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經方葛根芩連湯之藥物動力學研究—從體內到體外、從動物到人體 (2-1)

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摘　要

葛根芩連湯由葛根、炙甘草、黃芩及黃連組成，具有清解表裏、瀉熱和中、止利之功效。本計畫所使用的製劑，係以同一批原生藥，由GMP中藥廠製備濃縮製劑與水煎劑，再以大鼠為動物模式進行葛根芩連湯所含指標成分受腸道菌體作用之循環前代謝與血藥及尿藥動力學之研究並進行兩種劑型間於大鼠體內之口服生可用率之比較。本研究以HPLC-UV定量葛根芩連湯水煎劑及濃縮散劑中各指標成分之含量及分析口服藥物後血清與尿液檢品中的指標成分與其代謝物之含量。並藉以比較水煎劑與濃縮散劑之生體可用率及生體相等性。

分析大鼠口服水煎劑及濃縮散劑之血清及尿液檢品後發現，血中及尿中並未檢出各成分之原型化合物。而daidzein、baicalein、wogonin均以結合態代謝物(sulfates/glucuronides)存在於血清及尿液中，顯示多酚成分主要以sulfates/glucuronides型態吸收並從尿液排除。大鼠口服葛根芩連湯水煎劑或濃縮散劑後，水煎劑各成分之吸收及總排除量與濃縮劑型並無顯著差異，除wogonin之外，daidzein、baicalein皆達生體相等性。由血藥經時變化圖及各時段之排除率(% of dose/h)顯示各成分皆有腸肝循環現象。各成分排除半衰期(t1/2)介於1~28 h，各成分間變異性頗大，個體間之差異亦大。

關鍵詞：葛根芩連湯、中藥藥物動力學、動物、口服

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Pharmacokinetics of Ge Gen Huang Qin Huang Lian Tang – in vitro to in vivo and Animals to Humans (2-1)

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ABSTRACT

Ge Gen Huang Qin Huang Lian Tang (GGCLT) is composed of Pueraria Radix, Scutellariae Radix, Glycyrrhizae Radix and Coptidis Rhizoma. This prescription possessed various biological effects including antipyretic, antibacteria, antivirus and antiarrhythmia etc. This study investigates the metabolism and pharmacokinetics of the flavonoid constituents in GGCLT. Serum and urine samples were assayed for the concentrations of daidzein, baicalein, wogonin and their conjugated metabolites before and after hydrolysis with sulfatase and glucuronidase. Noncompartment model of WINNONLIN was used for calculation of pharmacokinetic parameters. Paired Student's test was used to compare the bioavailabilities of various compounds between two dosage forms. The results showed that no free form of daidzein, baicalein and wogonin was detected and they were found predominantly as sulfates/glucuronides in the serum and urine. These two dosage forms were found bioequivalent concerning the pharmacokinetics of daidzin and baicalin, whereas those of wogonin were not. All metabolites demonstrated possible enterohepatic circulation. The excretion half-lives of all constituents ranged from 1 to 28 h and the variability among individuals was rather large.

Keywords：Ger-Gen-Chin-Lien Tang, pharmacokinetics, animal

壹、前言

數種藥物分別以君、臣、佐、使之角色，組合成方劑使用於臨床，為中醫藥有別於世界上其他醫學體系的用藥特色之一。相對於單味藥物，中藥方劑實為一極複雜的化學組合體系，因此其中何者成分為主要產生療效之基礎物質，長期以來一直是個幾乎無法回答的基本問題，有許多急待釐清之處[1-2]。物質進入生物體後，體外化學成分組合經體內複雜的代謝系統作用後，其質與量之組成必然迥異於前；本研究室先前之研究曾發現，與不同背景或輔料共存之同一成分，其口服吸收後之動力學行為是顯然不同[3-5]。

在本研究室先前累積的單味中藥代謝動力學研究之基礎上[3-16]，從93年度迄今，持續以「三黃瀉心湯」為模型方劑，從動物到人體進行一系列該方中指標成分的動物血藥動力學與人體尿藥與血藥動力學研究，此些研究的結果顯示，投藥後大白鼠的血清與人體的尿液中並未檢測出此方中所含之生物鹼成分，顯示其原形無法進入體循環，而方劑中所含之多酚成分除rhein尚有原型存在外，其他多以sulfates及glucuronides等代謝產物存在於體循環。95年度所執行的人體血藥與尿藥動力學研究的結果亦顯示，此些生物鹼成分的原形分子亦不存在於人體之血液中。

上述的研究結果顯示，口服中藥後體內存在的分子型態，與現行針對天然植物成分以體外試驗評估中藥活性之思維有落差。因此若僅試圖從單味藥物或方劑之化學組成，尋找方劑藥物之療效基礎物質，可能會與真正體內發揮作用的物質有相當的差距。當前對於中藥方劑的研究，多集中於其藥理作用之評估與成分之定量分析，對於傳統方劑口服給藥後，所含成分之生體轉化動態的相關研究領域，僅有少數研究工作者投入其中，相關研究報告並不多見。在過去幾年中，本研究室分別進行過單味中藥黃芩中baicalin、baicalein及wogonin[12, 15-16]、甘草中glycyrrhizin及glycyrrhetic acid[4-6]與葛根中puerarin、daidzin及daidzein等成分之口服代謝動力學研究[17]，在此些研究中發現，此些成分以原形分子出現於體循環之比例極低，多數以結合態型式之代謝物存在於體內。另有其他學者對於大豆中daidzin的研究顯示，配糖體成分不能直接通過小腸壁而吸收，推測係因其極性太高，而人和動物的腸道菌群*Lactobacilli, Biofidobacteria, Bacteroides*等對藥物具有代謝能力。傳統上中草藥多以水煎劑、丸劑等劑型口服給藥，進入腸腔後直接暴露於腸道菌群中，因而受其代謝轉化，因此中藥中的配醣體成分會被腸道中存在的細菌水解成為低極性之非醣體aglycone後，才能為人體吸收利用[18-19]。因此本研究室以近年進行的相關研究基礎上，續以葛根芩連湯為標

的藥物，從體內到體外、從動物到人體進行相關血藥與尿藥之藥物動力學之研究，建立更多中藥方劑體內動態的參考數據。

葛根芩連湯出於傷寒論三十四條，「太陽病，桂枝証，醫反下之，利遂不止，脈促者，表未解也；喘而汗出者，葛根黃芩黃連湯主之」，中醫藥委員會所公告的基準方中，葛根芩連湯由葛根（12g）、炙甘草（3g）、黃芩（4.5g）及黃連（4.5g）組成，具有清解表裡、瀉熱和中、止利之功效。中醫臨床上使用於太陽表邪內陷所致之腸熱下痢症[20]。而除傳統的治療功效外，另有文獻顯示，葛根芩連湯尚具有解熱[21-22]、抗菌[22-23]、抗缺氧[24]、改善化療放療後腸炎泄瀉[25-26]與降血糖[27-28]等生物活性；另外此方在定量分析上常以baicalin、baicalein、wogonin、puerarin、daidzin、daidzein、berberine、palmatine、coptisine、glycyrrhizin及glycyrrhetic acid等成分含量作為品質評價之評估對象，此些成分具許多重要的生物活性，如黃芩及其成分baicalin、baicalein與wogonin等具抗發炎[29]、抗菌[30]、抗氧化[31]、抗病毒、抗腫瘤[32-33] 等活性。黃連及其成分berberine具抗菌、抗腫瘤、抗發炎[34-37]等活性。葛根及其成分puerarin、daidzin及daidzein具抗心律不整及擴張冠狀動脈血管[38-40]，抗血小板凝集[41]、降血脂[42]、抗腫瘤[43]、增強小鼠免疫功能[44]與抗氧化[45]等藥理活性。甘草與glycyrrhizin（甘草酸）及glycyrrhetic acid（甘草次酸）等具抗炎、抗氧化、抗病毒等作用[46-53]。另有研究報導，甘草主成分甘草酸可抑制冠狀病毒之複製的作用，同時亦抑制病毒進入細胞，另外其代謝物甘草次酸有更強抗發炎、促進巨噬細胞分泌NO等作用[54] 。因此不論從傳統或現代醫學角度觀之，葛根芩連湯為一極重要且具開發潛力之方劑藥物。

另外在95年度本研究室所參與的葛根芩連湯對MTX交互作用風險評估之研究中顯示，葛根芩連湯顯著增高MTX於鼠體內之全身暴露及滯留時間，初步結果顯示葛根芩連湯可能抑制了MTX之排除進而造成毒性。近年研究顯示MTX於體內之轉運、外排與MRP1、MRP2、MRP3、MRP4及OAT1、OAT2、OAT3與 OAT4等運送蛋白有關[55-60]。因此口服葛根芩連湯後，那些成分吸收入體內而影響上述運送蛋白造成不良反應，極待透過in *vitro* 及 in *vivo*之藥物動力學研究來釐清。因此，基於我們過去對葛根芩連湯中各組成單味藥物藥動學的基礎，以及相關中西藥交互作用風險評估研究中的發現，本研究選擇以經方「葛根芩連湯」做為研究標的，除可累積更多的中藥方劑臨床藥動學資訊外，亦可協助釐清葛根芩連湯與MTX交互作用發生之機制。

由於台灣特殊之醫療環境，健保僅給付濃縮製劑，因此臨床上使用科學濃縮製劑之比率遠超過傳統水煎劑，但在此兩劑型間，由於其藥物形式、

賦型劑以及藥物成分組成之質與量等差異，其在生體內之吸收代謝情形必然有所不同。目前台灣民眾使用的濃縮製劑數量極大，但除本研究室所進行三黃瀉心湯的相關研究外，尚未見對於水煎劑與濃縮製劑兩種劑型間口服生可用率比較之報導，因此本計畫另進行葛根芩連湯兩種劑型間口服生可用率之比較，以提供臨床使用之參考。

本年度之計畫乃為葛根芩連湯之人體臨床藥物動力學之實驗先導試驗，以SD大鼠為動物模式，建立葛根芩連湯的大鼠藥物動力學數據，並據以為申請人體試驗進行的基礎依據。我們以大鼠為實驗動物一系列評估葛根芩連湯在其體外到體內的代謝動力學行為包含腸道菌群對中藥成分的體循環前代謝之研究及血藥與尿藥動力學研究，並嘗試以西藥BA/BE的試驗模式進行不同製劑間指標成分生可用率之比較。此外，在本年度計畫中，亦將下一年度擬執行之葛根芩連湯之人體試驗計畫之分析條件開發完成，同時亦完成人體試驗委員會之試驗案申請。

貳、材料與方法

一、藥材之採購及基原鑑定

採購葛根芩連湯中各組成藥材，經五官及顯微組織學鑑定，確認其基原並建檔，作為本研究之材料。葛根芩連湯之組成為葛根、黃芩、黃連、炙甘草(12:4.5:4.5:3)。

二、葛根芩連湯之製備與指標成分之定量分析

(一) 葛根芩連湯之製備

1. 水煎劑部分：採購葛根、黃芩、黃連與甘草原藥材，並經生藥組織學鑑定後，委託GMP中藥廠以其廠規之方式，比例為12:4.5:4.5:3，製備濃縮抽提物，取其一部分加入適量二次水還原為水煎劑備用。
2. 濃縮製劑部分：
   (1)將上述GMP中藥廠所製備之濃縮抽提物，取其一部分製備為濃縮散劑備用。
   (2)市售品則自六家GMP中藥廠所生產之濃縮葛根芩連湯製劑。
   (3)上述水煎劑與濃縮散劑均以HPLC定量其中所含的puerarin、daidzin、coptisine、baicalin、daidzein、palmatine、berberine、baicalein、glycyrrhizin及wogonin等成分含量後備用。

(二) 濃縮散劑與水煎劑中指標成分之定量

取經水稀釋60倍的水煎劑3mL，加甲醇7mL振盪混合，離心15min (10,000 g)去沉澱，取上清液160 μL，加入40 μL之內標準甲醇溶液(amyl paraben, 100.0 μg/mL)混合後，離心15min (10,000g)，取上清液20 μL注入HPLC分析。將上述溶液以各成分（puerarin、daidzin、coptisine、baicalin、daidzein、palmatine、berberine、baicalein、glycyrrhizin及wogonin）與內部標準品之波峰面積比值，代入檢量線之方程式，求出各成分之含量。

(三) HPLC分析條件

層析管：Apollo C18, 5 μm (4.6 × 250 mm)

移動相：0.1 % H_3PO_4：CH_3CN

0.1 % H3PO4的梯度變化如下(層析時間為75分鐘)：

梯度變化	層析時間 (分鐘)
89 → 82	25
82 → 70	45
70 → 57	54
57 → 53	59
53 → 35	65
35 → 89	75

流　　速：1.0 mL/min

檢測波長：250 nm

內 標 準：amyl paraben (100.0 μg/mL)

三、大鼠口服葛根芩連湯後體循環前代謝之研究

(一) 腸道菌懸浮液之製備

取未進行實驗之SD大鼠所排遺的新鮮糞便，加入人工腸液，以1：3之比例混合後利用攪拌器混合均勻，再以紗布過濾於4℃冰櫃中保存，2小時內備用。

(二) 腸道菌群體循環前代謝分析樣品之製備與反應

分別配製上述已定量完成指標成分含量之葛根芩連湯水煎劑與濃縮散劑之水懸浮液（每 mL 含 0.1g 之原生藥材量）各 3.0mL，各加入 27.0mL 之大鼠腸道菌懸浮液，以攪拌器混勻後，用微量分注器分別取混合液 600μL 置於避光試管中，栓上血清塞並用針筒將空氣移除模擬腸道生態，先各取 6 管立即貯存於冰上，其餘再置於 37℃水浴槽中，以 100rpm 振搖，令其反應，並於 30 秒、1 分鐘、30 分鐘、1、2、4 及 8 小時，分別各取出 6 管，立即置於冰上停止反應，待後續檢品處理[65]。

(三) 分析樣品HPLC分析條件之開發

1. 檢品處理

於上述之檢品中，分別加入0.1N鹽酸溶液100μL及乙酸乙酯700μL（含內標amyl paraben 10 μg/mL），經試管震盪器震盪後高速離心15分鐘。取乙酸乙酯層，用氮氣吹乾後，加入甲醇100μL以超音波震盪器震盪使之完全溶解。再經高速離心15分鐘，取上清液20μL注入HPLC分析。

2. 檢品中指標成分HPLC分析條件

分析葛根芩連湯中所含配醣體成分如baicalin、wogonoside、daidzin經腸道菌體代謝後之動態變化。

層析管：Apollo C18, 5 μm (4.6 × 250 mm)

移動相：0.1 % H_3PO_4：CH_3CN

0.1 % H_3PO_4 的梯度變化如下(層析時間為75分鐘)：

梯度變化	層析時間 (分鐘)
85 → 70	20
70 → 57	40
57 → 54	53
54 → 30	63
30 → 85	75
35 → 89	75

流　　速：1.0 mL/min

檢測波長：250 nm

內 標 準：amyl paraben (10.0 μg/mL)

四、口服葛根芩連湯後指標成分於鼠體之代謝與吸收

(一)給藥方法與檢品採集

1. 動物與給藥

選用SD大白鼠6隻，體重介於300-500 g，實驗前先禁食12小時。經胃管灌食給予葛根芩連湯水煎劑(每公斤給予相當於原生藥量6 g之水煎劑)。3小時後自由進食。

2. 血液採集

大白鼠於給藥後適當時間，由心臟穿刺採血，每次採血量為1mL，將血液檢品以10,000 g高速離心15分鐘，取上層血清，貯存於-20 ℃俟後分析。採血時間點為給藥後15、30、60、120、360、480、720、1440、2160、2880、4320及5760分鐘。

3. 尿液採集

大白鼠於給藥前禁食12小時並同時收集其空白尿液。並於給藥後適當時間，採集尿液。服藥後於0-2、2-5、5-8、8-12、12-24、24-34、34-48、48-58及58-72小時，共收集九個時段之尿液，每段尿液分別測量並記錄其體積後，各取1 mL之尿液置於1.5 mL微量離心管中並與剩餘之尿液一併置於- 30 ℃之冷凍櫃中貯存，待後續分析之用。

(二)血清指標成分之glucuronides及sulfates代謝物之定量

取200μL血清檢品置於避光玻璃管中，分別加入50μL β-glucuronidases (1000 units/mL溶於pH 5.0之acetate buffer)或sulfatases (1000 units/mL，內含20880 units/mL之β-glucuronidases)和50μL維生素C溶液(200 mg/mL)，充分混合後，蓋上血清塞，抽氣，置於37℃之恆溫水槽分別反應2小時及30分鐘。反應完成後，立即置於冰上終止反應，隨即加入50μL 0.1N鹽酸溶液，並以350μL乙酸乙酯萃取(含內標propyl paraben 1μg/mL)，充分混合後，經10,000g高速離心15分鐘，取乙酸乙酯層，用氮氣吹乾後，以50μL甲醇溶解，取20μL供HPLC分析。檢品中指標成分與內標準之波峰面積比值，代入檢量線方程式，求得濃度。

(三)血清中指標成分及其代謝物之HPLC分析條件

分析條件如下所述，並進一步評估此方法之精密度(precision)、準確度(accuracy)、靈敏度(sensitivity)與回收率(recovery)。

層析管：Apollo C18, 5 μm (4.6 × 250 mm)

移動相：0.1 % H_3PO_4：CH_3CN

0.1 % H_3PO_4 的梯度變化如下(層析時間為45分鐘)：

梯度變化	層析時間(分鐘)
72 → 72	12
72 → 58	28
58 → 58	35
58 → 72	40
72 → 72	45

流　　速：1.0 mL/min

檢測波長：250 nm

內 標 準：propyl paraben (1.0 μg/mL)

(四)尿液指標成分之glucuronides 及 sulfates代謝物之定量

取100μL尿液檢品置於避光玻璃管中，分別加入50μL β-glucuronidases (1000 units/mL溶於pH 5.0之acetate buffer)或sulfatases (1000 units/mL，內含20880 units/mL之β-glucuronidases)和50μL維生素C溶液(200 mg/mL)，充分混合後，蓋上血清塞，抽氣，置於37℃之恆溫水槽分別反應30分鐘。反應完成後，立即置於冰上終止反應，隨即加入50μL 0.1N鹽酸溶液，並以250μL乙酸乙酯萃取(含內標propyl paraben 4μg/mL)，充分混合後，經10,000g高速離心15分鐘，取乙酸乙酯層，用氮氣吹乾後，以50μL甲醇溶解，取20μL供HPLC分析。檢品中指標成分與內標準之波峰面積比值，代入檢量線方程式，求得濃度。

(五)尿液中指標成分及其代謝物之HPLC分析條件

分析條件如下所述，並進一步評估此方法之精密度(precision)、準確度(accuracy)、靈敏度(sensitivity)與回收率(recovery)。

層析管：Apollo C18, 5 μm (4.6 × 250 mm)

移動相：0.1 % H_3PO_4：CH_3CN

0.1 % H3PO4的梯度變化如下(層析時間為45分鐘)：

梯度變化	層析時間 (分鐘)
72 → 72	12
72 → 58	28
58 → 58	35
58 → 72	40
72 → 72	45

流　　速：1.0 mL/min

檢測波長：250 nm

內標準：propyl paraben (4.0 μg/mL)

五、口服葛根芩連湯水煎劑與濃縮散劑於鼠體生可用率之比較

(一)給藥方法與檢品採集

1. 動物與給藥

選用SD大白鼠，體重介於300-500g，實驗前先禁食12小時。將大白鼠隨機分為3組，每組至少7隻，實驗採交叉設計。經胃管灌食分別給予自製之葛根芩連湯水煎劑、濃縮散劑及市售濃縮散劑（各指標成分含量最高者），每公斤給予相當於原生藥量6 g之劑量。3小時後自由進食。

2. 血液及尿液採集

血液及尿液採集之方法與採血及收集尿液時間同前所述。

(二)血清與尿液檢品之前處理步驟同前。

(三)血清與尿液中指標成分及其代謝物分析條件之開發步驟同前。

六、數據分析

使用 WINNONLIN (version 3.0；Pharsight Corp., U.S.A.)軟體計算動力學參數。其後再以 paired Student's t-test 對生體可用率參數進行組間差異之比較，其α值定為 0.05，以了解劑型間之差異。

七、人體血漿與尿液檢品中指標成分及其代謝物 HPLC 分析條件之開發-預試驗

(一) 血漿中指標成分及其代謝物之HPLC分析條件

層析管：Apollo C18, 5 μm (4.6 × 250 mm)

移動相：0.1 % H_3PO_4：CH_3CN

0.1 % H3PO4 的梯度變化如下(層析時間為45分鐘)：

梯度變化	層析時間 (分鐘)
72 → 72	12
72 → 58	28
58 → 58	35
58 → 72	40
72 → 72	45

流　　速： 1.0 mL/min

檢測波長： 250 nm

內 標 準： propyl paraben (1.0 μg/mL)

(二) 尿液中指標成分及其代謝物之HPLC分析條件

層析管：Apollo C18, 5 μm (4.6 × 250 mm)

移動相：0.1 % H_3PO_4：CH_3CN

0.1 % H3PO4 的梯度變化如下(層析時間為45分鐘)：

梯度變化	層析時間 (分鐘)
72 → 72	12
72 → 58	28
58 → 58	35
58 → 72	40
72 → 72	45

流　　速： 1.0 mL/min　　檢測波長： 250 nm

內 標 準： propyl paraben (4.0μg/mL)

