



## Acute and sub-chronic toxicity study of the ethanol extract from leaves of *Aralia elata* in rats



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### ABSTRACT

**Ethnopharmacological relevance:** *Aralia elata* Seem. (*A. elata*) is a well-known medicinal plant which has been used as a tonic, anti-arthritic and anti-diabetic agent in traditional Chinese medicine. This investigation aimed to evaluate the potential toxicological properties of the ethanol extract from leaves of *A. elata*, namely ethanol leaves extract (ELE), in rats by acute and sub-chronic toxicity studies.

**Materials and methods:** In the acute toxicity study, rats were orally administrated with ELE at doses of 1.00, 2.15, 4.64, and 10.00 g/kg to determine the oral medial lethal dose (LD<sub>50</sub>). Abnormal behavior, toxic symptom, and death were observed for 14 consecutive days. In the sub-chronic toxicity study, rats were orally administrated with ELE at doses of 0, 60, 180, and 540 mg/kg for 12 weeks and followed-up a 4-week recovery period. At the end of the treatment and recovery periods, the rats were sacrificed for hematological, biochemical, and histopathology analyses.

**Results:** The acute toxicity study showed that oral administration of ELE induced the incidence of adverse effects. The death rate also increased in a dose-dependent manner. The LD<sub>50</sub> value was 3.16 g/kg for female rats, and 5.84 g/kg for male rats, respectively. The sub-chronic toxicity study showed that daily oral administration of ELE induced no significant difference in food consumption. However, the body weight of male rats in high dose group increased slowly compared with the control group during the recovery period. The hematological and biochemical analysis showed that compared with the control group, HGB and MCV levels were significantly increased in ELE treatment groups at the end of the treatment period, while TP and GLB levels were significantly decreased at the end of the recovery period. The absolute and relative weight of thymus, brain and adrenal gland showed a significant difference in low or high dose group at the end of the treatment period, although no histological changes were observed in various organs.

**Conclusion:** The results of this study provided evidence that oral administration of ELE at dose of 540 mg/kg is safe in rats and may not exert severe toxic effects.

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**Abbreviations:** ELE, ethanol leaves extract; WBC, white blood cell; RBC, red blood cell; HCT, hematocrit; HGB, hemoglobin; MCH, mean corpuscular; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; LYM, lymphocytes; PLT, platelet; MON, monocytes; NEUT, neutrophil granulocytes; BAS, basophils; EOS, eosinophils; Ret, reticulocyte; APTT, activated partial thromboplastin time; PT, prothrombin time; ALT, alanine transaminase; ALP, alkaline phosphatase; AST, aspartate transaminase; ALB, albumin; GLB, globulin; A/G, albumin-globulin ratio; TP, total protein; TBIL, total bilirubin; CREA, creatinine; UA, uric acid; UREA, urea; CK, creatine kinase; TG, triglyceride; TCHO, total cholesterol; LDH, lactate dehydrogenase; GLU, glucose; LD<sub>50</sub>, medial lethal dose; CFDA, China Food and Drug Administration; NOAEL, no observe adverse effect level; HED, human equivalent dose.

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## 1. Introduction

Traditional Chinese herbal medicines have played an important role in promoting people's health and alleviating diseases for thousands of years (Lee et al., 2012). As alternative treatments for diseases, herbal medicines have advantages in reducing side effects, promoting immune system, and even prolonging survival time of people with cancer (Konkimalla and Efferth, 2008; Qi et al., 2010). *Aralia elata* Seem., locally called "Ci Lao Ya", is a shrub or small tree widely distributed in the northeast states of China, as well as in Japan, Korea, and Russia (Wang et al., 2014b). As a traditional Chinese herbal medicine, its leaves, roots and bark have been used to treat neurasthenia, diabetes mellitus, rheumatoid arthritis, hepatitis, gastrospasm (Gao et al., 1983; Luo et al., 2015; Saito et al., 1993; Zhang et al., 2012; Chung et al., 2005).

Given the increasing consumption of herbal medicine worldwide, the safety of herbal medicines has become a major concern. The young leaf of *A. elata* has unique flavor and good taste, which makes it a well-known edible plant in Asia (Zhang et al., 2013a). Saponins and flavonoids are the main bioactive components in its leaves (Wang et al., 2011; Zhang et al., 2013b). Phytochemical studies showed that plants with complex mixtures of saponins, flavonoids, and alkaloids, caused an increased risk of adverse reactions or synergistic effects of chemical interactions (Saad et al., 2006). However, to the best of our knowledge, the toxicological evaluation of ethanol extract from leaves of *A. elata* has not been conducted.

Previous study reported that total saponins extracted from leaves of *A. elata* possessed significant antitumor effect on human breast cancer *in vivo* and *in vitro* (Li et al., 2013). In order to confirm the safety of chemical substances in humans, toxicological studies in experimental animals were performed to evaluate the potential toxicity and provide a direction for determining a dose regimen for human use (Gao et al., 2011). The present study was carried out to collect preclinical data on the safety of the ELE by acute and sub-chronic oral administration in rats in order to provide a direction for selecting a safety range of dose for human use and complement earlier efficacy studies of this plant.

