

Bioactive constituents of some plant species from the mountain Galičica

Iris Djordjević

Faculty of Veterinary medicine, University of Belgrade, Bul. Oslobođenja 18, 1100 Belgrade, Serbia

Introduction

Between 2008 and 2010 the pharmacognostic investigation of phytomedicinal potential of the species inhabiting mt. Galičica was organized by the Galičica National Park (GNP) through the KFW project entitled "Support to Galičica National Park". In the search for biologically active and new compounds, the project included the targeted collection of wild-growing mostly endemic plants growing on mt. Galičica. The choice of plants was based on chemotaxonomic and ethnomedicinal information of the corresponding genera. The phytochemical investigation of these species is presented in this lecture.

***Centaurea* spp. (Asteraceae)** (Tešević et al., 2014)

The aerial parts of the investigated species (*C. galicicae*, *C. tomorosii* and *C. soskae*) were collected during the flowering period (17 July 2010). Crude extracts of the ground dried aerial parts of the studied species (Et₂O/MeOH/Petrol ether, 1:1:1). According to HPLC/PDA/ESI HR TOF MS analysis, all the studied taxa contained cnicin, the germacranolide exhibiting numerous biological activities, as the main component. The flavonoid patterns of *C. galicicae* and *C. soskae* were rather similar, differing only in the relative amounts of the constituents. The flavonoid complex of *C. tomorosi* contained an additional component, cirsimaritin. The ¹H NMR quantitative analysis demonstrated high content of germacranolide cnicin (2.9 – 9.6%, calcd. per weight of the dried plant material) in the extracts.

***Helichrysum zivojini* Černjavski & Soška (Asteraceae)** (Aljančić et al., 2014)

The aerial parts of *H. zivojinii* were collected at Tomoros (ca. 1600 m altitude), Mt. Galičica (North Macedonia) during the flowering (17 July 2010). The combination of CC of *n*-BuOH extract by column chromatography (CC) on polyamide and semi-prep HPLC, afforded two new compounds, *i.e.* bisdihydrochalcone diglucoside containing a cyclobutane ring (tomoroside A) and a methylene-bridged bischalconeglycoside (tomoroside B), probably dimers of the co-occurring chalcone isosalipurposide. Seven known naringenin-, apigenin-kaempferol- and luteoline glucosides were also detected. Tomorosids A and B exhibited significant anticancer activities. Tomoroside B synergized with Tipifarnib showing potential to improve the action of this new chemotherapeutic involved in the modulation of mitogene activated protein (MAP) kinase signaling pathway.

***Cephalaria ambrosioides* (Sibth. & Sm.) Roem. & Schult (Dipsacaceae)** (Godevac et al. 2010)

The aerial parts of *C. ambrosioides* (endemic species of the Balkans) were collected on the slopes of Mt. Galičica between Ohrid and Prespa lakes in July 2008. The combination of Sephadex LH-20 and silica-gel CC of the 90% MeOH extract of air-dried aerial parts of *C. ambrosioides* afforded a new allose-containing triterpenoid saponin, together with a known saponin leucanthoside A, isolated previously in our laboratory from *C. leucantha*. (Godevac et al., 2006)

Leucantoside A exhibited a microtubule-stabilizing activity in the tubulin assay ($IC_{50} = 50 \mu M$). Under the same conditions, paclitaxel, used as a positive control, was about a hundred times more active.

***Sideritis raeseri* Boiss. and Heldr. subsp. *raeseri* (Lamiaceae)** (Menković et al., 2013)

Sideritis raeseri Boiss. and Heldr. subsp. *raeseri* is widely used in folk medicine as a tea to alleviate the symptoms of common colds, coughs, and bronchitis, as well as in the treatment of gastrointestinal disorders and inflammations, and as a tonic. The aerial parts of *S. raeseri* subsp. *raeseri* were collected in NPG in the zone of sustainable collection in the phase of full flowering (July, 2010) on three different localities. The aim of the study was the analysis of bioactive compounds especially those with anti-inflammatory activity. Combination of the UV and MS data of the ethanol extract (soxhlet extraction) allowed the characterization of 17 compounds, which could be classified into flavonoid glycosides (isoscuteallarein and hypolaetin derivatives) or hydroxycinnamic acid derivatives. The presence of phenylpropanoid glycoside martynoside was reported for the first time in the wild growing *S. raeseri* subsp. *raeseri*. Hypolaetin derivatives, known for their anti-inflammatory activity, dominated and were more abundant in *S. raeseri* subsp. *raeseri* grown in NPG in comparison with *S. scardica* grown nearby the NPG.