參、結果與討論

一、葛根芩連湯中指標成分之定量分析

本研究利用HPLC方法定量GMP中藥製造廠依廠規所製備之水煎劑及濃縮散劑，兩種製劑乃使用同一批經基源鑑定之藥材製備，以利基於生藥等量計算生體相等性。葛根芩連湯濃縮製劑與水煎劑中活性指標成分之定量方法參考自本研究室先前所開發之條件[62]，採用梯度沖提方式，於75分鐘內完成分析，層析圖如Fig. 1所示。以各標準品與內標準之波峰面積比值為Y軸，各標準品之濃度為X軸進行直線迴歸，求得各成分之檢量線方程式及相關係數，如Table 1所示，結果顯示皆有良好線性關係。分析方法之精密度及準確度，如Table 2~11所示。各成分之同日內和異日間之變異係數及相對誤差皆在可接受的範圍內，確效結果顯示本分析系統之精密度及準確度良好。此外，puerarin、daidzin、coptisine、baicalin、daidzein、palmatine、berberine、baicalein、glycyrrhizin及wogonin之可定量極限 (LOQ) 分別為5.6、0.8、1.3、12.5、0.9、1.3、3.8、0.6、2.5及0.6 μg/mL，可偵測極限(LOD)分別為0.01、0.01、0.01、0.01、0.01、0.01、0.01、0.01、0.04及0.01 μg/mL。水煎劑及濃縮散劑指標成分之定量結果，如Table 12所示，結果顯示兩劑型中各成分間之差異不大。此外，購自六家GMP中藥廠所生產之濃縮葛根芩連湯製劑之定量亦為相同分析方法。其指標成分之定量結果，如Table 13~15所示，不同廠商所製造之葛根芩連湯濃縮散劑每公克分別含puerarin 0.4±0.0~12.4±3.6 mg、daidzin 0.1±0.0~1.8±0.3 mg、coptisine 0.3±0.0~2.7±0.3 mg、baicalin 3.3±0.1~14.0±0.8 mg、daidzein 0.0_3±0.0~0.3±0.0mg、palmatine 0.4±0.0~1.9±0.2 mg、berberine 0.7±0.0~6.7±0.4 mg、baicalein 0.2±0.0~1.4±0.1 mg、glycyrrhizin 0.3±0.0~2.1±1.2 mg、wogonin 0.1±0.0~0.4±0.0 mg。就此些指標成分的含量而言，各家產品之差異極大，可能與各家廠商的抽提方式、濃縮倍數與賦型劑比例等因素相關，亦可能因藥材來源不同而導致品質之差異。

二、大鼠口服葛根芩連湯後體循環前代謝之研究

本計畫欲分析之葛根芩連湯的配醣體成分，在先前以人工腸液所進行之試驗中發現，胃液的酸度與正常的體內溫度37℃無法分解破壞配醣體成分，顯示這些中藥成分可安全經過胃部而進到腸道內。因此本研究以腸道菌群探討對中藥的影響。利用HPLC方法定量以鼠便腸道菌水解之葛根芩連湯水煎劑與濃縮散劑中daidzein、baicalein、wogonin之含量，採用梯度沖提方式。各成分受鼠便腸道菌水解之經時變化圖如Fig. 2所示。

以鼠便腸道菌與葛根芩連湯水煎劑及濃縮散劑培養後，結果顯示兩種製劑中，daidzein、baicalein及wogonin於培養後，其濃度先增後降。而於培養後，發現水煎劑之baicalein及wogonin濃度在四小時後趨於平緩，而濃縮散劑之baicalein及wogonin濃度則漸少，推估雖然腸道菌可將各成分配醣體之醣基水解，使之轉變形成苷元，因此會造成初始的濃度漸增，但鼠體腸道菌亦能將苷元降解，致使其濃度因培養時間增長而逐漸降低。

葛根芩連湯所含之黃酮類成分主要以配醣體的形式存在，水溶性頗佳，一般中藥多使用水煎煮，因此黃酮配醣體極易溶於傳統水煎劑中，然而此些化合物能否吸收，攸關其藥效。以化學觀點而言，配醣體極性高，不易穿透細胞膜吸收，黃酮配醣體一般先於腸道被glucosidases/hydrolases，如CBG、LPH，水解形成其苷元[63-64]而後才由腸黏膜吸收進入血液，並於肝或腸中藉uridine-diphosphate glucuronosyltransferases (UGTs) 或 sulfonyl-transferases (PSTs)作用，形成sulfates及glucuronides結合態代謝物。且由預試驗之研究顯示口服給予葛根芩連湯製劑後，血液中並無黃酮配醣體如puerarin、daidzin、baicalin及wogonoside存在，此些配醣體主要以非醣體之結合態代謝物型式出現在血循環中。因此本研究利用鼠糞便腸道菌水解此些黃酮類成分，以模擬腸道內黃酮配醣體之水解情境，以定量daidzein、baicalein及wogonin濃度之改變。

本研究室先前將Puerarin及daidzin置於鼠便懸浮液中反應24小時，結果顯示並無法測得任何daidzein [65]。但Kim (1998)等人的研究將puerarin及daidzin分別置於人的腸內菌中培養24小時，發現此二者均會轉變成daidzein[66]；另有Simons (2005)等提出人體糞便腸道菌亦無法將puerarin水解為daidzein[67]。Puerarin為*C*-glycoside，化學性質上無法以酸水解成苷元。若能水解，勢必仰賴特殊之腸道菌，或藉由特殊之運輸蛋白使其原型分子進入細胞。本研究結果與Kim (1998)等人的結果雖不相符，但與Simons (2005)等人的結果相符，是否因種族或飲食習慣等造成腸內菌叢之差異，因而導致水解之結果不同，此歧異尚待進一步針對腸道菌叢之差異進行比較。另外，本研究室先前的研究也指出，將baicalein及wogonin置於鼠便懸浮液中反應24小時，結果顯示wogonin較不易被降解，而此化合物由於其結構具有methoxy基團，推測可能A環上的methoxy基團有保護不被降解的作用。而baicalein，很快被降解。此些結果也與本次實驗的結果相符。

三、不同葛根芩連湯劑型於鼠體之動力學研究與生可用率之比較

(一)血藥動力學

爲探討葛根芩連湯於大鼠之藥物動力學行為，本研究室開發分

析血清中指標成分與其結合態代謝物之HPLC分析方法，HPLC層析圖如Fig. 3所示，各成分分離效果良好，每一檢品可於45分鐘內完成分析。以各標準品與內標準之波峰面積比值為Y軸，各標準品之濃度為X軸進行直線迴歸，求得各成分之檢量線方程式及相關係數，如Table 16所示，結果顯示皆有良好線性關係。分析方法之精密度及準確度，如Table 17~20所示。各成分之同日內和異日間之變異係數及相對誤差皆在可接受的範圍內，確效結果顯示本分析系統之精密度、準確度及回收率皆良好。此外，daidzein、baicalein及wogonin之可定量極限(LOQ)分別為0.3、0.2及0.1 μg/mL，可偵測極限(LOD)皆為0.04 μg/mL。

為探討葛根芩連湯傳統水煎劑與現代濃縮散劑於鼠體之代謝與吸收情形，本實驗進行了兩種製劑於鼠體內之生體可用率研究。動物給藥採交叉設計，餵予含相等原生藥量之水煎劑與濃縮散劑(6 g/kg)。為了定量血清中之結合態代謝物(sulfates/glucuronides)，各血清檢品先經過前處理，亦即在抗壞血酸保護下，分別以sulfatase及β-glucuronidase於37℃恆溫震盪水槽中酶解30分鐘及2小時，之後以含內標準品之乙酸乙酯進行萃取，最適化之酶解時間及抗壞血酸用量等皆經過預試驗決定。

大鼠血清中各成分之濃度如Table 21~Table 32所示，濃度經時變化如Fig. 4~5及Fig. 7所示。各動力學參數之計算係使用WINNONLIN軟體，採非室體模式，C_{max}、$AUC_{0\text{-}5760}$、MRT及AUC/dose等參數如Table 39~Table 40所示。

綜合以上結果，所有成分皆無以原型存在於大鼠血清中。daidzein、baicalein、wogonin則均以結合態代謝物形式(sulfates/glucuronides)存在，顯示此些黃酮類成分於吸收過程中，極易受腸、肝細胞代謝而接上sulfuric acid 或glucuronic acid，轉化為高水溶性分子，以利於在血液中運輸及從尿中排泄。比較兩劑型間個別指標成分之吸收情形，如Table 42 所示，其中daidzein sulfates/glucuronides、baicalein sulfates/glucuronides、wogonin sulfates/glucuronides於服用水煎劑時AUC/dose皆略高於濃縮散型。口服濃縮散劑後，各成分AUC/dose 之90 %信賴區間，除wogonin sulfates/glucuronides外，皆落於水煎劑組參數平均值之80%~120%間，初步顯示daidzein sulfates/glucuronides及baicalein sulfates/glucuronides於兩劑型皆達生體相等性，進一步數據的分析

評估仍繼續進行中。

(二)尿藥動力學

在葛根芩連湯的尿藥動力學研究部分，動物口服相當於6 g原生藥之葛根芩連湯水煎劑及濃縮散劑，並以代謝籠分段收集服藥後72小時內各區間之尿液，以評估各種指標成分於鼠體吸收之差異。以HPLC-UV分析尿中指標成分之結合態代謝物之含量，移動相採取梯度沖提方式進行分析，每一檢品可於45分鐘內完成分析，尿液檢品酶解後層析圖如Fig. 8所示。各成分於尿中可定量之濃度範圍及其檢量線如Table 44所示，均有良好之線性關係($r > 0.9999$)，分析方法之確效結果如Table 45~ 47所示，變異係數與相對誤差均在可接受範圍內，顯示再現性和準確度良好。各成分之回收率評估，結果如Table 48所示，各檢品回收率介於50.3 ~ 98.4 %。綜合上述之結果，此分析方法精確可行。

實驗結果顯示尿中並未檢出各成分之原型化合物，亦未檢測出coptisine、palmatine、berberine，顯示此三個生物鹼化合物原型之生可用率極低，可能因為它們皆為帶正電的氮陽離子，導致無法滲透進入腸細胞，因而吸收不易，但亦有可能此些生物鹼化合物於體內代謝成其他形式之代謝物[68]，因而無法檢出其原型分子。

Daidzein、baicalein、wogonin主要皆以結合態代謝物(sulfates/glucuronides)存在於尿中，顯示多酚成分於體內吸收後，多以sulfates/glucuronides從尿液排除。此結果與本研究室先前對於黃芩之中藥代謝動力學的研究結果相符。

各段尿液檢品定量後，分別計算各時段之排出量，並以各成分總排出量佔服用劑量之百分比，評估兩劑型相對的吸收程度。而各時段之排藥量、總排藥量及排出率經計算後，結果如Table 49~60所示，各成分之累積排除量如Fig. 9 ~ 10所示。比較各成分從尿液回收的結果顯示，daidzein、baicalein與wogonin於兩劑型間並無明顯差異，顯示水煎劑與濃縮散劑對於此些成分的吸收程度相當。進一步比較各時段之平均排除率(% of dose/h)，如Fig. 12~17及Fig. 21所示，結果亦顯示兩種劑型之間，尿藥的排除動態未見明顯差異，而腸肝循環現象則較為明顯。

本研究依Sigma-minus method，以體內待排除藥物剩餘量之自然對數與時間迴歸，求得排除速率常數後，換算成排除半衰期。尿藥數據如Table 49~60所示，各代謝產物排除半衰期之個體差異頗

大，由Table 67所示，口服水煎劑後各成分間排除半衰期變異性頗大，如daidzein sulfates/glucuronides可長達15~28 h以上，而baicalein sulfates/ glucuronides、wogonin sulfates/glucuronides在1~16 h左右，因此基於各成分之排除半衰期，臨床一日兩次或三次的服藥方式可視為合理，但以一日三次的服藥方式需考慮部分代謝物蓄積的可能性。

本實驗除比較葛根芩連湯水煎劑與濃縮散劑間於血清中及尿中之相對生可用率外，另比較市售之濃縮散劑與本研究中水煎劑間之吸收代謝情形，血藥動力學部分如Fig. 6~7、Fig. 11及Table 33~38、Table 41~42所示；尿藥動力學部分如Fig. 18~20、Fig. 22及Table 61 ~ 67所示。及血藥及尿藥動力學結果顯示，兩劑型間之相對生可用率並未達生體相等性，可能由於各家廠商製造濃縮散劑的製程有異，進而影響各成分於鼠體間之吸收行為。

為能順利進行第二年之葛根芩連湯於人體之試驗計畫，本研究已於第一年計畫中，開發人體血漿與尿液檢品高效液相層析之分析條件，層析圖如Fig. 24所示。

肆、結論與建議

一、本研究結果顯示大鼠口服葛根芩連湯水煎劑及濃縮散劑後，血清及尿液檢品中並未檢出各成分之原型化合物，daidzein、baicalein、wogonin 主要皆以結合態代謝物 (sulfates/glucuronides) 存在。此部份之研究結果與傳統上中藥研究均以指標成分評估其活性之現況很不相同。此一訊息應可提供後續進行相關之體外實驗或藥效學研究之參考。

二、本研究委託國內 GMP 科學中藥製造廠以其廠規與相同來源之藥材製備葛根芩連湯水煎劑及濃縮散劑，以利基於生藥等量計算生體相等性，在血藥及尿藥動力學部分，同一來源製備的水煎劑與濃縮劑型間，各成分之吸收及代謝情形差異不大，除 wogonin 外，其他成分均符合生體相等性之概念。但當比較抽樣之市售濃縮散劑與傳統水煎劑間之相對生可用率時，發現其並未達生體相等性，此一結果可能由於各家廠商製造濃縮散劑的製程有異，進而影響各成分於動物體內的吸收行為。因此，同一方劑由不同 GMP 藥廠製造之製劑其生可用率可能有極大的差異，值得注意與探討。

三、本研究模式可作為未來進行中藥方劑藥物動力學與生可用率研究之基礎，建立與臨床療效較具相關性之製劑品質評估模式，做為健保局藥品給付決策之參考，並期望能加速中醫藥現代化之腳步。

誌謝

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陸、圖、表

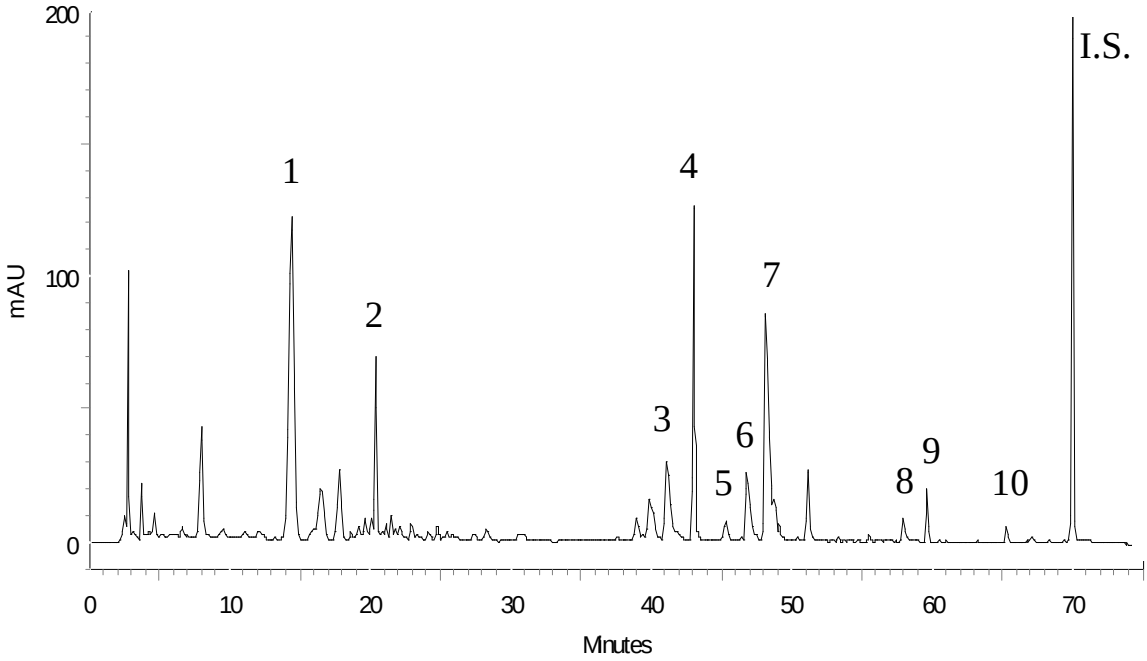
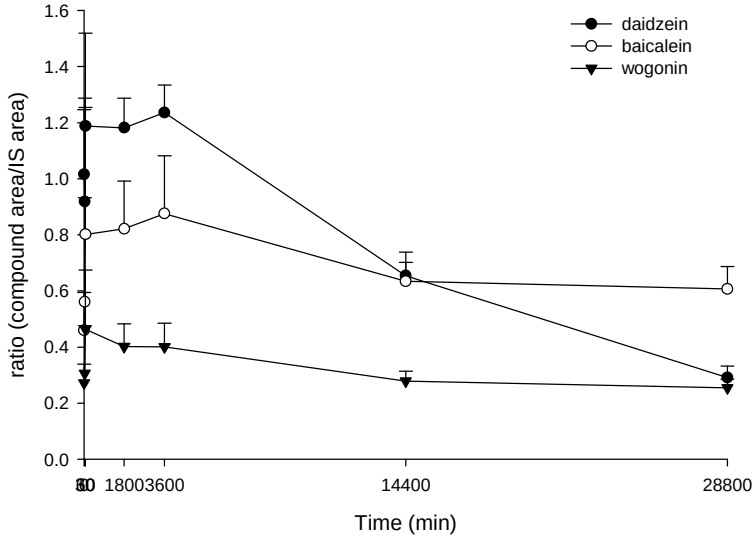


Fig 1 HPLC chromatogram of GGCLT decoction

1: puerarin, 2: daidzin, 3: coptisine, 4: baicalin, 5: daidzein, 6: palmatine, 7: berberine, 8: baicalein, 9: glycyrrhizin, 10: wogonin, I.S.: amyl paraben

(a)



(b)

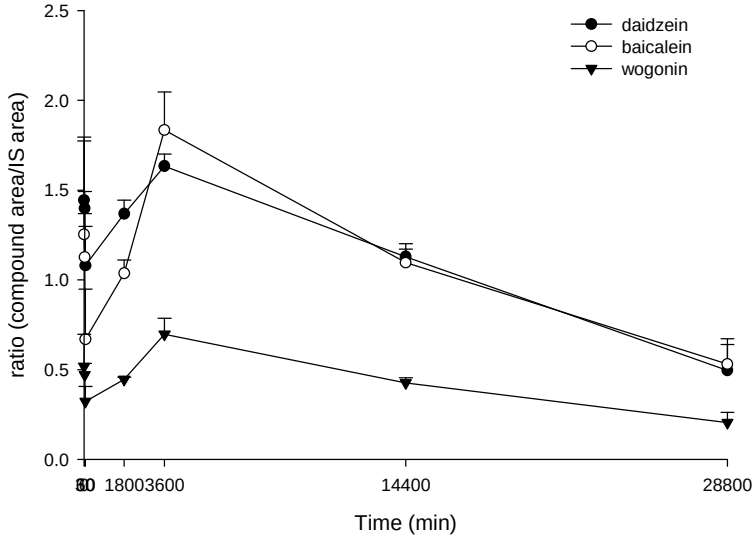


Fig 2 Mean (±S.D.) ratio-time profiles of daidzein, baicalein and wogonin after incubation of GGCLT decoction (a) and GGCLT commercial extract (b) with rat feces (n=3).

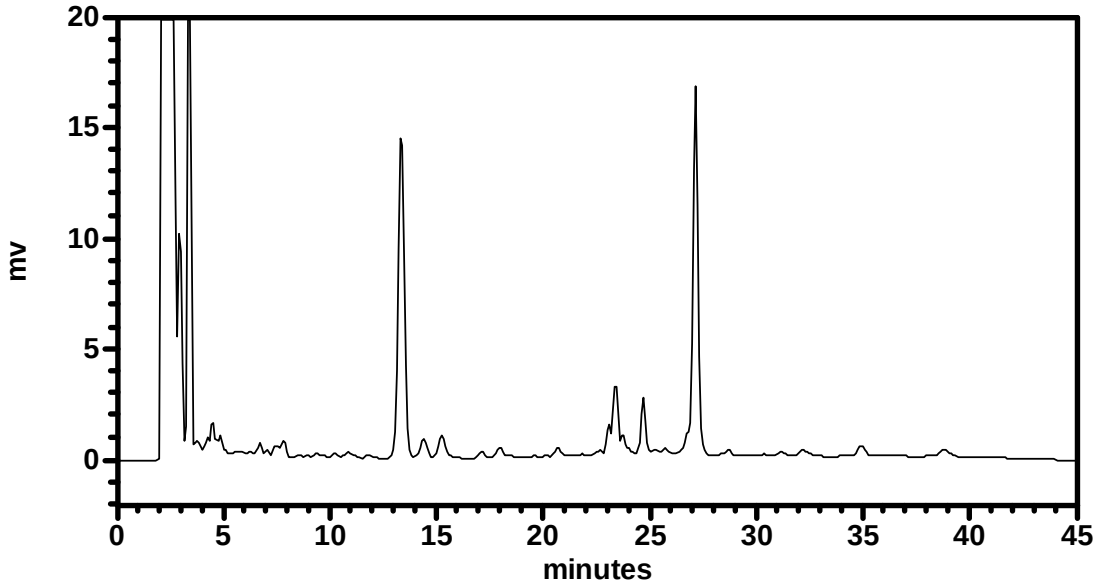


Fig.3 HPLC chromatogram of rat serum after sulfatase treatment.

