PHARMACOLOGY AND TOXICOLOGY OF HERBAL MEDICINE:  
SUBACUTE TOXICITY OF COMMONLY  
USED CHINESE DRUGS  

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INTRODUCTION

The subacute toxicological and behavioral effects of 50% ethanol crude extracts of the following traditional Chinese medicinal drugs administered in single dosage (5, 10 g/kg, p.o., per day for 14 days) were evaluated quantitatively: 1. Cheqianze 2. Digupi 3. Fuling 4. Houpo 5. Madouling 6. Mutong 7. Niuxi 8. Qingxiangzi 9. Qianhu 10. Shandougen 11. Tainnazixing 12. Weilingxian 13. Xiakucao 14. Xianmao and 15. Xinyi, respectively. The toxicological assessments included A). the lethal dose (LD50); B). Gross examination (e.g. food consumption, water intake, urinary output, and body weight changes) was measured on 1st, 5th and 12th day; C). hematological tests & clinical chemistry (e.g. hemoglobin concentration, total WBC counts, SGPT, total protein, albumin, creatinine and blood urine nitrogen), urinalysis (e.g. pH, protein, uric acid) were examined on 1st, 4th, 11th and 15th days; D). locomotor activity was monitored on the 2nd, 3rd, 9th and 10th days; and E). post-mortem histopathologic examinations in male Sprague-Dawley rats were investigated. The maximal tolerable doses ranging from 1/10 to 1/5 of LD50 were used as the reference dosages in this 14-day subacute experiments. The following results were found:

In gross examinations, it was found the water intake was decreased significantly after continuous oral administration of Xiakucao, and the urinary output was increased after continuous treatment of Cheqianze or Digupi. In hematological assessment, it was found that total WBC counts were affected by Digitipi, Madouling, Mutong, Qingxiangzi, Weilingxian, and Xinyi. In clinical blood chemistry evaluation, the following results were found: the whole body nutrient standard references values such as plasma total protein (T-P), or serum albumin content (ALB) was affected by Cheqianze, Madouling, Niuxi, Qingxiangzi, Shandougen, & Xianmao. The reference standard for protein catabolism such as BUN was affected by Digupi, Fuling, Houpo, Qianhu, Shandougen, Tiannanxing, Xiakucao, and Xinyi. The liver functional standard test such as alanine aminotransferase (ALT or SGPT) was affected by Cheqianze, Houpo, Mutong, Niuxi, Tiananxaming, Weilingxian, Xiakucao, and Xianmao. The kidney functional standard test such as creatinine were affected by Cheqinze, Houpo, & Madouling. In urinary analysis, the protein urea, a common symptom in control group, but its value was significantly increased after continuous treatment of Qixiangzi, Qianhu, Weilingxian, Xiakucao, Xianmao or Xinyi. In behavioral toxicological evaluations, it was found that Cheqianze, Fuling, Niuxi, Qingxiangzi, Shandougen, & Tiannanxing, & Xianmao elicited a moderate to marked degree of inhibition, while Qianhu, & Xiakucao elicited moderate degree of stimulation on the locomotor activity when compared with the control group. The tissue pathological reference standards such as the net tissue weight or water content of heart, liver, lung or kidney during post-mortem examination were affected by Cheqianze, Digupi, Fuling, Madouling, Mutong, Qingxiangzi, Qianhu, Shandougen, Tiannanxing, Weilingxian, Xiakucao, Xianmao, and Xinyi. No evidence of any irreversible visible pathological damage or mortality attributable to any of the test drugs occurred during the experimental period of 15 days. A comprehensive summary reflecting the toxicological profiles of individual tested Chinese herbal drug, the following descriptive forms were also presented.

