行政院國家科學委員會補助專題研究計畫 ■ 成 果 報 告 □期中進度報告

中藥黃酮多酚及其代謝產物之組織分佈、代謝物之製備及其與 carbamezepine 之交互作用與機制探討

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中　華　民　國　九十七　年　十　月　卅　日

中文摘要

化橘紅、槐花水煎劑富含柚皮苷與芸香苷等黃酮多酚，目前多酚之體外活性研究多針對黃酮多酚之非醣體。多酚口服後，主要代謝成 sulfates、glucuronides 等，此等代謝物之動力學或藥理活性尚鮮少報導。

Carbamazepine 為臨床常用之抗癲癇藥，治療指數狹窄其代謝與運輸排除與 CYPs、P-gp 及 MRP2 有關。近來許多研究顯示，黃酮多酚對 Pgp、CYP3A4 具調控作用，而且內源性或外源性的葡萄糖醛酸與硫酸代謝物於體內之轉運、外排與 MRPs 有關，因此吾人臆測併服黃酮多酚時，carbamazepine 之吸收與代謝可能受其影響，而且黃酮多酚所衍生之葡萄糖醛酸與硫酸等代謝物可能會與 carbamazepine 競搶 MRP2。

本計畫第二年以大鼠探討口服芸香科植物化橘紅及其成分柚皮苷、豆科植物槐花與其成分芸香苷對於口服 carbamazepine 之代謝動力學影響，利用 HPLC 定量血清中 Carbamazepine 及活性代謝物 Carbamazepine-10, 11-epoxide 之濃度。結果顯示，併服柚皮苷後 Carbamazepine 之血峰濃度(C_{max})顯著增加，而血藥曲線下面積(AUC_{0-t})及平均滯留時間(MRT)均未有顯著差異，Carbamazepine-10, 11-epoxide 之 C_{max}、AUC_{0-t} 及 MRT 均無顯著差異，僅血峰時間(T_{max})降低。併服化橘紅後 Carbamazepine 及 Carbamazepine-10, 11-epoxide 之 C_{max}、AUC_{0-t} 及 MRT 均無顯著差異，顯見其於大鼠體內暴露並無顯著影響。

大鼠併服單劑量槐花、柚皮苷、芸香苷，對口服 Carbamazepine 之血藥面積及血峰濃度皆顯著增加。因此為確保用藥安全，服用 Carbamazepine 的病患須避免併服芸香苷、柚皮苷及含此成分之中草藥。

關鍵字：Carbamazepine、化橘紅、槐花、柚皮苷、芸香苷、藥物動力學

英文摘要

Huajuhung (*Citrus grandis*) and Huaihua (*Sophora japonica* L.) contain naringin and rutin as their major constituents, respectively. Recent *in vitro* screenings for bioactivities of these flavonoid polyphenols almost focused on the aglycones. However, our previous studies on the biological fates of polyphenols indicated that sulfates and glucuronides were the major forms in circulation after oral intake.

Carbamezepine is an anti-epileptic with narrow therapeutic window. CBZ was known as substrates for Pgp, CYP3A4 and MRPs. Recent biochemical studies indicated that flavonoids may modulate Pgp and CYP3A4, and the transport of endogenous and xenobiotic sulfates and glucuronides were associated with MRP2. Therefore, we hypothesize that the intake of flavonoid may alter the absorption and disposition of carbamazepine, moreover, the sulfates and glucuronides of flavonoids may compete for MRP2 with carbamazepine. The 2nd year of this project investigated the interactions between the above-mentioned flavonoids and herbal decoctions with carbamazepine. HPLC method will be used for the assay of carbamazepine and carbamazepine-epoxide in blood. Statistical comparison will be used to analyze the difference between treatments. The results showed that naringin and Huajuhung exerted no conspicuous alteration on systemic exposure of carbamazepine and the active metabolite carbamazepine-10, 11-exposide. Only naringin significantly increased the C_{max} of carbamazepine. In addition, coadministration of Huaihua and rutin with carbamazepine, the C_{max} and AUC of carbamazepine and carbamazepine-10, 11-exposide would increase. The systemic exposure of carbamazepine was markedly enhanced by coadministrations of Huajuhung, Huaihua, naringin and rutin.

It is anticipated to provide important drug safety information, moreover, to develop a cocktail therapy using nontoxic herb to enhance the efficacy of CBZ. Therefore, patients treated with carbamazepine should avoid concurrent use naringin, rutin or Chinese herbs containing naringin, rutin in order to ensure the safety.

Key words: Carbamazepine, Huajuhung, Huaihua, naringin, rutin, pharmacokinetic

目錄

附圖目錄

附表目錄

前言

天然多酚之化學結構依碳骨架可分為 flavonoid、anthraquinone、lignan、isoflavone 及 aromatic acid 等類，主要以配醣體之形式廣泛存在於植物界，如植物、水果和蔬菜中。流行病學研究顯示，對於心血管系統、內分泌系統及癌症具有預防保護之良好效果(Anekonda & Reddy, 2004; Christofidou-Solomidou & Muzykantov; 2006; Doraiswamy, 2002; Dryden et al., 2006; Duarte et al., 2002; Fugh-Berman & Cott, 1999; Pan et al., 2003; Thelen et al., 2005; Van Meeteren et al., 2005)。現代藥理研究顯示，該類化學物質具有諸多生物活性例如抗氧化、抗發炎、抗過敏、抗病毒、抑制血小板凝集、抗腫瘤等 (Aherne & O'Brien, 1999; Bilto & Abdalla, 1998; Cushnie & Lamb, 2005; Goniotaki et al., 2004; Gryglewski et al., 1987; Jeong et al., 2005; Lindahl & Tagesson, 1997; Middleton & Drzewiecki, 1984; Pearce et al., 1984)。

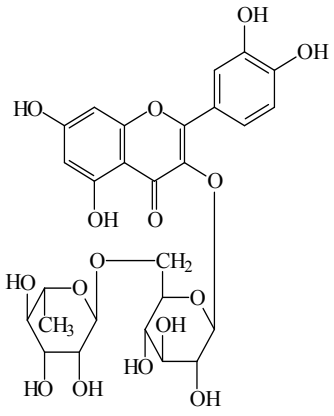
有關黃酮多酚的吸收、代謝、組織分佈等體內動力學真相，直到近幾年來才逐漸揭露，大鼠或人攝食後，黃酮配醣體於腸道中必須受腸內酵素或腸道細菌水解成較低極性的非醣體，方能被腸細胞吸收(Victor and Winter 1987; Mackey et al., 2002; Wilkinson et al., 2003; Bokkenheuser et al., 1987;)。然而，此些非醣體旋又受到腸及肝細胞之代謝，轉化成 sulfates、glucuronides 等結合態代謝物而循環於血中；此些代謝物部分從尿中排出，另有部分從膽汁排除後，旋而進入腸肝循環，重覆進入體中利用(Walle, 1997; Hanasaki et al., 1994; Li et al., 1997; Ratty and Das, 1988)，許多 sulfates 及 glucuronides 等結合態代謝物在體內之轉運、排泄與多藥物抗藥性蛋白如 MRP1、MRP2、MRP3 及負離子轉運蛋白如 OAT 等相關(Cui et al., 1999; Hirohashi et al., 1999; Kawabe et al., 1999; O'Leary et al., 2003; van Aubel et al., 1998; Grim et al., 2003; Emoyo et al., 2002) 。

