Journal of Food and Drug Analysis, Vol. 10, No. 2, 2002, Pages 75-80 藥物食品分析 第十卷 第二期

Relative Flavone Bioavailability of Scutellariae Radix between Traditional Decoction and Commercial Powder Preparation in Humans

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(Received: January 17, 2002; Accepted: March 15, 2002)

ABSTRACT

Baicalin, baicalein, wogonoside and wogonin are bioactive flavone constituents of Scutellariae Radix with a wide range of beneficial activities. The purpose of this study attempted to compare the absorption of baicalin, baicalein, wogonoside and wogonin between traditional decoction and a commercial powder preparation of Scutellariae Radix. Eight healthy male volunteers received 90 mL traditional decoction (equivalent to 9 g crude drug) and 4.3 g commercial powder preparation (comparable to 9 g crude drug) of Scutellariae Radix in a randomized crossover design. The contents of baicalin, baicalein, wogonoside and wogonin in traditional decoction and commercial preparation as well as their metabolites in urine were determined by HPLC methods. The relative flavone bioavailability was obtained by comparing urinary recoveries of glucuronides/sulfates of wogonin and baicalein within 36 hr after dosing.

The mean (± S.E.) cumulated renal excretion of glucuronides/sulfates of baicalein and wogonin after intake of traditional decoction were 66.0 ± 8.7 μmol (4.0 ± 0.5% of dose) and 30.8 ± 8.2 μmol (7.1 ± 1.8% of dose), whereas those for commercial preparation were 40.2 ± 6.0 μmol (2.2 ± 0.3% of dose) and 14.7 ± 3.7 μmol (4.1 ± 1.0% of dose), respectively.

The results indicated that the bioavailability of wogonin/wogonoside was about two times when compared to that of baicalein/baicalin from either traditional decoction or the commercial preparation. The flavone bioavailability from commercial preparation was significantly lower by 44.2± 0.1% for baicalin/baicalein and by 42.3 ± 0.1% for wogonoside/wogonin than those from traditional decoction.

Key words: flavone, baicalin, baicalein, wogonin, Scutellariae Radix

INTRODUCTION

In recent years, flavonoids are receiving increasing interest because of their beneficial biological activities including anti-inflammatory, antioxidant, antiviral, antitumor and antiallergic effects[1,2]. However, limited information about their bioavailability was available. Baicalin, baicalein, wogonin and wogonoside are the bioactive flavone constituents of Scutellariae Radix, the root of *Scutellariae baicalensis* Georgi (Labiatae), which is widely used in clinical Chinese medicine as a remedy for the treatment of fever, cough, inflammation and allergic diseases. Baicalin, baicalein and wogonin have been reported to show anti-inflammatory[3,4], anti-allergic[5], antioxidant[6] and antitumor activities[7,8]. In addition, baicalin was also shown to possess antiviral activity[9] and baicalein was reported to show hypotensive effect [10,11].

Chinese medicines are traditionally administered as decoction. In recent decades, preparation in granule or powder form has been commercialized for clinical use and is the only dosage form of Chinese medicine covered by the national health insurance in Taiwan. The object of this study was to compare the absorption of these flavones after oral administrations between traditional decoction and a commercial powder preparation of Scutellariae Radix in healthy males.

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MATERIALS AND METHODS

I. *Chemicals*

Baicalin, baicalein and wogonin were obtained from Wako (Osaka, Japan). β-Glucuronidase/sufatase (HP-2, from *Helix pomatia*), ethyl paraben and propyl paraben were purchased from Sigma Chemical Co. (St. Louis, MO, U.S.A.). Acetonitrile, methanol and ethyl acetate were LC grade and purchased from Mallinckrodt Baker, Inc. (Phillipsburg, NJ, U.S.A.). L(+)-Ascorbic acid was obtained from RdH Laborchemikalien GmbH & Co. KG (Seelze, Germany). Other reagents were HPLC grade or reagent grade. Milli-Q plus water (Millipore, Bedford, MA, U.S.A.) was used throughout this study.

