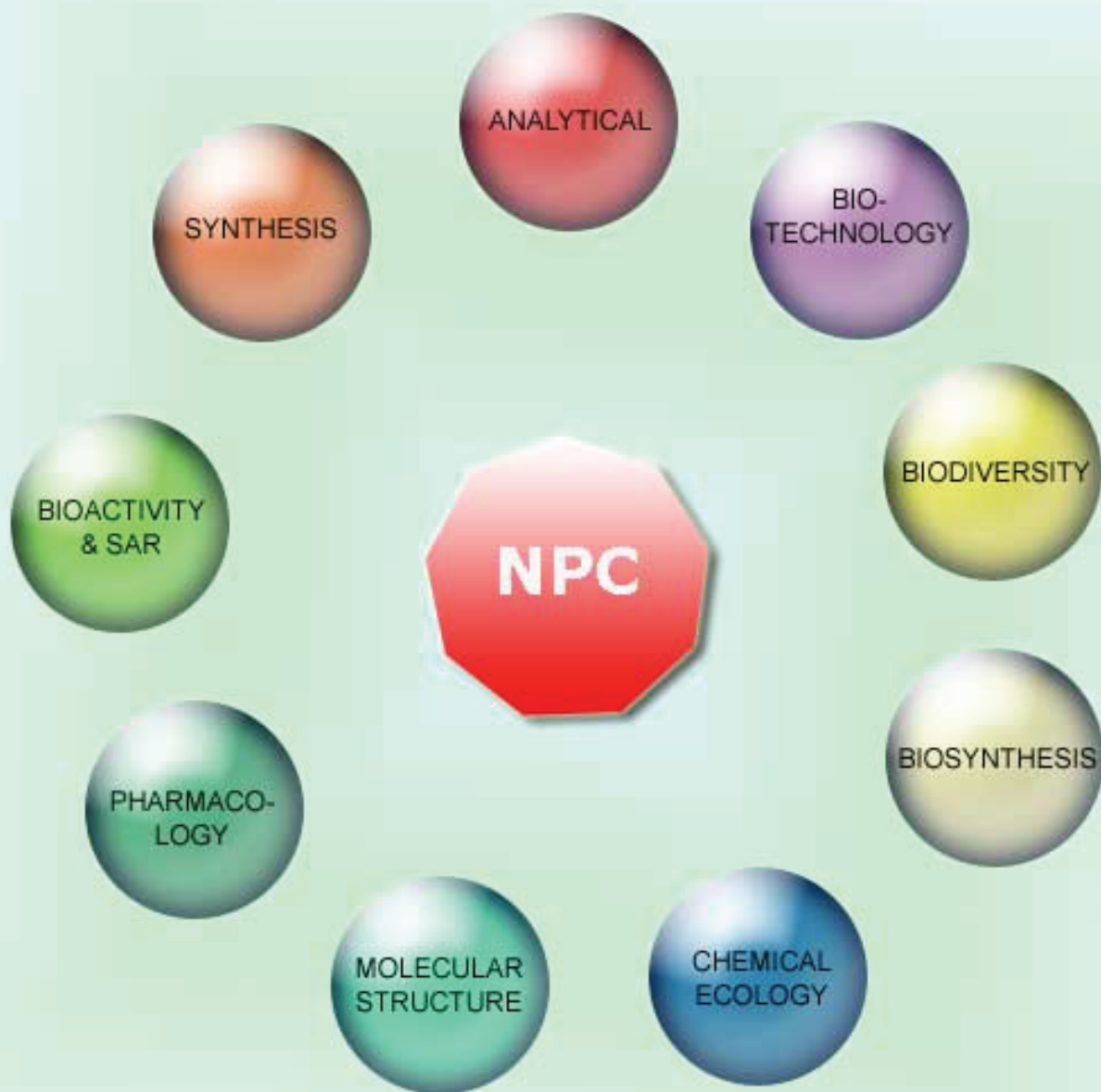


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Anti-inflammatory Activity of *Melampyrum barbatum* and Isolation of Iridoid and Flavonoid Compounds

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Melampyrum barbatum Waldst. & Kit. ex Willd. (Scrophulariaceae) has been used in traditional medicine for the treatment of rheumatic complaints and different skin diseases. In the course of our study the anti-inflammatory activity of the aerial parts of *M. barbatum* was evaluated. A MeOH extract was prepared and consecutively partitioned with CHCl₃, EtOAc and *n*-BuOH. The fractions were assayed in *in vivo* carrageenan-induced rat paw oedema model. The intraperitoneally administered *n*-BuOH phase exerted marked inhibitory effect (33.6 %, $p < 0.01$). Multistep chromatographic separation afforded mussaenoside and aucubine from *n*-BuOH fraction. Moreover, 8-epiloganin, loganic acid and mussaenoside were obtained from EtOAc fraction and apigenin, luteolin, benzoic acid and galactitol from CHCl₃ fraction. These data validate the ethnomedicinal use of *M. barbatum* for the treatment of inflammatory diseases and reveal that iridoids and flavonoids could be responsible for the anti-inflammatory effect of this species.

