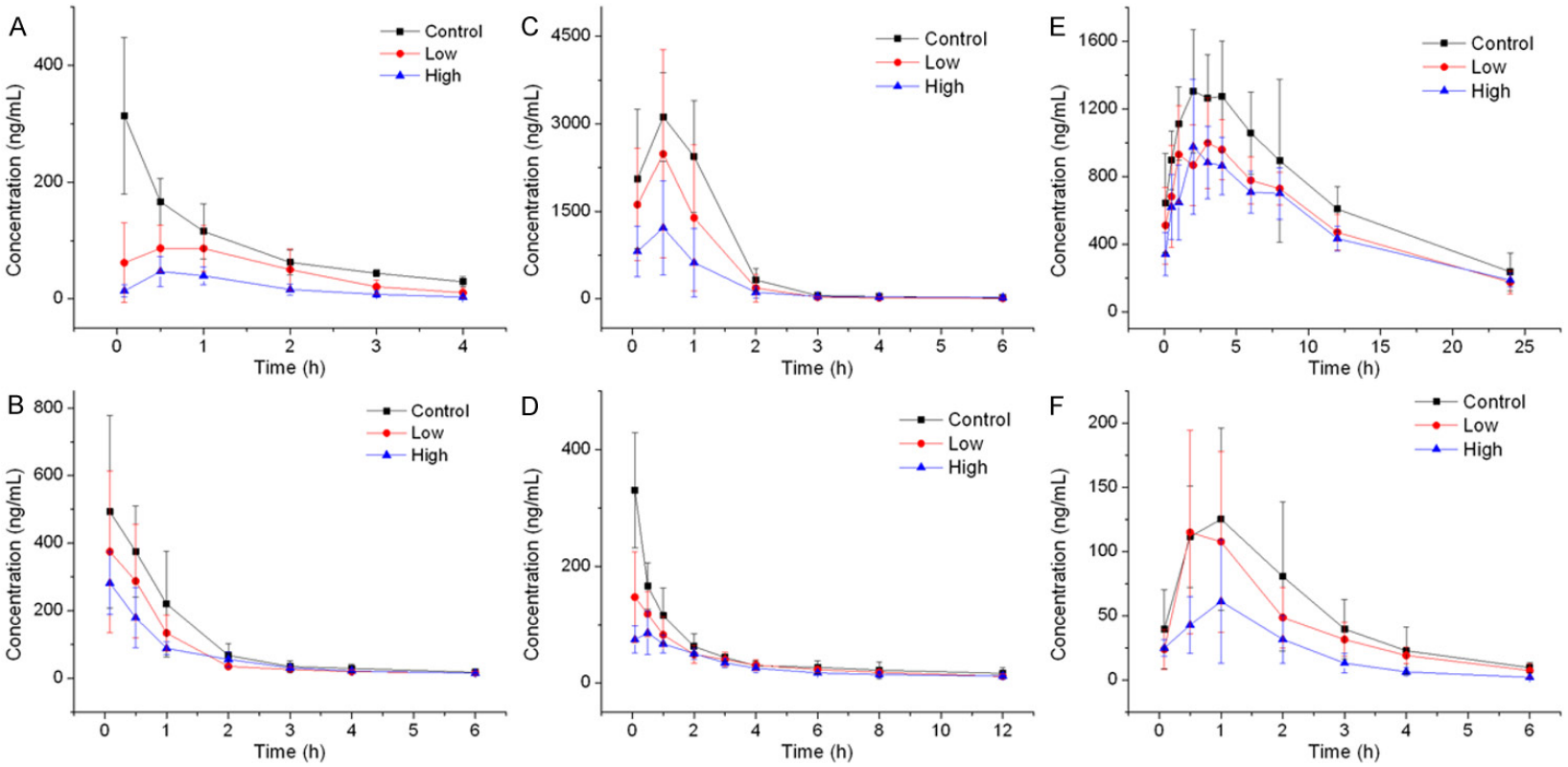

Figure 2. The pharmacokinetic profiles of bupropion (A), omeprazole (B), phenacetin (C), testosterone (D), tolbutamide (E), metroprolol (F) in control group and chronic Zhu-Tan Tong-Luo decoction group (Low, High) rats (n=8).

