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Excretion of tectoridin metabolites in rat urine and bile orally administrated at different dosages and their inhibitory activity against aldose reductase

Jialin Qu [a], Zhizhen Wu [b], Jie Gao [a], Hao Wen [a], Tao Wang [b,**], Dan Yuan [a,*]

[a] *Department of Traditional Chinese Medicine, Shenyang Pharmaceutical University, 103 Wenhua Road, Shenyang 110016, China*
[b] *Institute of Traditional Chinese Medicine, Tianjin University of Traditional Chinese Medicine, 312 Anshanxi Road, Nankai District, Tianjin 300193, China*

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ABSTRACT

This study investigated the urinary and biliary excretion of tectoridin, a major active isoflavonoid found in the flowers of *Pueraria thomsonii* Benth. and the rhizomes of *Belamcanda chinensis* (L.) DC. Using UHPLC/Q-TOFMS, seven glucuronides and/or sulfated metabolites and four Phase I metabolites were simultaneously quantified in rat urine after oral administration of tectoridin at 100 and 200 mg/kg. Over a 72-h period, 14.2% and 14.7% of the tectoridin were excreted as eleven metabolites in urine, among which, two major metabolites tectorigenin-7-*O*-β-D-glucuronide (Te-7G) and tectorigenin accounted for 5.5–5.5% and 4.3–4.4%. Furthermore, the cumulative excretion of four glucuronides and sulfated metabolites in bile accounted for 7.3% and 3.9% of the dose within 60 h, among which, Te-7G and tectorigenin-7-*O*-glucuronide-4′-*O*-sulfate (Te-7G-4′S) accounted for 2.3–3.0% and 1.4–3.9%, respectively. The results indicate that the urine was the primary elimination route, and glucuronidation after deglycosylation at C-7 position was the major metabolic pathway of tectoridin in vivo. Moreover, the inhibitory activities of tectoridin and its five metabolites on rat lens aldose reductase were confirmed (IC_{50}: 1.4–15.5 μM), whereas irisolidone-7-*O*-glucuronide (Ir-7G) and irisolidone showed little activity.

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1. Introduction

Tectoridin (structure shown in Fig. 1) is a major isoflavonoid found in the rhizomes of *Belamcanda chinensis* (L.) DC [1]. and the flower of *Pueraria thomsonii* Benth. [2], and possesses hepatoprotective [3], estrogenic [4], hypoglycemic [5], antioxidative [6], and anti-inflammatory activities [7]. Several studies reported the transformation of tectoridin to aglycone tectorigenin by human and rat intestinal flora [8,9], the identification of seven glucuronides and sulfate conjugates of tectorigenin in urine and bile after oral administration of tectoridin and tectorigenin [10,11], and the quantification of tectorigenin in rat urine using enzyme hydrolysis after oral administration of tectoridin [12]. In previous studies, we reported the isolation and structural identification of ten urinary and biliary metabolites [13,14] and the determination of plasma pharmacokinetics of three conjugated metabolites in

Abbreviations: AR, aldose reductase; Dihydro-Te, dihydrotectorigenin; EIC, extracted ion chromatograms; HE, high energy; IR, infrared radiation; Ir-7G, irisolidone-7-*O*-glucuronide; IS, internal standard; Iso-Te, isotectorigenin; LE, low energy; LLOQ, lower limit of quantitation; MS, mass spectrometry; m/z, mass-to-charge ratio; NMR, nuclear magnetic resonance; 6-OH BiA-G, 6-OH Biochanin A-glucuronide; PLNO, partial loop needle overfill; QC, quality control; RE, relative error; RSD, relative standard deviation; Te-7G, tectorigenin-7-*O*-β-D-glucuronide; Te-4′G, tectorigenin-4′-*O*-β-D-glucuronide; Te-7G-4′S, tectorigenin-7-*O*-glucuronide-4′-*O*-sulfate; Te-7S, tectorigenin-7-*O*-sulfate; Te-4′S, tectorigenin-4′-*O*-sulfate; UGT, glucuronyl transferase; UHPLC/Q-TOF MS, ultra-performance liquid chromatography/quadrupole time-of-flight mass spectrometry; UV, ultraviolet spectrum.

* Corresponding author. Tel./fax: +86 24 23986502.
** Corresponding author. Tel.: +86 22 59596163.
E-mail addresses: wangtao@tjutcm.edu.cn (T. Wang), yuandan_kampo@163.com (D. Yuan).