II. *Crude Drug and Commercial Powder Preparation*

The crude drug of Scutellariae Radix and commercial powder preparation were purchased from a Chinese drug

store in Taichung. The origin of the crude drug was identified by microscopic examination. A specimen was deposited in the Institute of Chinese Pharmaceutical Sciences, China Medical College. The commercial powder preparation used in this study was the product containing the highest flavone content among ten brands assayed in our previous study[12].

III. *HPLC Conditions*

The HPLC apparatus included a pump (LC-6AD, Shimadzu, Japan), an UV spectrophotometric detector (SPD-6A, Shimadzu, Japan) and chromatopac (C-R6A, Shimadzu, Japan) with an automatic injector (Series 200 Autosampler, Perkin Elmer, U.S.A.). The Inertsil ODS-2 column (4.6 × 250 mm, 5 μm) was equipped with a guard column (4.6 × 50 mm, 5 μm) (GL Science Inc., Tokyo, Japan).

IV. *Herbal Decoction Preparation*

A quantity of 120.0 g of crude drug was used for preparing decoction. A volume of 4.8 L water was added and heating was carried out on a gas stove. After boiling, gentle heating continued for another 2.5 hr until the volume was reduced to less than a quarter of the original volume. The mixture was filtered while hot and sufficient hot water was added to make 1.2 L which was immediately divided into aliquots (90 mL each) and then frozen at –30˚C for later use.

V. *Acid Hydrolysis of Traditional Decoction*

The decoction was diluted with methanol (3:7, v/v) and centrifuged at 9860 x g for 15 min. The supernatant was added with an equal volume of 5% HCl, then divided into three aliquots (2 mL each). Each sample was covered with aluminum foil and hydrolysis was carried out at 100˚C in a water bath for 1.5 hr. The hydrolysates obtained were added with sufficient methanol to make 2 mL and then frozen at –30˚C for later analysis.

VI. *Extraction of Commercial Powder Preparation*

The commercial powder preparation (0.5 g) was extracted two times with 50 mL 70% aqueous methanol by ultrasonic shaking for 2 hr before filtering. Sufficient amount of methanol was added to the combined filtrates to make 100 mL and then frozen at –30˚C for later analysis.

VII. *Acid Hydrolysis of Commercial Powder Preparation*

The extract of commercial powder preparation was added with an equal volume of 5% HCl, then divided into three aliquots (2 mL each). The acid hydrolysis was carried out in triplicates using method mentioned above for the decoction. The hydrolysates obtained were added with sufficient methanol to make 2 mL and then frozen at –30˚C for later analysis.

VIII. *Quantitation of Baicalin, Baicalein, Wogonoside and Wogonin in Decoction, Commercial Powder Preparation and Their Hydrolysates*

The assay method and validation was reported in our previous study[12]. Two hundred microliter of sample was added with 200 μL ethyl paraben solution (20.0 μg/mL in methanol) as internal standard and 20 μL were subjected to HPLC analysis. The mobile phase consisted of acetonitrile –0.005% phosphoric acid (36:64, v/v) for baicalin, baicalein and wogonin assays. The detection wavelength was set at 270 nm and flow rate was 1.0 mL/min. The contents of baicalin, baicalein and wogonin were determined directly, whereas wogonoside was calculated by subtraction of free form wogonin from the total wogonin after acid hydrolysis.

IX. *Subjects*

Eight healthy Chinese males, 22-28 years and 56-85 kg in body weight, provided their informed consents. Routine biochemical tests indicated that their hepatic and renal functions were in good condition. They did not smoke or drink and had taken no medication for at least 2 weeks and throughout the experiment.

