• 系統編號	RN9406-0588		
• 計畫中文名稱	桔皮甘對應力所誘發血管內皮細胞基因表現的作用以及細胞內的分子機轉		
• 計畫英文名稱	Cellular and Molecular Mechanism of the Effect of Hesperidin on Cyclic Strain-Induced Gene Expression in Vascular Endothelial Cells		
• 主管機關	行政院國家科學委員會	• 計畫編號	NSC92-2320-B038-034
• 執行機構	臺北醫學大學醫學系		
• 本期期間	9208 ~ 9307		
• 報告頁數	6 頁	• 使用語言	英文
• 研究人員	陳保羅 Chan, Paul		
• 中文關鍵字	桔皮甘; 循環性應力; 內皮素; 增殖; 訊息傳遞; 內皮細胞；活性氧族群		
• 英文關鍵字	Hesperidin; Cyclic strain; Endothelin; Proliferation; Signal transduction; Endothelial cell ? FReactive oxygen species		
• 中文摘要	桔皮甘 (hesperidin)是傳統中藥”陳皮”中所富含具強力抗氧化能力的物質，於動物實驗上，證實可抑制動脈硬化的發生以及降 低血膽固醇，臨床上已有商品名爲 Daflon 500 mg 的含桔皮之藥品，普遍運用於改善慢性靜脈閉鎖不全。然而，目前對於其在血管系統的細胞作用與分子生物機轉仍不明確。（ 1）內皮細胞(endothelial cells; ECs)是血管系統內層的細胞，具有調節血管舒張或收縮及其他重要功能。內皮細胞可受到機械力的作用而產生一些血流動力學上 (hemodynamic) 的變化。在實驗上，常以循環性應力 (cyclic strain)的模式模擬血管收縮，舒張的作用，來探究培養中內皮細胞的變化。近來實驗發現；循環性應力可增加內皮細胞素-1(endothelin-1；ET-1)的基因表現。有此種作用與細胞內活性氧族群 (reactive oxygen species; ROS)有關。實驗發現，循環性應力可誘發 ROS 的產生，ROS 進一步激活 Ras/Raf 的訊息傳導路徑並活化 nuclear factor-KB 和 activator protein-1 (AP-1)等轉錄因子來促進 ET-1 的基因表現。因桔皮甘爲抗氧化劑可減少 ROS 的產生。所以本研究即以循環性應力的模式來探究桔皮甘對於培養中內皮細胞分泌 ET-1 的影響及其分子生物機轉。桔皮甘有抑制應力增加內皮素基因表現的作用。		
• 英文摘要	The pure polyphenol hesperidin is common in juices, ascorbic acid, and the citrus juices and has beneficial properties such as being strong antioxidants. In a hamster model of atherosclerosis, the juices were able to significantly inhibit atherosclerosis and lowered cholesterol and triglycerides. Furthermore, hesperidin is clinically used in the formular of purified micronized flavonoid fraction		

(S5682 or registered as Daflon; containing 90% diosmin and 10% hesperidin). It is concluded that Daflon is of benefit to patients with chronic venous insufficiency. However, the cellular and molecular mechanisms of the beneficial effect of hesperidin in the vascular system remain to be elucidated. Endothelial cells (ECs) are constantly under the influence of mechanical forces, including cyclic strain, as a consequence of vessel contraction and relaxation. Activation of several signal transduction systems has been demonstrated by hemodynamic forces in ECs. Recently, it has been proposed that the reactive oxygen species (ROS) function as second messengers in cells exposed to cyclic strain. Activation of nuclear factor-kB and activator protein-1 (AP-1), which can be regulated by ROS, are believed to be involved in the upregulation of certain genes by hemodynamic forces. Cyclic strain-induced ROS appear to be involved in the cyclic strain-induced gene expression of plasminogen activator inhibitor-1, monocyte chemotactic protein-1, and endothelin-1 (ET-1). ROS are also involved in the cyclic strain-induced expression of the ET-1 gene through modulation of Ras/Raf/extracellular signal-regulated kinase pathway in ECs. However, the effect of hesperidin on cyclic strain-induced ET-1 gene expression and the intracellular mechanism remains to be determined. In this project, we investigate whether hesperidin affects cyclic strain-induced ET-1 gene expression and explore its molecular mechanism in culture system. Hesperidin inhibited the strain-induced ET-1 gene expression as revealed by Nothern blotting and promoter activity assay. Hesperidin also inhibited strain-increased intracellular ROS generation as measured by a redox sensitive fluorescent dye, 2' 7'-dichlorofluorescin diacetate, and ERK phosphorylation. In summary, our results suggest that Hesperidin inhibits strain-induced ET-1 gene expression, partially by interfering with the ERK pathway via attenuation of ROS generation.