



Effects of dihydropyrano coumarins from *Ferulago macrocarpa* on VEGF, MMP9, MMP2 and study of binding modes using computational methods

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Background and objectives: *Ferulago macrocarpa* of Apiaceae (Umbelliferae) is native to the highlands of the west of Iran which contains dihydrocoumarins from phenolic class. Studies have shown that phenolic compounds at physiological concentrations could inhibit two groups of gelatinase matrix metalloproteinases (MMP2, MMP9). Due to the high diversity of coumarins in the plant, the possibility of the compounds to inhibit plant enzymes seem to be mentioned. **Methods:** Acetone extract of the plant was prepared and then winterized. Afterwards, dihydropyrano coumarins were purified using normal phase column chromatography and preparative HPLC, and their structures were verified. After culturing the cells, at confluence step, supernatants were collected at 24 and 48 h soup and non-proliferation medium containing 2% albumin. The pure substances were applied on cell lines U87MG and WEHI for evaluation of VEGF, MMP-2 and 9 activities. In the computational processing, the structures were docked in the active site of metalloproteinases 9, and significant interactions were determined. Subsequently, ligand-protein complexes were subjected to molecular dynamics simulation in water, and thermodynamic properties were calculated. (MMP9 code= 1L6J, MMP2 code= 1CK7). **Results:** Regarding cytotoxicity results, IC₅₀ of prantschimgin and grandivitin in WEHI cell line were 521.63, 232.66, and in U87MG cell line were 575.58, 322.0 lpg/mL, respectively. **Conclusion:** Two coumarins, prantschimgin and grandivitin with the potential inhibitory effects on the activity of MMP 2,9 and anti-angiogenesis were purified from *F. macrocarpa* fruits. The application can be expected to have therapeutic efficacy in cancer cell lines U87MG and WEHI.

Keywords: *Ferulago macrocarpa*, grandivitin, matrix metalloproteinase, ovarian cancer, prantschimgin