中藥槐花為豆科植物槐 *Sophora japonica* L. 的乾燥花及花蕾，為中醫常用的收斂止血劑。其主成分為黃酮類成分 (rutin、quercetin、kaempferol、isorhamnetin、genistein、sophorin A)；皂苷及其苷元 (betulin、sophoradiol、soyasaponin、kaikasaponin)；其它成分 (tannin、vitamine 等)。槐花含有豐富具生物活性之黃酮類配醣體－芸香苷。芸香苷口服後經腸內菌水解成其苷元－槲皮素，隨即再代謝成硫酸及葡萄糖醛酸結合態代謝物，循環於全身。芸香苷能保持毛細血管正常的抵抗力，減少血管通透性，可使因脆性增加而出血的毛細血管恢復正常的彈性 (董艷芬與李堅，2001)。抗炎作用及抑菌(江蘇新醫學院，1997；黃敏，2000)抗病毒、真菌作用(Wacker and Eilmers, 1978)對心血管系統則產生刺激心臟擴張血管及抑制血小板凝集(Hitoshi et al., 1987)。

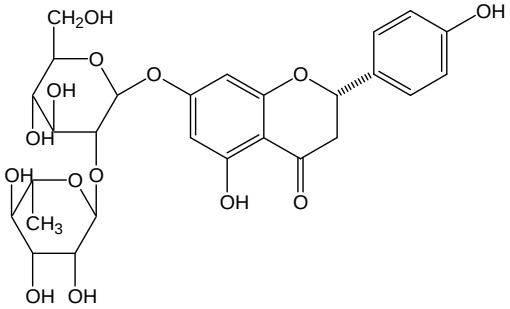
化橘紅為芸香科(Rutaceae)植物化州柚 *Citrus grandis* (L.) Osbeck var. tomentosa 或柚 *Citrus grandis* (L.) Osbeck 之成熟或未成熟乾燥果皮，其味苦辛性溫。現代藥理作用研究指出其具抑制豚鼠支氣管平滑肌收縮、降血脂(Gorinstein et al., 2004)及抗高血壓之作用(Reshef et al., 2005)。其主成分為黃酮類成分 (naringin, narigenin, neohesperidin, poncirin, furanocoumarins)、揮發油(citral, geraniol, limalool, limomene, cadinene, dipenten 及 methlanthranilate 等)，以及其他成分如 stachydrine, cis-3-hexenol, aurapten 等(Pallati et al., 2004; Mokbel and Suganuma, 2006)。Naringin 為 flavanones 主要存在於柑橘屬植物，如葡萄柚的果皮及果肉，中藥枳實、枳殼及化橘紅。其具抗氧化、降低膽固醇、預防癌症、抗菌、抗過敏等作用。柚皮苷具有清除自由基、抑制 xanthine oxidase 活性、抗脂質過氧化、保護 DNA 免於裂解、抗氧化作用、提高血漿高密度脂蛋白、抑制 HMG-CoA reductase 活性、降低血漿及肝臟膽固醇、抗潰瘍、預防肺癌、腸胃道解痙及抑制反應性抗體（reagenic antibody）產生的被動皮膚過敏反應等作用。此外，柚皮苷對酵母菌與真菌有抑制作用，對

細菌有抗突變作用。另外，投予 500 mg naringin 於人體無不良反應，服用單劑量 2 g 後，亦無毒性反應。

Carbamazepine 為抗癲癇藥物、用於大發作、精神運動型癲癇與混合行發作及治療三叉神經痛藥物，具有抗膽鹼激素、抗利尿、肌肉鬆弛及心律不整等活性(Brodie and Dichter, 1996; Tibballs, 1992)。常見副作用以鎮靜暈眩疲勞等中樞神經系統問題，噁心嘔吐等腸胃道問題，視覺模糊及震顫等勢力問題為主，另有皮膚及 Stevens-Johnson symdrome 等 (Tibballs, 1992; Keating and Blahunka, 1995)。於體內吸收完全口服生可用率達 85%，4-8 小時達血中最高濃度(Bertilsson and Tomson et al., 1986; Levy and Kerr, 1988)。蛋白質結合率 76%，可通過胎盤蓄積胎兒體內(Rane et al., 1975)。於肝臟受 CYP3A4 之代謝，形成具藥理活性之 Carbamazepine-10, 11-epoxide 及其 N-或 O-glucuronides，多以代謝物排除僅少量原形(3%)，Carbamazepine-10, 11-epoxide 血中蛋白質結合率為 50-60%，主要由尿液(72%)及糞便(28%)排除(Bertilsson and Tomson et al., 1986; Levy and Kerr, 1988)。其於體內之轉運與 MRPs 有關。



Rutin



Naringin

藥物動力學研究指出，這些富含黃酮類成分之中藥及其成分，於大鼠體內主要以其硫酸及葡萄糖醛酸結合態代謝物之型態存再於血液循環中。更有報告指出硫酸及葡萄糖醛酸結合態代謝物之轉運及外排與 MRP2 及 OATs 等有關(van Aubel et al., 1998; Grim et al., 2003; Emoyo et al., 2002 ; Gibbs et al., 2004 ; Kruh and Belinsky, 2003)。因而，吾人推論含柚皮苷 (narigin)及芸香苷 (rutin) 之藥物，可能競爭該等運送蛋白而與 carbamazepine 產生交互作用，預期將會提升西藥之血中濃度而增加療效或毒性。

本研究以大鼠探討柚皮苷與化橘紅水煎劑、芸香苷與槐花水煎劑對 carbamazepine 動力學之影響，研究皆以平行設計進行，分別予以單獨口服 carbamazepine 及併服柚皮苷與化橘紅水煎劑、芸香苷與槐花水煎劑。給藥後特定時間點心臟採血，以 HPLC 分析法測定血清中 Carbamazepine 及 Carbamazepine-10, 11-epoxide 濃度。