1: daidzein, 2: baicalein, 3: wogonin, I.S.: propyl paraben

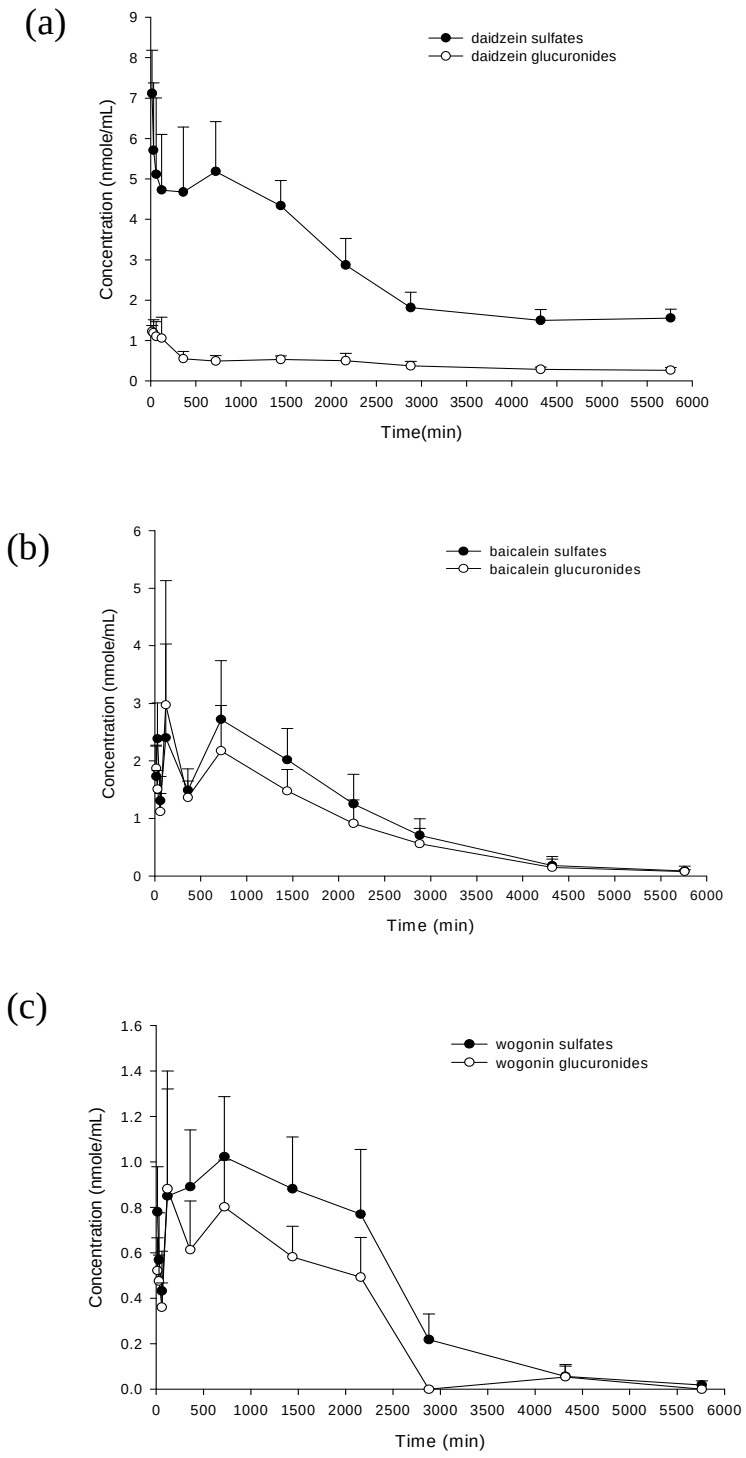


Fig.4 Mean (±S.E.) serum concentration - time profiles of the conjugate metabolites of (a): daidzein; (b): bacalein; (c): wogonin in six rats after oral administration of GGCLT decoction.

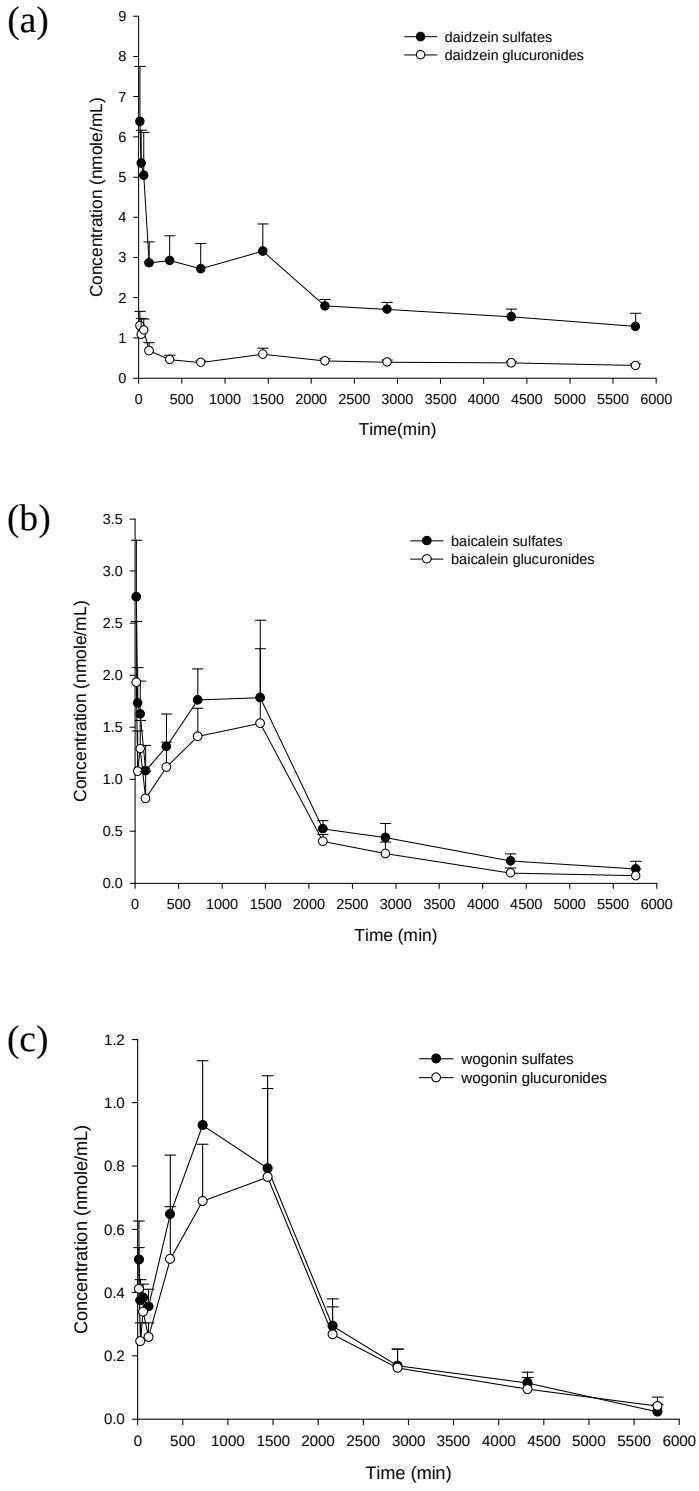


Fig.5 Mean (±S.E.) serum concentration - time profiles of the conjugate metabolites of (a): daidzein; (b): bacalein; (c): wogonin in six rats after oral administration of GGCLT commercial extract I.

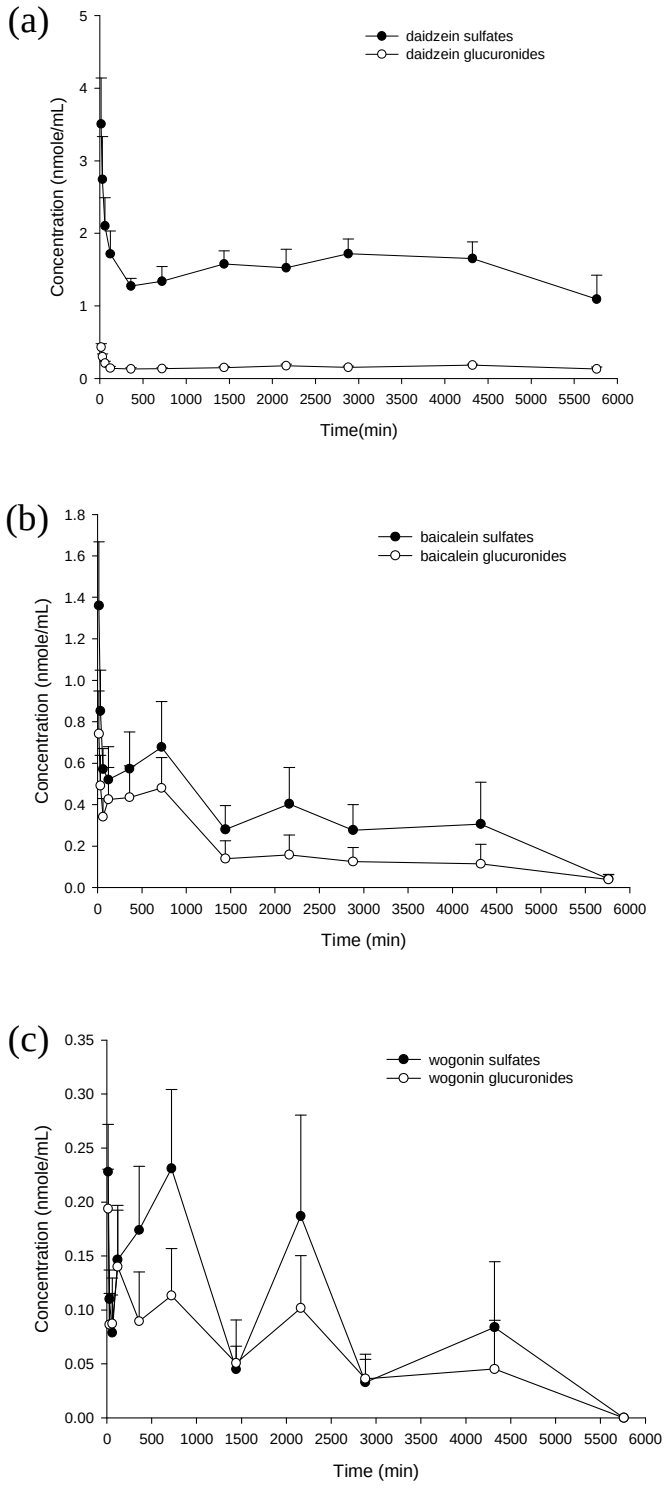


Fig.6 Mean (±S.E.) serum concentration - time profiles of the conjugate metabolites of (a): daidzein; (b): bacalein; (c): wogonin in six rats after oral administration of GGCLT commercial extract II.

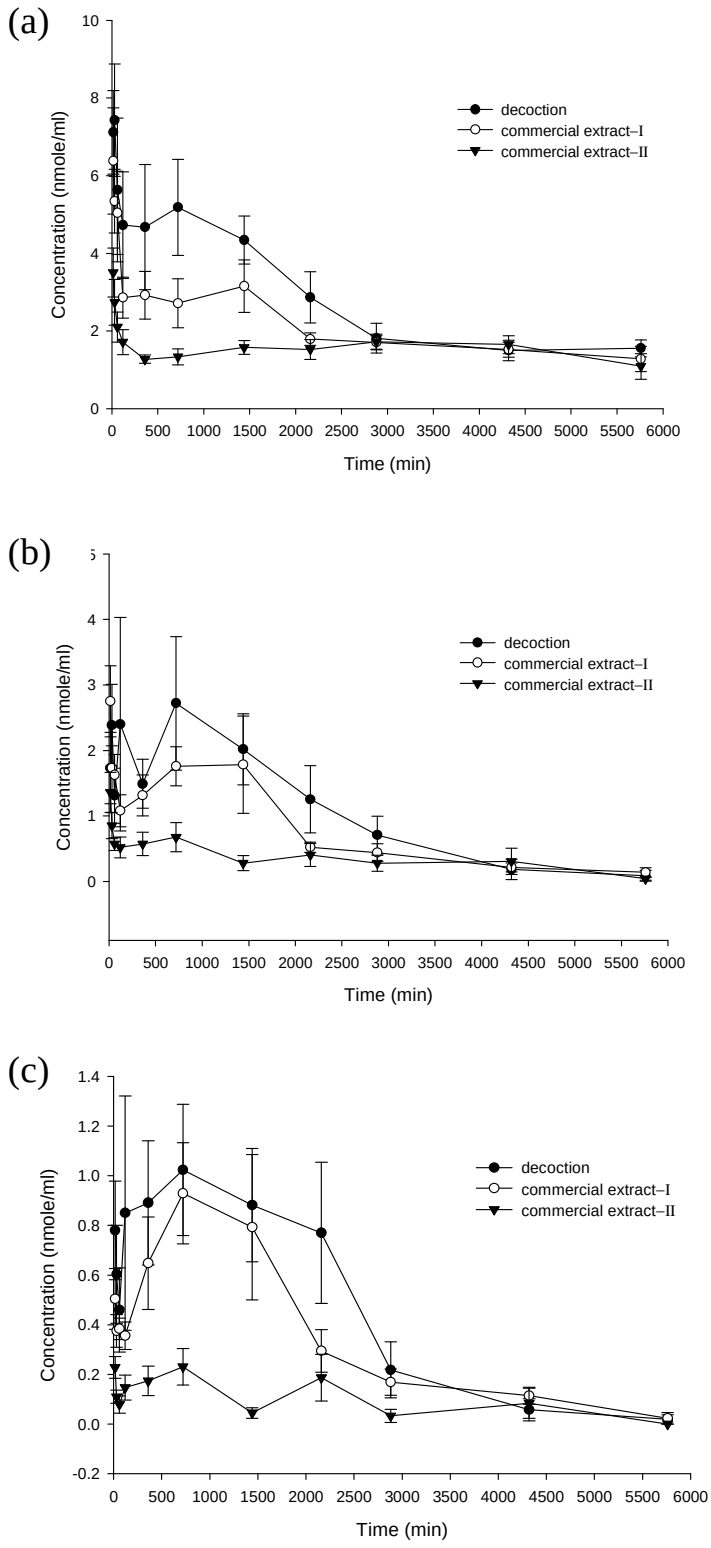


Fig.7 Comparison of mean (±S.D.) serum concentration-time profiles of (a) daidzein (b) baicalein (c) wogonin conjugates after oral administration of the decoction and commercial extracts of GGCLT.

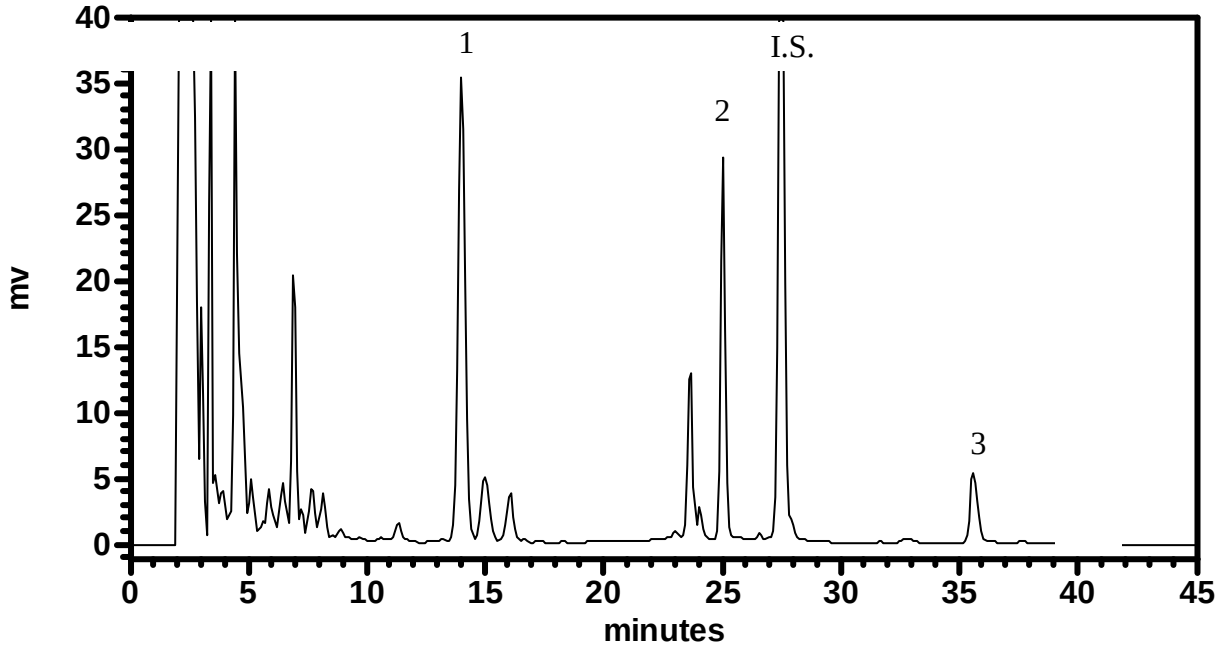


Fig.8 HPLC chromatogram of rat urine after sulfatase treatment. 1: daidzein, 2: baicalein, 3: wogonin, I.S.: propyl paraben

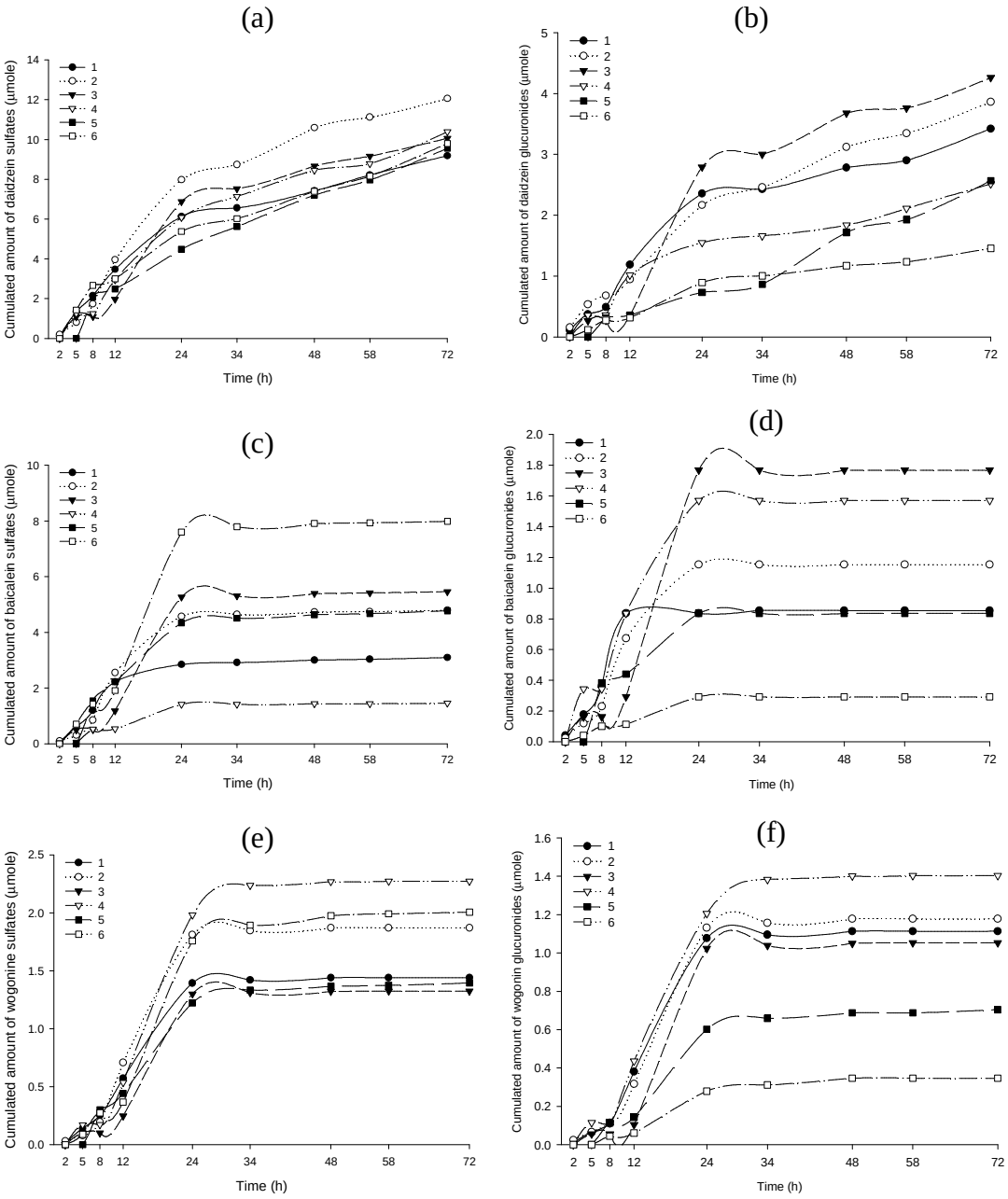


Fig.9 Cumulated excretion of (a) daidzein sulfates (b) daidzein glucuronides (c) baicalein sulfates (d) baicalein glucuronides (e) wogonin sulfates (f) wogonin glucuronides in urine of six rats after intake of decoction of GGCLT.