Keywords: *Melampyrum barbatum*, Scrophulariaceae, Iridoids, Flavonoids, Anti-inflammatory activity.

Melampyrum species (Scrophulariaceae) were widely applied in traditional medicine as anticonvulsant, sedative, cardiovascular and anti-inflammatory agents [1,2]. Chemical and pharmacological studies of *Melampyrum* genus afforded the identification of flavonoids, phenylcarboxylic acids, alkaloids, iridoids, triterpenoids and sterols [3-6]. Pharmacological studies demonstrated that *Melampyrum* species have antioxidant, free radical scavenging and anti-inflammatory properties, and sedative effect targeting GABAergic neurotransmission [2,7,8]. No data on the chemical constituents of this species have been reported earlier.

In the present work the aerial parts of *M. barbatum*, collected from wild stock in Hungary, were extracted with MeOH-H₂O 7:3, and then liquid-liquid partition was performed with CHCl₃, EtOAc and *n*-BuOH. These fractions were examined for anti-inflammatory activity using *in vivo* carrageenan-induced rat paw oedema test after intraperitoneal (i.p.) administration of the samples. The *n*-BuOH extract (MBAR Bu) had pronounced inhibitory effect (33.6 %, $p < 0.01$) at 10 mg/kg dose, whereas the EtOAc and CHCl₃ extracts (MBAR EtOAc and MBAR CHL) did not influence the intensity of the inflammatory reaction significantly ($p > 0.05$) (Figure 1).

The CHCl₃, EtOAc and *n*-BuOH fractions of *M. barbatum* were subjected CC, VLC and preparative TLC separations. The isolated compounds were identified by 1D and 2D NMR analyses. Apigenin, luteolin, benzoic acid and galactitol were isolated from CHCl₃ fraction; 8-epiloganin, loganic acid and mussaenoside from EtOAc fraction; and mussaenoside and aucubin were obtained from the *n*-BuOH fraction.

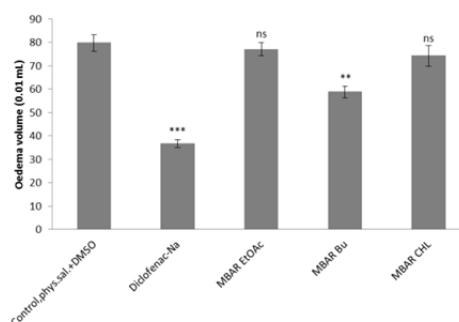


Figure 1: Inhibitory effects of *M. barbatum* extracts (10 mg/kg, i.p.) and diclofenac-Na (5 mg/kg, i.p.) on carrageenan-induced paw oedema volume in rats. Each column indicates the mean \pm SEM. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; compared with physiological saline and DMSO (5 mL/kg) in the control group.

Recent studies have shown the anti-inflammatory activity of aucubin in the same *in vivo* model (inhibition 37.9%, $p < 0.001$ at 5.0 mg/kg) [9]. The anti-inflammatory effect of 8-epiloganin and mussaenoside was investigated, and found that both compounds suppressed the production of nitric oxide (NO) and prostaglandin E₂, and the expression of inducible NO synthase and cyclooxygenase-2 (COX-2) induced by lipopolysaccharide (LPS) in the RAW264.7 murine macrophage cell line. 8-Epiloganin and mussaenoside also inhibited the release of pro-inflammatory cytokines induced by LPS, namely, tumor necrosis factor- α and interleukin-1 β [10]. Anti-inflammatory effects of loganic acid on carrageenan-induced mouse paw oedema and TPA-induced mouse ear oedema models was demonstrated [11]. Moreover, loganic acid

was found to be a potent anti-inflammatory agent when iridoids were evaluated for their potential to inhibit COX-1 and COX-2 enzymes. In these assays, loganic acid exhibited COX-1 (36.0±0.6%) and COX-2 (80.8±4.0%) inhibition at 10 µM concentration [12]. Apigenin and luteolin were found to significantly inhibit TNF α -induced NF- κ B transcriptional activation due to inhibition of the activity of GAL4-NF- κ B p65 fusion protein. Furthermore, the administration of apigenin and luteolin markedly inhibited acute carrageenan-induced paw edema in mice [13].