一、中藥水煎劑、黃酮多酚溶液之製備

1. 化橘紅及槐花水煎劑

精確稱取化橘紅及槐花各 250 g，加入 5 L 一次水靜置半小時，於瓦斯爐上加熱至沸騰，沸騰後轉為小火繼續加熱至體積減至 2.5 L 以下，以紗布趁熱過濾取濾液後，將藥渣濾除，濾液以小火繼續煎煮至體積低於 500 mL，加水定容至 500 mL，混合均勻後分裝於 50 mL 離心管，置於-30℃冰存備用。

上述水煎劑並分別以 HPLC 定量所含黃酮多酚含量，化橘紅所定支指標成分為 narigin 及 narigenin；而槐花則為 rutin 與 quercetin。

2. 柚皮苷與芸香苷溶液

(1) 精確稱取芸香苷，加熱水定容後以超音波震盪，配製 50 mg/mL 的柚皮苷溶液。
(2) 使用前新鮮製備。精確稱取 400 mg 之芸香苷，加熱水定容至 10.0 mL，超音波震盪，得 40 mg/mL 的芸香苷溶液。

二、口服中藥黃酮多酚對 carbamazepine 動力學之影響

1. 血清標準溶液之製備及定量前處理

分別精確稱取carbamazepine 與 carbamazepine epoxide，以甲醇溶解並稀釋定容，製備介於 4.0～1000.0 g/mL 間九種濃度標準溶液，各取 100 µL 標準溶液，加入 900 µL 空白血清，得濃度分別為 0.4、0.8、1.6、3.1、6.3、12.5、25.0、50.0 及 100.0 µg/mL 之血清標準溶液。

2. 檢量線之繪製

取 100 µL 血清標準溶液，加 100 µL含內標準 (2.0 µg/mL 5,7-dimethoxycoumarin) 之乙酸乙酯萃取，用試管振盪器振盪 20 秒後高速離心 (9860 *g*) 15 分鐘，取乙酸乙酯層，用氮氣吹乾後，以 50 µL 氯甲烷溶解，取 20 µL 供 HPLC 分析。

3. 給藥與採血

(1) 口服化橘紅與柚皮苷對 carbamazepine 動力學之影響

實驗前禁食 12 小時，給藥設計採交叉試驗模式。將大白鼠隨機分成三組，第一組以胃管投予 carbamazepine (400 mg/kg)，第二、三組分別投予柚皮苷溶液 213.2 mg/kg (367 µmol/kg)，或化橘紅水煎劑 2 g/kg 後併服 carbamazepine。單服 carbamazepine 組則併服等體積的水。

口服投藥後於 10、30、60、120、240、480、720、1440、2160、2880、3600 和 4320 分鐘，以心臟穿刺採血。每次採血量為 0.4 mL，將血液檢品置於微量離心管，高速離心 (9860 *g*) 15 分鐘，貯存於 -30 ℃，俟後分析。

(2) 口服化橘紅與柚皮苷對 carbamazepine 動力學之影響

實驗前禁食12小時，給藥設計採交叉試驗模式。將大白鼠隨機標記每組六隻以上，第一組槐花水煎劑組，分成對照組單服carbamazepine 400 mg/kg與carbamazepine並服槐

花水煎劑2 g/kg組、4 g/kg組，第二組芸香苷組，分成對照組單服carbamazepine 400 mg/kg與CBZ並服芸香苷160 mg/kg組、320 mg/kg組，每次給藥至少間隔兩週之wash out後。單服carbamazepine時則併服等體積的水。

口服投藥後於10、30、60、120、240、480、720、1440、2160、2880和4320分鐘，以心臟穿刺採血。每次採血量為0.5 mL，將血液檢品置於微量離心管，高速離心 (10000 *g*) 15 分鐘，貯存於 -30 ℃，俟後分析。

4. 血清檢品之前處理及定量

血清中 carbamazepine及其 epoxide 之定量係取 100 μL 血清檢品，加100 μL 含內標準 (2.0 g/mL 5,7-dimethoxycoumarin) 之乙酸乙酯萃取，用試管振盪器振盪 20 秒後高速離心 (9860 *g*) 15 分鐘，取乙酸乙酯層，用氮氣吹乾後，以 50 μL 氰甲烷溶解，取 20 μL 供 HPLC 分析。

5. 高效液相層析分析條件

層析管：Apollo ® C18, 5 μm (150 × 4.6 mm)

流速：1.0 mL/min

檢測波長：214 nm

移動相：氰甲烷：0.1 % 磷酸 (45:55, v/v) 之混合液

6. 分析系統及方法之確效

(1). 精密度 (precision)

將各濃度之血清標準溶液，分別於同日內早、午、晚及連續三日之異日間各進行一次層析，並以獲得之檢量線方程式求得每次實驗濃度。以三次同日內及三次異日間實驗濃度分別求其平均值 (mean)、標準偏差 (standard deviation, S.D.)及變異係數 (coefficient of variation, C.V.)。

(2). 準確度 (accuracy)

同日內三次及異日間三次實驗濃度平均值與理論濃度間之相對誤差(relative error) 表示之。

(3). 靈敏度 (sensitivity)

將 naringenin 血清標準溶液一再稀釋，直到其波峰為雜訊三倍之濃度為偵測極限。

(4). 回收率 (recovery)

將 CBZ、CBZ epoxide 標準溶液 (溶於甲醇)，分別加入空白血清及水中，製備 100.0, 6.3 及 0.4 μg/mL 等三種濃度之血清及水標準溶液各三份，所測得之血清標準溶液之波峰面積比值除以各對應濃度之水標準溶液之波峰面積比值，即為回收率。

7. 數據分析

以 WINNONLIN (version 1.1, SCI software, Statistical Consulting Inc., Apex, NC, USA) 之非室性模式計算 CBZ 之藥物動力學參數，以 one way ANOVA with Sheffe's test 檢定各組間之差異性。

結果與討論

本研究探討口服併用化橘紅與其主成分柚皮苷、槐花及其主成分芸香苷對 Carbamazepine 動力學之影響。

一、carbamazepine 與 Carbamazepine -10, 11-epoxide 分析方法

本研究利用 HPLC 定量 carbamazepine 與 Carbamazepine-10, 11-epoxide 之經時變化，所採用之高效液相層析條件係以乙腈：0.1 %磷酸溶液（45：55, v/v）混液為移動相，流速為 1.0 mL/min，檢測波長 214 nm。以 5, 7-dimethoxycoumarin 為內部標準品。結果顯示定量 carbamazepine 與 Carbamazepine-10, 11-epoxide 之方法在同日內及異日間皆有良好之精確度，其變異係數（C.V.）值均小於 10 %，相對誤差(relative error)均小於 14 % (Table 1 與 Table 2)。Carbamazepine 與 Carbamazepine-10, 11-epoxide 之回收率(recovery)分別為 94.5~98.3 %、92.7~97.8 %、101.4~105.1 %、96.5~104.7 %如 Table 3~4 所示。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。

