利用 HPLC 分析方法預測中草藥與藥物之交互作用：探討 furanocoumarins 對肝臟代謝酵素 CYP3A4 所引起交互作用之研究

Predicting Herb-drug Interactions by HPLC Analysis: Furanocoumarin-based Metabolic Interactions with CYP3A4

中文摘要

本研究以逆相高效液相層析 (RP-HPLC) 方法預測中草藥與藥物因代謝而發生交互作用之可能性。以二十九種結構相關且已知會抑制藥物代謝 phase-I 細胞色素 P450 3A4 (CYP3A4) 的 furanocoumarins 爲模式藥物利用 RP-HPLC 進行預測中草藥與藥物之交互作用。將其中五個 furanocoumarins 標準品利用已經確效的 RP-HPLC 系統分析，將所得的容量因子 (capacity factor) 值與用 Molsuite 2000 molecular modeling pro plus software (ChemSW®) 軟體計算出的 furanocoumarins 分配係數 (log P) 進行關聯分析。利用此關聯曲線可求得這系列 furanocoumarins 之容量因子。結果顯示絕大部分的 furanocoumarins 其容量因子介於 1.65 和 10.57 之間 (滯留時間 10 到 40 分鐘)，也就是相當於 RP-HPLC 分析時分離層 3 到 8 (fraction 3~8) 之間。每一個分離層利用對 nifedipine 氧化反應的抑制之程度來表示酵素 CYP3A4 受抑制之程度。在定量性預測中草藥與藥物交互作用時，Ru 被定義爲層析反應單位的總合，可利用方程式 Ru = R / 7.79 ?e 105 表示，其中 R 代表每一個層析峰或是任一個分離層內所有層析峰其面積的總合 (sum of the peak area)。結果顯示，CYP3A4 酵素抑制百分比 (y) 與層析反應單位的總合 (Ru，x) 呈乙狀 (sigmoidal) 的關係，方程式爲 y = 85.36 x (14.86 + x)-1 其相關係數爲 0.63。這乙狀的曲線可以分爲低、中和高風險三個範圍，用來代表中草藥或複方濃縮中草藥粉與藥物發生代謝交互作用的風險程度。經由本研究"風險類別"的預測分類結果，可以提供有用的資訊來評估中草藥與藥物之交互作用。

英文摘要

An attempt made in this study was to predict the potential for metabolic interactions of herbal extracts of drugs based on their chromatographic profiles in reverse-phase high-performance liquid chromatography (RP-HPLC) analysis. Twenty-nine structurally related furanocoumarin compounds with known effect on cytochrome P450 3A4 (CYP3A4), which is important for phase-I drug metabolism, were selected as a model system, and analyzed using an RP-HPLC system developed for this study. Log values of the partition coefficients (log P) of these furanocoumarin derivatives calculated using Molsuite 2000 molecular modeling pro plus software (ChemSW®) were used to interpolate the capacity factors from a validated correlation curve constructed using five standard references that covered the elution time range in the

RP-HPLC analysis system developed in the lab. The obtained correlations were then used to estimate the capacity factor for all of the furanocoumarin derivatives collected from the literatures with reported herb-drug interaction activity in CYP3A4. The capacity factors for most of the furanocoumarins were between 1.65 and 10.57 (with retention times of 10~40 min), a range approximately equivalent to fractions 3 to 8 (Fr3~8) in the RP-HPLC fraction analysis. Each fraction was examined for its inhibition of microsomal nifedipine oxidation represented as the CYP3A4 inhibitory potency. Ru was designated the total response unit and expressed as Ru = R / 7.79 ?e 105; this was calculated for each single peak or each fraction in terms of the sum of the peak area (R) for all chromatographic peaks appearing in the chromatographic analysis. A sigmoidal relationship was established between the CYP3A4 inhibitory potency (y) and the RP-HPLC peak response unit (Ru ، x) as y = 85.36 x (14.86 + x)-1 with a correlation coefficient of 0.63. The sigmoidal curve could be divided into three ranges designated low, medium, and high risk that were used to indicate the relative inhibitory potency of the metabolic interactions of herbs or traditional Chinese herb medicines with CYP3A4. These predictive classifications provide information and might be useful for “risk category” decisions concerning herb-drug interactions.