

中文摘要

環孢靈為一個治療指數狹窄之免疫抑制劑。它是 CYP 3A4 及 P-glycoprotein (Pgp) 之受質。槲皮素是 CYP 3A4 之抑制劑，亦會調控 Pgp。芸香為槲皮素之配醣體，於大腸中代謝成槲皮素而吸收。此研究的目的係探討槲皮素、芸香對環孢靈動態學的影響。

大白鼠或豬口服環孢靈及併服槲皮素、芸香。環孢靈之血中濃度以單株螢光偏極免疫法定量。統計方法採 Student' t-test 分析。以體外翻腸試驗評估槲皮素、芸香對 Pgp 功能之影響。

結果顯示於豬及大白鼠體內，槲皮素顯著降低環孢靈之吸收達 56 % 及 43 %，而芸香於大白鼠體內顯著降低環孢靈之吸收達 57 %。然而翻腸試驗顯示槲皮素、芸香對 Pgp 功能均為抑制的作用。

吾人建議當槲皮素、芸香與環孢靈或其他 CYP 3A4 / P-glycoprotein (Pgp) 之受質併用時，應密切監測危險西藥之血中濃度。

關鍵詞：槲皮素、芸香、環孢靈、交互作用

Abstract

Cyclosporin, an immunosuppressant with narrow therapeutic window, is a substrate for both CYP 3A4 and P-glycoprotein (Pgp). Quercetin is an inhibitor of CYP 3A4, and a modulator of Pgp. Rutin is a glycoside of quercetin and absorbed as quercetin in large intestine. The aim of this study was to measure the effect of quercetin and rutin on the absorption and disposition of cyclosporin in pigs and rats.

Cyclosporin was orally administered without and with a concomitant dose of quercetin or rutin to pigs or rats. Cyclosporin concentrations in blood samples were determined by a specific monoclonal fluorescence polarization immunoassay. Student's t-test was used for statistical comparison. Everted intestine sac study was carried out to evaluate the effect on intestinal Pgp function.

The coadministration of quercetin significantly decreased cyclosporin AUC_{0-3} by 56 % and AUC_{0-t} by 43 % in pigs and rats, respectively. The coadministration of rutin significantly decreased cyclosporin AUC_{0-t} by 57 % in rats. However, sac study showed that quercetin and rutin significantly

inhibited the function of intestinal Pgp.

It is suggested that concurrent use of quercetin or rutin with cyclosporin or other medications whose absorption and metabolism are mediated by Pgp and/or CYP 3A4 should require close monitoring.

Keywords: Rutin, Quercetin, Cyclosporin, Interaction

二、緣由與目的

Cyclosporin is a widely used immunosuppressant with narrow therapeutic window. Cyclosporin and its metabolites have nephrotoxic, hepatotoxic, and neurotoxic side effects. Cyclosporin is metabolized by CYP 3A4 [1] and is also a substrate of P-glycoprotein (Pgp), the multi-drug efflux transporter [2]. The significant role of CYP 3A4 for drug - drug interactions was well recognized. Pgp is a membrane protein expressed in various normal human tissues such as small intestine, kidney, liver and capillary endothelial cells of brain and testes [3-5], and its significant roles for chemoprevention of organisms and drug - drug interaction had been proposed [6-8].

Flavonoids have attracted much attention in recent years because of their beneficial pharmacological activities and furthermore, their additional abilities to modulate both CYP 3A4 and Pgp [9-12]. Grapefruit juice was reported to increase the absorption of cyclosporin [13,14]. Early efforts to identify the active CYP 3A4 inhibitor in grapefruit juice focused on flavonoids such as naringenin and quercetin, however, both compounds failed to reproduce the inhibition in human studies [15,16]. Quercetin was shown to be a potent inhibitor of CYP3A4 in in vitro studies [17,18]. Regarding its modulation on Pgp, quercetin has been initially identified as an inducer in multidrug-resistant breast cancer cells and HCT-15 colon cells [19,20], but later it was shown to be an inhibitor of Hoechst 33342 transport by Pgp [21].

Quercetin is widely distributed mainly as glycosides in daily diet like onions, apples, berries, tea and red wine as well as in herbal remedy and dietary supplements worldwide. Evidence showed that orally administered quercetin glycosides like rutin were significantly broken down to absorbable quercetin by the enterobacteria. The present study attempted to measure the influence of quercetin and rutin on the absorption and disposition of cyclosporin in pigs and

rats.

三、結果與討論

Fig. 1, and Fig. 2 depict the blood profiles of cyclosporin (Sandimmun) after administration of cyclosporin alone and with quercetin in pigs and rats, respectively. Our results showed that quercetin did significantly reduce AUC_{0-3} by 56 % in pigs. As in rats, coadministration of quercetin significantly decreased AUC_{0-t} by 43 %. However, no significant changes on T_{max} , MRT and elimination rate of cyclosporin were found for quercetin coadministration in pigs and rats. Fig. 3 and Fig. 4 depict the blood profiles of cyclosporin (Neoral) after administration of cyclosporin alone and with quercetin and rutin, respectively, in rats. Our results showed that quercetin and rutin did significantly reduce the AUC_0 of cyclosporin by 43 % and 57 %, respectively.