二、口服化橘紅、柚皮苷對 carbamazepine 動力學之影響

化橘紅水煎劑 naringin 含量為 1739.1 μg/g 及 naringenin 含量為 20.5 μg/g。

單服 Carbamazepine 約 2.5 小時達血峰濃度，其活性代謝物 Carbamazepine-10, 11-epoxide 則約 48 小時達血峰濃度(Table 5 與 Table 6)。

大鼠併服 naringin (213 mg/kg)後，其 Carbamazepine 之 Carbamazepine 之血峰濃度(C_{max})顯著增加，而血藥曲線下面積(AUC_{0-t})及平均滯留時間(MRT)均未有顯著差異，Carbamazepine -10, 11-epoxide 之 C_{max}、AUC_{0-t} 及 MRT 均無顯著差異，僅血峰時間(T_{max})降低。Carbamazepine 及 Carbamazepine-10, 11-epoxide 之 C_{max}、AUC_{0-t} 及 MRT 均無顯著差異，顯見其於大鼠體內暴露並無顯著影響(Figure 1 與 2；Table 7 與 Table 8)。併服化橘紅後 Carbamazepine 及 Carbamazepine-10, 11-epoxide 之 C_{max}、AUC_{0-t} 及 MRT 均無顯著差異(Figure 1 與 2；Table 9 與 Table 10)，顯見其於大鼠體內暴露並無顯著影響(Table 11 與 Table 12)。

文獻報導 Carbamazepine 於為中之吸收率受劑型、物化性質、在胃中之溶離及胃排空率之影響(Morselli et al., 1975; Levy et al., 1975)，因而與 naringin 併用時因而增加其吸

收速率加快藥效作用，因而其併用之安全性應進一步評估。Carbamazepine 多於肝臟代謝僅約 3%以原形排除(Petit et al., 1991; Lertrananangkoon and Horning, 1982)，其於體內主要轉化為 Carbamazepine-10, 11-epoxide (Kerr et al., 1991)，再由 microsomal epoxide hydrolase 水解成 trans-dihydrodiol，而 Carbamazepine-10, 11-epoxide 為具活性之代謝產物(Bertilsson et al., 1986)。化橘紅水煎劑含大量 naringin 及苷元 naringenin 可競爭外排運輸蛋白，另化橘紅含 furannocoumarins 可抑制腸中 CYP3A4 活性，因此臆測應可增加 Carbamazepine 之暴露，但本實驗結果未達顯著差異。

三、口服槐花及芸香苷對 carbamazepine 動力學之影響

併服槐花後，高劑量組(4 g/kg)對於大鼠之 Carbamazepine 及 Carbamazepine -10, 11-epoxide 之 C_{max} 及 AUC_{0-t} 顯著增加，另低劑量組(2 g/kg)之 C_{max} 亦顯著升高，而 MRT 均無顯著差異，顯見槐花可增加大鼠體內之暴露(Figure 5 and Table 13)。

大鼠併服 rutin 後，高劑量組(320 mg/kg)之 Carbamazepine 之 C_{max} 及 AUC_{0-t} 顯著增加，而低劑量組(160 mg/kg)之 Carbamazepine 及 Carbamazepine -10, 11-epoxide 之 AUC_{0-t} 均顯著增加，至於 MRT 無論槐花高低劑量，無論於 Carbamazepine 及 Carbamazepine -10, 11-epoxide 均未有顯著差異(Figure 6 and Table 14)。

Carbamazepine 為 CYP3A4、P-gp 及 MRP2 之受質，口服芸香苷配醣體後會於體內代謝成負離子之 sulfates 與 glucuronide，在體內與 Carbamazepine 競爭排除，使 Carbamazepine 滯留於體內的時間延長。有報告指出 sulfates、glucuronides 與 MRP2 有關(Chu et al., 2004; Phillip et al., 2004; Akiko et al., 2000)，因而推測口服後之結合態代謝物對 Carbamazepine 產生抑制排除作用可能與 MRP2 有關。另外芸香苷於體內會水解形成其苷元槲皮素，，並以槲皮素結合態代謝物及極少量的槲皮素苷元之形式存在於血中，槲皮素會抑制 P-gp 及 CYP3A 的活性(Sarkar, 1997) 槲皮素亦有誘導 P-gp 之報導(Critchfielset al., 1994)，Carbamazepine 之血中濃度應降低，但實驗結果與此相反，其交互作用另有其他機轉存在，值得更進一步研究。

實驗進行中發現，Carbamazepine 與化橘紅、柚皮苷併用時，大鼠昏睡時間顯著較單服 Carbamazepine 長，此現象是否與柚皮苷結合態代謝物競爭 BBB 上之外排運輸蛋

白有關，使 Carbamazepine 及其代謝物滯留腦中失量增加以致大鼠昏睡。此一機轉應再進一步研究及討論。

Carbamazepine 為中樞抑制劑，治療癲癇大發作及運動型癲癇以及三叉神經痛，可穿透 BBB，其副作用為口乾、頭暈、嗜睡、運動失調等，較嚴重之副作用包含 Stevens-Johnson syndrome、骨髓抑制、心臟傳導異常等，為 2003 年台灣地區申請藥害救濟第一位(高與戴，2003)，因此其與中藥之交互作用不容小覷。

結論

1. 大鼠併服narigin後Carbamazepine之血峰濃度顯著增加，Carbamazepine及Carbamazepine -10, 11-epoxide之暴露則無顯著影響。併服化橘紅後Carbamazepine及Carbamazepine -10, 11-epoxide之血峰濃度、暴露均無顯著影響。
2. 大鼠併服槐花後，Carbamazepine及Carbamazepine -10, 11-epoxide之血峰濃度、曲線下面積均顯著增加。併服rutin後Carbamazepine及Carbamazepine -10, 11-epoxide之血峰濃度與曲線下面積亦顯著增加，平均滯留時間俱未受影響。併服槐花與rutin對大鼠之Carbamazepine暴露均顯著增加。
3. 為確保用藥安全，服用 Carbamazepine 的病患須避免併服芸香苷、柚皮苷及含此成分之中草藥。