## 2. Materials and methods

### 2.1. Plant material and preparation of extract

The leaves of *A. elata* were collected from the Heilongjiang province of China in July 2011 and were identified by Prof. Zhenyue Wang (Heilongjiang University of Chinese Medicine). A voucher specimen (No.1990063) has been deposited in Herbarium of Heilongjiang University of Chinese Medicine, Harbin, China. The air-dried leaves were extracted three times with 95% ethanol for 2 h at each time. The solution was filtered and eluted by macroporous resin column with water, 30% and 70% ethanol, respectively. The 70% ethanol solution was evaporated and concentrated to obtain the ELE. Ultimately, about 10 kg air-dried leaves obtained 170 g ELE.

### 2.2. Sample preparation for HPLC

Two reference standards (Congmuyenoside G and Congmuyenoside I) were dissolved in methanol in the concentration of 1 mg/ml and stored at 4 °C. The ELE (550 mg) was dissolved in methanol (50 ml) and extracted by using heating reflux extraction method for four hours. Then, the filtrates were concentrated under

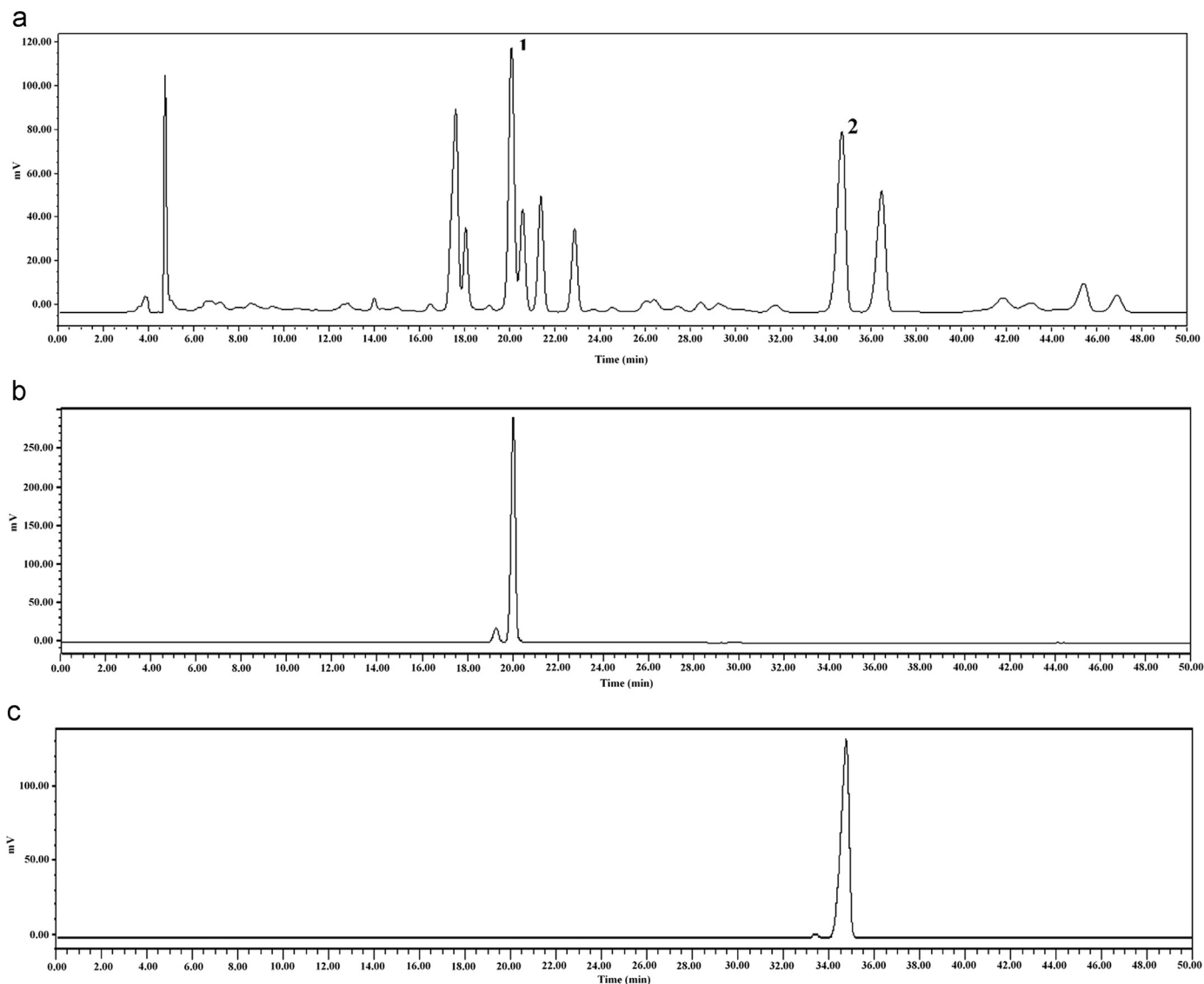


Fig. 1. HPLC chromatograms of ethanol extract of *Aralia elata* Seem leaves and standards. (a) Ethanol extract; (b) Congmuyenoside G; (c) Congmuyenoside I.

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