X. *Drug Administration and Urine Collection*

After overnight fast, frozen herbal decoction (90 mL each) warmed in a microwave oven and commercial powder preparation (4.3 g each) were administered to eight volunteers in a randomized crossover design. Each volunteer was then supplied with 120 mL and 210 mL warm water immediately following the decoction and commercial powder preparation, respectively. Urine samples were collected before and 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-24 and 24-36 hr after drug administration. Food was withheld for 3 hr after dosing.

XI. *Quantitation of Glucuronides/Sulfates of Baicalein and Wogonin in Urine*

The concentrations of conjugated metabolites of baicalein and wogonin in urine were determined after enzyme treatment. Two hundred microliter of urine was mixed with 100 μL β-glucuronidase/sulfatase (2207/84 units/mL in pH 5 acetate buffer), 20 μL ascorbic acid (200 mg/mL) and then incubated at 37˚C for 7 hr under anaerobic condition and protected from light. After hydrolysis, the urine was acidified by adding 50 μL 0.1 N HCl and partitioned with 350 μL ethyl acetate (containing 8.0 μg/mL of propyl paraben as internal standard). The ethyl acetate layer was evaporated under N_2 to dryness and reconstituted with an appropriate volume of mobile phase prior to HPLC analysis.

For calibrator preparation, 200 μL urine spiked with various concentrations of baicalein and wogonin were added with 100 μL buffer (pH 5) . The later procedure was the same as that described above for urine samples. The mobile phase of HPLC was modified to acetonitrile-0.05% phosphoric acid

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(38:62, v/v)[12]. The calibration curve was plotted after linear regression of the peak area ratio (baicalein or wogonin to internal standard) with concentrations of baicalein or wogonin.

XII. *Validation of Assay Methods for Urine*

The system suitability was evaluated by the intraday and interday precision and accuracy. The recovery study was conducted by spiking baicalein and wogonin into blank urine and water, respectively, then comparing the concentrations obtained in blank urine to the corresponding ones in water were compared.

XIII. *Data Analysis*

The concentrations of baicalein and wogonin measured in urine were multiplied by the respective urinary volumes to obtain the amount excreted at the sampling time. The summarized amount of glucuronides/sulfates of baicalein and wogonin was transformed into molar percentage of the dose which was calculated as total intake of baicalin/baicalein and wogonoside/wogonin, respectively. The urinary excretion rates of the metabolites per hour during each collection interval were calculated.

XIIII. *Statistical Analysis*

The paired Student's t-test was used to compare the differences of renal recoveries of baicalin/baicalein and wogonin/wogonoside within 36 hr between the two treatments.

RESULTS AND DISCUSSION

Biological activities of flavonoids depend on their bioavailability. The chemical structures and physicochemical properties of flavonoids determine their rate and extent of intestinal absorption and the nature of the metabolites circulating in the plasma[13]. The traditional decoction of Scutellariae Radix contains a major constituent baicalin with its aglycone baicalein in much less abundance. Another flavonoid glycoside wogonoside is also in presence with its aglycone wogonin. Because authentic wogonoside was not available, its quantitation was carried out indirectly by subtracting aglycone wogonin from the total wogonin after acid hydrolysis. Quantitation of the decoction indicated that each dose (90 mL, equivalent to 9 g crude drug) contained baicalin 1380.1 μmol (616.0 mg), baicalein 263.1 μmol (71.1 mg), wogonoside 289.5 μmol (133.3 mg) and wogonin 145.6 μmol (41.4 mg), and those in the commercial powder preparation (4.3 g) were 1516.0 μmol (676.7 mg), 280.0 μmol (75.7 mg), 223.1 μmol (102.7 mg), and 136.1 μmol (38.7 mg), respectively. The result indicated that the contents of baicalin and wogonoside were much higher than their corresponding aglycones in both traditional decoction and commercial powder preparation.