誌謝

本計畫案由本計畫總主持人李珮端教授實驗室完成及提供結果，謹此致謝。

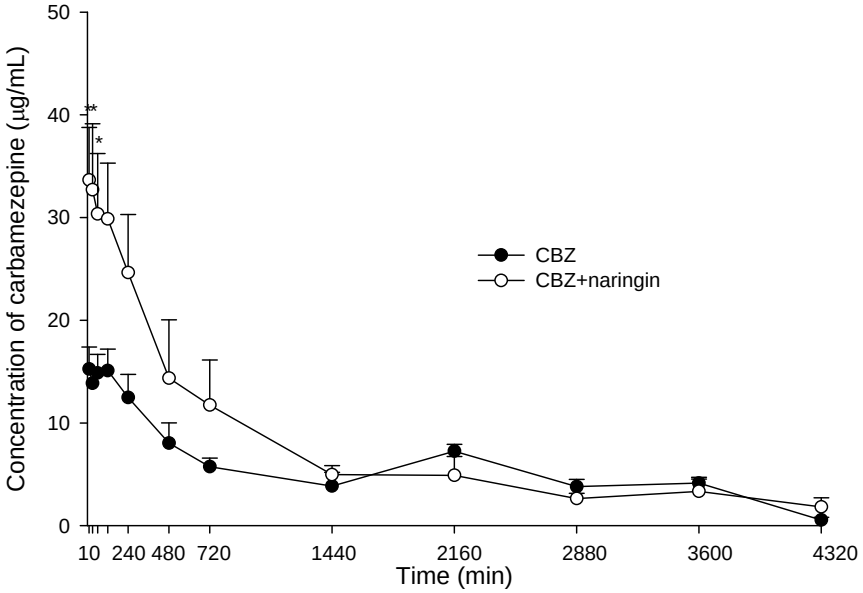


Figure 1. Serum concentration-time profiles of CBZ (mean±S.E.) after oral administration of CBZ alone (400 mg/kg) (●) and coadministrations with 213 mg/kg naringin (○).

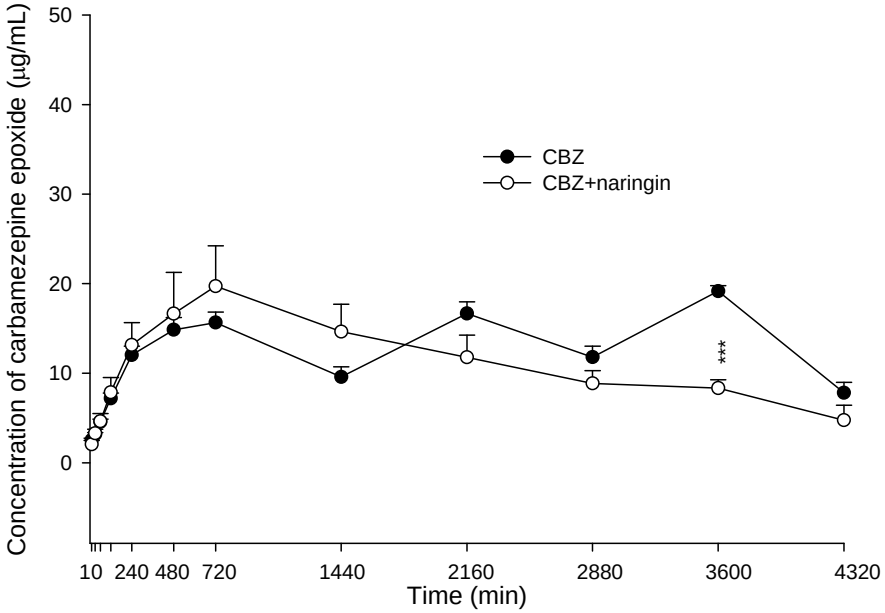


Figure 2. Serum concentration-time profiles of CBZ epoxide (mean±S.E.) after oral administration of CBZ alone (400 mg/kg) (●) and coadministrations with 213 mg/kg naringin (○).

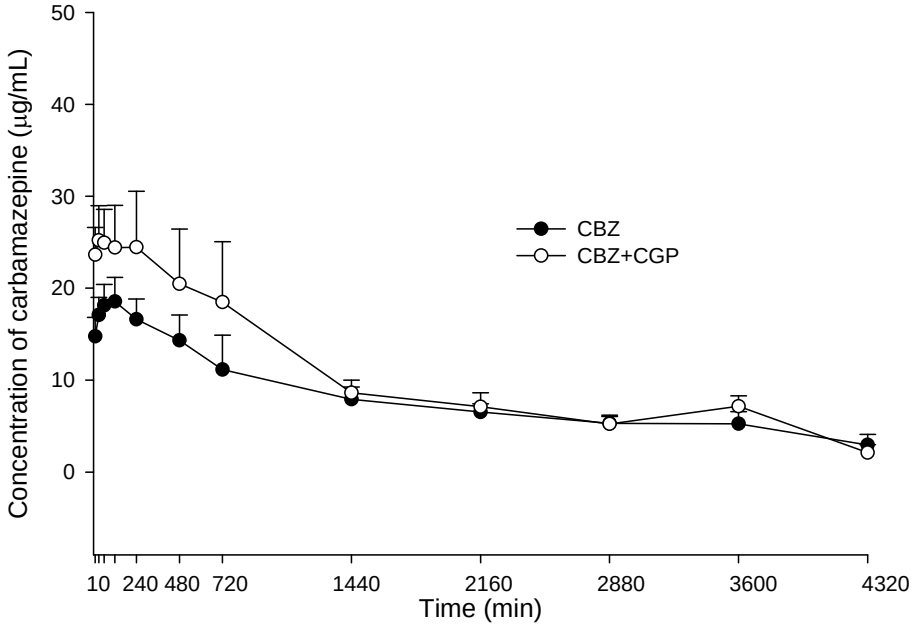


Figure 3. Serum concentration-time profiles of CBZ (mean±S.E.) after oral administration of CBZ alone (400 mg/kg) (●) and coadministrations with 2 g/kg CGP (○).

