• 計畫中文名稱	吳茱萸次鹼衍生物之合成與其第一型拓樸異構脢抑制活性鑒定		
• 計畫英文名稱	Synthesis and Identification of Rutaecarpine Derivatives as Topoisomerase I Inhibitors		
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• 研究人員	林俊茂,黃聲東		
• 中文關鍵字	抗藥性；吳茱萸鹼；吳茱萸次鹼；拓樸異構?；		
• 英文關鍵字	Drug resistance； Evodiamine； Rutaecarpine； Topoisomerase；		
• 中文摘要	DNA 拓樸異構酶(Topoisomerase, Top)在 DNA 進行複製或轉錄過程中扮演調節拓樸 狀態的角色，Top 可切割 DNA 磷雙酯鍵形成缺口，讓 DNA 進行鬆解變異之拓樸狀態後再 重新接合以維持雙股 DNA 正常功能。由於 Top 活性涉及許多細胞週期過程，一些以抑制 Top 爲標的化合物物被應用作爲抗腫瘤、抗病毒、抗菌、及免疫調節等醫療應用。 吳茱萸鹼及吳茱萸次鹼是由五個環狀所組成之雜環化合物，其本是緣自芸香科植物 吳茱萸所分離的生物鹼，根據報導指出具有血管舒張、抗肥胖、抗癌、抗發炎等生理功 能，並且探討過其作用於細胞內之分子機轉，惟現有文獻並無其直接作用之分子目標被 揭露。 本研究團隊首度揭露吳茱萸鹼及吳茱萸次鹼透過穩定 Top-DNA 中間體結構，使無法 完成 Top 再接合步驟，造成第一型 Top (TopI)及 DNA 正常功能被抑制。此一揭露將加速 吳茱萸鹼及吳茱萸次鹼的醫藥應用，並進一步發展爲新藥開發平台。 由 TopI 及其抑制劑結構-活性關係分析，A 環及 E 環的取代官能基可以決定性增加 與 Top 的結合力，因此增強對 Top 的抑制能力。本計劃提出合成 A 環的鹵化物衍生物， 及 E 環的硝化或氨基衍生物，預期可以增強與 TopI-DNA 之結合力。共有 12 種化合物被 合成，其中有 8 種是未曾揭露之全新化合物，其將分別利用電腦分子立體模擬、表面電 漿共振、及 DNA 鬆解等技術探討其活體外 TopI 的抑制能力。活體內 TopI 的抑制力將利 用高度表現 TopI 的癌細胞株測試。一旦確立具有較佳作用，則將於種植癌細胞老鼠測 試所合成之吳茱萸次鹼衍生物是否透過 TopI 的抑制力而具有同等的生物活性。 儘管現有 TopI 抑制劑發展爲抗癌或抗病毒藥物在臨床應用相當成功，但仍然因容 易誘發化學抗藥性而受限。本計劃之完成將確定吳茱萸鹼衍生物的作用模式與目標，其 將啓動吳茱萸鹼衍生物更專一性的新藥開發平台，所設計合成之		

	全新化合物，將可改善 既有藥物在生物活性應用所遭遇之限制。同時建立有機合成吳茱萸次鹼新衍生化合物的 製備方法。
• 英文摘要	DNA topoisomerases regulate the topological state of DNA that is crucial for replication, transcription, and other nuclear processes. Topoisomerases play roles on regulatory checkpoints during cell cycle progression. The enzymatic mechanism involves two sequential transesterification reactions through cleaving the phosphodiester backbone and forming a covalent linkage to the DNA, and then relegated to restore the DNA double strands. Topoisomerase inhibitors have been developed for antitumor, antiviral, antibacterial, anti-protozoa, and immunomodulation applications. Evodiamine (EVO) and rutaecarpine, alkaloidal compounds originally isolated from Evodia rutaecarpa (Juss.), have been reported to possess many physiological functions including vasorelaxation, antiobesity, anticancer, and anti-inflammatory effects. Even the cellular response to these compounds have been reported, the direct molecular targets of compounds have not been addressed yet. EVO and rutaecarpine derivatives are first reported to be the TopI inhibitor that acts by stabilizing the covalent complex between Top I and DNA, which results in a blockade of DNA function. It provides beneficial effects of EVO to develop a variety of therapeutic applications and drug design platform. According to the structure-activity relationship analysis on TopI inhibitor, modifications of A- and B-rings are expected to increase the DNA-TopI trapping ability and result in increased DNA damage. Halide substitutions on A-ring and nitro- or amino- substitutions on E-rings are designed in this proposal, and those are expected to be more potent in TpoI inhibition. There are 12 rutaecarpine derivatives to be synthetized, in which 8 derivatives are new compounds. The in vitro TopI inhibition activity will be assessed using computer-aid molecular modeling, surface plasmon plasmon resonance, and DNA relaxation assay. The in vivo assay will be performed in high TopI-expression cells. The potent derivatives will be further assessed in cancer cell-implanted mice. Even TopI inhibitors are well applied on clinical cancer therapy, development of multiple drug resistance upon drug use hampers their feasibility. Achievement of this proposal will confirm the action target of rutaecarpine derivatives, which will prompt a new drug development platform. The synthetic compounds will break through the limitation of TopI inhibitor application on clinical. In addition, the synthetic process of new rutaecarpine derivatives will become well established.