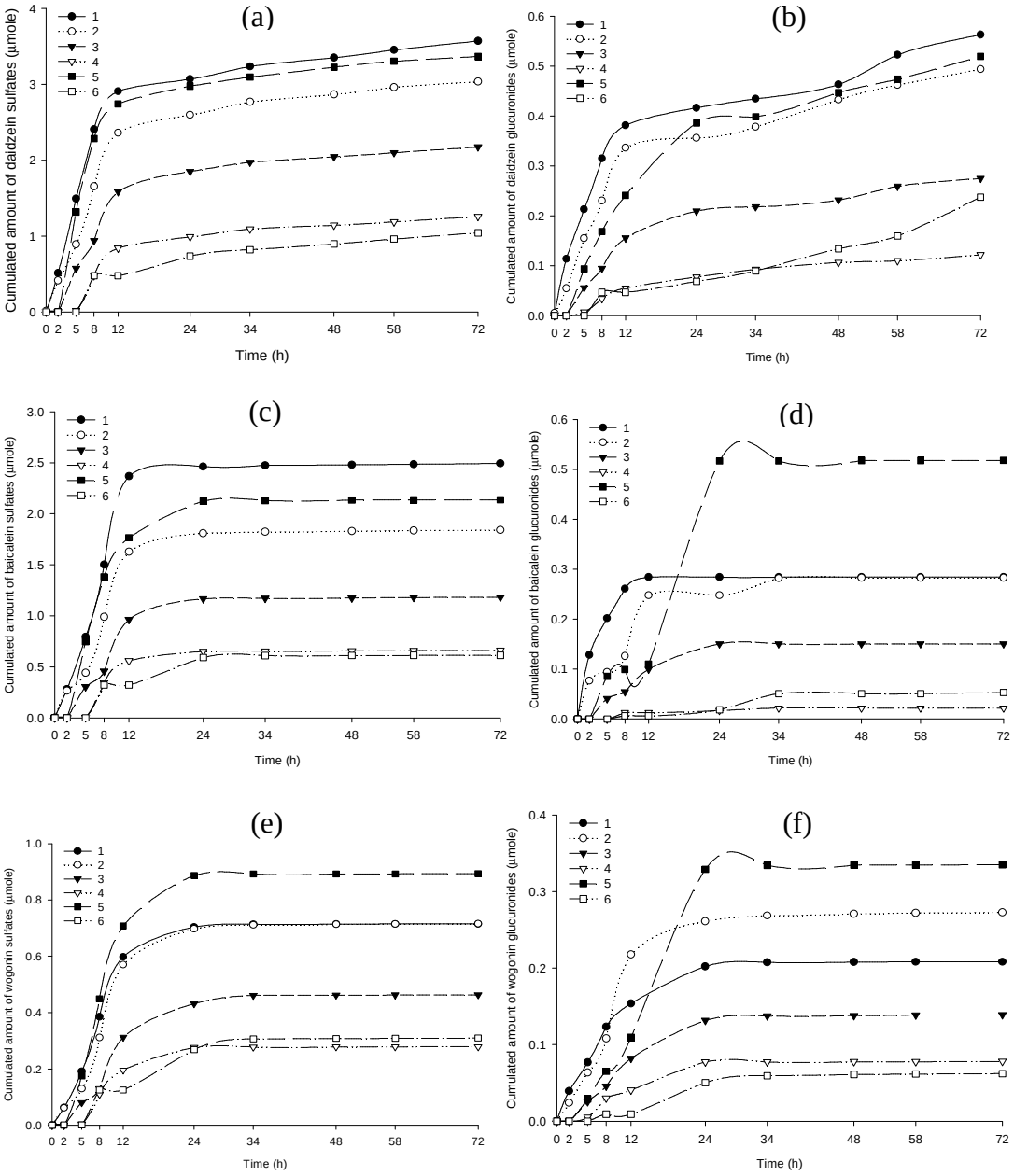


Fig.10 Cumulated excretion of (a) daidzein sulfates (b) daidzein glucuronides (c) baicalein sulfates (d) baicalein glucuronides (e) wogonin sulfates (f) wogonin glucuronides in urine of six rats after intake of commercial extract I of GGCLT.

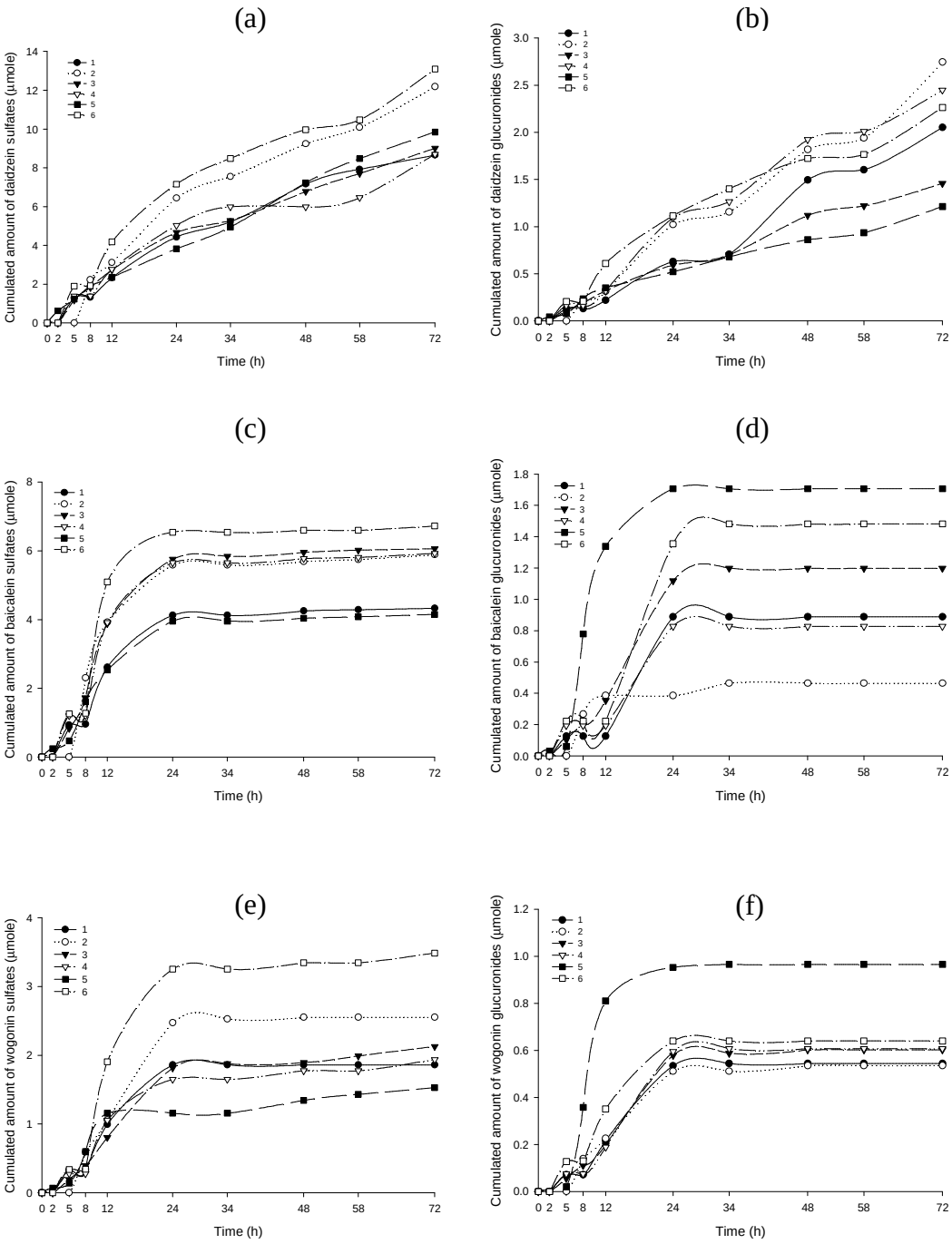


Fig. 11 Cumulated excretion of (a) daidzein sulfates (b) daidzein glucuronides (c) baicalein sulfates (d) baicalein glucuronides (e) wogonin sulfates (f) wogonin glucuronides in urine of six rats after intake of commercial extract II of GGCLT.

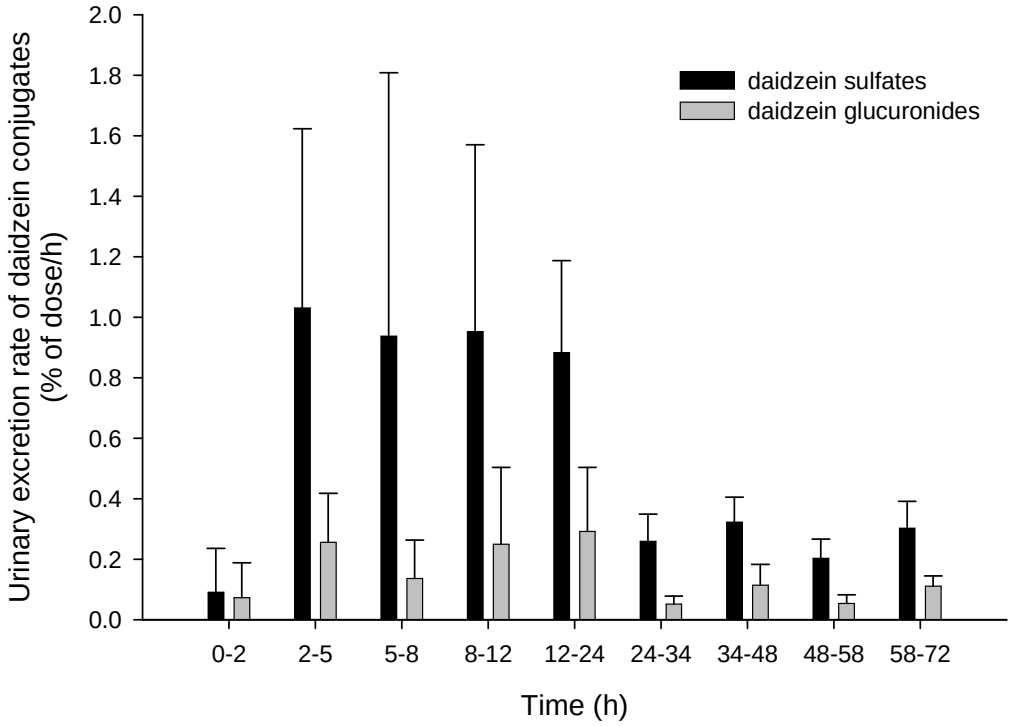


Fig.12 Mean (±S.D.) urinary excretion rate (% of dose/h) of daidzein conjugates in six rats after intake of GGCLT decoction (6 g/kg) during each time interval.

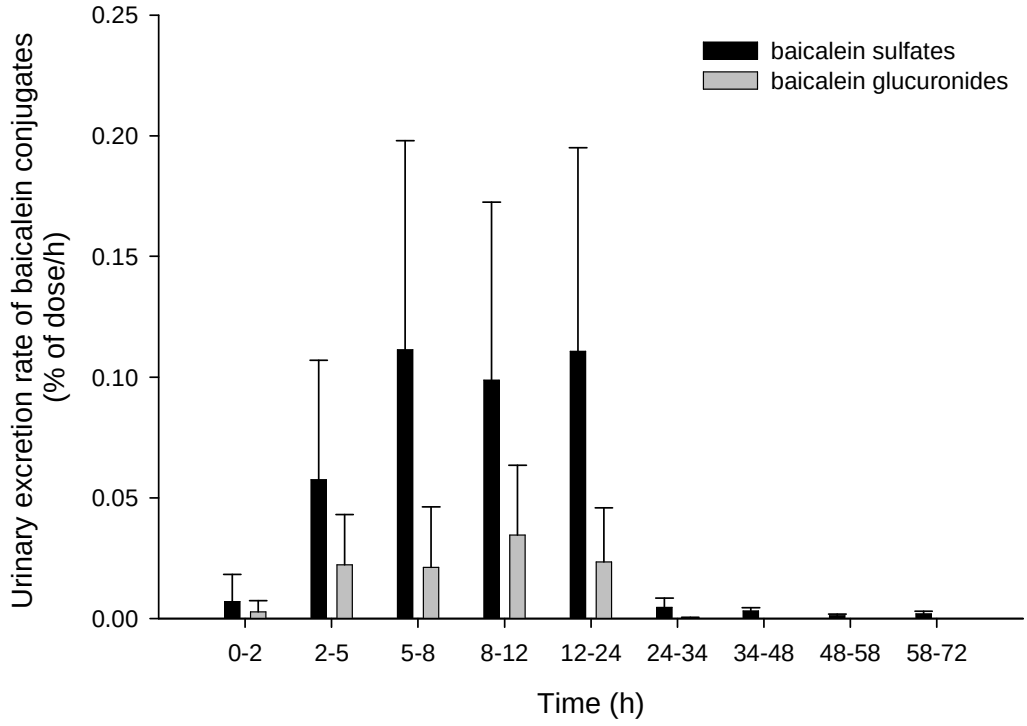


Fig.13 Mean (±S.D.) urinary excretion rate (% of dose/h) of baicalein conjugates in six rats after intake of GGCLT decoction (6 g/kg) during each time interval.

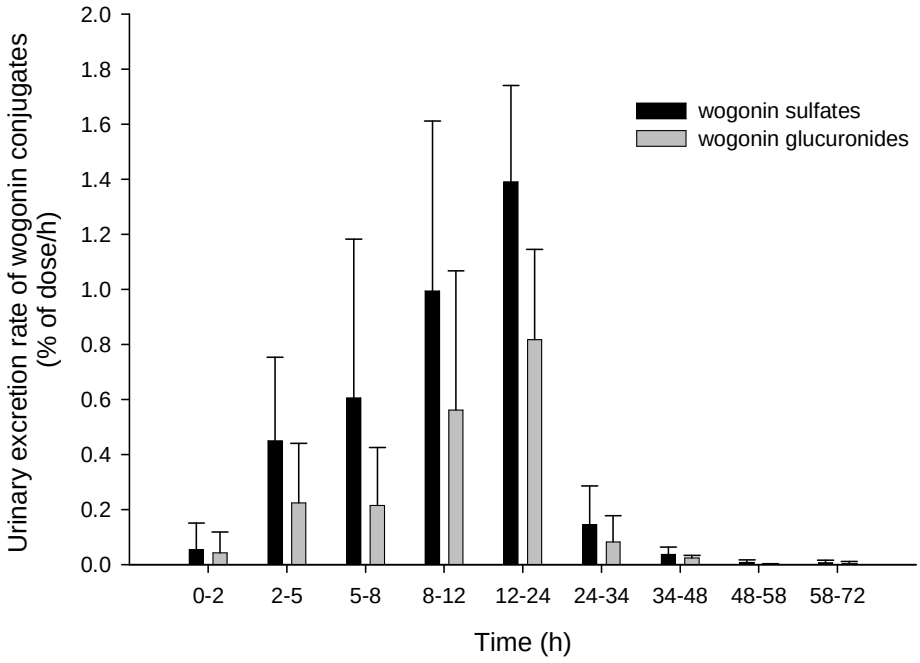


Fig. 14 Mean (±S.D.) urinary excretion rate (% of dose/h) of wogonin conjugates in six rats after intake of GGCLT decoction (6 g/kg) during each time interval.

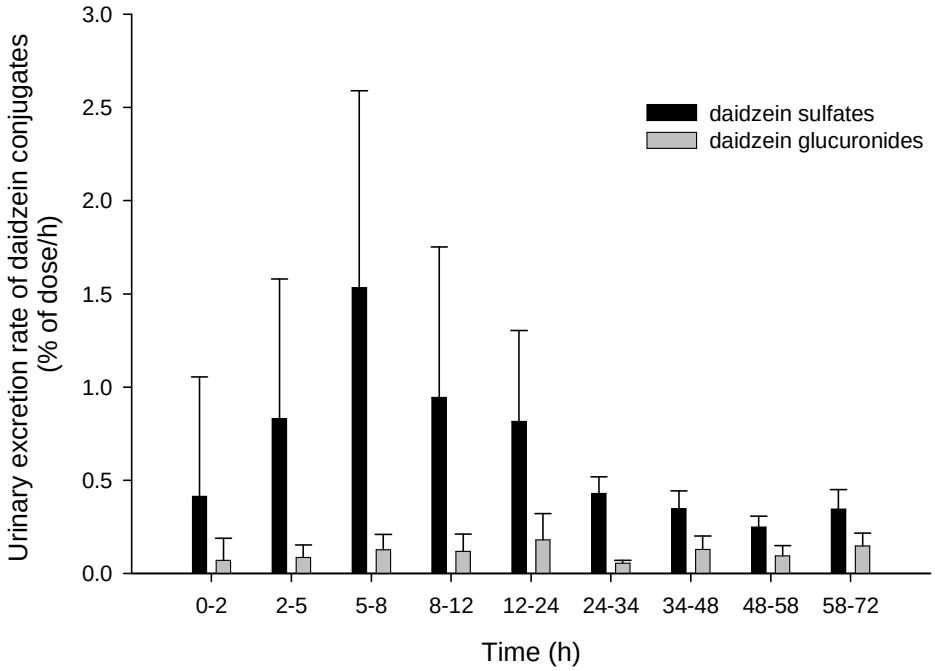


Fig. 15 Mean (±S.D.) urinary excretion rate (% of dose/h) of daidzein conjugates in six rats after intake of commercial extract I of GGCLT (6 g/kg) during each time interval.

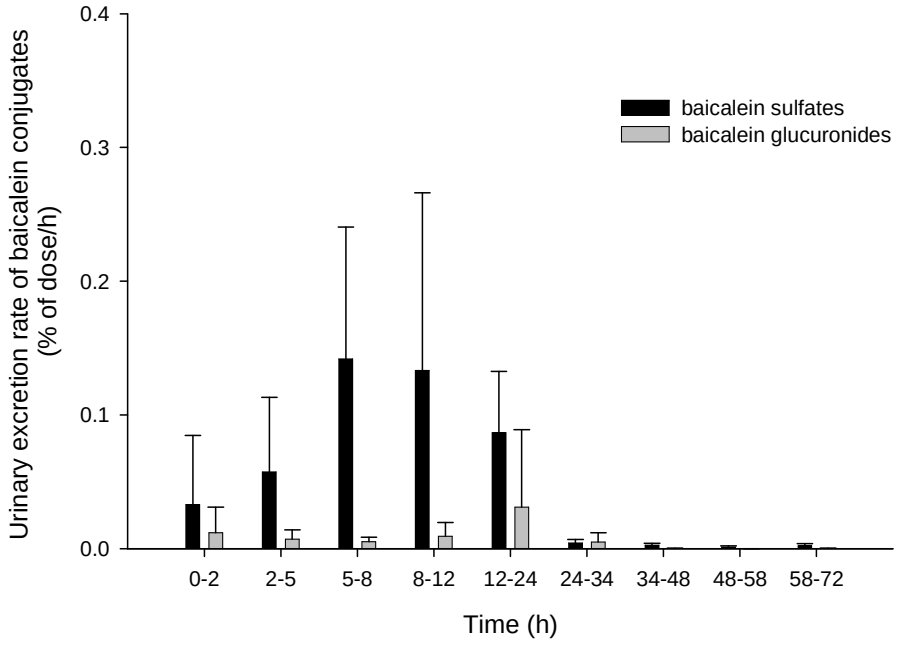


Fig. 16 Mean (±S.D.) urinary excretion rate (% of dose/h) of baicalein conjugates in six rats after intake of commercial extract I of GGCLT (6 g/kg) during each time interval.

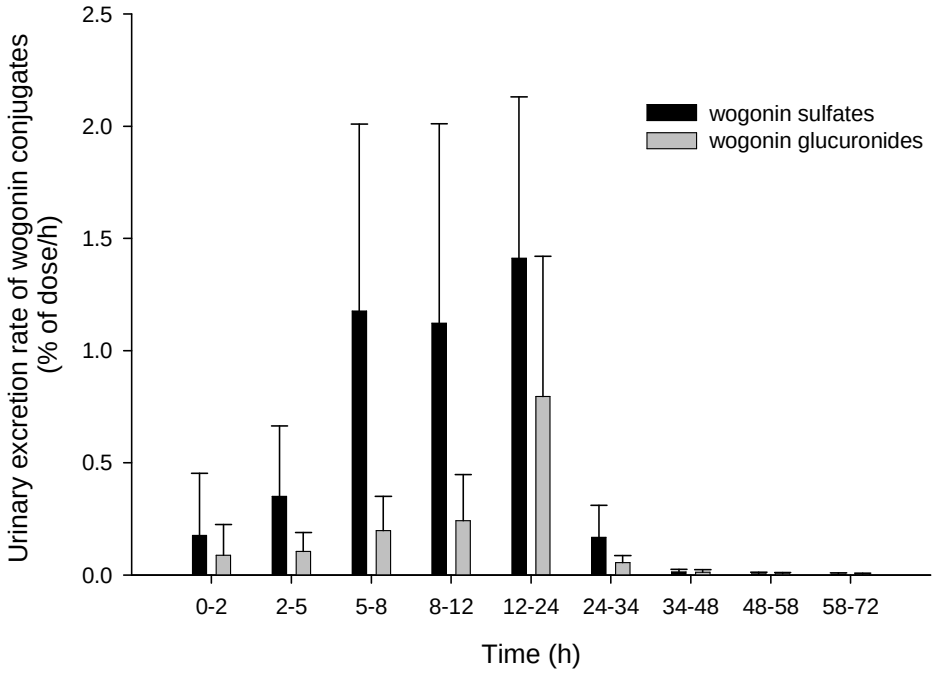


Fig. 17 Mean (±S.D.) urinary excretion rate (% of dose/h) of wogonin conjugates in six rats after intake of commercial extract I of GGCLT (6 g/kg) during each time interval.

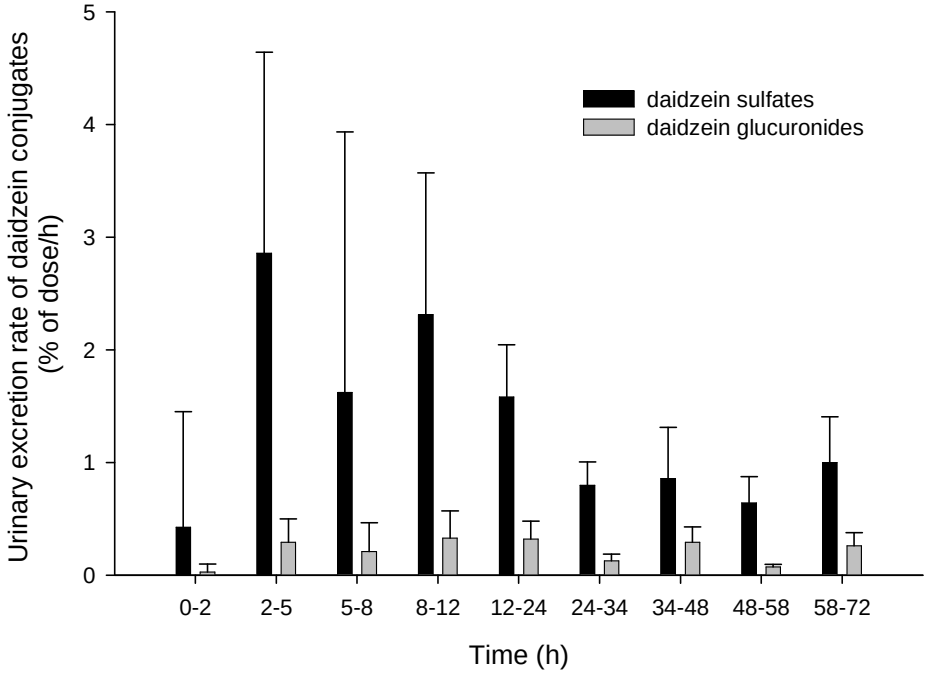


Fig. 18 Mean (±S.D.) urinary excretion rate (% of dose/h) of daidzein conjugates in six rats after intake of commercial extract II of GGCLT (6 g/kg) during each time interval.