All of the above studies indicate that iridoids and flavonoids are responsible for the anti-inflammatory activity of *M. barbatum* extract. The highest activity of the *n*-BuOH phase most probably is the consequence of the high accumulation of iridoids in this fraction. Our study validates the ethnomedicinal use of the plant for the treatment of inflammatory diseases, and are in good agreement with earlier results reported for *M. pratense*, which anti-inflammatory activity was proved on peroxisome proliferator-activated receptors- (PPARs)- α and - γ , activation of NF- κ B, induction of interleukin-8 (IL-8) and E-selectin *in vitro* [2].

Experimental

Plant material: *M. barbatum* Waldst. & Kit. ex Willd. was gathered in Öskü (Hungary) in July 2013 and identified by Gy. Pinke and G. Király. A voucher specimen (MBAR No 35) was deposited in the Herbarium of Institute of Pharmacognosy, University of Szeged. The plant material was stored at -20 °C until processing.

Extraction and Isolation: The ground aerial parts (4 kg) were extracted with 17 L MeOH-H₂O 7:3 for 3×20 minutes using an ultrasonic bath. The extract obtained was concentrated in vacuum and fractionated using solvent-solvent partition with CHCl₃ (3.5 L), EtOAc (3.5 L) and *n*-BuOH (3.5 L). On evaporation of the CHCl₃ phase, galactitol was crystallised. The mother liquor of CHCl₃ phase (10.88 g) was subjected to CC on polyamide using MeOH-H₂O mixtures (1:4, 2:3, 3:2, 4:1, v/v) as eluents. In MeOH-H₂O (2:3) eluate crystal formation (benzoic acid) was observed. Fraction obtained with MeOH-H₂O (3:2) was separated

by prep TLC on silica gel with *n*-hexane-acetone (3:2, v/v), yielding apigenin (5.9 mg) and luteolin (10.2 mg). The EtOAc fraction (2.98 g) was purified by prep TLC on silica gel using CHCl₃-MeOH (4:1, v/v) as eluent. The detection was performed by spraying with *p*-dimethylamino-benzaldehyde + cc. HCl solution. By this means mussaenoside (56.4 mg) [5], 8-epiloganin (15.6 mg) [5] and loganic acid (12.2 mg) [3] were isolated. The *n*-BuOH phase (33.48 g) was separated by VLC on silica gel G (15 µm, Merck) using gradient system of CH₂Cl₂-EtOAc-MeOH-H₂O (1:1:0:0, EtOAc, 0:4:1:0, 0:1:1:0, MeOH, 0:0:1:1 v/v/v/v), to obtain 13 fractions (I-XIII). Fraction VI was further purified by preparative TLC on silica gel with EtOAc-MeOH-H₂O (5:2:3, v/v/v), affording mussaenoside (18.6 mg) and aucubin (49.6 mg) [5].

In vivo anti-inflammatory effect on carrageenan-induced paw oedema model: The anti-inflammatory effect was investigated in carrageenan-induced inflammatory paw oedema model in rats as described in ref [9]. The animals were treated in accordance with 86/609/ECC Directives and the Hungarian Act for the Protection of Animals in Research (Article 32 of Act XXVIII), with the approval of the Hungarian Ethics Committee for Animal Research (No IV/198/2013). Each experimental group comprised ten rats. The animals received 10 mg/kg i.p. of the CHCl₃, EtOAc and *n*-BuOH phases. Physiological saline-DMSO mixture was used as control. Diclofenac-Na (5 mg/kg i.p.) was administered as positive control (inhibition 37%, *p* < 0.001).

Statistical analysis was performed with Prism 5.0 software (GraphPad, San Diego, CA, USA). The differences in the extents of paw oedema between the treated and control groups were determined by one-way analysis of variance (ANOVA) with Dunett's test. The criterion for statistical significance was *p* < 0.05. All values are expressed as mean ± SEM.

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Synthesis of Ficusnotins, Rare 1,4-Diarylbutanoids Derived from <i>Ficusnota</i>, via Ruthenium-Catalyzed Conjugate Addition Jeong A Yoon, Sungwan Ahn and Young Taek Han	351
Identification of the Metabolites of a Novel Anti-MRSA Compound, Kaempferol-3-O-Alpha-L-(2",3"-di-<i>p</i>-coumaroyl)rhamnoside (KCR), Extracted from American Sycamore Jiajiu Shaw, Kenneth Swartz, Frederick Valeriote, Joseph Media, Ben Chen, Mark T. Hamann and Xiaojuan Wang	355
Anthocyanins from the Red Flowers of <i>Meconopsis wallichii</i> in Bhutan Tsukasa Iwashina, Rinchen Yangzom, Yoshinori Murai, Kencho Dorji, Takayuki Mizuno and Choki Wangmo	359
New Polyisoprenylated Polycyclic Phloroglucines from <i>Clusia gundlachii</i> Jin Zhang, Jianping Zhao, Volodymyr Samoylenko, Surendra Jain, Babu L. Tekwani and Ilias Muhammad	361
Polyisoprenylated Acylphloroglucinols from <i>Garcinia nervosa</i> Alfarius Eko Nugroho, Hitomi Nakamura, Daisuke Inoue, Yusuke Hirasawa, Chin Piow Wong, Toshio Kaneda, A. Hamid A. Hadi and Hiroshi Morita	367
Synergy between Essential Oils of <i>Calamintha</i> Species (Lamiaceae) and Antibiotics Marina Milenković, Jelena Stošović and Violeta Slavkovska	371