The HPLC assay method of baicalein and wogonin in urine after enzymatic hydrolysis was developed and validated in this study. The chromatogram of a urine sample is

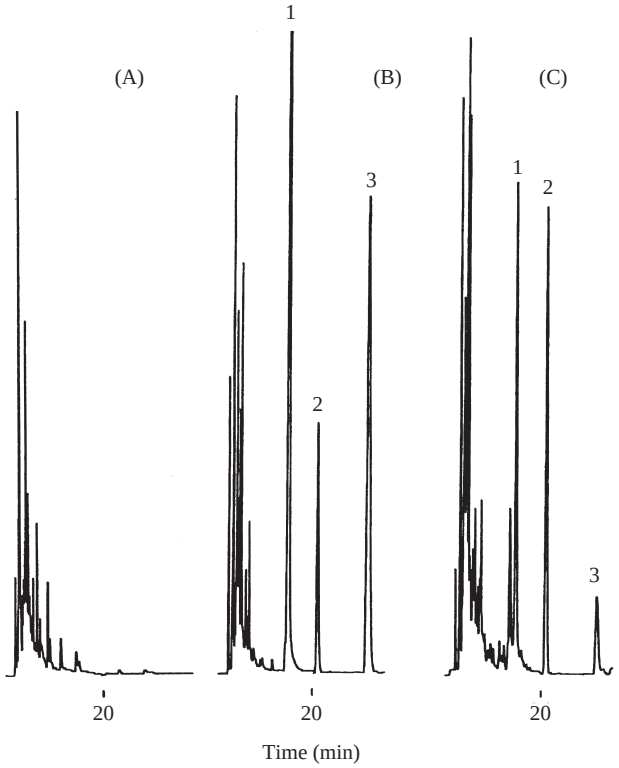

Figure 1. HPLC chromatograms of (A) drug free urine; (B) baicalein and wogonin with internal standard in urine; (C) urine sample with internal standard; 1: baicalein; 2: internal standard (propyl paraben); 3: wogonin.

Table 1. Intraday and interday analytical precision and accuracy of baicalein assay in urine

Concentration (μg/mL)	Intraday (n=3) Precision Mean ± S.D. (C.V.%)	Intraday (n=3) Accuracy R. E. (%)	Interday (n=3) Precision Mean ± S.D. (C.V.%)	Interday (n=3) Accuracy R. E. (%)
40.0	$39.7 \pm 0.0_3$ (0.1)	-0.8	39.6 ± 0.3 (0.8)	-1.1
20.0	$21.0 \pm 0.1_3$ (0.6)	4.9	20.8 ± 0.2 (0.8)	4.0
10.0	$10.1 \pm 0.2_3$ (2.4)	1.3	10.1 ± 0.1 (1.2)	1.0
7.5	$7.3 \pm 0.3_3$ (4.4)	-2.4	7.2 ± 0.5 (7.0)	-3.8
5.0	5.0 ± 0.1 (1.2)	-0.7	4.9 ± 0.1(2.6)	-2.0
2.5	2.2 ± 0.1 (3.1)	-11.0	$2.3 \pm 0.0_3$ (1.3)	-9.7
1.3	$1.2 \pm 0.0_1$ (0.7)	-5.8	1.2 ± 0.1(7.5)	7.7
0.6	$0.7 \pm 0.0_4$ (5.4)	7.7	0.6 ± 0.1(11.3)	-2.0

shown in Figure 1. Good linear relationships were obtained for baicalein and wogonin in the concentration ranges 0.3-40.0 μg/mL (Y = 0.13 X - 0.01, r = 0.9991) and 0.3-20.0 μg/mL (Y = 0.12 X - 0.02, r = 0.9989) in urine, respectively. The intraday and interday precision and accuracy analysis of baicalein and wogonin in urine indicated that the both coefficients of variations were below 11.3 and 7.3% and the relative errors were below 11.0% and 9.6%, respectively, as shown in Table 1 and Table 2. The LOQ (limits of quantitation) and LOD (limits of detection) were 2.5 μg/mL and 0.2 μg/mL for both baicalein and wogonin. The recoveries of baicalein and wogonin from urine as shown in Table 3 were 102.2-114.5% and 106.3-114.1%, respectively, indicating almost quantitative recoveries.

