中文摘要

肝癌是世界上最常見的惡性腫瘤之一。尤其在台灣，由於 B 型肝炎、C 型肝炎的盛行及酗酒等因素，使得國人肝癌的罹病率較國外為高，而且發病的族群集中在青壯年人口。所以，肝癌不僅僅是一種威脅個人健康的疾病，對國家的經濟發展也有相當大的損害。目前用於肝癌的治療方法非常多樣，但對於佔大多數的較晚發現、合併肝硬化，甚至發生肝外擴散的病人，經動脈化學藥物栓塞或化學治療則是重要的治療方式。

柔紅黴素主要被用來治療乳癌、食道癌、各種惡性肉瘤以及淋巴癌；近年來，應用在胃癌、胰臟癌、肝癌及膽管癌的治療也有不錯的效果。柔紅黴素的抗癌機轉主要是透過對 Topoisomerase II 的抑制，因而影響 DNA 雙股的分離，並進一步抑制 DNA 合成，使細胞週期中的 G2-M 期比例增加。

黃酮類是一種天然的多酚化合物，蔬菜、水果、穀物及飲料中都有他們的蹤跡。目前已知它們具有抗發炎、抗氧化、抗病毒、抗過敏及抗癌等療效；甚至有些黃酮類還可以透過抑制抗癌藥在細胞內的代謝或改變細胞膜對抗癌藥的輸送，使細胞內的抗癌藥物濃度上升，而增強抗癌藥的效果。

基於想要進一步瞭解黃酮類化合物對接受化學藥物治療中的肝癌病人有何影響，我們利用不同癌化程度的人類肝細胞株來模擬肝癌的各臨床分期，在將不同的藥物加入細胞後，用流式細胞儀進行分析，以 G2-M 期所佔的比例是否上升做為判斷的準則，試圖搜尋出具有增效作用的藥物。

透過本研究，我們建立了一個以分析細胞週期為基礎的抗癌藥物搜尋平台，並利用此一平台對有代表性的黃酮類化合物做搜尋，結果找到 apigenin 這個可以促使 Chang liver/AP-1 細胞產生 G2-M arrest 的藥物。在對 apigenin 做進一步的分析後，我們發現 apigenin 除了可以單獨使用，在 50 μM 以上的濃度使 Chang liver/AP-1 細胞產生 G2-M arrest；它也可與柔紅黴素發生協同作用，在 50 μM 以上的濃度時使 Chang liver/AP-1 細胞的 G2-M 期比例上升，因此可能在接受柔紅黴素治療的病人體內發揮增效的功效。

Abstract

Primary hepatocellular carcinoma (HCC) is one of the most common tumors in the world. It is especially prevalent in Taiwan, where the annual incidence is up to 28.71 cases per 100,000 population. The most important reason for the high incidence of HCC is the frequency of chronic infection with hepatitis B virus and hepatitis C virus. In addition, alcohol abuse contributes to the development of HCC. There are many therapeutic strategies for the treatment of HCC. For patients who combined with liver cirrhosis or extra-hepatic metastasis, transarterial chemoembolization and chemotherapy are the important treatment applications in clinic.

Daunorubicin is an effective anti-cancer drug, which has been used for treating a wide variety of cancers, such as breast and esophageal carcinomas, osteosarcoma, Kaposi's sarcoma, soft-tissue sarcomas, hepatocellular carcinoma, and Hodgkin's and non-Hodgkin's lymphomas. Topoisomerase II is likely to be the major target of daunorubicin. Daunorubicin also inhibits DNA synthesis, DNA strand unwinding, and helicase activity. All of these mechanisms contribute to the G2-M arrest in various cells.

Flavonoids are a class of benzo-gamma-pyrone derivatives, which are ubiquitous in vegetables, fruits, grains, and beverages. Previous studies indicate that they have great potentialities in the anti-inflammation, anti-oxidation, anti-virus infection, anti-allergy, and anti-cancer cell proliferation. Some of them also alter intra-cellular metabolism or change the transportation behavior of cell membrane to enhance the effect of anti-cancer drugs.

In order to study the interaction between flavonoids and daunorubicin, we used different hepatic cell lines to represent the different clinical stages of HCC. After the addition of different agents into these cells, the cell distribution was analyzed by flow cytometer. The results revealed that apigenin, a member of flavone, arrested the cells in the G2-M phase in a dose-dependent manner. Apigenin also worked with daunorubicin, resulting in the increase of the cell distribution in G2-M phase. In conclusion, our results suggested that apigenin exhibited the synergic effect with daunorubicin in Chang liver/AP-1 cells to enhance the daunorubicin-induced cell growth inhibition, G2-M arrest, and apoptosis.