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1. Cheqianze 車前子 (5, 10 g/kg)
   - Origin
   - Clinical Indication diuretics for eliminating dampness
   - LDS50 21 (14.4-30.7) g/kg, i.p., >50 g/kg, p.o. in ICR mice
   - Spontaneous Locomotor Activity (subacute, initial phase)
   - Subacute Toxicity Profile
     a. Food Consumption
     b. Water Intake
     c. Urinary output
     d. Hematological SGPT, total protein, albumin, & creatinine
     e. Urinary Analysis protein
     f. Organ water content & weight heart wet & dry weight
     liver & kidney dry weight
     lung wet & dry weight, and water content

2. Diguji 地骨皮 (5, 10 g/kg)
   - Origin
   - Clinical Indication heat-clearing
   - LDS50 8.8 (7.5-10.3) g/kg, i.p.; >50 g/kg, p.o. in ICR mice
   - Spontaneous Locomotor Activity (subacute)
   - Subacute Toxicity Profile
     a. Food Consumption
     b. Water Intake
     c. Urinary output all tested doses
     d. Hematological WBC (high dose), & BUN
     creatinine (late phase)
     e. Urinary Analysis protein
     f. Organ water content & weight heart wet & dry weight
     liver & lung dry weight

3. Fuling 茯苓 (5, 10 g/kg)
   - Origin
   - Clinical Indication diuretics for eliminating dampness
   - LDS50 >50 g/kg in ICR mice, p.o.
   - Spontaneous Locomotor Activity (subacute, late phase)
   - Subacute Toxicity Profile
     a. Food Consumption
     b. Water Intake
     c. Urinary output
     d. Hematological BUN (at high dose)
     e. Urinary Analysis protein
     f. Organ water content & weight Liver wet weight and water content

4. Houpo 厚朴 (5, 10 g/kg)
   - Origin
   - Clinical Indication regulating Qi flow
   - LDS50 8.5 (6.4-12.1) g/kg, i.p.; >50 g/kg, p.o. in ICR mice
   - Spontaneous Locomotor Activity
   - Subacute Toxicity Profile
     a. Food Consumption
     b. Water Intake
     c. Urinary output
     d. Hematological SGPT (high dose), creatinine (initial phase)
     BUN (initial phase)
     e. Urinary Analysis protein
     f. Organ water content & weight
5. **Madouling** 馬兜鈴 (5, 10 g/kg)
   - **Origin**
   - **Clinical Indication**
   - **LD50**
   - **Spontaneous Locomotor Activity**
   - **Subacute Toxicity Profile**
     a. Food Consumption
     b. Water Intake
     c. Urinary output
     d. Hematological
     e. Urinary Analysis
     f. Organ water content & weight

6. **Mutong** 木通 (5, 10 g/kg)
   - **Origin**
   - **Clinical Indication**
   - **LD50**
   - **Spontaneous Locomotor Activity**
   - **Subacute Toxicity Profile**
     a. Food Consumption
     b. Water Intake
     c. Urinary output
     d. Hematological
     e. Urinary Analysis
     f. Organ water content & weight

7. **NiuXi** 牛膝 (5, 10 g/kg)
   - **Origin**
   - **Clinical Indication**
   - **LD50**
   - **Spontaneous Locomotor Activity**
   - **Subacute Toxicity Profile**
     a. Food Consumption
     b. Water Intake
     c. Urinary output
     d. Hematological
     e. Urinary Analysis
     f. Organ water content & weight

8. **Qingzhi** 菲枳子 (5, 10 g/kg)
   - **Origin**
   - **Clinical Indication**
   - **LD50**
   - **Spontaneous Locomotor Activity**
   - **Subacute Toxicity Profile**
     a. Food Consumption
     b. Water Intake
     c. Urinary output
     d. Hematological
     e. Urinary Analysis
     f. Organ water content & weight
9. **Qianhu** 前胡 (5, 10 g/kg)
   - **Origin**: dry root of *Peucedanum praeruptorum* DUNN (Umbelliferae)
   - **Clinical Indication**: latent heat-clearing, expectorant
   - **LD50**: > 25 g/kg, p.o. in ICR mice
   - **Spontaneous Locomotor Activity**: ↑ (subacute, late phase)
   - **Subacute Toxicity Profile**
     - a. Food Consumption:  
     - b. Water Intake:  
     - c. Urinary output:  
     - d. Hematological: ↑ BUN
     - e. Urinary Analysis: ↑ protein
     - f. Organ water content & weight: ↑ lung wet and dry weight