The metabolites of baicalin and baicalein in human plasma after oral administration were identified as baicalein 7-*O*-glucuronide and baicalein 6-*O*-sulfate[10]. The quantitation of the conjugated metabolites in urine was based on the determination of baicalein/wogonin after enzymatic hydrolysis with β–glucuronidase/sulfatase. The hydrolysis procedure was conducted with the addition of ascorbic acid, under anaerobic condition and protected from light. Regarding the hydrolysis time, 7 hr was previously determined as the optimal duration. No free form of baicalein or wogonin was detected in urine. The molar percentages absorbed from baicalin/baicalein and wogonoside/wogonin in decoction and commercial powder preparation calculated from the recovery of the conjugated metabolites of the aglycones were shown in Table 4. Total amounts of 66.0 ± 8.7 μmol (4.0 ± 0.5% of dose) and 30.8 ± 8.2 μmol (7.1 ± 1.8% of dose) for conjugated metabolites of baicalein and wogonin were recovered in urine, respectively, after the intake of decoction, whereas those after intake of the commercial powder preparation were 40.2 ± 6.0 μmol (2.2 ± 0.3% of dose) and 14.7 ± 3.7 μmol (4.1 ± 1.0% of dose). The mean cumulated urinary excretion and the mean urinary excretion of the eight individuals in each time interval during 36 hr were shown in Figure 2 and Figure 3, respectively, after intake of the decoction and commercial powder preparation.

Baicalin and wogonoside are glycosides which are polar and thus are not able to permeate through enterocytes, whereas their aglycones baicalein and wogonin are more lipophilic and absorbable by the intestine. The relatively high early exposure of baicalein and wogonin during 0-2 hr of both traditional decoction and commercial powder preparation could be explainable by the major contribution of the rapid absorption of these aglycones in the small intestine. A second peak between 6-8 hr was mainly due to the absorption of baicalein/wogonin from their glycosides baicalin/wogonoside which were later absorbed only after gradual hydrolysis in the colon by microflora. Therefore, baicalin/wogonoside are like natural sustained-released prodrugs of baicalein/wogonin. The third peak between 10–12 hr might be due to intake of dinner, because eating was known to stimulate emptying of the gall bladder and to result in more enterohepatic circulation of the conjugated metabolites[13]. It could be speculated that enterohepatic circulation of the conjugated metabolites resulted in long half lives of these molecules which is generally preferable because greater efficacy could

Table 2. Intraday and interday analytical precision and accuracy of wogonin assay in urine

	Intraday (n=3)		Interday (n=3)	
Concentration (μg/mL)	Precision Mean ± S.D. (C.V.%)	Accuracy R. E. (%)	Precision Mean ± S.D. (C.V.%)	Accuracy R. E. (%)
20.0	20.2 ± 0.1 (0.3)	1.1	20.2 ± 0.1 (0.4)	0.8
10.0	$9.5 \pm 0.0_2$ (0.2)	-5.3	$9.5 \pm 0.0_4$ (0.5)	-5.0
5.0	5.1 ± 0.1 (2.5)	2.1	5.0 ± 0.1 (1.4)	-0.1
2.5	2.4 ± 0.1 (3.8)	-2.4	$2.4 \pm 0.0_2$ (1.0)	-5.0
1.3	$1.3 \pm 0.0_4$ (3.1)	4.3	$1.3 \pm 0.0_4$ (3.3)	4.7
0.6	0.7 ± 0.1 (7.3)	9.6	$0.7 \pm 0.0_4$ (6.0)	8.7

Table 3. Recoveries (%) of baicalein and wogonin from urine (n=3)