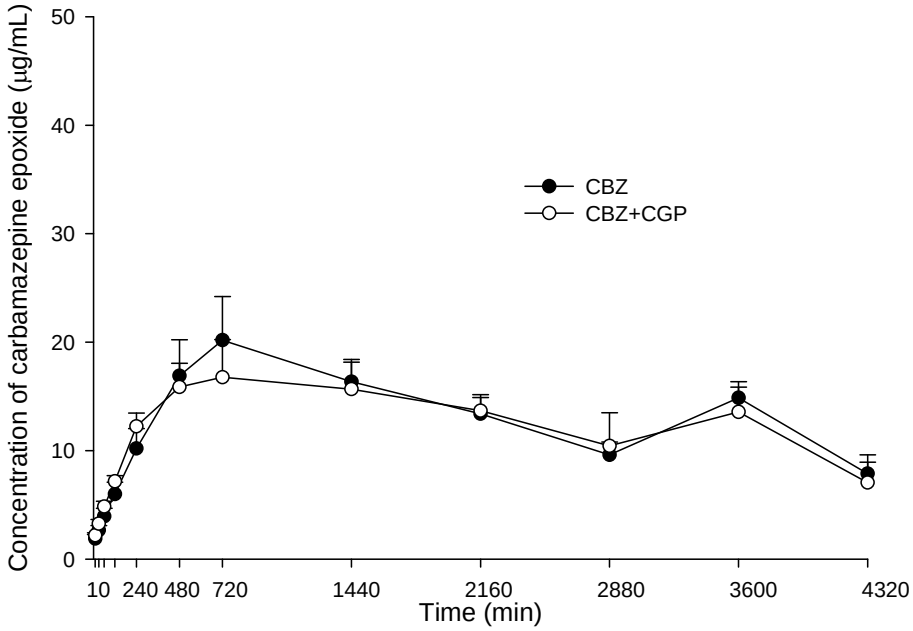
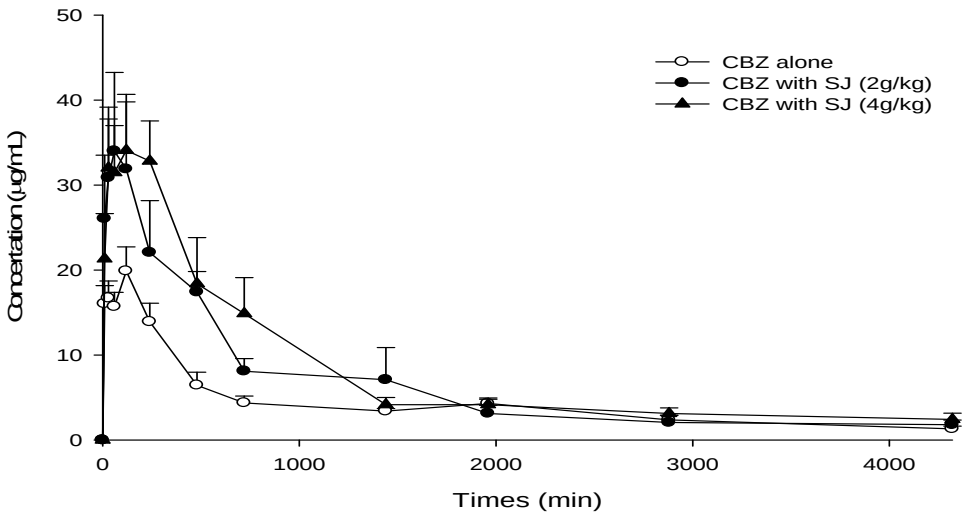


Figure 4. Serum concentration-time profiles of CBZ epoxide (mean±S.E.) after oral administration of CBZ alone (400 mg/kg) (●) and coadministrations with 2 g/kg CGP (○).

(a)



(b)

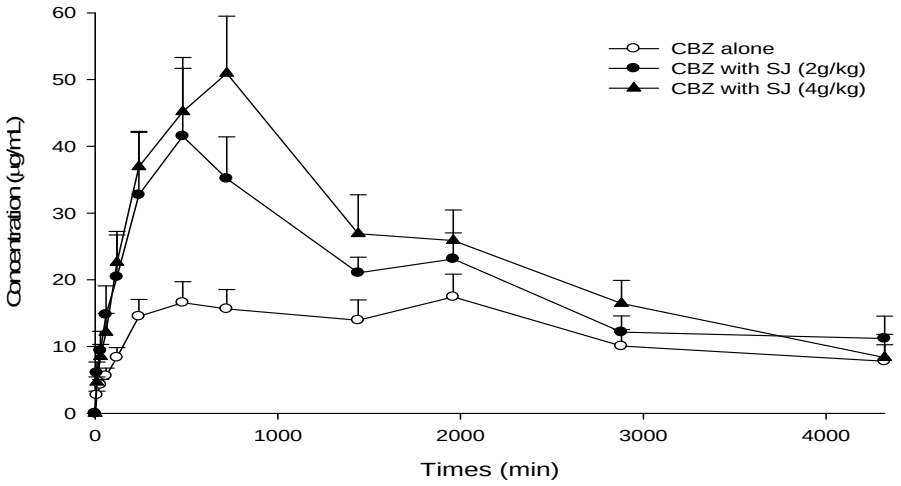


Figure 5. Mean (±S.E.) serum concentration-time profiles of CBZ (a) and CBZ epoxide (b) after oral administration of CBZ alone (400 mg/kg) (○), coadministration with 2 g/kg (●) and 4 g/kg (▲) of SJ decoction in seven rats.

