(-)-vitisin B 誘導人類血癌細胞凋亡分子機轉之探討

Study the molecular mechanisms of (-)-vitisin B on the induction of apoptosis in human leukemia cells

中文摘要

小葉葡萄 (Vitis thunbergii var. taiwaniana，簡稱 VTT) 是一台灣原生葡萄，在台灣被用來當作一種民間傳統藥物。它富含多酚類化合物 (Polyphenols) ，特別是槲皮素 (Quercetin) 、白藜蘆醇 (Resveratrol)，這些多酚類化合物在許多研究中，被證實具有保護心血管疾病、抗癌、抗衰老及改善腦神經退化性疾病 (Neurodegenerative diseases)。 (-)-vitisin B 是白藜蘆醇 (Resveratrol) 的衍生物，是由小葉葡萄中萃取之富含多酚類的化合物。本篇研究以人類急性骨髓性血癌第三型細胞 (HL-60：急性前骨髓性白血病) 爲研究模式，探討 (-)-vitisin B 誘導 HL-60 細胞凋亡分子機轉。首先，我們發現 (-)-vitisin B 具有抑制細胞增殖和誘導細胞凋亡的能力，這些現象受到 (-)-vitisin B 的作用時間和劑量影響，隨 (-)-vitisin B 劑量增加，細胞 SubG1 時期有明顯增加的趨勢。此外，給予 6.25 μM 劑量的 (-)-vitisin B ，發現其細胞週期停滯於 S 和 G2/M 時期有明顯增加的現象，這些結果皆指出 (-)-vitisin B 能誘導 HL-60 產生細胞凋亡。分析細胞凋亡蛋白表現，結果發現以不同濃度之 (-)-vitisin B 處理細胞後， PARP 裂解, 活化 caspase-3, -8, -9 凋亡蛋白之表現隨 (-)-vitisin B 濃度增加有增加的情形，並且誘導細胞凋亡之 Bax 蛋白表現亦有增加的趨勢。再者，以 (-)-vitisin B 處理細胞後，細胞亦有磷酸化 JNK, p38, 及 FasL 蛋白增加之情形，由以上結果得知 (-)-vitisin B 會藉由磷酸化 JNK, p38 以及 Fas 外因性細胞凋亡傳遞路徑誘導細胞凋亡。 H 具有發展成抗血癌藥物的潛力。

英文摘要

Vitis thunbergii var. taiwaniana (VTT) is a Taiwan original wild grape, and has been used as a folk medicine in Taiwan. VTT is rich in polyphenols, especially quercetin and resveratrol's derivatives, which have been demonstrated that exhibited an inhibitory activity on the carcinogenesis and prevented some of neurodegenerative diseases.

(-)-vitisin B is a resveratrol's derivative and extracted from VTT. In this study, we have investigated the mechanisms of (-)-vitisin B on the induction of apoptosis in human HL-60 promyelocytic leukemia cells. First, we found that (-)-vitisin B significantly inhibited cell proliferation and induced cell apoptosis. This effect appears to occur in a time- and dose-dependent manner. Cell cycle distribution was also examined and found that

(-)-vitisin B significantly induced SubG1 population in a dose-dependent manner. In

addition, (-)-vitisin B markedly increased the cell cycle population in S and G2/M phases at 6.25?峪. These results indicated that (-)-vitisin B might alter cell cycle distribution in HL-60 cells. When analyzing the expression of cell apoptosis-related proteins, we found that (-)-vitisin B dose-dependently induced PARP cleavage, activated caspase-3, -8, and -9, and increased proapoptotic bax protein expression. Moreover,
(-)-vitisin B treatment also resulted in the increase of phosphorylation of JNK and p38, and FasL expression. These results suggest that (-)-vitisin B -induced cell apoptosis might be mediated through the activation of JNK and p38 and Fas death signal transduction.