Constituents spiked	Concentration (μg/mL)	Recoveries (%) (Mean ± S.D.)
Baicalein	5.0	102.2 ± 0.0
	20.0	110.9 ± 0.0
	40.0	114.5 ± 0.0
Wogonin	2.5	114.1 ± 2.9
	5.0	110.7 ± 1.8
	10.0	106.3 ± 1.0

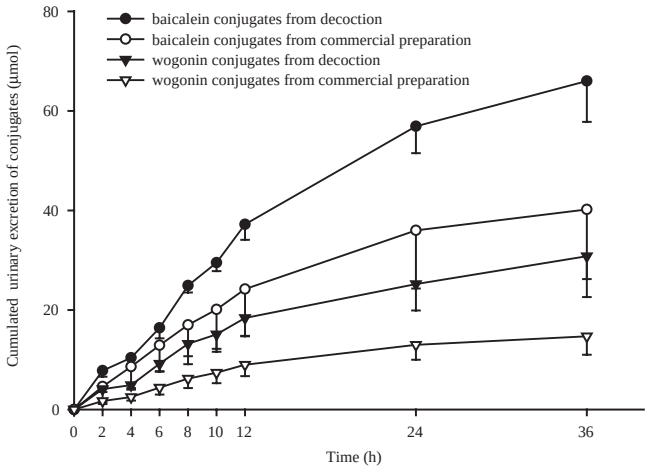

Figure 2. Mean (± S.E.) cumulative excretion of conjugated metabolites of baicalein and wogonin in urine of eight volunteers after intake of Scutellariae Radix decoction and commercial preparation.

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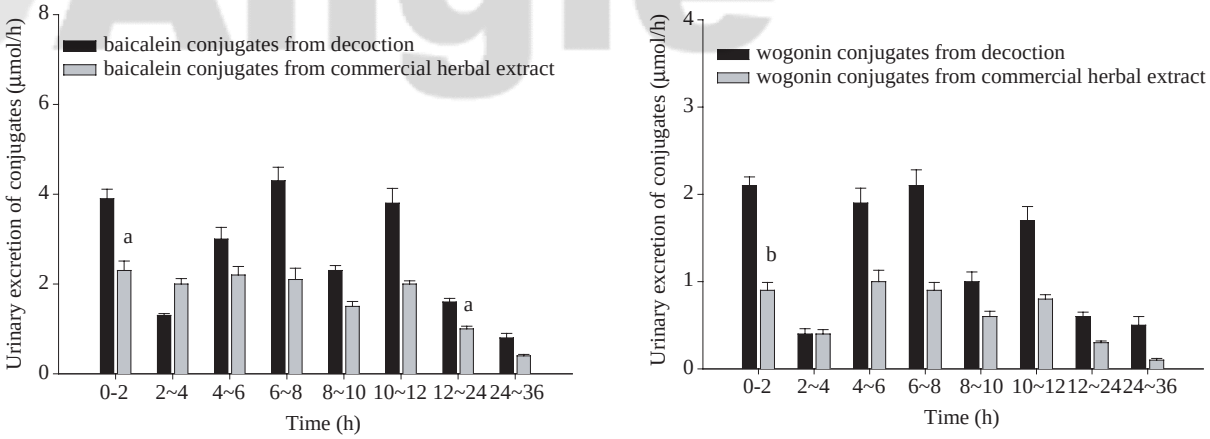
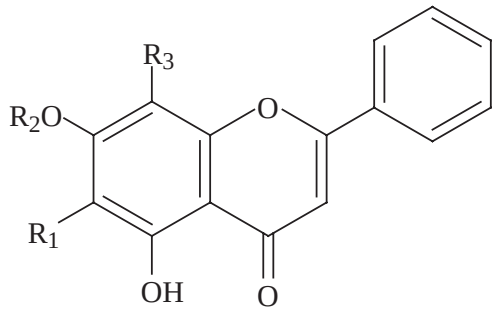


Figure 3. Mean (± S.E.) urinary excretion rate of (A) baicalein and (B) wogonin conjugates of eight volunteers after administration of Scutellariae Radix decoction and commercial preparation in each time interval (μmol/h).
[a] P<0.05, [b] P<0.01.

