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Study on the role of hepatic first-pass elimination in the low oral bioavailability of scutellarin in rats

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In the present study, we compared the systemic exposure of scutellarin following intraportal with intravenous administration to understand the contribution of presystemic hepatic elimination to the low oral bioavailability. Results showed that the hepatic first-pass elimination of scutellarin played an insignificant role in the presystemic elimination of orally administered scutellarin. Moreover, our results suggested that the site of first pass extraction was not the liver, but the gastrointestinal tract.

Scutellarin, a flavone glucuronide, is the main effective component of breviscapine and isolated from *Erigeron breviscapus* (Vant.) Hand-Mazz. Recent studies have shown that scutellarin possesses potent pharmacological effects (Ding 1999; Liu et al. 2002), and it is widely used in the treatment of cerebravascular diseases currently (Deng 2002; Ding 1999; He and Zeng 2002). However, the oral bioavailability of scutellarin was found to be quite poor in rats (Zhong et al. 2003). This study was intended to determine the role of hepatic first-pass elimination in limiting scutellarin absorption following oral administration.

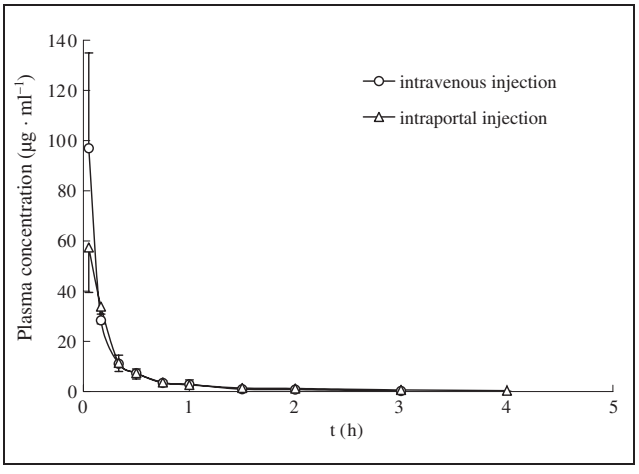

Fig.: Scutellarin plasma concentration-time profiles after intravenous and intraportal administration. Each values was the mean ± SD (n = 6)

Table: Pharmacokinetic parameters of scutellarin following intravenous and intraportal administration to rats (n = 6)

Parameters	Route of scrutellarin administration	
	Intravenous (i.v.)	Intraportal (i.p.)
AUC_{0-t} (μg · h/ml)	20.75 ± 4.43	19.09 ± 2.95
K(1/h)	1.22 ± 0.21	0.67 ± 0.34
Cl (ml/h)	248 ± 57	258 ± 40
F_{liver}[a]		92%

Values were mean ± SD (n = 6)
[a] F_{liver} calculated by $\frac{AUC/dose\ (i.p.)}{AUC/dose\ (i.v.)}$

Scutellarin was administered to rats by intravenous or intraportal injection. Blood samples were collected at designated times following administration and analyzed using HPLC with the UV detector. All the drug concentration data were analyzed using a non-compartmental method to obtain pharmacokinetic parameters. The plasma concentration-time curves were illustrated in the Fig. Unexpectedly, the concentration-time curves showed an overlapping contour. Accordingly, the data strongly suggest that first-pass hepatic elimination did not exert a significant role in the low oral bioavailability.

Pharmacokinetic parameters of scutellarin following intravenous and intraportal injection of 20 mg · kg^{-1} to Wistar rats are summarized in the Table. $AUC_{0\text{-}t}$ (up to 4 h) for intravenous administration and intraportal administration were 20.8 ± 4.43, 19.1 ± 2.9 μgh/ml, respectively. The percentage of scutellarin escaped first-pass hepatic elimination was approximately 92% available in the systemic exposure following intraportal injection. A high percentage of scutellarin entered the systemic circulation without undergoing significant presystemic hepatic elimination. Consequently, hepatic first-pass elimination of scutellarin did not have a considerable effect in the presystemic elimination of orally administered scutellarin. Our results also suggest that factors within the gastrointestinal tract such as the low oral solubility in gastrointestinal fluid, limited membrane permeability, transporter mediated intestinal secretion, or gut wall metabolism might contribute significantly to the low oral bioavailability of scutellarin (Yan et al. 2002).

It is known that the small intestine has the ability to metabolize a variety of drugs by numerous pathways, including both phase I and phase II reactions (Ilett et al. 1990). Recent studies showed that intestinal first-pass elimination of flavoniods was the main reason for low oral bioavailability of flavonoids (Liu and Hu 2002).

Experimental

1. Regents and chemicals

Scutellarin was supplied by Yunnan Yuxi Wanfang Natural Medicine Co. (China), Ltd. The internal standard, rutin, was purchased from the National Institute for the Control of Pharmaceutical and Biological Products (China).