Everted intestine sac study showed that quercetin and rutin inhibited the efflux transport of rhodamine 123, from serosal side to mucosal side for both jejunum and ileum in a dose-dependent manner, indicating that quercetin and rutin significantly inhibited the function of intestinal Pgp.

Quercetin was reported to be an inhibitor of CYP 3A4 and modulator of Pgp (18, 20). Based on our result of everted sac study, quercetin is an inhibitor of intestinal Pgp, which was correspondent to the study of Hoechst 33342 transport by reconstituted Pgp (21). Being inhibitors of CYP 3A4 and Pgp based on *in vitro* evidences, quercetin and rutin are likely to enhance the absorption of cyclosporin, substrate of CYP 3A4/ Pgp. However, unexpectedly, our results of *in vivo* studies indicated that quercetin and rutin significantly inhibited cyclosporin absorption, suggesting that the effect of quercetin and rutin on cyclosporin absorption can not be attributable to its modulation on CYP 3A4 or Pgp. It clearly indicated here that these *in vitro* evidences could not be extrapolated to *in vivo* effects of quercetin and rutin. Prior to the quercetin - cyclosporin interaction study was conducted, the pharmacokinetic properties of “the precipitant drug” – quercetin had been investigated in rabbits and rats in our laboratory. The pharmacokinetic studies indicated that quercetin was rapidly absorbed and simultaneously glucuronidated after oral administration in both animals and circulated almost exclusively as glucuronides in the plasma, which was in good agreement with the results from a previous study of pigs. From the

pharmacokinetic properties of quercetin, the *in vivo* effects of quercetin glucuronides on CYP 3A4 and Pgp might be more important than quercetin itself. Therefore, it is plausible to propose that quercetin glucuronides, instead of quercetin might play a key role in modulating CYP 3A4 and/or Pgp to result in altered absorption of cyclosporin. To investigate the effects of quercetin glucuronides on CYP 3A4 and Pgp in *in vitro* systems could be helpful to clarify the mechanism of this *in vivo* interaction. In our recent study, the effect of quercetin glucuronides on CYP 3A4 of mice liver microsomes was investigated using testosterone as a model substrate. Our primary results indicated that both quercetin glucuronides and quercetin inhibited the function of CYP 3A4. Moreover, the effect of quercetin glucuronides on Pgp remains to be studied in our laboratory in the future. It is suggested that a better understanding of the pharmacokinetic properties of “the precipitant drug” would be helpful to elucidate the mechanism of interaction with “the object drug”.

In summary, quercetin and rutin significantly inhibited the absorption of cyclosporin in pigs and rats. It is suggested that concurrent use of quercetin, rutin or dietary supplement containing them with CYP 3A4/Pgp substrates should require close monitoring of the critical therapeutic drugs.

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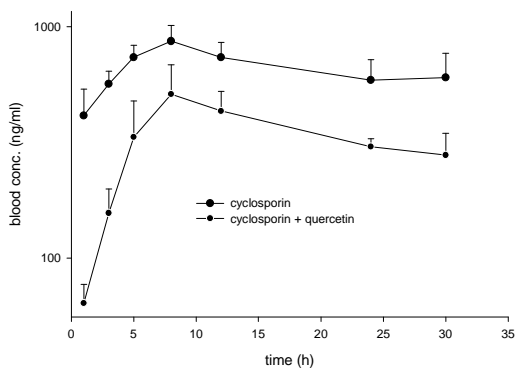


Fig. 1

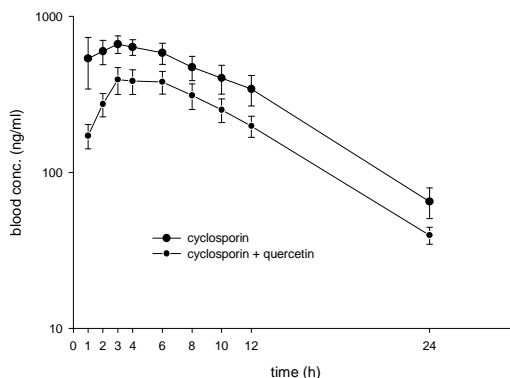


Fig. 2

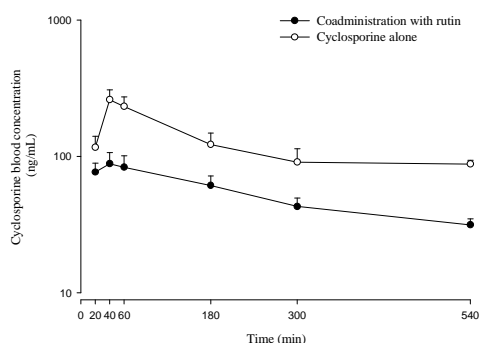


Fig. 3

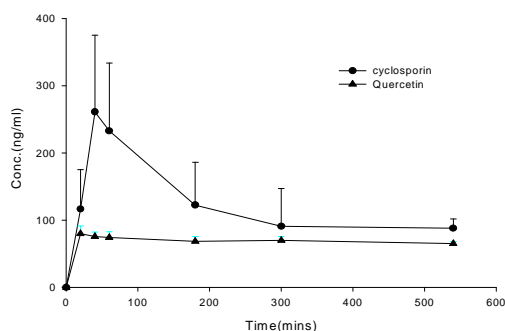


Fig. 4