10. **Shandougen** 山豆根 (5, 10 g/kg)
    - **Origin**: dry root and rhizoma of *Sophora subprostrata* CHUN et T. CHEN (Leguminosae)
    - **Clinical Indication**: heat-clearing and expelling miasma
    - **LD50**: 14 (11.0-18.5) g/kg, i.p.; and > 20 g/kg, p.o. in ICR mice
    - **Spontaneous Locomotor Activity**: ↓ (subacute, initial phase)
    - **Subacute Toxicity Profile**
      - a. Food Consumption:  
      - b. Water Intake:  
      - c. Urinary output:  
      - d. Hematological: ↓ albumin, ↑ BUN
      - e. Urinary Analysis: ↑ protein
      - f. Organ water content & weight: ↑ heart wet, dry weight, and water content (high dose)

11. **Tainnanxing** 天南星 (5, 10 g/kg)
    - **Origin**: dry aerial part of *Arisaema contortum* SCHOTT (Araceae)
    - **Clinical Indication**: expectorants, diuretic, sedative
    - **LD50**: 3.2 (2.34-4.38) g/kg, i.p.; and > 25 g/kg, p.o. in ICR mice
    - **Spontaneous Locomotor Activity**: ↓ (acute, low dose, i.p.);
      ↑ (subacute, at low dose, p.o.)
    - **Subacute Toxicity Profile**
      - a. Food Consumption:  
      - b. Water Intake:  
      - c. Urinary output:  
      - d. Hematological: ↑ SGPT (at high dose) ↓ BUN (at high dose)
      - e. Urinary Analysis: ↑ protein (at high dose)
      - f. Organ water content & weight: ↑ heart dry weight

12. **Weilingxian** 威靈仙 (5, 10 g/kg)
    - **Origin**: dry root of *Clematis chinensis* OSBECK (Ranunculaceae)
    - **Clinical Indication**: antirheumatics
    - **LD50**: > 50 g/kg, i.p., and p.o. in ICR mice
    - **Spontaneous Locomotor Activity**:  
      - **Subacute Toxicity Profile**
      - a. Food Consumption:  
      - b. Water Intake:  
      - c. Urinary output: ↑ (at low dose)
      - d. Hematological: ↑ WBC (late phase), ↓ SGPT
      - e. Urinary Analysis: ↑ protein
      - f. Organ water content & weight: ↑ heart & liver wet weight and water content (high dose)
13. *Xiakucao* 夏枯草 (5, 10 g/kg)
   • Origin: the fruit cluster of *Prunella vulgaris* L. (Labiatae)
   • Clinical Indication: heat-clearing
   • LD50: > 50 g/kg, p.o. in ICR mice
   • Spontaneous Locomotor Activity: ↑ (subacute)
   • Subacute Toxicity Profile:
     a. Food Consumption: ➖
     b. Water Intake: ➖
     c. Urinary output: ➖
     d. Hematological: ↓ SGPT, ↑ BUN
     e. Urinary Analysis: ↑ protein
     f. Organ water content & weight: ↑ heart wet weight

14. *Xianmao* 仙茅 (5, 10 g/kg)
   • Origin: dry rhizoma of *Curculigo orchioides* GAERTNER (Amaryllidaceae)
   • Clinical Indication: tonic prescriptions, reinforcing “Yang”
   • LD50: 15.0 (12.3 - 18.6) g/kg in ICR mice (i.p.)
   • Spontaneous Locomotor Activity: ▼ (subacute, high dose)
   • Subacute Toxicity Profile:
     a. Food Consumption: ➖
     b. Water Intake: ➖
     c. Urinary output: ↑ (at high dose)
     d. Hematological: ↓ SGPT, ↑ Albumin (all tested doses)
     e. Urinary Analysis: ↑ protein
     f. Organ water content & weight: ↑ heart wet weight and water content (at high dose)
     ▼ liver wet weight; and water content (at high dose)

15. *Xinyi* 辛夷 (5, 10 g/kg)
   • Origin: flower buds of *Magnolia denudata* DESR. (Magnoliaceae)
   • Clinical Indication: relieving exterior disorder
   • LD50: 20.4 (14.8 - 27.6) g/kg, i.p., and > 50 g/kg, p.o. in ICR mice
   • Spontaneous Locomotor Activity: ➖
   • Subacute Toxicity Profile:
     a. Food Consumption: ➖
     b. Water Intake: ➖
     c. Urinary output: ➖
     d. Hematological: ↑ WBC (late phase), BUN (initial phase)
     ▼ creatinine (initial phase)
     e. Urinary Analysis: ↑ protein
     f. Organ water content & weight: ↑ heart wet & dry weight (at high dose)