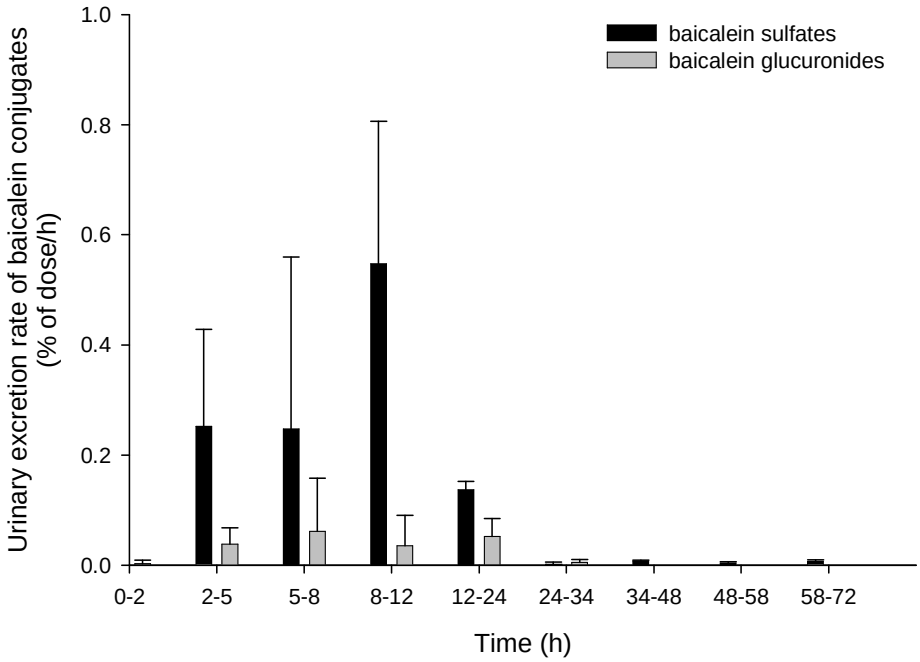


Fig. 19 Mean (±S.D.) urinary excretion rate (% of dose/h) of baicalein conjugates in six rats after intake of commercial extract II of GGCLT (6 g/kg) during each time interval.

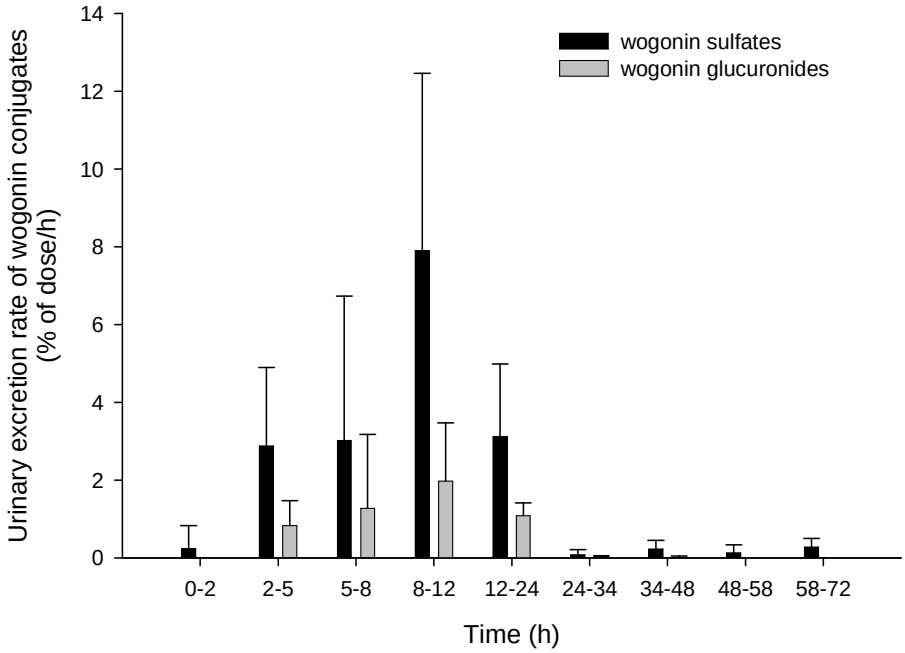
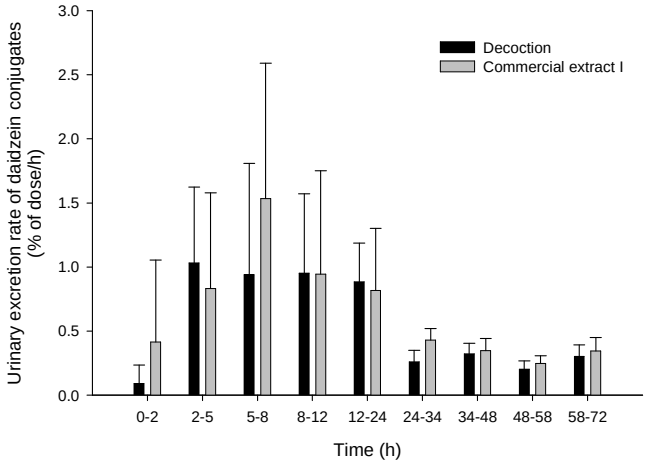
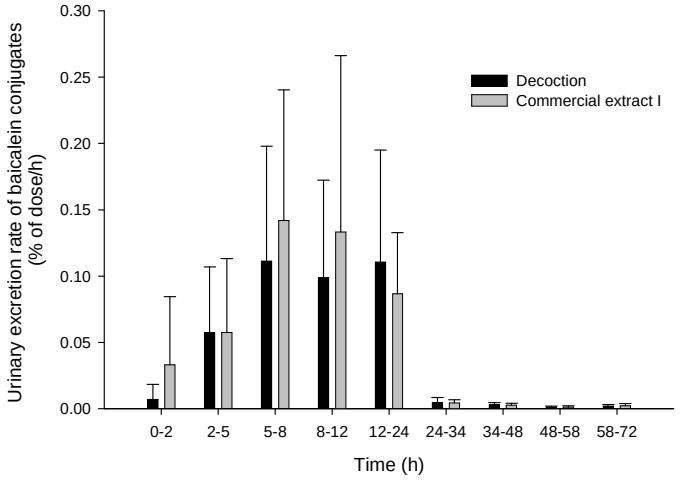


Fig. 20 Mean (±S.D.) urinary excretion rate (% of dose/h) of wogonin conjugates in six rats after intake of commercial extract II of GGCLT (6 g/kg) during each time interval.

(a)



(b)



(c)

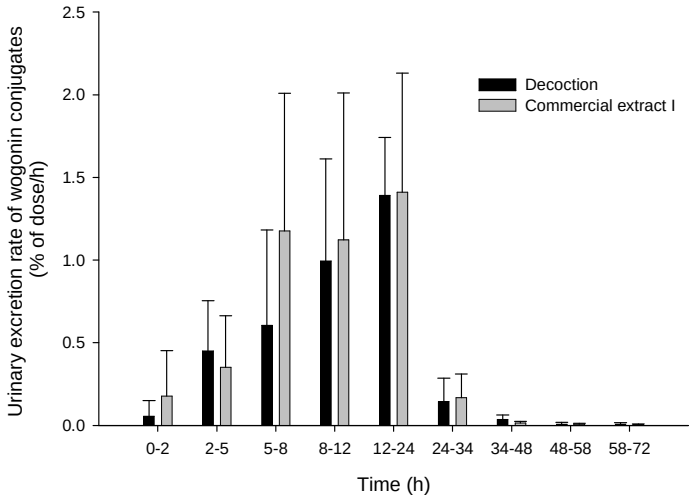
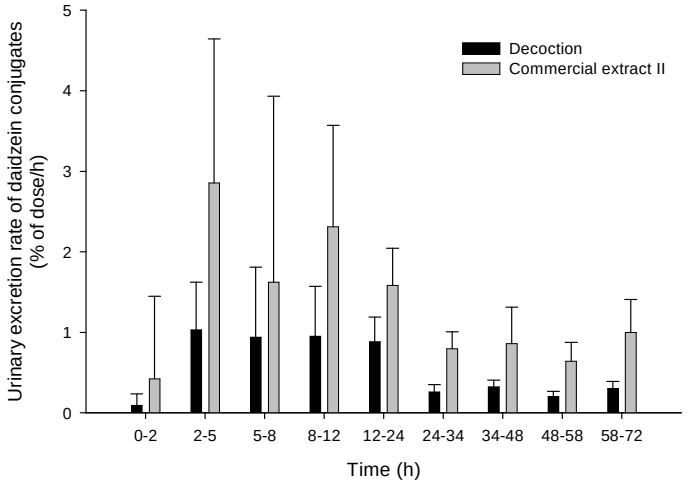
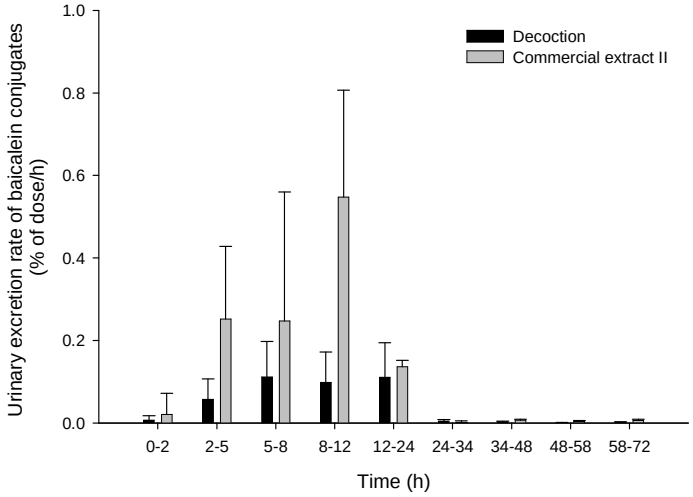


Fig. 21 Mean (±S.D.) urinary excretion rate (% of dose/h) of (a) daidzein (b) baicalein (c) wogonin conjugates in six rats after intake of decoction and commercial extract I of GGCLT during each time interval.

(a)



(b)



(c)

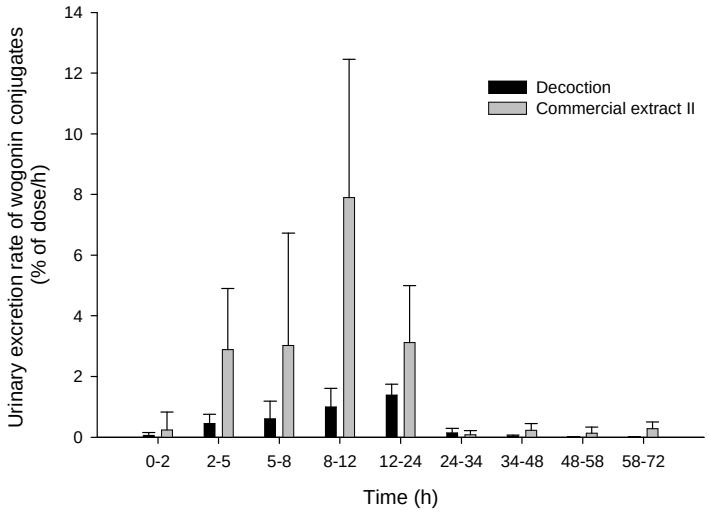


Fig 22 Mean (±S.D.) urinary excretion rate (% of dose/h) of (a) daidzein (b) baicalein (c) wogonin conjugates in six rats after intake of decoction and commercial extract II of GGCLT during each time interval.

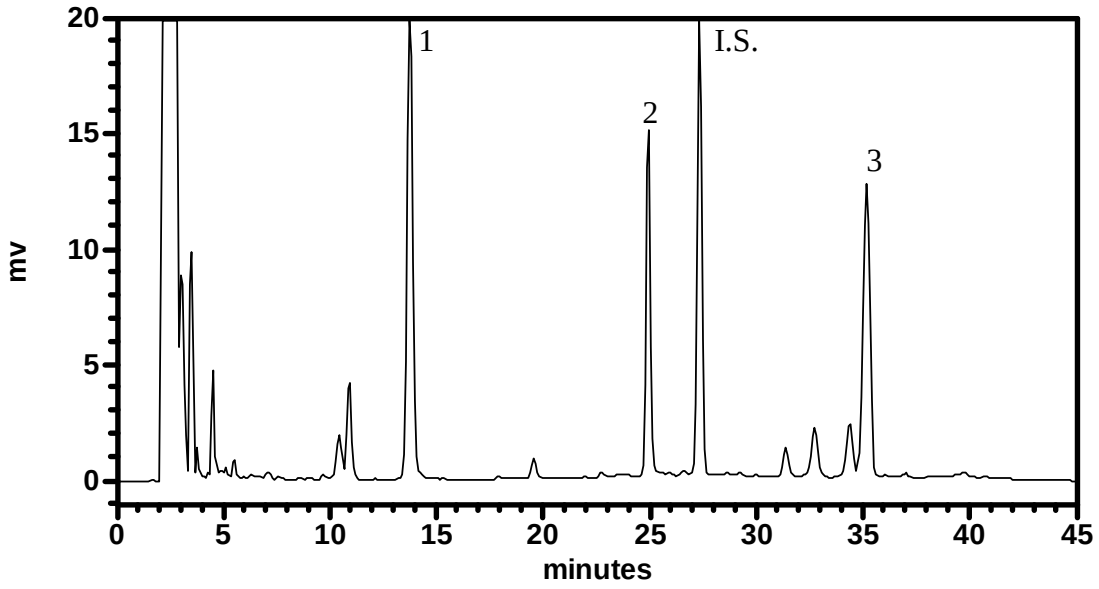


Fig.23 HPLC chromatogram of human plasma after spiked with 1: daidzein, 2: baicalein, 3: wogonin, I.S.: propyl paraben

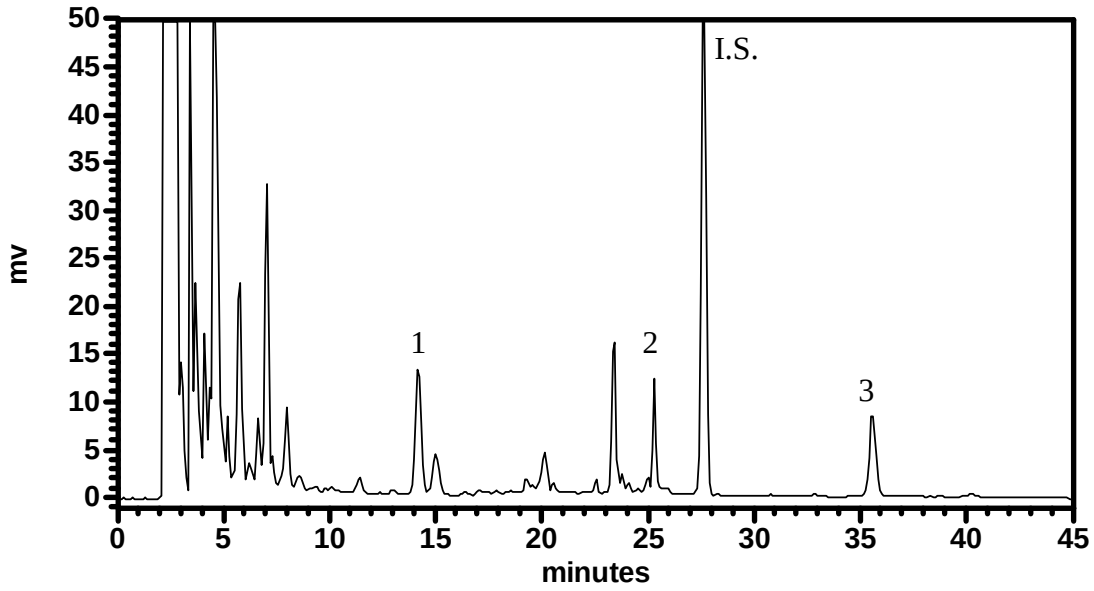


Fig.24 HPLC chromatogram of human urine after spiked with 1: daidzein, 2: baicalein, 3: wogonin, I.S.: propyl paraben

Table 1 The regression equations, concentration ranges and correlation coefficients of various constituents of GGCLT

Constituents	Regression equations	Conc. range (μg/mL)	r
Puerarin	Y=0.025X-0.008	5.6~180.0	0.9995
Daidzin	Y=0.027X-0.001	0.8~25.0	0.9995
Coptisine	Y=0.020X+0.001	1.3~40.0	0.9995
Baicalin	Y=0.013X-0.001	12.5~400.0	0.9995
Daidzein	Y=0.058X-0.001	0.9~30.0	0.9999
Palmatine	Y=0.022X-0.013	1.3~40.0	0.9999
Berberine	Y=0.025X-0.033	3.8~120.0	0.9999
Baicalein	Y=0.027X-0.017	0.6~20.0	0.9998
Glycyrrhizin	$Y=0.005X+0.000_1$	2.5~80.0	0.9999
Wogonin	$Y=0.023X+0.000_5$	0.6~20.0	0.9999

Table 2 Intra-run and inter-run analytical precision and accuracy of puerarin in MeOH

	Intra-run			Inter-run		
Conc	Precision		Accuracy	Precision		Accuracy
(μg/mL)	Mean± S.D.	(C.V.%)	(%)	Mean± S.D.	(C.V.%)	(%)
180.0	179.9±1.9	1.1	-0.1	179.5±2.0	1.1	-0.3
90.0	90.7±5.2	5.7	0.8	90.8±5.9	6.5	0.9
45.0	43.9±2.4	5.4	-2.5	46.0±4.2	9.1	2.2
22.5	22.4±0.7	2.9	-0.2	21.6±0.5	2.1	-4.1
11.3	11.7±0.5	4.6	4.4	11.3±0.1	0.8	0.5
5.6	5.7±0.5	8.0	1.4	5.2±0.4	6.7	-6.9

n=3

Table 3 Intra-run and inter-run analytical precision and accuracy of daidzin in MeOH

	Intra-run			Inter-run		
Conc	Precision		Accuracy	Precision		Accuracy
(μg/mL)	Mean± S.D.	(C.V.%)	(%)	Mean± S.D.	(C.V.%)	(%)
25.0	25.1±0.1	0.3	0.6	24.9±0.2	0.9	-0.3
12.5	12.1±0.3	2.6	-2.9	12.7±0.6	5.0	1.2
6.3	6.4±0.4	5.6	2.1	6.3±0.4	6.6	0.6
3.1	3.1±0.1	3.5	-0.3	$3.0\pm0.0_2$	0.7	-3.0
1.6	1.6±0.1	4.0	4.6	$1.6\pm0.0_3$	2.0	1.9
0.8	$0.8\pm0.0_4$	5.2	2.3	$0.7\pm0.0_4$	5.7	-7.0

n=3

Table 4 Intra-run and inter-run analytical precision and accuracy of coptisine in MeOH

	Intra-run			Inter-run		
Conc	Precision		Accuracy	Precision		Accuracy
(μg/mL)	Mean± S.D.	(C.V.%)	(%)	Mean± S.D.	(C.V.%)	(%)
40.0	39.7±0.1	0.2	-0.6	39.9±0.2	0.5	-0.4
20.0	20.5±0.1	0.3	2.5	20.5±0.5	2.6	2.7
10.0	10.2±0.3	2.7	2.1	9.5±0.5	4.8	-5.3
5.0	4.7±0.2	3.5	-6.2	5.0±0.3	6.7	0.0
2.5	2.3±0.1	5.3	-6.3	2.4±0.2	8.2	-4.4
1.3	1.3±0.1	9.2	1.2	1.5±0.1	5.0	18.8

n=3

Table 5 Intra-run and inter-run analytical precision and accuracy of baicalin in MeOH

Conc	Intra-run			Inter-run		
	Precision		Accuracy	Precision		Accuracy
(μg/mL)	Mean± S.D.	(C.V.%)	(%)	Mean± S.D.	(C.V.%)	(%)
400.0	400.5±2.7	0.7	0.1	397.2±1.5	0.4	-0.7
200.0	199.2±7.5	3.7	-0.4	207.4±3.9	1.9	3.7
100.0	99.2±3.8	3.8	-0.8	96.5±2.0	2.1	-3.5
50.0	50.1±1.1	2.1	0.2	49.9±1.1	2.1	-0.1
25.0	25.9±0.6	2.2	3.7	25.3±0.6	2.5	1.2
12.5	12.5±0.8	6.2	0.2	11.2±0.8	7.5	-10.8

n=3

Table 6 Intra-run and inter-run analytical precision and accuracy of daidzein in MeOH

