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Isolation, characterization and investigation of antiproriferative activity of two isolated flavonoids from *Scutellaria liwinowii* and underlying apoptosis mechanism in cancer cell lines

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The *Scutellaria* species (Lamiaceae) is used as a source of flavonoids to treat a variety of diseases in traditional medicine. In spite of many reports about the cytotoxic and antitumor effects of some species of this genus the anti-cancer researches on one of the Iranian species, *S. litwinowii*, have not yet been conducted. In an attempt to isolate, characterize and investigate the cytotoxic properties of wogonin and neobaicalein two active flavonoids isolated from the plant, silica gel column chromatography employing gradient elution with petroleum ether/ethyl acetate solvent mixture and semi-preparative HPLC were done. Structure elucidation of wogonin, and neobaicalein were performed by ^{1}H, and ^{13}C NMRs. Wogonin and neobaicalein were isolated for the first time in *S. litwinowii*. The cytotoxic properties of total methanol, different fractions, and wogonin and neobaicalein two isolated flavonoids from *S. litwinowii* root extract were investigated on different cancer cell lines. Meanwhile, the role of apoptosis in this toxicity was explored. To elucidate the apoptotic mechanism we choose two myeloid cell lines, apoptosis-proficient HL60 cells and apoptosis-resistant K562 cells. An increase in the activity of caspases-3, -8 and -9; poly (ADP ribose) polymerase (PARP) cleavage; detection of phosphatidylserine on the outer layer of cell membrane; and sub-G1 peak in the flow cytometry histogram of treated cells, activation of the caspase-3 suggested the induction of apoptosis. *S. litwinowii* also increased the Bax/bcl-2 ratio. It could be concluded that *S. litwinowii* induced apoptosis in both apoptosis-proficient and apoptosis-resistant leukemic cells. To sum up, neobaicalein caused cytotoxicity and induced apoptosis in HL60 and K562 cells through interaction with the mitochondrial membrane proteins involved in apoptosis. Neobaicalein was demonstrated to induce apoptosis in both myelogenous leukemia cells and merits further investigation regarding therapeutic options in the treatment of hematological malignancies.

Keywords: apoptosis; Bax; caspase; Fas receptor; *Scutellaria litwinowii*; poly (ADP ribose) polymerase; neobaicalein