Table 4. Comparison of renal recoveries (% of dose) of baicalein and wogonin conjugates after intake of Scutellariae Radix decoction and commercial preparation

Metabolites	Traditional decoction	Commercial preparation	Difference
Baicalein conjugates	4.0 ± 0.5	2.2 ± 0.3	-44.2 ± 0.1[b]
Wogonin conjugates	7.1 ± 1.8	4.1 ± 1.0	-42.3 ± 0.1[a]

Data expressed as mean ± S.E.
[a] P<0.01, [b] P<0.05.



Baicalin : R_1 = OH, R_2 = glucuronic acid, R_3 = H
Baicalein : R_1 = OH, R_2 = H, R_3 = H
Wogonoside: R_1 = H, R_2 = glucuronic acid, R_3 = OCH_3
Wogonin : R_1 = H, R_2 = H, R_3 = OCH_3

be anticipated. In addition, the results indicated that the bioavailability of wogonin/wogonoside was about two times of that for baicalein/baicalin from either traditional decoction or the commercial powder preparation. This might be accounted for by the higher lipophilicity of wogonin based on its longer retention time of reversed-phase HPLC as shown in Figure 1.

In summary, the flavone bioavailability from commercial powder preparation was significantly lower by 44.2 ± 0.1% for baicalin/baicalein and by 42.3 ± 0.1% for wogonoside/wogonin than those from traditional decoction. It could be concluded that traditional decoction was the better dosage form for immediate and higher absorption. If the administration of commercial powder preparation of Scutellariae Radix would achieve the comparable efficacy of traditional decoction, higher dose should be prescribed. Otherwise, further improvement on formulation of the commercial powder preparation is needed.

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黃芩傳統水煎劑與濃縮散劑於人體內生體可用率之比較

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（收稿：January 17, 2002 ；接受：March 15, 2002）

摘　要

黃芩為富含黃酮類成分之傳統中藥。本研究探討黃芩傳統水煎劑及濃縮散劑中之黃酮類成分—黃芩苷、黃芩苷元、漢黃芩苷和漢黃芩素在人體內吸收之比較。八位受試者以隨機交叉設計給藥，分別口服給予90毫升之傳統水煎劑（相當於9克之藥材）或4.3克之濃縮散劑（約相當於9克之藥材），以高效液相層析法測定傳統水煎劑及濃縮散劑中黃芩苷、黃芩苷元、漢黃芩苷和漢黃芩素以及它們在尿中之結合態代謝物之含量。尿液中代謝物之檢測是經由β-葡萄糖醛酸酶及硫酸酶水解之後，定量其黃芩苷元和漢黃芩素之濃度。兩種劑型相對生體可用率係比較服藥後之三十六小時內，其尿中結合態代謝物之總排出率。

定量結果顯示，口服傳統水煎劑後，尿中黃芩苷元及漢黃芩素代謝物之平均總排出量分別為66.0 ±8.7 μmol（平均排出率為4.0 ±0.5%）及30.8 ±8.2 μmol（平均排出率為7.1 ±1.8%），而濃縮散劑則為40.2 ±6.0 μmol（2.2 ±0.3%）及14.7 ±3.7 μmo（4.1 ± 1.0%）。因此口服濃縮散劑之黃芩苷／黃芩苷元和漢黃芩苷／漢黃芩素平均生體可用率，比傳統水煎劑分別顯著減少了44.2 ±0.1%及42.3 ± 0.1%。此結果顯示黃芩之傳統水煎劑與濃縮散劑無生物相等性。

關鍵詞：黃酮類，黃芩，黃芩苷，黃芩苷元，漢黃芩苷，漢黃芩素