Conc	Intra-run			Inter-run		
	Precision		Accuracy	Precision		Accuracy
(μg/mL)	Mean± S.D.	(C.V.%)	(%)	Mean± S.D.	(C.V.%)	(%)
30.0	$30.0\pm0.0_2$	0.1	-0.1	29.9±0.1	0.3	-0.4
15.0	$15.1\pm0.0_4$	0.2	0.9	15.3±0.2	1.3	1.7
7.5	7.4±0.1	0.9	-1.1	7.5±0.1	0.9	-0.4
3.8	$3.7\pm0.0_2$	0.5	-0.6	$3.7\pm0.0_4$	1.0	-0.9
1.9	$1.9\pm0.0_4$	1.9	0.8	1.8±0.1	4.3	-1.6
0.9	$0.9\pm0.0_1$	1.0	0.3	$0.9\pm0.0_5$	5.1	-5.3

n=3

Table 7 Intra-run and inter-run analytical precision and accuracy of palmatine in MeOH

Conc	Intra-run			Inter-run		
	Precision		Accuracy	Precision		Accuracy
(μg/mL)	Mean± S.D.	(C.V.%)	(%)	Mean± S.D.	(C.V.%)	(%)
40.0	39.8±0.2	0.6	-0.5	40.0±0.1	0.2	-0.1
20.0	20.3±0.5	2.4	1.7	20.3±0.2	1.0	1.4
10.0	10.3±0.2	2.1	2.8	9.7±0.3	3.4	-2.8
5.0	4.7±0.2	4.0	-5.8	4.7±0.2	4.6	-5.3
2.5	2.3±0.1	4.2	-8.4	2.6±0.2	8.6	3.4
1.3	1.3±0.1	9.7	5.6	1.5±0.1	5.0	18.3

n=3

Table 8 Intra-run and inter-run analytical precision and accuracy of berberine in MeOH

Conc	Intra-run			Inter-run		
	Precision		Accuracy	Precision		Accuracy
(μg/mL)	Mean± S.D.	(C.V.%)	(%)	Mean± S.D.	(C.V.%)	(%)
120.0	119.4±0.7	0.6	-0.5	119.4±0.2	0.1	-0.5
60.0	61.4±1.6	2.6	2.4	62.1±0.4	0.6	3.5
30.0	29.9±2.0	6.6	-0.3	28.4±0.7	2.3	-5.4
15.0	14.5±0.9	6.4	-3.5	14.4±1.0	6.8	-4.3
7.5	7.0±0.5	6.7	-6.2	7.6±0.2	2.2	0.7
3.8	4.0±0.3	7.0	7.0	4.5±0.3	6.8	18.7

n=3

Table 9 Intra-run and inter-run analytical precision and accuracy of baicalein in MeOH

Conc	Intra-run			Inter-run		
	Precision		Accuracy	Precision		Accuracy
(μg/mL)	Mean± S.D.	(C.V.%)	(%)	Mean± S.D.	(C.V.%)	(%)
20.0	20.1±0.1	0.3	0.5	20.1±0.2	0.8	0.3
10.0	9.8±0.1	0.9	-1.7	9.9±0.4	4.1	-0.6
5.0	5.0±0.2	3.9	-0.9	4.8±0.2	3.2	-3.5
2.5	2.4±0.1	4.2	-2.0	2.5±0.2	7.0	-0.8
1.3	$1.3\pm0.0_3$	2.3	6.6	$1.3\pm0.0_2$	1.8	6.4
0.6	0.7±0.1	9.2	14.0	$0.7\pm0.0_4$	6.2	16.9

n=3

Table 10 Intra-run and inter-run analytical precision and accuracy of glycyrrhizin in MeOH

Conc	Intra-run			Inter-run		
	Precision		Accuracy	Precision		Accuracy
(μg/mL)	Mean± S.D.	(C.V.%)	(%)	Mean± S.D.	(C.V.%)	(%)
80.0	79.9±0.1	0.1	-0.2	79.8±0.1	0.1	-0.2
40.0	40.7±0.5	1.2	1.6	40.7±0.2	0.4	1.7
20.0	19.1±0.6	3.2	-4.5	19.3±0.1	0.6	-3.3
10.0	10.0±0.1	1.0	0.4	10.0±0.1	0.8	-0.3
5.0	5.3±0.1	1.4	5.9	$5.2\pm0.0_4$	0.9	4.6
2.5	2.5±0.1	3.5	1.4	$2.5\pm0.0_2$	0.7	-1.9

n=3

Table 11 Intra-run and inter-run analytical precision and accuracy of wogonin in MeOH

Conc	Intra-run			Inter-run		
	Precision		Accuracy	Precision		Accuracy
(μg/mL)	Mean± S.D.	(C.V.%)	(%)	Mean± S.D.	(C.V.%)	(%)
20.0	20.0±0.1	0.3	0.2	$20.0\pm0.0_3$	0.1	-0.1
10.0	10.0±0.1	0.8	0.1	10.1±0.1	0.7	1.3
5.0	4.8±0.1	2.9	-4.4	$4.8\pm0.0_5$	1.0	-4.2
2.5	$2.5\pm0.0_1$	0.5	-0.3	$2.5\pm0.0_2$	0.9	-1.1
1.3	1.4±0.1	5.3	8.8	$1.3\pm0.0_3$	2.5	5.6
0.6	0.7±0.1	9.0	10.0	$0.7\pm0.0_3$	3.9	8.5

n=3

Table 12 The contents (μmoL) of various constituents in each gram of GGCLT decoction and commercial extract I and II

Contents / Compound	Decoction	Commercial extract I	Commercial extract I
Puerarin	28.5	21.3	12.1
Daidzin	5.0	4.1	2.1
Copsitine	10.2	7.6	3.3
Balcalin	30.1	28.8	16.3
Daidzein	0.9	0.9	0.0
Palmatine	6.7	6.5	2.7
Berberine	25.0	20.6	8.9
Baicalein	2.1	2.1	0.8
Glycyrrhizin	3.7	3.1	2.0
Wogonin	1.1	1.3	0.4

Table 13 Contents (mg) of puerarin, daidzin, coptisine and baicalin in each gram commercial extracts of GGCLT

Samples	puerarin	daidzin	coptisine	baicalin
a	0.4±0.0	0.1±0.0	0.3±0.0	3.3±0.1
b	5.0±0.4	0.9±0.0	1.2±0.1	7.3±0.4
c	6.7±0.2	0.9±0.0	0.8±0.3	3.9±0.3
d	12.4±3.6	1.8±0.3	2.7±0.3	14.0±0.8
e	0.5±0.0	0.1±0.0	0.9±0.1	4.2±0.1
f	1.5±0.0	0.3±0.0	1.7±0.3	4.4±0.2

Data expressed as mean±S.D.
n=3

Table 14 Contents (mg) of daidzein, palmatine and berberine in each gram commercial extracts of GGCLT

Samples	daidzein	palmatine	berberine
a	0.0_3±0.0	0.4±0.0	0.7±0.0
b	0.2±0.0	1.0±0.1	3.0±0.2
c	0.1±0.0	0.8±0.0	2.1±0.1
d	0.3±0.0	1.9±0.2	6.7±0.4
e	0.0±0.0	0.8±0.0	2.5±0.2
f	0.1±0.0	1.3±0.1	4.4±0.3

Data expressed as mean±S.D.
n=3

Table 15 Contents (mg) of baicalein, glycyrrhizin and wogonin in each gram commercial extracts of GGCLT

Samples	baicalein	glycyrrhizin	wogonin
a	0.3±0.0	0.3±0.0	0.1±0.0
b	0.2±0.0	1.6±0.1	0.1±0.0
c	0.7±0.0	1.2±0.0	0.2±0.0
d	0.6±0.1	2.1±1.2	0.4±0.0
e	0.6±0.0	1.9±0.1	0.3±0.0
f	1.4±0.1	1.8±0.0	0.4±0.0

Data expressed as mean±S.D.
n=3

Table 16 The regression equations, concentration ranges and correlation coefficients of daidzein, baicalein and wogonin in rat serum.

Constituents	Conc. ranges (μg/ml)	Regression equations	r
Daidzein	0.3 ~ 10.0	$Y=0.65X+0.00_1$	0.9999
Baicalein	0.2 ~ 5.0	$Y=0.25X+0.00_5$	0.9999
Wogonin	0.1 ~ 2.5	$Y=0.24X+0.00_1$	0.9999

Table 17 Intraday and interday analytical precision and accuracy of daidzein in rat serum

Conc (μg/mL)	Intraday Precision Mean± S.D.	(C.V.%)	Accuracy (%)	Interday Precision Mean± S.D.	(C.V.%)	Accuracy (%)
10.0	10.0± 0.0_5	0.5	0.4	10.0± 0.0_2	0.2	0.5
5.0	4.9±0.2	3.1	-2.0	4.9±0.0_4	0.8	-2.0
2.5	2.5± 0.1	3.5	0.9	2.5± 0.0_3	1.0	-0.6
1.3	1.3±0.0_1	1.1	3.0	1.3±0.0_5	4.1	0.8
0.6	0.6±0.0_1	0.8	0.7	0.7±0.0_3	4.8	5.6
0.3	0.3± 0.0_1	3.3	-1.0	0.3± 0.0_1	4.4	6.3

n=3

Table 18 Intraday and interday analytical precision and accuracy of baicalein in rat serum

Conc (μg/mL)	Intraday Precision Mean± S.D.	(C.V.%)	Accuracy (%)	Interday Precision Mean± S.D.	(C.V.%)	Accuracy (%)
5.0	5.0± 0.0	0.6	0.7	5.0± 0.0_3	0.5	0.7
2.5	2.4± 0.1	3.8	-3.9	2.4± 0.1	3.4	-3.3
1.3	1.3± 0.0	5.1	3.8	1.3± 0.1	5.7	1.9
0.6	0.6± 0.0	2.8	2.2	0.6± 0.0_2	2.8	2.2
0.3	0.3± 0.0	7.8	-2.6	0.3± 0.0_3	8.6	-0.4
0.2	0.2± 0.0	4.1	6.1	0.2± 0.0_1	4.8	8.8

n=3

Table 19 Intraday and interday analytical precision and accuracy of wogonin in rat serum

Conc (μg/mL)	Intraday Precision Mean± S.D.	(C.V.%)	Accuracy (%)	Interday Precision Mean± S.D.	(C.V.%)	Accuracy (%)
2.5	2.5± 0.0	1.6	0.8	2.5± 0.0	1.0	-0.4
1.3	1.2± 0.1	8.9	-4.0	1.3± 0.1	5.6	2.7
0.6	0.6± 0.0	6.7	2.7	0.6± 0.0	6.8	-5.0
0.3	0.3± 0.0	8.1	0.8	0.3± 0.0	2.6	4.5
0.2	0.2± 0.0	5.3	3.2	0.2± 0.0	7.7	-0.9
0.1	0.1± 0.0	8.8	6.5	0.1± 0.0	3.5	-5.9

n=3

Table 20 Recoveries (%) of various constituents of GGCLT from rat serum

Constituents	Conc. Spiked (μg/mL)	1	2	3	Recoveries (%). Mean± S.D
Daidzein	5.0	95.2	96.9	98.2	96.8±1.5
	2.5	98.7	100.3	100.6	99.9±1.0
	1.3	98.6	101.1	100.4	100.0±1.3
Baicalein	2.5	82.4	82.2	84.5	83.0±1.3
	1.3	91.2	92.5	86.5	90.1±3.1
	0.6	88.9	92.9	95.0	92.3±3.1
Wogonin	1.3	97.3	98.7	100.1	98.7±1.4
	0.6	100.5	99.0	99.1	99.5±0.8
	0.3	106.7	107.5	106.2	106.8±0.6

n=3

Table 21 The serum concentrations (nmol/mL) of daidzein sulfates/glucuronides in six rats after oral administration of GGCLT decoction (6 g/kg).

Time (min) \ Rats	1	2	3	4	5	6	Mean±S.E.
15	9.5	4.6	10.5	3.9	6.3	7.9	7.1±1.1
30	7.2	9.0	13.7	4.2	5.0	5.5	7.4±1.4
60	6.2	1.0	14.2	3.7	4.6	4.1	5.6±1.9
120	5.4	1.1	11.0	3.4	4.2	3.3	4.7±1.4
360	4.4	2.6	12.5	3.9	2.6	2.1	4.7±1.6
720	5.9	2.8	10.5	6.2	2.9	2.8	5.2±1.2
1440	5.1	2.6	4.2	4.2	6.9	3.1	4.3±0.6
2160	2.9	4.6	1.6	5.0	1.7	1.3	2.9±0.7
2880	2.4	2.2	2.3	2.5	1.2	0.2	1.8±0.4
4320	2.3	1.0	1.2	1.2	1.0	2.3	1.5±0.3
5760	1.7	1.1	2.5	1.1	1.3	1.5	1.6±0.2

Table 22 The serum concentrations (nmol/mL) of daidzein glucuronides in six rats after oral administration of GGCLT decoction (6 g/kg).

Time (min) \ Rats	1	2	3	4	5	6	Mean±S.E.
15	1.5	0.8	1.8	1.0	1.3	1.0	1.2±0.1
30	1.3	0.5	2.6	1.4	0.7	0.6	1.2±0.3
60	1.0	0.4	2.8	1.3	0.7	0.4	1.1±0.4
120	0.6	0.4	3.6	0.9	0.5	0.3	1.1±0.5
360	0.3	0.3	1.3	0.8	0.3	0.3	0.6±0.2
720	0.6	0.2	0.5	1.1	0.4	0.4	0.5±0.1
1440	0.6	0.2	0.4	0.7	0.8	0.4	0.5±0.1
2160	0.5	0.5	0.3	1.4	0.4	0.1	0.5±0.2
2880	0.4	0.4	0.4	0.9	0.3	0.0	0.4±0.1
4320	0.4	0.2	0.3	0.5	0.2	0.3	0.3±0.0
5760	0.4	0.4	N.D.	0.4	0.2	0.3	0.3±0.1

N.D.：not detected

Table 23 The serum concentrations (nmol/mL) of baicalein sulfates/glucuronides in six rats after oral administration of GGCLT decoction (6 g/kg).

Time (min) \ Rats	1	2	3	4	5	6	Mean±S.E.
15	0.1	0.9	4.0	1.7	1.6	2.0	1.7±0.5
30	1.6	4.5	4.2	1.5	1.3	1.1	2.4±0.6
60	1.2	0.0	3.2	1.2	1.3	0.9	1.3±0.4
120	1.2	0.0	10.5	1.1	0.7	0.9	2.4±1.6
360	1.3	0.7	2.9	2.3	1.0	0.7	1.5±0.4
720	2.3	0.8	6.3	5.4	0.9	0.6	2.7±1.0
1440	1.5	0.7	3.5	2.3	3.5	0.5	2.0±0.5
2160	0.5	0.9	0.6	3.6	1.6	0.3	1.3±0.5
2880	0.0	1.1	0.1	1.8	1.1	0.2	0.7±0.3
4320	0.0	0.0	N.D.	N.D.	0.1	1.0	0.2±0.2
5760	0.0	0.0	N.D.	N.D.	N.D.	0.5	0.1±0.1

N.D.：not detected

Table 24 The serum concentrations (nmol/mL) of baicalein glucuronides in six rats after oral administration of GGCLT decoction (6 g/kg).

Time (min) \ Rats	1	2	3	4	5	6	Mean±S.E.
15	2.0	0.9	3.7	1.6	1.6	1.6	1.9±0.4
30	1.2	1.1	3.1	1.5	1.1	1.1	1.5±0.3
60	1.1	0.5	2.6	1.0	0.6	0.9	1.1±0.3
120	1.1	0.4	13.7	0.7	1.1	0.8	3.0±2.2
360	1.0	1.0	2.5	2.0	0.8	0.8	1.4±0.3
720	1.9	0.8	4.8	4.4	0.6	0.6	2.2±0.8
1440	1.0	0.6	2.8	1.9	2.0	0.5	1.5±0.4
2160	0.3	0.6	0.2	2.8	1.2	0.3	0.9±0.4
2880	0.0	0.8	0.0	1.7	0.7	0.1	0.6±0.3
4320	N.D.	N.D.	N.D.	0.0	N.D.	0.9	0.1±0.2
5760	N.D.	0.0	N.D.	0.2	0.2	0.0	0.1±0.0

N.D.：not detected

Table 25 The serum concentrations (nmol/mL) of wogonin sulfates/glucuronides in six rats after oral administration of GGCLT decoction (6 g/kg).

Time (min) \ Rats	1	2	3	4	5	6	Mean±S.E.
15	0.8	0.5	1.7	0.8	0.6	0.3	0.8±0.2
30	0.4	0.4	1.5	0.7	0.4	0.1	0.6±0.2
60	0.3	0.1	1.2	0.6	0.4	0.1	0.5±0.2
120	0.6	0.1	3.2	0.6	0.3	0.3	0.8±0.5
360	1.1	0.5	1.9	1.2	0.5	0.2	0.9±0.3
720	1.6	0.5	1.7	1.6	0.5	0.3	1.0±0.3
1440	1.0	0.4	0.7	1.6	1.4	0.2	0.9±0.3
2160	1.6	0.5	0.1	1.7	0.5	0.2	0.8±0.3
2880	0.2	0.1	0.1	0.8	0.2	N.D.	0.2±0.1
4320	N.D.	0.1	N.D.	N.D.	N.D.	0.3	0.1±0.0
5760	N.D.	0.1	N.D.	N.D.	N.D.	N.D.	0.0±0.0

ND：not detected

Table 26 The serum concentrations (nmol/mL) of wogonin glucuronides in six rats after oral administration of GGCLT decoction (6 g/kg).

Time (min) \ Rats	1	2	3	4	5	6	Mean±S.E.
15	0.7	0.1	1.1	0.6	0.3	0.3	0.5±0.1
30	0.7	0.3	0.8	0.6	0.3	0.2	0.5±0.1
60	0.4	0.1	0.8	0.5	0.2	0.1	0.4±0.1
120	0.6	0.1	3.4	0.4	0.3	0.4	0.9±0.5
360	0.6	0.1	1.5	0.9	0.3	0.2	0.6±0.2
720	1.2	0.3	1.3	1.3	0.3	0.3	0.8±0.2
1440	0.6	0.3	0.5	1.1	0.8	0.3	0.6±0.1
2160	0.3	0.4	0.3	1.4	0.3	0.3	0.5±0.2
2880	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0.0±0.0
4320	N.D.	N.D.	N.D.	N.D.	N.D.	0.3	0.0±0.0
5760	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0.0±0.0

ND：not detected

Table 27 The serum concentrations (nmol/mL) of daidzein sulfates/glucuronides in six rats after oral administration of GGCLT commercial extract I (6 g/kg).

Time (min) \ Rats	1	2	3	4	5	6	Mean±S.E.
15	8.6	6.1	9.2	0.5	8.9	5.1	6.4±1.4
30	7.2	4.4	6.3	3.8	7.7	2.6	5.3±0.8
60	5.9	3.9	9.5	2.7	5.8	2.4	5.0±1.1
120	3.6	1.5	4.3	1.9	4.1	1.8	2.9±0.5
360	2.8	1.7	4.6	2.3	4.9	1.3	2.9±0.6
720	1.9	3.2	5.6	2.6	1.8	1.3	2.7±0.6
1440	3.2	2.1	2.7	3.6	6.1	1.3	3.2±0.7
2160	2.4	2.1	1.4	1.8	1.4	1.6	1.8±0.2
2880	2.4	1.8	1.8	1.3	1.5	1.3	1.7±0.2
4320	1.6	1.7	1.9	1.9	0.6	1.5	1.5±0.2
5760	1.2	1.2	1.4	2.8	0.5	0.7	1.3±0.3

Table 28 The serum concentrations (nmol/mL) of daidzein glucuronides in six rats after oral administration of GGCLT commercial extract I (6 g/kg).

Time (min) \ Rats	1	2	3	4	5	6	Mean±S.E.
15	1.6	2.1	1.1	0.1	2.3	0.6	1.3±0.4
30	N.D.	1.4	1.0	0.7	2.8	0.5	1.1±0.4
60	1.0	1.1	1.2	0.7	2.5	0.6	1.2±0.3
120	0.6	0.4	0.5	0.5	1.7	0.5	0.7±0.2
360	0.3	0.4	0.4	0.4	1.0	0.2	0.5±0.1
720	0.4	0.6	0.4	0.4	0.4	0.3	0.4±0.0
1440	0.5	0.7	0.3	1.3	0.4	0.3	0.6±0.2
2160	0.5	0.6	0.2	0.4	0.4	0.4	0.4±0.1
2880	0.5	0.6	0.3	0.4	0.3	0.3	0.4±0.1
4320	0.4	0.6	0.3	0.3	0.3	0.3	0.4±0.0
5760	0.3	0.4	0.3	0.5	0.2	0.2	0.3±0.0

N.D.：not detected

Table 29 The serum concentrations (nmol/mL) of baicalein sulfates/glucuronides in six rats after oral administration of GGCLT commercial extract I (6 g/kg).

Time (min) \ Rats	1	2	3	4	5	6	Mean±S.E.
15	4.0	2.6	2.6	0.5	4.2	2.6	2.8±0.5
30	2.4	1.4	1.3	1.0	3.1	1.1	1.7±0.3
60	1.4	1.2	2.0	1.3	3.0	0.8	1.6±0.3
120	0.8	0.5	1.2	0.8	2.2	0.9	1.1±0.2
360	1.0	0.8	1.4	0.8	2.8	1.1	1.3±0.3
720	1.4	1.5	2.1	0.7	2.8	2.1	1.8±0.3
1440	1.3	1.3	0.6	2.1	5.2	0.2	1.8±0.7
2160	0.7	0.7	0.2	0.4	0.6	0.5	0.5±0.1
2880	0.4	1.0	0.2	0.7	0.0	0.4	0.4±0.1
4320	0.2	0.1	0.5	0.2	0.1	0.3	0.2±0.1
5760	0.1	0.0	0.5	0.1	0.1	0.2	0.1±0.1

N.D.：not detected

Table 30 The serum concentrations (nmol/mL) of baicalein glucuronides in six rats after oral administration of GGCLT commercial extract I (6 g/kg).

