



Phellopterin-Induced Caspase-Dependent Apoptosis Through PI3K/AKT Pathway Inhibition in SMMC-7721 Human Hepatoma Cells

Rongrui BAO¹ #, Shuai WANG¹ #, Xinxin YANG¹, Gang CHEN² & Xiansheng MENG¹ *

¹ College of Pharmacy, Liaoning University of Traditional Chinese Medicine,
Dalian 116600, P. R. China

² School of Traditional Chinese Materia Medica, Shenyang Pharmaceutical University,
Shenyang 110016, China

SUMMARY. Phellopterin is a natural furanocoumarin isolated from the fruits *Heracleum mantegazzianum*, dating back to 1965. However, so far the detailed bio-activities of it were barely known. In this paper, we for the first time found it to be a potent natural antitumor agent against human liver cancer both *in vivo* and *in vitro*. Phellopterin inhibited SMMC-7721 cell proliferation dose-dependently with concentration ranging from 1 to 40 μ M. Both flow cytometry and Hoechst 33258 nuclear staining experiments showed that phellopterin could cause apoptosis in SMMC-7721 cells. Western blot results substantiated the inhibition on PI3K/AKT pathway by phellopterin. *In vivo* antitumor experiment with 18 weeks rat model of DEN-induced hepatoma showed that both 10 and 25 mg/kg phellopterin significantly suppressed the tumor growth with low toxicity. All these results suggested that phellopterin is a natural anti-tumor chemotherapeutic agent against liver cancer.

RESUMEN. Phellopterina es una furanocumarina natural aislada de los frutos de *Heracleum mantegazzianum*, que se remonta a 1965. Sin embargo, hasta el momento se conocían poco sus actividades biológicas. En este artículo, por primera vez, descubrimos que era un potente agente antitumoral natural contra el cáncer de hígado humano tanto *in vivo* como *in vitro*. Phellopterina inhibió la proliferación celular de SMMC-7721 de forma dependiente de la dosis con una concentración que oscila entre 1 y 40 μ M. Tanto la citometría de flujo como los experimentos de tinción nuclear Hoechst 33258 demostraron que la phellopterina podría causar apoptosis en células SMMC-7721. Los resultados de Western blot confirmaron la inhibición en la vía PI3K/AKT por la phellopterina. El experimento antitumoral *in vivo* con un modelo de rata de 18 semanas de hepatoma inducido por DEN demostró que tanto la phellopterina de 10 como la de 25 mg/kg suprimieron significativamente el crecimiento del tumor con baja toxicidad. Todos estos resultados sugieren que la phellopterina es un agente quimioterapéutico antitumoral natural contra el cáncer de hígado.

KEY WORDS: apoptosis, liver cancer, phellopterin, PI3K/AKT.

These authors contributed equally to this work.

* Author to whom correspondence should be addressed. E-mail: mxsvvv@163.com