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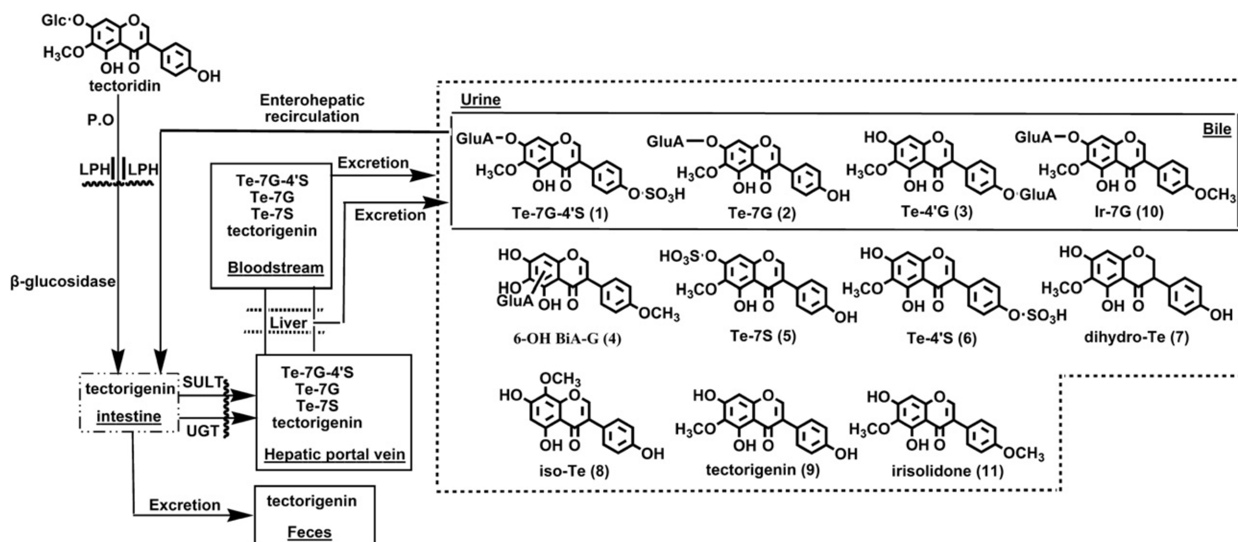

Fig. 1. Chemical structure of tectoridin and its proposed metabolic fates in rat urine and bile.

rat after oral administration of tectoridin [14]. However, the urinary and biliary excretion of conjugated metabolites after tectoridin intake has not been reported yet.

As a successive study on tectoridin metabolism, the urinary and biliary excretion kinetics of tectoridin metabolites, including seven glucuronides and sulfate conjugates, dihydrotectorigenin (dihydro-Te), isotectorigenin (iso-Te), tectorigenin and irisolidone, were determined by a UHPLC/Q-TOF MS method. Moreover, the inhibition activity of tectoridin and its major metabolites on aldose reductase from rat lens was assayed for the first time.

2. Material and methods

2.1. Chemicals and reagents

The standard compounds used in the qualitative and quantitative determinations were obtained as described previously. Tectoridin, tectorigenin and irisolidone were isolated from the flowers of *P. thomsonii* and *Pueraria lobata* [15,16], iso-Te, Te-7G, Ir-7G, tectorigenin-7-*O*-sulfate (Te-7S), tectorigenin-4′-*O*-sulfate (Te-4′S) and Te-7G-4′S were isolated from bile or urine of rats orally administered tectoridin or kakkalide [13,14,17]. The identification of these compounds was confirmed by spectral analysis including ultraviolet (UV), infrared radiation (IR), ^{1}H and ^{13}C NMR, and MS. The purity of tectoridin as evaluated by high performance liquid chromatography (HPLC)/UV was 98.4%, while that of the other compounds was greater than 95%. Daidzein, used as an internal standard (IS), was purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan), and had a purity of more than 98%.

Acetonitrile (HPLC grade) and formic acid were purchased from Fisher (Hampton, NH, USA). Ultra-pure water (18.2 MΩ) was prepared with a Milli-Q water purification system (Millipore, Molsheim, France).

Li_2SO_4 (Sinopharm Chemical Reagent Co., Ltd., P. R. China), DL-glyceraldehyde (Sigma, St. Louis, USA), NADPH (Sino-American Biotechnology Co., Ltd., P. R. China) and imidazole (Tianjin Concord Technology Co., Ltd, P. R. China) were used in the activity assay experiment.

2.2. Animals

Male Sprague–Dawley rats (200 ± 20 g body weight about 6–8 week-old) purchased from the Animal Center of Shenyang Pharmaceutical University were maintained in a breeding room under controlled temperature (25 °C), humidity (55 ± 5%) and lighting (12 h light, 12 h dark) conditions. Animals were acclimatized in metabolic cages with soy-free food for two weeks and fasted overnight before the experiments with free access to water. All experimental protocol was approved by the Ethics Review Committee for Animal Experimentation of Shenyang Pharmaceutical University.

2.3. Collection of urine and bile samples

Male rats were housed individually in a glass metabolism cage for urine collection. They were fasted for 12 h before the experiments. Tectoridin was suspended in 0.5% carboxymethylcellulose solution and the suspension was administered orally to rats at a dose of 100 and 200 mg/kg by gavage. The urine samples were collected for 12 h before dosing, and 0, 2, 4, 8, 12, 24, 36, 48, 60 and 72 h after dosing. During the collection, water and sugar were available freely. All the bio-samples were collected in ice-chilled glass containers, and stored at −20 °C until analysis. Sixteen fasted rats were fixed on a wooden plate and anesthetized by intraperitoneal injection of urethane (at the dose of 1.0 g/kg). An abdominal incision was made and the common bile duct was cannulated with PE-10 tubing for collection of the bile samples. And then, the tectoridin suspension was administered to rats at a dose of 100 and 200 mg/kg by oral gavage. The bile samples were collected for 1 h before dosing, and 0, 2, 4, 8, 12, 24, 36, 48 and 60 h after dosing, respectively. All the bile samples were stored at −20 °C until analysis.

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