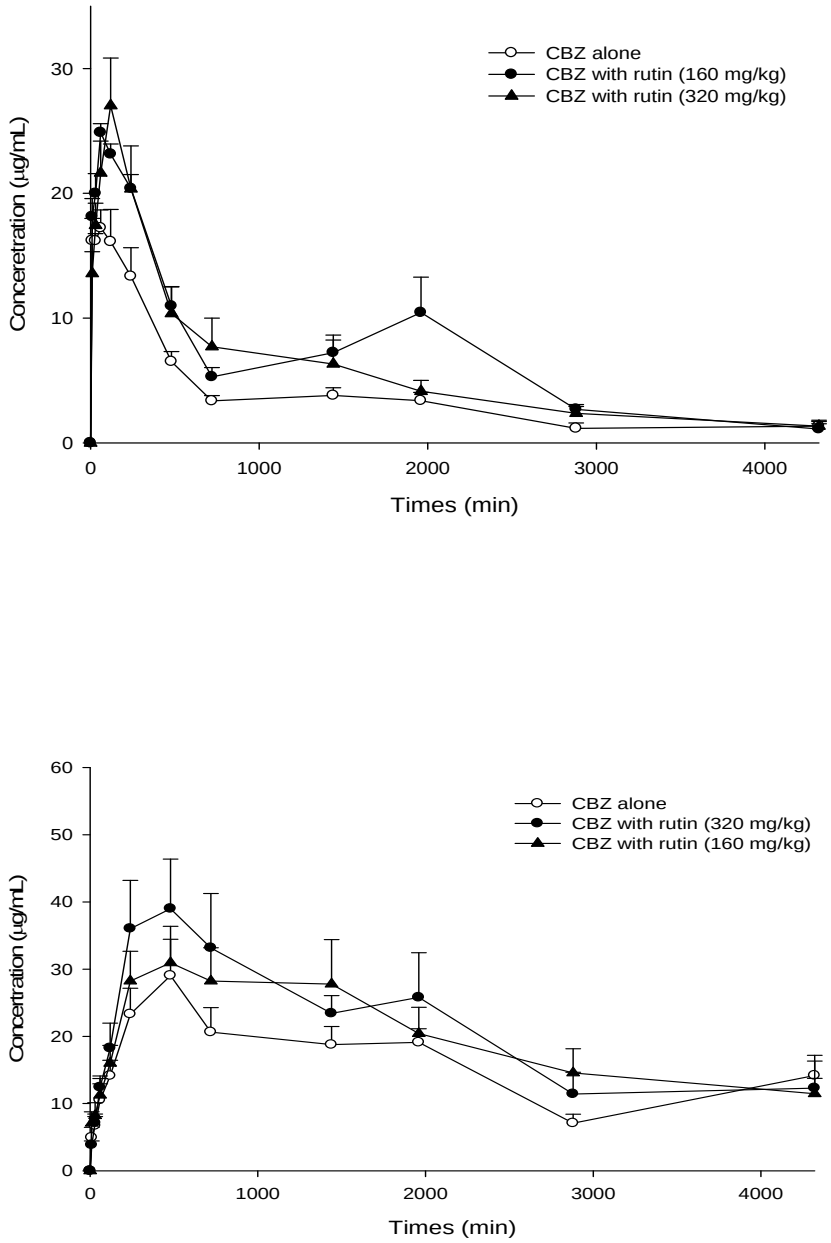


Figure 6. Mean (±S.E.) serum concentration-time profiles of CBZ (a) and CBZ epoxide (b) after oral administration of CBZ alone (400 mg/kg) (○), coadministration with 160 mg/kg (●) and 320 mg/kg (▲) of SJ decoction in seven rats.

Table 1. Intraday and interday analytical precision and accuracy of CBZ in serum by HPLC analysis

Conc. (μg/mL)	Intra-day			Inter-day		
	Precision		Accuracy	Precision		Accuracy
	Mean ± S.D.	(C.V.%)	Relative error (%)	Mean ± S.D.	(C.V.%)	Relative error (%)
0.4	0.44 ± 0.01	(1.9)	12.7	0.46 ± 0.01	(1.3)	13.0
0.8	0.82 ± 0.01	(0.0)	5.4	0.83 ± 0.02	(0.3)	6.4
1.6	1.67 ± 0.03	(1.6)	6.8	1.57 ± 1.17	(0.4)	0.4
3.1	3.30 ± 0.02	(0.7)	5.6	3.28 ± 1.05	(4.9)	4.9
6.3	6.54 ± 0.04	(0.6)	4.6	6.38 ± 0.86	(2.0)	2.0
12.5	13.47 ± 0.02	(0.2)	7.7	13.31 ± 0.50	(6.5)	6.5
25.0	27.77 ± 0.04	(0.1)	11.1	27.50 ± 0.07	(1.0)	10.0
50.0	54.57 ± 0.03	(0.1)	9.1	54.31 ± 0.20	(8.6)	8.6
100.0	98.54 ± 0.15	(0.2)	-1.5	98.57 ± 0.20	(-1.4)	-1.4

Table 2. Intraday and interday analytical precision and accuracy of CBZ epoxide in serum by HPLC analysis

Conc. (μg/mL)	Intra-day			Inter-day		
	Precision		Accuracy	Precision		Accuracy
	Mean ± S.D.	(C.V.%)	Relative error (%)	Mean ± S.D.	(C.V.%)	Relative error (%)
0.4	0.34 ± 0.01	1.86	-12.0	0.33 ± 0.01	3.59	-13.4
0.8	0.71 ± 0.01	0.44	-9.5	0.67 ± 0.03	4.50	-13.7
1.6	1.50 ± 0.02	1.40	-4.2	1.46 ± 0.01	0.70	-6.5
3.1	3.36 ± 0.01	0.34	7.6	3.17 ± 0.05	1.72	1.4
6.3	6.04 ± 0.06	1.03	-3.4	6.15 ± 0.02	0.39	-1.6
12.5	12.66 ± 0.12	0.98	1.2	12.85 ± 0.11	0.83	2.8
25.0	24.82 ± 0.27	1.11	-0.7	25.29 ± 0.25	0.98	1.2
50.0	50.30 ± 0.06	0.12	0.6	49.72 ± 0.58	1.17	-0.6
100.0	99.88 ± 0.80	0.80	-0.1	100.03 ± 0.30	0.30	0.0

Table 3. Recovery (%) of CBZ from rat serum (n=3)

Conc. (μg/mL)	1	2	3	Mean± S.D.
0.4	95.5	92.5	98.2	95.4± 2.8
6.3	94.5	97.3	96.9	96.3± 1.5
100.0	95.5	96.4	98.3	96.7± 1.4

Table 4. Recovery (%) of CBZ epoxide from rat serum (n=3)

Conc. (μg/mL)	1	2	3	Mean± S.D.
0.4	93.6	92.7	93.3	93.2± 0.5
6.3	94.2	97.8	96.4	96.2± 1.8
100.0	96.3	97.5	97.2	97.0± 0.6

Table 5. Individual pharmacokinetic parameters of CBZ after oral administration of 400 mg/kg CBZ alone to six rats

Parameter \ Rat	1	2	3	4	5	6	Mean ± S.E
$AUC_{0\text{-}4320}$ ($\mu mol \cdot min \cdot mL^{-1}$)	161.8	125.9	145.3	217.7	89.9	122.5	143.8± 17.8
C_{max} ($nmol \cdot mL^{-1}$)	114.3	111.5	95.0	94.7	45.5	86.5	91.2± 10.1
T_{max} (min)	720.0	60.0	120.0	480.0	10.0	60.0	241.7± 118.3
MRT (min)	1289.6	1409.3	1488.3	1751.8	1722.8	1917.1	1596.5± 97.3

Table 6. Individual pharmacokinetic parameters of CBZ epoxide after oral administration of 400 mg/kg CBZ alone to six rats

Parameter \ Rat	1	2	3	4	5	6	Mean± S.E
$AUC_{0\text{-}4320}$ ($\mu mol \cdot min \cdot mL^{-1}$)	246.0	264.5	163.1	203.4	219.5	289.1	230.9± 18.5
C_{max} ($nmol \cdot ml^{-1}$)	88.3	85.9	51.8	61.4	61.3	154.3	83.8± 15.3
T_{max} (min)	1440.0	3600.0	1440.0	4320.0	3600.0	720.0	2520.0± 609.5
MRT (min)	1968.1	2077.6	2110.1	2283.0	2155.7	1691.7	2047.7± 82.6

Table 7. Individual pharmacokinetic parameters of CBZ after oral coadministration of 400 mg/kg CBZ with naringin (213 mg/kg) to six rats

Parameter \ Rat	1	2	3	4	5	6	Mean ± S.E
AUC_{0-4320} ($\mu mol \cdot min \cdot mL^{-1}$)	138.2	88.1	197.9	183.9	265.6	218.6	182.1 ± 25.4
C_{max} ($nmol \cdot mL^{-1}$)	113.2	50.5	128.0	128.6	172.6	157.4	125.0 ± 17.3
T_{max} (min)	30.0	10.0	120.0	60.0	120.0	480.0	136.7 ± 71.1
MRT (min)	1688.2	1851.0	1170.0	1920.7	1163.2	1195.8	1498.1 ± 147.2