Table 7. Biochemical results of control group and acute Zhu-tan Tong-luo decoction group rats (mean ± SD, n=8)

Group	Alanine aminotransferase (ALT)	Aspartate aminotransferase (AST)	Alkaline phosphatase (ALP)	Creatinine (Cr)	Uric Acid (UA)	Albumin (ALB)
Control	35.4	122.7	207.1	30.4	79.4	22.5
Low	40.5	121.3	229.0	26.5	77.0	23.1
High	39.7	124.3	192.1	29.7	71.3	23.9

Table 8. Biochemical results of control group and chronic Zhu-tan Tong-luo decoction group rats (mean ± SD, n=8)

Group	Alanine aminotransferase (ALT)	Aspartate aminotransferase (AST)	Alkaline phosphatase (ALP)	Creatinine (Cr)	Uric Acid (UA)	Albumin (ALB)
Control	54.6	158.3	251.1	23.6	84.7	25.2
Low	46.5	140.2	247.3	24.5	108.7	21.8
High	48.2	113.4	263.4	27.4	107.2	21.6

Concentration of plasma probe drugs versus time was analyzed by Version 3.0 Data Analysis System (Wenzhou Medical University, China). The main pharmacokinetic parameters of the Zhu-Tan Tong-Luo decoction group and control group were analyzed by SPSS I8.0 statistical software; statistical significance was assessed by t-test ($P<0.05$ was considered as statistically significant).

UPLC-MS/MS determination of probe drugs

The concentration of bupropion, omeprazole, phenacetin, testosterone, tolbutamide and metroprolol in rat plasma were simultaneously determined by a sensitive and simple UPLC-MS/MS method [6]. The compounds were analyzed by a UPLC-MS/MS with ACQUITY I-Class UPLC and a XEVO TQD triple quadrupole mass spectrometer that equipped with an electrospray ionization (ESI) interface (Waters Corp., Milford, MA, USA). Data acquisition and instrument control were performed on the Masslynx 4.1 software (Waters Corp., Milford, MA, USA).

Bupropion, omeprazole, phenacetin, testosterone, tolbutamide, metroprolol and diazepam (IS) were separated using a Waters BEH C18 column (2.1 mm × 100 mm, 1.7 μm) at constant temperature 40°C. The initial mobile phase consisted of 0.1% formic acid and acetonitrile with gradient elution at a flow rate of 0.4 mL/min and an injection volume of 2 μL. Elution was in a linear gradient, with the acetonitrile changing from 30 to 60% in 0.3-1.8 min and increasing up to 95% over 0.2 min. The acetonitrile content was maintained at 95% for 0.5 min and decreased to 30% within 0.1 min, and then maintained at 30% for 0.4 min.

The mass spectrometric detection was performed in a positive mode. Nitrogen was used as the cone gas (50 L/h) and desolvation gas (1000 L/h). The mass conditions were set as follows: source temperature 150°C; capillary voltage 2.5 kV; desolvation temperature 500°C. The multiple reaction monitoring (MRM) mode with m/z 240.1→184.1 for bupropion, m/z 346.1→197.8 for omeprazole, m/z 180.1→109.9 for phenacetin, m/z 289.0→97.0 for testosterone, m/z 271.2→155.1 for tolbutamide, m/z 268.1→115.8 for metroprolol, and m/z 285.1→193.1 for IS was used for quantitative analysis.

The LLOQ for each probe drug in plasma was 2 ng/mL. The RSD of the six probe drugs were less than 15%. The calibration plot of the probe drugs is in the range of 2-2000 ng/mL ($r>0.995$). The intra-day and inter-day accuracy ranged from 90% to 115%. The matrix effects were more than 82% or less than 113%. The extraction recoveries were better than 85%.

Biochemical tests

After pharmacokinetic study, the blood was collected from the tail vein for biochemical tests of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), creatinine (Cr), uric acid (UA), albumin (ALB). Serum samples were analyzed to

measure the serum activities of ALT, AST, ALP, Cr, UA and ALB, which was used to evaluate the liver and kidney function.

Results

The main pharmacokinetic parameters of bupropion, omeprazole, phenacetin, testosterone, tolbutamide and metroprolol calculated from non-compartment model analysis were summarized in **Tables 1**-**6**. The representative profiles of concentration of drugs (bupropion, omeprazole, phenacetin, testosterone, tolbutamide and metroprolol) vs. time were presented in **Figures 1** and **2**.

From the **Tables 1**-**3**, acute Zhu-tan Tong-luo decoction group compared with the control group, no difference in pharmacokinetic behaviors can be observed between low, high dosage group and control group for bupropion. While the pharmacokinetic behaviors of omeprazole in low and high dosage group compared with the control group, $AUC_{(0-t)}$ decreased ($P<0.01$), CL increased ($P<0.05$), C_{max} decreased ($P<0.05$). The pharmacokinetic behaviors of phenacetin in low and high dosage group compared with the control group, $AUC_{(0-t)}$ decreased ($P<0.05$), C_{max} decreased ($P<0.05$). The similar results were found in testosterone, tolbutamide and metroprolol, $AUC_{(0-t)}$ decreased, CL increased, C_{max} decreased, ($P<0.05$). The results were consistent with the **Figure 1**.