2. Apparatus and chromatographic conditions

The Shimadzu HPLC system (Kyoto, Japan) consisted of a LC-10AT pump, a SPD-10A UV detector, and a 7725i sample injector. The analytical column used was Hypersil C_{18} (4.6 mm × 200 mm, 5 μm) from Dalian Elite Analytical Instruments Co., Ltd. (China). The column temperature was maintained at room temperature. The UV detector was set at 335 nm, and the flow rate was 0.8 mL · min^{-1}. The mobile phase consisted of acetonitrile-water (23 : 77, v/v), adjusted to pH 2.5 with 1 mol · L^{-1} phosphoric acid.

3. Sample preparation

To aliquots of 100 μL plasma, 10 μL internal standard (100 $\mu g \cdot mL^{-1}$, rutin in methanol) and 50 μL 0.5 $mol \cdot L^{-1}$ phosphoric acid were added. The mixture was vortex-mixed and extracted with 2 mL of ethyl acetate by shaking for 10 min. the organic phases were separated by centrifugation for 10 min (3 000 rpm), transferred to another tube and evaporated to dryness in a water bath at 40 °C under a flow of nitrogen. The residue was dissolved in 50 μL mobile phase. A 20 μL aliquot of the solution was injected into the HPLC system for analysis.

4. Pharmacokinetics study and data analysis

All animal studies were performed according to the Guidelines for the Care and Use of Laboratory Animals that was approved by the Committee of Ethics of Animal Experimentation of Shenyang Pharmaceutical University. Wistar rats (Male and female, 240–300 g) were provided by the Animal Center of Shenyang Pharmaceutical University (Shenyang, China). Animals were housed in a room with controlled temperature and humidity, and had free access to food and water. They were fasted overnight before the experiments. Two groups (6 rats/group) were randomly assigned to receive scutellarin solution via injection into the tail vein or intraportal injection at a single dose of 20 mg/kg, respectively. All rats were anesthetized with an intraperitoneal injection of urethane (250 $mg \cdot ml^{-1}$) at a dose of 1000 $mgkg^{-1}$ The jugular vein was cannulated and blood samples were collected at 0.05, 0.17, 0.33, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, and 4.0 h after the initiation of injection. The plasma samples were transferred into microcentrifuge tubes and stored at −20 °C until analysis.
The plasma concentration-time data were analyzed by noncompartmental analysis with 3p97 sofeware, a practical pharmacokinetic program (the Chinese Society of Mathematical Pharmacology).

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Effect of aqueous extract of *Pterocarpus marsupium* wood on alloxan-induced diabetic rats

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An aqueous extract of *Pterocarpus marsupium* wood was screened for hypoglycemic activity on alloxan-induced diabetic rats. During both acute and sub-acute tests, the water extract, at an oral dose of 250 mg/kg, showed statistically significant hypoglycemic activity.

Pterocarpus marsupium Roxb. (Leguminosae), commonly called as Bijasal, is a moderate sized to large deciduous tree, up to 30 m high, found commonly in hilly regions from Deccan Peninsula and entering to Gujarat, Madhya Pradesh, Uttar Pradesh, Bihar and Orissa (Kirtikar and Basu 1991; Anonymous 2001). In the traditional system of medicine it is used as an astringent, bitter, acrid, cooling, anti-inflammatory, haemostatic, antihelmintic, constipating, anodyne, alterant and rejuvenating agent, in fractures, bruises, leprosy, skin diseases, leucoderma, urethrorrhea, diabetes, rectalgia, rectitis, verminosis, diarrhoea, dysentery, gout, rheumatoid arthritis, cough, asthma, bronchitis and greyness of hair (Vaidyaratnam 1995; Nadkarni 1985; Chopra et al. 1956). An aqueous infusion of the wood is said to be useful in diabetes and water stored in vessels made of the wood is reported to have anti-diabetic qualities (Anonymous 1969a; Rastogi and Mehrotra 1990). Liquirtigenin, isoliquiritigenin, alkaloids, resins, essential oil, semidrying oil, tannins (Rastogi and Mehrotra 1991; Rastogi and Mehrotra 1993), terpenes, catechol, gallic acid and yellow colouring matter have been isolated from the plant (Anonymous 1969b).
The effect of an aqueous extract of the heartwood of *P. marsupium* on diabetic rats was evaluated in this study. The results indicated that *P. marsupium* wood possessed statistically significant hypoglycemic activity as was evident during acute and sub-acute treatments. It is generally accepted that the sulphonylureas, including gliclazide produce hypoglycaemia in normal animals by stimulating the pancreatic β-cells to release more insulin. These drugs, however, do not reduce blood glucose in alloxan diabetic animals. In contrast to the oral anti-diabetic agents, the exogenous administration of insulin is known to produce hypoglycaemia in both normal and alloxan-induced subjects. It is, therefore, conceivable that the hypoglycemic principle(s) in the aqueous extract of *P. marsupium* exert a direct effect in diabetic rats. In diabetic rats, aqueous extract cannot act indirectly by stimulating the release of insulin since alloxan treatment causes permanent destruction of β-cells (Pari and Maheshwari 1999). The antihy-