Time (min) \ Rats	1	2	3	4	5	6	Mean±S.E.
15	3.9	2.2	1.8	0.1	3.1	0.5	1.9±0.6
30	N.D.	1.1	1.5	1.1	2.6	0.1	1.1±0.4
60	1.0	1.4	1.7	1.0	2.3	0.4	1.3±0.3
120	0.5	0.4	0.8	0.7	2.1	0.5	0.8±0.3
360	1.0	0.7	0.9	0.8	2.3	1.0	1.1±0.2
720	1.0	1.0	2.0	0.6	2.3	1.6	1.4±0.3
1440	1.0	0.9	0.5	4.9	1.8	N.D.	1.5±0.7
2160	0.6	0.5	0.2	0.3	0.5	0.3	0.4±0.1
2880	0.3	0.7	0.2	0.5	0.1	N.D.	0.3±0.1
4320	0.1	N.D.	0.3	0.1	N.D.	N.D.	0.1±0.0
5760	N.D.	N.D.	0.4	N.D.	N.D.	N.D.	0.1±0.1

N.D.：not detected

Table 31 The serum concentrations (nmol/mL) of wogonin sulfates/glucuronides in six rats after oral administration of GGCLT commercial extract I (6 g/kg).

Time (min) \ Rats	1	2	3	4	5	6	Mean±S.E.
15	0.9	0.7	0.4	N.D.	0.5	0.5	0.5±0.1
30	0.6	0.2	0.3	0.2	0.5	0.4	0.4±0.1
60	0.3	0.4	0.4	0.2	0.5	0.4	0.4±0.0
120	0.3	0.3	0.4	0.2	0.6	0.4	0.4±0.1
360	0.7	0.5	0.6	0.3	1.5	0.3	0.6±0.2
720	1.2	1.0	1.5	0.3	1.3	0.4	0.9±0.2
1440	0.6	0.9	0.4	0.6	2.2	0.1	0.8±0.3
2160	0.5	0.6	0.1	0.2	0.2	0.1	0.3±0.1
2880	0.2	0.4	0.1	0.2	N.D.	0.1	0.2±0.1
4320	0.1	0.1	0.3	0.1	N.D.	0.1	0.1±0.0
5760	N.D.	N.D.	0.1	N.D.	N.D.	N.D.	0.0±0.0

N.D.：not detected

Table 32 The serum concentrations (nmol/mL) of wogonin glucuronides in six rats after oral administration of GGCLT commercial extract I (6 g/kg).

Time (min) \ Rats	1	2	3	4	5	6	Mean±S.E.
15	0.8	0.7	0.3	N.D.	0.4	0.2	0.4±0.1
30	N.D.	0.3	0.3	0.2	0.4	0.2	0.2±0.1
60	0.3	0.3	0.4	0.2	0.5	0.3	0.3±0.0
120	0.2	0.1	0.2	0.2	0.4	0.3	0.3±0.0
360	0.6	0.4	0.3	0.2	1.3	0.3	0.5±0.2
720	0.6	0.5	1.3	0.3	1.1	0.3	0.7±0.2
1440	0.7	1.0	0.4	2.0	0.4	0.1	0.8±0.3
2160	0.6	0.5	0.2	0.2	0.1	0.1	0.3±0.1
2880	0.2	0.4	0.1	0.2	N.D.	0.1	0.2±0.1
4320	0.2	N.D.	0.2	0.1	N.D.	0.1	0.1±0.0
5760	0.1	N.D.	0.2	0.0	N.D.	N.D.	0.0±0.0

N.D.：not detected

Table 33 The serum concentrations (nmol/mL) of daidzein sulfates/glucuronides in six rats after oral administration of GGCLT commercial extract II (6 g/kg).

Time (min) \ Rats	1	2	3	4	5	6	Mean±S.E.
15	2.6	4.7	5.9	3.2	3.2	1.5	3.5±0.6
30	2.1	3.3	5.4	2.1	2.2	1.4	2.7±0.6
60	1.5	2.6	3.8	1.4	2.1	1.3	2.1±0.4
120	1.1	1.7	3.0	1.1	2.2	1.1	1.7±0.3
360	1.0	1.3	1.7	1.1	1.2	1.3	1.3±0.1
720	0.9	0.9	1.3	1.2	1.5	2.3	1.3±0.2
1440	1.7	1.7	1.1	2.3	1.2	1.5	1.6±0.2
2160	1.4	2.7	1.0	1.0	1.7	1.4	1.5±0.3
2880	1.4	2.7	1.4	1.8	1.6	1.5	1.7±0.2
4320	1.7	1.2	2.1	0.8	2.3	1.7	1.7±0.2
5760	1.7	1.9	1.8	0.4	0.5	0.2	1.1±0.3

Table 34 The serum concentrations (nmol/mL) of daidzein glucuronides in six rats after oral administration of GGCLT commercial extract II (6 g/kg).

Time (min) \ Rats	1	2	3	4	5	6	Mean±S.E.
15	0.6	0.5	0.5	0.3	0.5	0.3	0.4±0.0
30	0.4	0.3	0.4	0.2	0.3	0.2	0.3±0.0
60	0.2	0.3	0.2	0.1	0.3	0.2	0.2±0.0
120	0.1	0.1	0.1	0.1	0.3	0.1	0.1±0.0
360	0.1	0.1	0.1	0.2	0.1	0.1	0.1±0.0
720	0.1	0.1	0.1	0.2	0.2	0.2	0.1±0.0
1440	0.2	0.1	0.1	0.2	0.1	0.1	0.1±0.0
2160	0.2	0.3	0.1	0.1	0.2	0.2	0.2±0.0
2880	0.2	0.2	0.1	0.2	0.2	0.2	0.2±0.0
4320	0.2	0.2	0.1	0.1	0.2	0.2	0.2±0.0
5760	0.2	0.2	0.2	0.1	0.1	0.0	0.1±0.0

Table 35 The serum concentrations (nmol/mL) of baicalein sulfates/glucuronides in six rats after oral administration of GGCLT commercial extract II (6 g/kg).

Time (min) \ Rats	1	2	3	4	5	6	Mean±S.E.
15	1.3	1.8	2.6	0.8	1.2	0.5	1.4±0.3
30	1.4	0.8	1.5	0.6	0.5	0.3	0.9±0.2
60	0.5	0.5	0.9	0.5	0.8	0.2	0.6±0.1
120	0.4	0.2	1.0	0.4	1.0	0.1	0.5±0.2
360	0.2	0.3	1.1	0.9	0.8	0.1	0.6±0.2
720	0.4	0.1	0.7	1.0	0.3	1.6	0.7±0.2
1440	0.3	N.D.	0.3	0.8	0.1	0.1	0.3±0.1
2160	0.4	1.2	0.1	0.2	0.4	0.1	0.4±0.2
2880	0.1	0.7	N.D.	0.1	0.6	0.1	0.3±0.1
4320	0.1	0.2	N.D.	0.1	1.3	0.1	0.3±0.2
5760	0.1	0.0	N.D.	N.D.	0.1	N.D.	0.0±0.0

N.D.：not detected

Table 36 The serum concentrations (nmol/mL) of baicalein glucuronides in six rats after oral administration of GGCLT commercial extract II (6 g/kg).

Rats / TimSe (min)	1	2	3	4	5	6	Mean±S.E.
15	0.4	0.8	1.7	0.7	0.7	0.2	0.7±0.2
30	0.2	0.4	1.0	0.4	0.8	0.1	0.5±0.1
60	0.1	0.3	0.5	0.4	0.7	0.1	0.3±0.1
120	0.1	0.3	0.9	0.3	0.9	0.0	0.4±0.2
360	0.0	0.2	0.9	0.7	0.6	0.1	0.4±0.2
720	0.1	0.1	0.6	0.7	0.4	1.0	0.5±0.1
1440	N.D.	N.D.	N.D.	0.5	0.2	0.1	0.1±0.1
2160	N.D.	0.5	0.0	N.D.	0.4	N.D.	0.2±0.1
2880	N.D.	0.3	0.1	0.0	0.3	N.D.	0.1±0.1
4320	0.0	0.0	N.D.	N.D.	0.6	0.1	0.1±0.1
5760	N.D.	N.D.	N.D.	N.D.	0.1	0.1	0.0±0.0

N.D.：not detected

Table 37 The serum concentrations (nmol/mL) of wogonin sulfates/glucuronides in six rats after oral administration of GGCLT commercial extract II (6 g/kg).

Rats / Time (min)	1	2	3	4	5	6	Mean±S.E.
15	0.2	0.3	0.4	0.3	0.2	0.1	0.2±0.0
30	0.1	0.1	0.2	0.0	0.2	0.1	0.1±0.0
60	0.1	N.D.	0.1	N.D.	0.2	0.1	0.1±0.0
120	0.	0.1	0.3	N.D.	0.3	0.1	0.1±0.1
360	N.D.	0.1	0.2	0.3	0.4	0.1	0.2±0.1
720	0.1	0.2	0.1	0.3	0.1	0.6	0.2±0.1
1440	0.1	0.1	N.D.	N.D.	N.D.	0.1	0.0±0.0
2160	0.1	0.6	N.D.	0.1	0.1	0.1	0.2±0.1
2880	N.D.	0.2	N.D.	N.D.	0.0	N.D.	0.0±0.0
4320	N.D.	N.D.	N.D.	0.1	0.4	N.D.	0.1±0.1
5760	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0.0±0.0

N.D.：not detected

Table 38 The serum concentrations (nmol/mL) of wogonin glucuronides in six rats after oral administration of GGCLT commercial extract II (6 g/kg).

Rats / Time (min)	1	2	3	4	5	6	Mean ±S.E.
15	0.2	0.2	0.4	0.2	0.2	0.1	0.2 ±0.0
30	0.1	N.D.	0.5	0.0	0.2	0.1	0.1 ±0.0
60	0.1	N.D.	0.1	N.D.	0.3	0.1	0.1 ±0.0
120	0.1	N.D.	0.3	0.0	0.3	0.1	0.1 ±0.1
360	N.D.	N.D.	0.1	0.1	0.3	0.0	0.1 ±0.1
720	N.D.	N.D.	0.1	0.2	0.1	0.3	0.1 ±0.0
1440	0.1	N.D.	N.D.	0.2	N.D.	N.D.	0.1 ±0.0
2160	0.1	0.3	N.D.	N.D.	0.1	0.1	0.1 ±0.1
2880	0.1	0.1	N.D.	N.D.	0.1	N.D.	0.0 ±0.0
4320	N.D.	N.D.	N.D.	N.D.	0.3	N.D.	0.0 ±0.1
5760	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0.0 ±0.0

N.D.：not detected

Table 39 Pharmacokinetic parameters of sulfates (S) and glucuronides (G) of daidzein, baicalein and wogonin in six rats after oral administration of GGCLT decoction (6 g/kg).

Parameters / Metabolites	C_{max}	AUC_{0-5760}	MRT	AUC/dose
Daidzein S/G	8.9±1.2***	15871.8±1787.8***	2315.7±122.6	529.0±59.6
Daidzein G	1.6±0.4	2529.4±459.0	2404.1±231.7	84.3±15.3
Baicalein S/G	4.7±1.3	5630.1±1127.9	1662.3±312.9	29.1±5.8
Baicalein G	4.1±2.0	4733.1±1122. 4	1600.3±278.4	24.5±5.8
Wogonin S/G	1.5±0.4	2336.4±486.2	1468.6±184.0	354.5±73.8
Wogonin G	1.3±0.5	1436.9±297.3	1202.1±178.8	218.0±45.1

*** $p < 0.001$ (compared with glucuronides)
Data expressed as mean ± S.E.
Cmax (nmol·ml-1): concentration of peak serum level.
AUC0-5760 (nmol·min·ml-1): area under serum concentration – time curve to 5760 min.
MRT (min): mean residence time.

Table 40 Pharmacokinetic parameters of sulfates (S) and glucuronides (G) of daidzein, baicalein and wogonin in six rats after oral administration of GGCLT commercial extract I(6 g/kg).

Parameters / Metabolites	C_{max}	AUC_{0-5760}	MRT	AUC/dose
Daidzein S/G	7.0±0.9**	11740.3±928.6***	2374.6±159.0	479.5±37.9
Daidzein G	1.6±0.3	2466.6±221.5	2570.2±121.3	100.7±9.0
Baicalein S/G	3.2±0.5	4197.3±631.1	1685.3±118.1	22.6±3.4
Baicalein G	2.9±0.5	3195.0±542.6	1385.9±187.7	17.2±2.9
Wogonin S/G	1.1±0.3	1863.6±319.2	1560.5±112.8	236.4±40.5
Wogonin G	1.1±0.2	1595.9±240.6	1536.9±181.7	202.4±30.5

** $p< 0.01$, *** $p < 0.001$ (compared with glucuronides)
Data expressed as mean ± S.E.
Cmax (nmol·ml-1): concentration of peak serum level.
AUC0-5760 (nmol·min·ml-1): area under serum concentration – time curve to 5760 min.
MRT (min): mean residence time.

Table 41 Pharmacokinetic parameters of sulfates (S) and glucuronides (G) of daidzein, baicalein and wogonin in six rats after oral administration of GGCLT commercial extract II (6 g/kg).

Parameters / Metabolites	C_{max}	$AUC_{0\text{-}5760}$	MRT	AUC/dose
Daidzein S/G	3.6±0.6**	8824.2±469.0***	2797.1±115.1	713.7±37.9
Daidzein G	0.4±0.1	906.8±51.0	2900.1±70.4	73.3±4.1
Baicalein S/G	1.6±0.2	1909.9±366.5	1824.9±386.1	19.4±3.7
Baicalein G	0.9±0.2	1021.6±303.3	1520.3±321.1	10.4±3.1
Wogonin S/G	0.4±0.1	429.7±94.4	253.5±68.6	184.1±40.5
Wogonin G	0.3±0.0	1421.6±303.8	1387.0±326.8	108.6±29.4

** p< 0.01, *** p < 0.001 (compared with glucuronides)
Data expressed as mean ± S.E.
Cmax (nmol·ml-1): concentration of peak serum level.
AUC0-5760 (nmol·min·ml-1): area under serum concentration – time curve to 5760 min.
MRT (min): mean residence time.

Table 42 AUC/dose (min/mL) of various constituent after administration of decoctions and commercial extract I of GGCLT to rats (n=6)

Constituents	Decoction	Commercial extract I	
	Mean	Mean	Confidence interval
Daidzein	529.0	479.5	403.1～555.9
Baicalein	29.1	22.6	15.8～29.5
Wogonin	354.5	236.4	154.8～318.0

Table 43 AUC/dose (min/mL) of various constituent after administration of decoctions and commercial extract II of GGCLT to rats (n=6)

Constituents	Decoction	Commercial extract II	
	Mean	Mean	Confidence interval
Daidzein	529.0	713.7	637.3～790.1
Baicalein	29.1	19.4	11.9～27.0
Wogonin	354.5	184.1	102.6～265.6

Table 44 The regression equations, concentration ranges and correlation coefficients of daidzein, baicalein and wogonin in rat urine.

Constituents	Conc. ranges (μg/ml)	Regression equations	r
Daidzein	0.6 ~ 20.0	Y=0.122X-0.003	0.99997
Baicalein	0.6 ~ 20.0	Y=0.033X+0.015	0.99994
Wogonin	0.3 ~ 10.0	Y=0.047X-0.001	0.99998

Table 45 Intraday and interday analytical precision and accuracy of daidzein in rat urine

Conc (μg/mL)	Intraday Precision Mean± S.D.	(C.V.%)	Accuracy (%)	Interday Precision Mean± S.D.	(C.V.%)	Accuracy (%)
20	20.0± 0.0_4	0.2	0.2	20.1± 0.0_6	0.3	0.3
10	9.9±0.1	-0.6	1.1	9.9±0.1	-1.1	1.1
5	5.0± 0.0_8	-0.2	1.6	5.0± 0.0_6	-0.2	1.2
2.5	2.4±0.1	-2.3	5.5	2.4±0.1	-2.9	5.1
1.3	1.3±0.0_6	6.5	4.3	1.4±0.0_7	8.0	4.9
0.6	0.6± 0.0_3	2.4	4.8	0.7± 0.0_4	5.0	5.8

n=3

Table 46 Intraday and interday analytical precision and accuracy of baicalein in rat urine

Conc (μg/mL)	Intraday Precision Mean± S.D.	(C.V.%)	Accuracy (%)	Interday Precision Mean± S.D.	(C.V.%)	Accuracy (%)
20	20.2± 0.2	1.2	0.8	20.2± 0.2	1.2	0.9
10	9.4± 0.5	-6.1	5.6	9.4± 0.5	-6.1	5.5
5	5.2± 0.4	4.2	8.6	5.2± 0.4	3.7	8.1
2.5	2.7± 0.1	8.7	4.6	2.7± 0.1	7.4	5.4
1.3	1.2± 0.1	-6.3	4.3	1.2± 0.0_7	-1.1	5.3
0.6	0.7± 0.0	5.5	5.6	0.6± 0.0_4	2.8	6.9

n=3

Table 47 Intraday and interday analytical precision and accuracy of wogonin in rat urine

Conc (μg/mL)	Intraday Precision Mean± S.D.	(C.V.%)	Accuracy (%)	Interday Precision Mean± S.D.	(C.V.%)	Accuracy (%)
10	10.0± 0.1	0.0	0.6	10.0± 0.0	-0.1	0.3
5	5.0± 0.2	-0.4	3.2	5.0± 0.1	0.2	1.3
2.5	2.6± 0.1	3.3	3.7	2.5± 0.1	1.3	2.0
1.3	1.2± 0.0	-2.5	3.6	1.2± 0.0	-0.3	2.0
0.6	0.6± 0.0	-1.0	4.3	0.6± 0.0	-0.5	2.9
0.3	0.3± 0.0	-6.0	7.9	0.3± 0.0	-7.9	4.1

n=3

Table 48 Recoveries (%) of various constituents of GGCLT from rat urine

Constituents	Conc. Spiked (μg/mL)	1	2	3	Recoveries (%) Mean± S.D
Daidzein	10.0	93.0	97.5	94.2	94.9±2.4
	5.0	89.5	94.1	96.2	93.3±3.4
	2.5	95.3	92.3	91.9	93.2±1.9
Baicalein	10.0	72.5	74.5	70.2	72.4±2.2
	5.0	59.1	62.3	63.2	61.6±2.2
	2.5	52.5	50.1	48.5	50.3±2.0
Wogonin	5.0	96.8	100.5	98.0	98.4±1.9
	2.5	91.1	96.1	98.6	95.3±3.8
	1.3	99.5	96.7	96.2	97.5±1.8

n=3

Table 49 The urine concentrations (μmole) of daidzein glucuronides in six rats after oral administration of decoction (6 g/kg) of GGCLT in each time interval.

Time (hr)	rats						Mean± S.D.
	1	2	3	4	5	6	
0-2	0.1	0.2	0.0	0.0	N.D.	N.D.	0.0± 0.1
2-5	0.3	0.4	0.3	0.4	N.D.	0.1	0.2± 0.1
5-8	0.1	0.1	0.0	0.0	0.3	0.2	0.1± 0.1
8-12	0.7	0.3	0.1	0.7	0.0	0.0	0.3± 0.3
12-24	1.2	1.2	2.4	0.5	0.4	0.6	1.1± 0.8
24-34	0.1	0.3	0.2	0.1	0.1	0.1	0.2± 0.1
34-48	0.4	0.7	0.7	0.2	0.9	0.2	0.5± 0.3
48-58	0.1	0.2	0.1	0.3	0.2	0.1	0.2± 0.1
58-72	0.5	0.5	0.5	0.4	0.6	0.2	0.5± 0.1
Total	3.4	3.9	4.3	2.5	2.6	1.5	3.0± 1.0
% of dose	11.4	12.9	14.2	8.4	8.6	4.8	10.0± 3.4
$t_{1/2}$ (hr)	19.9	19.6	16.4	22.8	28.7	19.8	21.2± 4.2

N.D.：not detected

Table 50 The urine concentrations (μmole) of daidzein sulfates/glucuronides in six rats after oral administration of decoction (6 g/kg) of GGCLT in each time interval.

Time (hr)	rats						Mean± S.D.
	1	2	3	4	5	6	
0-2	0.1	0.2	0.0	0.0	N.D.	N.D.	0.1± 0.1
2-5	1.2	0.6	1.1	1.2	N.D.	1.4	0.9± 0.5
5-8	0.8	0.9	0.0	0.0	2.1	1.2	0.8± 0.8
8-12	1.3	2.2	0.9	1.7	0.4	0.3	1.1± 0.7
12-24	2.7	4.0	4.9	3.1	2.0	2.4	3.2± 1.1
24-34	0.4	0.8	0.7	1.1	1.1	0.6	0.8± 0.3
34-48	0.9	1.9	1.1	1.3	1.6	1.4	1.4± 0.3
48-58	0.8	0.5	0.5	0.3	0.8	0.8	0.6± 0.2
58-72	1.0	0.9	0.9	1.6	1.6	1.6	1.3± 0.4
Total	9.2	12.1	10.1	10.4	9.6	9.8	10.2± 1.0
% of dose	30.6	40.2	33.5	34.6	31.8	32.6	33.9± 3.4
$t_{1/2}$ (hr)	18.3	15.0	15.5	19.8	22.1	19.8	18.4±2.7

N.D.：not detected

Table 51 The urine concentrations (μmole) of baicalein glucuronides in six rats after oral administration of decoction (6 g/kg) of GGCLT in each time interval.

