• 系統編號	RG9110-0554
• 計畫中文名稱	川芎的活性生物鹼 Tetramethylpyrazine 抑制血小板凝集反應的機轉研究
• 計畫英文名稱	Study of Antiplatelet Activity of Tmpz---An Alkaloid from Chung Chong
• 主管機關	行政院衛生署
• 計畫編號	CCMP89-RD-034
• 執行機構	台北醫學院醫學研究所暨藥理學科
• 本期期間	8807 ~ 8906
• 報告頁數	28 頁
• 使用語言	中文
• 研究人員	許準榕；林玟儀 Sheu, Joen-Rong
• 中文關鍵字	川芎；四甲基比井；抗血小板凝集；磷酸肌酐分解；一氧化氮；中草藥；血栓素 A2
• 英文關鍵字	Ligustici rhizoma；Tetramethylpyrazine (TMPZ)；Antiplatelet aggregation；Phosphoinositide breakdown；Nitric oxide (NO)；Chinese herbal medicine；Thromboxane A2
• 中文摘要	Tetramethylpyrazine(TMPZ)是傳統中藥川芎的主要活性成份。在本實驗中，我們將評估 TMPZ 的抗血小板能力。在人類的血小板中，TMPZ(0.5-1.5 mM)可依劑量的相關性而抑制不同的血小板活化劑(如 ADP、Collagen 和 U46619)所引起的血小板凝集反應及 ATP 釋放反應。TMPZ(0.5 mM)不會影響血小板細胞膜的流通性，即使濃度高到 1.5mM 亦然。再者，TMPZ(0.5-1.5 mM)可依劑量的相關性而抑制 Collagen 所引起血小板(/sup 3/H) Inositol monophosphate 的形成；另外，TMPZ(0.5-1.5mM)亦可依劑量的相關性而抑制 Collagen 所引起血小板內鈣的釋放。再者，TMPZ(0.5-1.5mM)亦可抑制 Collagen 所引起的 Thromboxane A/sub 2/的合成。在較高的濃度(1.0 mM)，我們亦發現 TMPZ 可干擾 FITC-triflavin 結合到血小板細胞膜醣蛋白受體 Glycoprotein IIb/IIIa complex. Triflavin 是一種蛇毒蛋白 Trimeresurus flavoviridis 所純化出的 Glycoprotein IIb/IIIa complex 的專一性拮抗劑。另一方面，TMPZ 在較低的濃度下(50-200μM)，我們發現 TMPZ 隨著時間及劑量的增加而可明顯的促進 Nitrate 及 cyclic GMP 的產生。由本研究顯示 TMPZ 抗血小板凝集作用可能經由兩種作用機轉：(1)在較低的濃度下(50-200 μM)，TMPZ 可促進血小板 NO 的釋放，導致 cyclic GMP 增加而降低細胞內鈣離子濃度。(2)在較高的濃度下(0.5-1.5 mM)，TMPZ 可抑制血小板的 Phosphoinositide 的分解以及 Thromboxane A2 的合成，進而降低細胞內鈣離子而抑制血小板凝集反應。
• 英文摘要	Tetramethylpyrazine (TMPZ) is the active ingredient of a Chinese herbal medicine. In this study, TMPZ was tested for its antiplatelet activities in human platelet suspensions. In human platelets, TMPZ (0.5-1.5 mM) dose-dependently inhibited both platelet aggregation and ATP-release reaction induced by a variety of agonists (i.e., ADP, collagen and U46619). TMPZ (0.5 mM) did not significantly change the fluorescence of platelet

membranes labeled with dipheylhexatriene (DPH), even at the high concentration (1.5 mM). Furthermore, TMPZ (0.5-1.5 mM) dose-dependently inhibited (/sup 3/H) inositol monophosphate formation stimulated by collagen (5 lμg/ml) in (/sup 3/H) myoinositol loaded platelets. In addition, TMPZ (0.5-1.5 mM) also dose-dependently inhibited the intracellular free Ca/sup +2/ rise of Fura 2-AM loaded platelets stimulated by collagen (5 μg/ml). Moreover, TMPZ (0.5-1.5 mM) inhibited thromboxane A/sub 2/ formation stimulated by collagen. At a higher concentration (1.0 mM), TMPZ has also been shown to influence the binding of FITC-triflavin to platelet glycoprotein IIb/IIIa complex. Triflavin, a specific glycoprotein IIb/IIIa complex antagonist purified from Trimeresurus flavoviridis venom. On the other hand, TMPZ (50-200 μM) significantly increased production of nitrate and cyclic GMP formation in human platelets within a 15-min incubation period. It is concluded that the antiplatelet activity of TMPZ may possibly involve two pathways: (1) at a lower concentration (50-200 μM), TMPZ may activate the nitric oxide and cyclic GMP formation. (2) at a higher concentration (1.0 mM), TMPZ is shown to inhibit phosphoinositide breakdown and thromboxane A/sub 2/ formation in human platelets.