***Crateagus orientalis* Pall. ex M. Bieb. (Rosaceae)** (Šavikin et al., 2017)

Plant material was collected at the Mt. Galičica (altitude 950 m). Leaves were collected in June 2010, while fruits were collected in October 2010. *Crateagus orientalis* Pall. ex M. Bieb., traditionally used by local people in southern parts of North Macedonia for preventing and treating cardiovascular diseases including angina, hypertension, arrhythmias, and congestive heart failure. The main objective of this study was to define the phenolic content, antioxidant and anti-inflammatory activity of the extracts. The content of 7 phenolics in ethanolic extracts of leaves and berries was studied using HPLC-DAD. The most dominant compounds were hyperoside, isoquercitrin and chlorogenic acid. The leaf extract was more effective as a DPPH radical scavenger than the berry extract, as well as in the relative reducing power on Fe^{3+} . Anti-inflammatory potential was studied by means of COX-1 and 12-lipoxygenase 12-LOX

inhibitory activity; both extracts evinced activity. Furthermore, *C. orientalis* leaf extract showed a concentration dependent inhibition of COX-1 pathway products 12-HHT and TXB2, reaching IC_{50} values below the lowest applied concentration. Although inhibitors such as acetylsalicylic acid and quercetin showed higher activity, this study demonstrated the potential of the investigated extracts as anti-inflammatory agents.

Acknowledgments

This research was funded by the Ministry of Education, Science and Technological Development of the Republic of Serbia through the Grant Agreement with the University of Belgrade – Faculty of Veterinary medicine No 451-03-68/2022-14/200143.

References

- Aljančić, I. S., Vučković, I., Jadranin, M., Pešić, M., Đorđević, I., Podolski-Renić, A., Stojković, S., Menković, N., Vajs V. E., Milosavljević S. M., 2014. Two structurally distinct chalcone dimers from *Helichrysum zivojinii* and their activities in cancer cell lines. *Phytochemistry*, 98, 190–196. <https://doi.org/10.1016/j.phytochem.2013.11.025>.
- Gođevac, D., Mandić, B., Vajs, V., Menković, N., Macura, S., Milosavljević, S., 2006. Complete assignments of 1H and ^{13}C NMR spectra of leucanthoside A, a new triterpenoid saponin from *Cephalaria leucantha* L., 2006. *Magn. Reson. Chem.* 44, 731-735. <https://doi.org/10.1002/mrc.1834>.
- Gođevac, D., Menković, N., Vujisić, Lj., Tešević, V., Vajs, V., Milosavljević, S., 2010. A new triterpenoid saponin from aerial parts of *Cephalaria ambrosioides*. *Nat. Prod. Res.* 24 (14), 1307-1312. <https://doi.org/10.1080/14786410903230383>.
- Menković N., Gođevac D., Šavikin K., Zdunić G., Milosavljević S., Bojadži A. and Avramoski O., 2013. Bioactive Compounds of Endemic Species *Sideritis raeseri* subsp. *raeseri* Grown in National Park Galičica. *Rec. Nat. Prod.* 7:3, 161-1689
- Tešević, V., Aljančić, I., Milosavljević, S., Vajs, V., Đorđević, I., Jadranin, M., Menković, N., Matevski, V., 2014. Secondary metabolites of three endemic *Centaurea* L. species *J. Serb. Chem. Soc.* 79 (11) 1355–1362 <https://doi.org/10.2298/JSC140318048T>.
- Šavikin, K. P., Krstić-Milošević, D. B., Menković, N. R., Bearac, I. N., Mrkonjić, Z. O., Pljevljakušić D. S., 2017. *Crataegus orientalis* Leaves and Berries: Phenolic Profiles, Antioxidant and Anti-inflammatory Activity. *Nat. Prod. Commun.* 12 (2), 159-162.