Time (hr)	rats						Mean± S.D.
	1	2	3	4	5	6	
0-2	0.0	0.0	N.D.	N.D.	N.D.	N.D.	0.0±0.0
2-5	0.1	0.1	0.2	0.3	N.D.	0.0	0.1±0.1
5-8	0.2	0.1	0.0	0.0	0.4	0.1	0.1±0.1
8-12	0.5	0.4	0.1	0.5	0.1	0.0	0.3±0.2
12-24	N.D.	0.5	1.5	0.7	0.4	0.2	0.5±0.5
24-34	0.0	N.D.	N.D.	N.D.	N.D.	N.D.	0.0±0.0
34-48	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0.0±0.0
48-58	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0.0±0.0
58-72	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0.0±0.0
Total	0.9	1.2	1.8	1.6	0.8	0.3	1.1±0.5
% of dose	0.4	0.6	0.9	0.8	0.4	0.2	0.6±0.3
$t_{1/2}$ (hr)	1.9	8.3	42.0	9.8	8.1	13.3	13.9±14.3

N.D.：not detected

Table 52 The urine concentrations (μmole) of baicalein sulfates/glucuronides in six rats after oral administration of decoction (6 g/kg) of GGCLT in each time interval.

Time (hr)	rats						Mean± S.D.
	1	2	3	4	5	6	
0-2	0.1	0.1	0.0	N.D.	N.D.	N.D.	0.0±0.0
2-5	0.5	0.2	0.5	0.1	N.D.	0.7	0.3±0.3
5-8	0.6	0.5	0.0	0.5	1.5	0.7	0.6±0.5
8-12	1.0	1.7	0.7	0.0	0.7	0.5	0.8±0.6
12-24	0.6	2.0	4.1	0.9	2.1	5.7	2.6±2.0
24-34	0.1	0.1	0.0	N.D.	0.2	0.2	0.1±0.1
34-48	0.1	0.1	0.1	0.0	0.1	0.1	0.1±0.0
48-58	0.0	0.0	0.0	N.D.	0.0	0.0	0.0±0.0
58-72	0.1	0.0	0.0	0.0	0.1	0.0	0.1±0.0
Total	3.1	4.8	5.5	1.5	4.8	8.0	4.6±2.2
% of dose	1.6	2.5	2.8	0.8	2.5	4.1	2.4±1.1
$t_{1/2}$ (hr)	9.8	7.5	7.2	6.5	9.2	6.7	7.8±1.4

N.D.：not detected

Table 53 The urine concentrations (μmole) of wogonin glucuronides in six rats after oral administration of decoction (6 g/kg) of GGCLT in each time interval.

Time (hr)	rats						Mean± S.D.
	1	2	3	4	5	6	
0-2	0.0	0.0	N.D.	N.D.	N.D.	N.D.	0.0±0.0
2-5	0.1	0.0	0.1	0.1	N.D.	N.D.	0.0±0.0
5-8	0.1	0.0	0.0	0.0	0.1	0.0	0.0±0.0
8-12	0.3	0.2	0.0	0.3	0.0	0.0	0.1±0.1
12-24	0.7	0.8	0.9	0.8	0.5	0.2	0.6±0.3
24-34	0.0	0.0	0.0	0.2	0.1	0.0	0.1±0.1
34-48	0.0	0.0	0.0	0.0	0.0	0.0	0.0±0.0
48-58	N.D.	N.D.	0.0	0.0	N.D.	N.D.	0.0±0.0
58-72	N.D.	N.D.	N.D.	N.D.	0.0	N.D.	0.0±0.0
Total	1.1	1.2	1.1	1.4	0.7	0.3	1.0±0.4
% of dose	16.9	17.9	16.0	21.3	10.7	5.3	14.7±5.7
$t_{1/2}$ (hr)	1.1	0.1	1.5	1.5	7.8	1.1	2.2±2.8

N.D.：not detected

Table 54 The urine concentrations (μmole) of wogonin sulfates/glucuronides in six rats after oral administration of decoction (6 g/kg) of GGCLT in each time interval.

Time (hr)	rats						Mean± S.D.
	1	2	3	4	5	6	
0-2	0.0	0.0	N.D.	N.D.	N.D.	N.D.	0.0± 0.0
2-5	0.1	0.0	0.1	0.2	N.D.	0.1	0.1± 0.1
5-8	0.1	0.1	0.0	0.0	0.3	0.2	0.1± 0.1
8-12	0.3	0.5	0.1	0.4	0.1	0.1	0.3± 0.2
12-24	0.8	1.1	1.1	1.4	0.8	1.4	1.1± 0.3
24-34	0.0	0.0	0.0	0.3	0.1	0.1	0.1± 0.1
34-48	0.0	0.0	0.0	0.0	0.0	0.1	0.0± 0.0
48-58	N.D.	N.D.	0.0	0.0	0.0	0.0	0.0± 0.0
58-72	N.D.	N.D.	N.D.	N.D.	0.0	0.0	0.0± 0.0
Total	1.4	1.9	1.3	2.3	1.4	2.0	1.7± 0.4
% of dose	21.9	28.4	20.1	34.5	21.2	30.4	26.1± 5.9
$t_{1/2}$ (hr)	1.0	4.5	4.6	4.7	2.0	2.0	3.1± 1.6

N.D.：not detected

Table 55 The urine concentrations (μmole) of daidzein glucuronides in six rats after oral administration of commercial extract I (6 g/kg) of GGCLT in each time interval.

Time (hr)	rats						Mean± S.D.
	1	2	3	4	5	6	
0-2	0.1	0.1	N.D.	N.D.	N.D.	N.D.	0.0±0.1
2-5	0.1	0.1	0.1	0.0	0.1	N.D.	0.1±0.0
5-8	0.1	0.1	0.0	0.1	0.1	0.2	0.1±0.1
8-12	0.2	0.2	0.2	0.0	0.1	N.D.	0.1±0.1
12-24	0.4	0.2	0.8	0.6	1.2	0.0	0.5±0.4
24-34	0.1	0.2	0.1	0.2	0.1	0.2	0.1±0.0
34-48	0.2	0.9	0.3	0.3	0.5	0.4	0.4±0.2
48-58	0.4	0.2	0.3	0.0	0.2	0.2	0.2±0.1
58-72	0.5	0.7	0.3	0.2	0.6	0.8	0.5±0.2
Total	2.2	2.6	2.0	1.5	2.9	1.8	2.1±0.5
% of dose	8.8	10.6	8.1	5.9	11.8	7.4	8.8±2.1
$t_{1/2}$ (hr)	32.7	31.3	20.9	16.3	23.7	49.2	29.0±11.7

N.D.：not detected

Table 56 The urine concentrations (μmole) of daidzein sulfates/glucuronides in six rats after oral administration of commercial extract I (6 g/kg) of GGCLT in each time interval.

Time (hr)	rats						Mean± S.D.
	1	2	3	4	5	6	
0-2	0.6	0.6	N.D.	N.D.	N.D.	0.0	0.2±0.3
2-5	0.8	0.5	1.1	0.0	1.3	N.D.	0.6±0.5
5-8	0.5	0.9	0.1	2.1	1.3	1.9	1.1±0.8
8-12	1.5	1.1	2.0	0.1	0.9	N.D.	0.9±0.8
12-24	1.7	2.1	3.9	4.3	1.9	0.5	2.4±1.4
24-34	1.2	1.3	1.0	1.0	1.1	0.7	1.1±0.2
34-48	0.9	1.6	1.4	1.2	1.3	0.8	1.2±0.3
48-58	0.8	0.8	0.5	0.5	0.6	0.5	0.6±0.1
58-72	1.6	1.6	1.4	0.9	0.8	0.8	1.2±0.4
Total	9.6	10.4	11.3	10.1	9.1	5.2	9.3±2.2
% of dose	39.0	42.7	46.3	41.2	37.3	21.0	37.9±8.9
$t_{1/2}$ (hr)	22.6	21.5	17.7	15.7	16.9	23.0	19.6±3.2

N.D.：not detected

Table 57 The urine concentrations (μmole) of baicalein glucuronides in six rats after oral administration of commercial extract I (6 g/kg) of GGCLT in each time interval.

Time (hr)	rats						Mean± S.D.
	1	2	3	4	5	6	
0-2	0.2	0.1	N.D.	N.D.	N.D.	N.D.	0.0±0.1
2-5	0.1	0.0	0.1	N.D.	0.1	N.D.	0.0±0.0
5-8	0.0	0.0	0.0	0.1	0.0	0.0	0.0±0.0
8-12	0.1	0.2	0.1	N.D.	0.0	N.D.	0.1±0.1
12-24	N.D.	N.D.	0.7	0.1	3.3	0.0	0.7±1.3
24-34	N.D.	0.3	N.D.	0.1	N.D.	0.3	0.1±0.1
34-48	N.D.	0.0	N.D.	N.D.	0.0	0.0	0.0±0.0
48-58	N.D.	N.D.	N.D.	N.D.	0.0	N.D.	0.0±0.0
58-72	N.D.	N.D.	N.D.	N.D.	0.0	0.0	0.0±0.0
Total	0.3	0.6	1.0	0.2	3.4	0.3	1.0±1.2
% of dose	0.2	0.3	0.5	0.1	1.8	0.2	0.5±0.6
$t_{1/2}$ (hr)	4.9	7.4	28.4	9.7	4.6	9.4	10.7±8.9

N.D.：not detected

Table 58 The urine concentrations (μmole) of baicalein sulfates/glucuronides in six rats after oral administration of commercial extract I (6 g/kg) of GGCLT in each time interval.

Time (hr)	rats						Mean± S.D.
	1	2	3	4	5	6	
0-2	0.3	0.4	N.D.	N.D.	N.D.	N.D.	0.1±0.2
2-5	0.4	0.2	0.6	0.0	0.7	N.D.	0.3±0.3
5-8	0.4	0.7	0.0	1.5	0.8	1.3	0.8±0.5
8-12	2.6	1.0	1.6	0.0	0.8	N.D.	1.0±0.1
12-24	1.0	1.6	2.9	2.6	2.9	0.5	1.9±0.1
24-34	0.1	0.1	0.0	0.0	0.1	0.2	0.1±0.0
34-48	0.0	0.1	0.1	0.1	0.0	0.0	0.1±0.0
48-58	0.0	0.0	0.0	0.0	0.0	0.0	0.0±0.0
58-72	0.1	0.1	0.0	0.0	0.0	0.0	0.1±0.0
Total	5.0	4.2	5.3	4.4	5.3	2.0	4.4±1.3
% of dose	2.7	2.3	2.9	2.4	2.9	1.1	2.4±0.6
$t_{1/2}$ (hr)	9.5	9.9	7.5	7.7	5.6	7.4	7.9±1.6

N.D.：not detected

Table 59 The urine concentrations (μmole) of wogonin glucuronides in six rats after oral administration of commercial extract I (6 g/kg) of GGCLT in each time interval.

Time (hr)	rats						Mean± S.D.
	1	2	3	4	5	6	
0-2	0.0	0.0	N.D.	N.D.	N.D.	N.D.	0.0±0.0
2-5	0.0	0.0	0.0	0.0	0.0	N.D.	0.0±0.0
5-8	0.0	0.1	0.0	0.1	0.0	0.0	0.0±0.0
8-12	0.1	0.2	0.1	0.0	0.1	N.D.	0.1±0.1
12-24	0.5	0.4	0.7	1.1	1.8	0.1	0.8±0.6
24-34	0.0	0.1	0.0	N.D.	0.0	0.1	0.0±0.0
34-48	0.0	0.0	0.0	0.0	0.0	0.0	0.0±0.0
48-58	0.0	0.0	0.0	N.D.	N.D.	0.0	0.0±0.0
58-72	N.D.	0.0	0.0	0.0	0.0	0.0	0.0±0.0
Total	0.7	0.8	1.0	1.2	2.0	0.2	1.0±0.11
% of dose	9.5	10.1	12.1	15.1	25.1	2.8	12.5±7.4
$t_{1/2}$ (hr)	4.9	8.7	6.9	5.8	5.1	9.7	6.8±2.0

N.D.：not detected

Table 60 The urine concentrations (μmole) of wogonin sulfates/glucuronides in six rats after oral administration of commercial extract I (6 g/kg) of GGCLT in each time interval.

Time (hr)	rats						Mean± S.D.
	1	2	3	4	5	6	
0-2	0.1	0.1	N.D.	N.D.	N.D.	0.0	0.0±0.0
2-5	0.1	0.1	0.2	0.0	0.2	N.D.	0.1±0.1
5-8	0.1	0.2	0.0	0.5	0.4	0.5	0.3±0.2
8-12	0.6	0.4	0.6	0.0	0.5	N.D.	0.4±0.3
12-24	1.1	1.1	1.7	2.3	1.4	0.3	1.3±0.7
24-34	0.1	0.1	0.2	0.0	0.1	0.3	0.1±0.1
34-48	0.0	0.0	0.0	0.0	0.0	0.0	0.0±0.0
48-58	0.0	0.0	0.0	0.0	N.D.	0.0	0.0±0.0
58-72	N.D.	0.0	0.0	0.0	0.0	0.0	0.0±0.0
Total	2.1	2.1	2.7	2.8	2.5	1.1	2.2±0.25
% of dose	27.0	26.3	34.5	36.0	32.2	14.1	28.3±8.0
$t_{1/2}$ (hr)	4.1	7.0	5.7	5.2	5.0	6.7	5.6±1.1

N.D.：not detected

Table 61 The urine concentrations (μmole) of daidzein glucuronides in six rats after oral administration of commercial extract II (6 g/kg) of GGCLT in each time interval.

Time (hr)	rats						Mean± S.D.
	1	2	3	4	5	6	
0-2	0.0	N.D.	N.D.	N.D.	0.0	N.D.	0.0± 0.0
2-5	0.1	N.D.	0.1	0.2	0.0	0.2	0.1± 0.1
5-8	N.D.	0.2	0.1	N.D.	0.2	0.0	0.1± 0.1
8-12	0.1	0.1	0.1	0.2	0.1	0.4	0.2± 0.1
12-24	0.4	0.7	0.3	0.8	0.2	0.5	0.5± 0.2
24-34	0.1	0.1	0.1	0.2	0.2	0.3	0.2± 0.1
34-48	0.8	0.7	0.4	0.7	0.2	0.3	0.5± 0.2
48-58	0.1	0.1	0.1	0.1	0.1	0.0	0.1± 0.0
58-72	0.4	0.8	0.2	0.4	0.3	0.5	0.5± 0.2
Total	2.1	2.7	1.5	2.4	1.2	2.3	2.0± 0.6
% of dose	16.6	22.2	11.8	19.8	9.8	18.3	16.4± 4.8
$t_{1/2}$ (hr)	25.4	30.1	22.0	21.5	27.1	24.0	25.0± 3.2

N.D.：not detected

Table 62 The urine concentrations (μmole) of daidzein sulfates/glucuronides in six rats after oral administration of commercial extract II (6 g/kg) of GGCLT in each time interval.

Time (hr)	rats						Mean± S.D.
	1	2	3	4	5	6	
0-2	N.D.	N.D.	N.D.	0.0	0.6	N.D.	0.1± 0.3
2-5	1.3	N.D.	1.2	1.4	0.6	1.9	1.1± 0.7
5-8	0.0	2.2	0.7	N.D.	0.7	0.0	0.6± 0.9
8-12	1.0	0.9	0.9	1.4	0.4	2.3	1.1± 0.6
12-24	2.1	3.3	1.9	2.3	1.5	3.0	2.3± 0.7
24-34	0.8	1.1	0.6	1.0	1.1	1.3	1.0± 0.3
34-48	2.0	1.7	1.5	N.D.	2.3	1.5	1.5± 0.8
48-58	0.8	0.8	0.9	0.5	1.2	0.5	0.8± 0.3
58-72	0.7	2.1	1.3	2.2	1.4	2.6	1.7± 0.7
Total	8.7	12.2	9.0	8.7	9.8	13.1	10.2± 1.9
% of dose	70.0	98.5	72.8	70.3	79.6	105.9	82.9± 15.6
$t_{1/2}$ (hr)	16.9	21.9	21.7	28.2	22.3	23.7	22.4± 3.6

N.D.：not detected

Table 63 The urine concentrations (μmole) of baicalein glucuronides in six rats after oral administration of commercial extract II (6 g/kg) of GGCLT in each time interval.

Time (hr)	rats						Mean± S.D.
	1	2	3	4	5	6	
0-2	N.D.	N.D.	N.D.	N.D.	0.0	N.D.	0.0±0.0
2-5	0.1	N.D.	0.1	0.2	0.0	0.2	0.1±0.1
5-8	N.D.	0.3	0.1	N.D.	0.7	N.D.	0.2±0.3
8-12	N.D.	0.1	0.2	N.D.	0.6	N.D.	0.1±0.2
12-24	0.8	N.D.	0.8	0.6	0.4	1.1	0.6±0.4
24-34	N.D.	0.1	0.1	N.D.	N.D.	0.1	0.0±0.1
34-48	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0.0±0.0
48-58	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0.0±0.0
58-72	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	0.0±0.0
Total	0.9	0.5	1.2	0.8	1.7	1.5	1.1±0.5
% of dose	0.9	0.5	1.2	0.8	1.7	1.5	1.1±0.5
$t_{1/2}$ (hr)	13.6	3.6	5.5	7.8	4.4	6.1	6.8±3.6

N.D.：not detected

Table 64 The urine concentrations (μmole) of baicalein sulfates/glucuronides in six rats after oral administration of commercial extract II (6 g/kg) of GGCLT in each time interval.

Time (hr)	rats						Mean± S.D.
	1	2	3	4	5	6	
0-2	N.D.	N.D.	N.D.	N.D.	0.2	N.D.	0.0±0.1
2-5	0.9	N.D.	0.8	1.2	0.2	1.3	0.7±0.5
5-8	0.0	2.3	0.9	N.D.	1.1	0.0	0.7±0.9
8-12	1.7	1.6	2.2	2.7	0.9	3.8	2.1±1.0
12-24	1.5	1.7	1.9	1.7	1.4	1.4	1.6±0.2
24-34	N.D.	N.D.	0.1	N.D.	N.D.	N.D.	0.0±0.0
34-48	0.1	0.1	0.1	0.1	0.1	0.1	0.1±0.0
48-58	0.0	0.1	0.1	0.0	0.0	N.D.	0.0±0.0
58-72	0.0	0.1	0.0	0.1	0.1	0.1	0.1±0.0
Total	4.3	5.9	6.1	5.9	4.2	6.7	5.5±1.0
% of dose	4.4	6.0	6.2	6.0	4.2	6.9	5.6±1.1
$t_{1/2}$ (hr)	8.1	2.0	7.4	2.0	9.1	7.0	6.0±3.1

N.D.：not detected

Table 65 The urine concentrations (μmole) of wogonin glucuronides in six rats after oral administration of commercial extract II (6 g/kg) of GGCLT in each time interval.

Time (hr)	rats						Mean± S.D.
	1	2	3	4	5	6	
0-2	0.0	0.0	0.0	0.0	N.D.	N.D.	0.0±0.0
2-5	0.1	N.D.	0.1	0.1	0.0	0.1	0.1±0.0
5-8	N.D.	0.1	0.1	N.D.	0.3	0.0	0.1±0.1
8-12	0.1	0.1	0.1	0.1	0.5	0.2	0.2±0.1
12-24	0.3	0.3	0.4	0.4	0.1	0.3	0.3±0.1
24-34	0.0	0.0	0.0	0.0	0.0	N.D.	0.0±0.0
34-48	N.D.	0.0	0.0	N.D.	0.0	N.D.	0.0±0.0
48-58	0.0	0.0	N.D.	0.0	0.0	0.0	0.0±0.0
58-72	0.0	0.0	N.D.	0.0	0.0	0.0	0.0±0.0
Total	0.5	0.5	0.6	0.6	1.0	0.6	0.6±0.2
% of dose	23.3	22.9	25.8	26.0	41.4	27.4	27.8±6.9
$t_{1/2}$ (hr)	0.7	1.1	1.1	0.7	0.7	9.3	2.3±3.5

N.D.：not detected

Table 66 The urine concentrations (μmole) of wogonin sulfates/glucuronides in six rats after oral administration of commercial extract II (6 g/kg) of GGCLT in each time interval.

Time (hr)	rats						Mean± S.D.
	1	2	3	4	5	6	
0-2	0.0	0.0	0.0	0.0	0.1	N.D.	0.0±0.0
2-5	0.3	N.D.	0.2	0.3	0.1	0.3	0.2±0.1
5-8	0.0	0.6	0.2	N.D.	0.5	0.0	0.2±0.3
8-12	0.7	0.5	0.4	0.8	0.6	1.6	0.7±0.4
12-24	0.9	1.4	1.0	0.6	0.0	1.3	0.9±0.5
24-34	0.0	0.1	0.1	0.0	0.0	N.D.	0.0±0.0
34-48	N.D.	0.0	0.0	0.1	0.2	0.1	0.1±0.1
48-58	N.D.	N.D.	0.1	0.0	0.1	0.0	0.0±0.0
58-72	0.0	N.D.	0.1	0.2	0.1	0.1	0.1±0.1
Total	1.9	2.6	2.1	1.9	1.5	3.5	2.2±0.7
% of dose	79.7	109.3	91.1	83.0	65.5	149.4	96.3±29.7
$t_{1/2}$ (hr)	9.7	4.3	13.5	14.4	16.1	10.6	11.4±4.2

N.D.：not detected

Table 67 Urinary excretion half-life of conjugate metabolites in six rats after intake of the decoction and commercial extracts of GGCLT

	Decoction	Commercial extract I	Commercial extract II
Daidzein S/G	18.4±2.7	19.6±3.2	22.4±3.6
Daidzein G	21.2±4.2	29.0±11.7 38 %	25.0±3.2
Baicalein S/G	7.8±1.4	7.9±1.6	6.0±3.1
Baicalein G	13.9±14.3	10.7±8.9	6.8±3.6
Wogonin S/G	3.1±1.6	5.6±1.1 81 %	11.4±4.2 268 %
Wogonin G	2.2±2.8	6.8±2.0 209 %	2.3±3.5