• 系統編號	RN9611-3513
• 計畫中文名稱	Sildenafil 和葡萄柚汁在 Cytochrome P450 的體外代謝交互作用之動力學模式探討(II)
• 計畫英文名稱	A Kinetic Model for the Metabolic Interaction of Sildenafil and Grapefruit Juice at the Active Site of Cytochrome P450 3A4 (II)
• 主管機關	行政院國家科學委員會
• 計畫編號	NSC94-2320-B038-012
• 執行機構	台北醫學大學藥學系
• 本期期間	9408 ~ 9507
• 報告頁數	23 頁
• 使用語言	中文
• 研究人員	何秀娥 Ho, Hsiu-O
• 中文關鍵字	--
• 英文關鍵字	Sildenafil; Testosterone; Carbamazepine; Drug interaction; CYP3A4
• 中文摘要	Sildenafil 經過人體吸收後最主要是經過肝臟酵素 CYP450 3A4 代謝成同樣具有藥理活性的代謝物 UK-103,320。實驗結果顯示，Sildenafil 在 microsome 的酵素動力學是遵循 Michaelis-Menten kinetic model，其 Vmax = 1.96 μMmin-1，Km = 27.31 μM.。利用 Testosterone 和 Carbamazepine 評估 Sildenafil 在 CYP3A4 的活性結合區的實驗，結果顯示 Sildenafi 與 Testosterone 和 Carbamazepine 進行代謝作用是屬於互相抑制的現象，彼此之間會相互影響，結果也顯示，Sildenafil 與 Testosterone 和 Carbamazepine，在 CYP3A4 的鍵結牽涉到一個以上活性位置的動力學模式。
• 英文摘要	The biotransformation of sildenafil to its major circulating metabolite, UK-103,320, was studied in male rat liver microsomes. The conversion of sildenafil to UK-103,320 by rat microsomes followed Michaelis-Menten kinetics, for which the parameters were Vmax = 1.96 .mu.M min-1and Km = 27.31 .mu.M. Using substrates of CYP3A4 of testosterone and carbamazepine, the active sites on CYP3A4 responsible for metabolizing sildenafil were also evaluated. Sildenafil biotransformation was inhibited in the individual presence of testosterone and carbamazepine. The most unusual results were the individual interactions of sildenafil with testosterone and carbamazepine. Although testosterone and carbamazepine can inhibit sildenafil demethylation in concentration- and incubation time-dependent manners, sildenafil did not inhibit testosterone hydroxylation or carbamazepine epoxidation. These results may be explained by a model in which multiple substrates or ligands can concurrently bind to the active site of a single CYP3A4 molecule. However, the contribution of separate allosteric sites and conformational heterogeneity to the atypical kinetics of CYP3A4 cannot be

ruled out in this study.