Table 8. Individual pharmacokinetic parameters of CBZ epoxide after oral coadministration of 400 mg/kg CBZ with naringin (213 mg/kg) to six rats

Parameter \ Rat	1	2	3	4	5	6	Mean ± S.E
AUC_{0-4320} ($\mu mol \cdot min \cdot mL^{-1}$)	240.8	242.2	187.9	213.8	266.8	151.6	217.2 ± 17.1
C_{max} ($nmol \cdot mL^{-1}$)	86.3	80.6	87.5	61.3	124.2	43.5	80.6 ± 11.2
T_{max} (min)	2880.0	3600.0	720.0	480.0	720.0	480.0	1480.0 ± 566.0
MRT (min)	2015.8	2315.5	1631.8	2216.2	1631.0	2216.3	2004.4 ± 124.5

Table 9. Individual pharmacokinetic parameters of CBZ after oral coadministration of 400 mg/kg CBZ with GCP (2 g/kg) to six rats

Parameter \ Rat	1	2	3	4	5	6	Mean ± S.E
AUC_{0-4320} ($\mu mol \cdot min \cdot mL^{-1}$)	217.5	300.0	227.5	199.7	151.9	195.8	215.4 ± 20.0
C_{max} ($nmol \cdot mL^{-1}$)	133.9	130.2	152.1	164.8	102.4	249.0	155.4 ± 20.6
T_{max} (min)	120.0	120.0	120.0	120.0	120.0	120.0	120.0 ± 0.0
MRT (min)	1770.6	2033.5	1708.5	1715.6	1703.1	1184.1	1685.9 ± 112.8

Table 10. Individual pharmacokinetic parameters of CBZ epoxide after oral coadministration of 400 mg/kg CBZ with GCP (2 g/kg) to six rats

Parameter \ Rat	1	2	3	4	5	6	Mean ± S.E
AUC_{0-4320} ($\mu mol \cdot min \cdot mL^{-1}$)	69.4	152.9	356.0	327.6	252.6	118.0	212.8± 47.8
C_{max} ($nmol \cdot mL^{-1}$)	46.2	65.6	109.1	106.1	77.5	54.7	76.5± 10.7
T_{max} (min)	60.0	120.0	2160.0	720.0	2160.0	480.0	950.0± 395.1
MRT (min)	1526.3	1821.4	2086.6	2048.5	2087.1	1568.7	1856.4± 105.9

GCP: Huajuhung; peel of *Citrus grandis*

Table 11. Comparison of pharmacokinetic parameters of CBZ in 6 rats given CBZ alone (400 mg/kg) and coadministered with 2 g/kg CGP (CBZ+CGP) decoction

Parameter \ Treatment	CBZ	CBZ + CGP	Difference (%)
AUC_{0-4320} ($\mu mol \cdot min \cdot mL^{-1}$)	143.8± 17.8	182.1± 25.4	26.6
C_{max} ($nmol \cdot mL^{-1}$)	91.2± 10.1	125.0± 17.3	37.1
T_{max} (min)	241.7± 118.3	136.7± 71.1	-43.4
MRT (min)	1596.5± 97.3	1498.1± 147.2	-6.2

Table 12. Comparison of pharmacokinetic parameters of CBZ epoxide in 6 rats given CBZ alone (400 mg/kg) and coadministered with 2 g/kg CGP (CBZ+CGP) decoction

Parameter \ Treatment	CBZ	CBZ + CGP	Difference (%)
AUC_{0-4320} ($\mu mol \cdot min \cdot mL^{-1}$)	230.9± 18.5	217.2± 17.1	-5.9
C_{max} ($nmol \cdot mL^{-1}$)	83.8± 15.3	80.6± 11.2	-3.8
T_{max} (min)	2520.0± 609.5	1480.0± 566.0	-41.3
MRT (min)	2047.7± 82.6	2004.4± 124.5	-2.1

Table 13. Pharmacokinetic parameters of CBZ and CBZ epoxide (CBZE) in seven rats receiving oral CBZ (400 mg/kg) alone and coadministration with SJ decoction (2, 4 g/kg)

Parameters	CBZ alone	CBZ + SJ (2 g/kg)	Difference (%)	CBZ + SJ (4 g/kg)	Difference(%)
C_{max} (CBZ)	93.8 ±7.2 [a]	167.5 ±32.5 [b]	81.2±42.3	173.3 ±14.1 [b]	82.1±19.5
AUC_{0-t} (CBZ)	79.2 ±8.5[a]	118.5 ±11.4 [b]	81.1±24.2	144.3 ±15.7 [b]	138.5±58.5
MRT_{0-t} (CBZ)	1419.9 ±62.7	1073.7 ±131.5	-22.8±11.2	1131.1 ±119.1	20.3±7.7
C_{max} (CBZE)	75.6 ±13.0 [a]	192.4 ±32.5 [b]	197.1±44.9	214.3 ±29.5 [b]	246.8±69.5
AUC_{0-t}(CBZE)	218.7 ±32.1[a]	333.4 ±43.9 [a]	75.2±12.5	418.4 ±63.1 [b]	120.5±27.2
MRT_{0-t}(CBZE)	1966.3 ±51.8 [a]	1700.9 ±119.6 [a]	-13.0±6.6	1577.0 ±49.2 [b]	-19.3±3.9

Table 14. Pharmacokinetic parameters of CBZ and CBZ epoxide in seven rats receiving oral CBZ (400 mg/kg) alone and coadministration with rutin (160, 320 mg/kg)

Parameters	CBZ alone	CBZ + rutin (160 mg/kg)	Difference (%)	CBZ + rutin (320 mg/kg)	Difference (%)
C_{max}	82.3 ±29.1 [a]	106.4 ±40.2 [a]	31.1±11.7	115.8 ±43.8 [b]	45.3±17.1
AUC_{0-t}	67.5 ±23.9 [a]	122.5 ±46.3 [b]	81.8±30.9	103.9 ±39.3 [b]	56.3±21.3
MRT_{0-t}	1208.4 ±427.2	1298.3 ±490.7	16.6±6.3	1145.4 ±432.9	-1.0±0.4
C_{max} -E	121.7 ±19.5	161.5 ±20.2	83.9±15.7	179.6 ±18.5	73.2±49.4
AUC_{0-t}-E	267.1 ±27.2[a]	379.4 ±33.0 [b]	63.8±13.6	355.6 ±40.4 [a]	56.4±49.0
MRT_{0-t} -E	1890.2 ±111.9	1707.6 ±101.1	-5.9±10.8	1789.2 ±60.5	-3.1±6.6

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