From the **Tables 4**-**6**, chronic Zhu-tan Tong-luo decoction group compared with the control group, no difference in pharmacokinetic behaviors can be observed between low group and control group for omeprazole, phenacetin, tolbutamide and metroprolol. While for bupropion, compared with the control group, $AUC_{(0-t)}$ decreased (Low, $P<0.01$; High, $P<0.01$), CL increased (Low, $P<0.05$; High, $P<0.01$), C_{max} decreased (Low, $P<0.01$; High, $P<0.01$), and for testosterone, $AUC_{(0-t)}$ decreased (Low, $P<0.05$; High, $P<0.01$), C_{max} decreased (Low, $P<0.01$; High, $P<0.01$). The high dosage group compared with the control group, pharmacokinetic behaviors for omeprazole, phenacetin, tolbutamide and metroprolol, $AUC_{(0-t)}$ decreased ($P<0.05$ or $P<0.01$). The results were consistent with the **Figure 2**.

There is no significant difference between control group and Zhu-Tan Tong-Luo group for biochemical results, **Tables 7** and **8**.

Discussion

A large number of drugs are metabolized by CYP enzymes in the liver, and more than 90% of drug-drug interactions occur at the CYP-catalyzed step [7, 8]. In general, changes in pharmacokinetics are thought to be caused by drug-drug or drug-food interactions [9]. Similarly, supplement-drug interactions involving CYP activity are occasionally found to cause considerable adverse events. For these reasons, we evaluated the effects of Zhu-Tan Tong-Luo decoction on the activity of CYP enzymes in *vivo*. We selected CYP isoforms CYP1A2, CYP3A4, CYP2C19, CYP2C9, CYP2B6, and CYP-2D6 because more than 90% of drugs are known to be metabolized by these 6 CYP enzymes [10-13].

From the **Tables 1**-**3**, acute Zhu-Tan Tong-Luo decoction group compared with the control group, no difference in pharmacokinetic behaviors can be observed between low, high dosage group and control group for bupropion. It suggested that the Zhu-Tan Tong-Luo decoction for one day was not able to induce or inhibit the activity of CYP2B6 enzyme. There significant difference for AUC, CL and C_{max} of omeprazole, phenacetin, testosterone, tolbutamide and metroprolol between the Zhu-Tan Tong-Luo decoction group (low, high) and control group was observed. It suggested that the Zhu-Tan Tong-Luo decoction for 1 day may induce the activity of CYP2C19, CYP1A2, CYP3A4, CYP2C9, CYP2D6 enzyme.

From the **Tables 4**-**6**, chronic Zhu-Tan Tong-Luo decoction group compared with the control group, no difference in pharmacokinetic behaviors can be observed between low group and control group for omeprazole, phenacetin, tolbutamide and metroprolol, it indicated that the low dosage Zhu-Tan Tong-Luo decoction intragastric administration for 14 days did not induce or inhibit CYP2C19, CYP1A2, CYP2C9, CYP2D6. The high dosage group compared with the control group, pharmacokinetic behaviors for omeprazole, phenacetin, tolbutamide and metroprolol, $AUC_{(0-t)}$ decreased ($P<0.05$ or $P<0.01$), it indicated that the high dosage Zhu-tan Tong-luo decoction intragastric administration for 14 days may slightly induce CYP2C19, CYP1A2, CYP2C9, CYP2D6. While for bupropion and testosterone, compared low and high group with the control group, $AUC_{(0-t)}$ decreased, C_{max} decreased, it indicated that the low and

high dosage Zhu-Tan Tong-Luo decoction intragastric administration for 14 days may induce CYP2B6 and CYP3A4.

As Zhu-Tan Tong-Luo decoction is always administrated in combination with other drugs, interactions between Zhu-Tan Tong-Luo decoction and other drugs would increase the risk of either diminished efficacy or adverse effects. In our study, we found that 1 and 14 days-intragastric administration of Zhu-Tan Tong-Luo decoction slightly induce the metabolism of CYP2B6, CYP2C19, CYP1A2, CYP3A4, CYP2C9, CYP2D6 of rats. Therefore, the metabolism and elimination of drugs would change if they are administrated in combination with Zhu-tan Tong-luo decoction.

Conclusion

The results observed in this study would provide us valuable information regarding the interactions of Zhu-Tan Tong-Luo decoction with other drugs. Induction of drug metabolizing enzyme CYP2B6, CYP2C19, CYP1A2, CYP3A4, CYP2C9, and CYP2D6 by Zhu-Tan Tong-Luo decoction would reduce the efficacy of other drug. Additional, there no statistical difference for biochemical results after 1 or 14 intragastric administration of Zhu-Tan Tong-Luo decoction.

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Disclosure of conflict of interest

None.

Address correspondence to: Wenzong Zhu, Department of Rehabilitation, Wenzhou Chinese Medicine Hospital, Wenzhou 325005, China. Tel: 8657788052781; E-mail: zhuwenzongwz@163.com

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