Accounts/Reviews

Pharmaceutical, Ethnopharmacological, Phytochemical and Synthetic Importance of Genus <i>Aerva</i>: A Review Sara Musaddiq, Kiran Mustafa, Sajjad Ahmad, Samina Aslam, Basharat Ali, Samia Khakwani, Naheed Riaz, Muhammad Saleem and Abdul Jabbar	375
--	-----

Natural Product Communications

2018

Volume 13, Number 3

Contents

Progress on Bioactive Secondary Plant Metabolites

(Guest Editor: Antonio Evidente)

Original Paper

Page

Anti-inflammatory Activity of *Melampyrum barbatum* and Isolation of Iridoid and Flavonoid Compounds

Erzsébet Háznagy-Radnai, Laura Fási, Edit Wéber, Gyula Pinke, Gergely Király, Anita Sztojtkov-Ivanov, Róbert Gáspár and Judit Hohmann

235

Phytotoxic Lignans from *Artemisia arborescens*

Andrea Labruzzo, Charles L. Cantrell, Alessandra Carrubba, Abbas Ali, David E. Wedge and Stephen O. Duke

237

Accounts/Reviews

Pseudoguaianolides: Recent Advances in Synthesis and Applications

Margherita Barbero and Cristina Prandi

241

Medical Cannabis for the Treatment of Inflammation

Dvory Namdar and Hinanit Koltai

249

A Review on Recent Syntheses of Amaryllidaceae Alkaloids and Isocarbostryls (Time period mid-2016 to 2017)

Willem A. L. van Otterlo and Ivan R. Green

255

Natural Phenylidihydroisocoumarins: Sources, Chemistry and Bioactivity

Serhat S. Çiçek, Sara Vitalini and Christian Zidorn

279

Allelopathy for Parasitic Plant Management

Alessio Cimmino, Marco Masi, Diego Rubiales, Antonio Evidente and Monica Fernández-Aparicio

289

Original Paper

Approach to Determination a Structure – Antioxidant Activity Relationship of Selected Common Terpenoids Evaluated by ABTS^{•+} Radical Cation Assay

Karolina A. Wojtnik-Kulesza, Łukasz M. Cieśla and Monika Waksmundzka-Hajnos

295

Oxygenated Terpenes from the Indo-Pacific Nudibranchs *Goniobranchus splendidus* and *Goniobranchus collingwoodi*

Louise C. Forster, Andrew M. White, Karen L. Cheney and Mary J. Garson

299

Cochlearoids L and M: Two New Meroterpenoids from the Fungus *Ganoderma cochlear*

Fu-Ying Qin, Yong-Ming Yan, Zheng-Chao Tu and Yong-Xian Cheng

303

Oxidation of 3 β -Acetoxy-21 β -acetyl-20 β ,28-epoxy-18 α ,19 β H-ursane into Novel gem-Chloronitro- and 1,2,4,5-tetraoxane derivatives

Emil Yu. Yamansarov, El'mira F. Khusnutdinova, Alexander N. Lobov, Oxana B. Kazakova and Kirill Yu. Suponitsky

307

Expression of Carotenoid Biosynthetic Genes and Carotenoid Biosynthesis during Seedling Development of *Momordica charantia*

Do Manh Cuong, Jae Kwang Kim, Jin Jeon, Tae Jin Kim, Jong Seok Park and Sang Un Park

311

Metabolic Profiling and Chemical-Based Antioxidant Assays of Green and Red Lettuce (*Lactuca sativa*)

Chang Ha Park, Hyeon Ji Yeo, Thanislas Bastin Baskar, Jae Kwang Kim and Sang Un Park

315

Effect of Guggulsterone on the Expression of Adiponectin in 3T3-L1 Cells

Indira Saikumar, Avinash A. Rasalkar, Bhadravathi M. Shivakumar, Divijendra N. Reddy and Rajyalakshmi Malempati

323

Synthesis of Analogues of (+)-Gomphoside, a Potent HIF-1 Inhibitor and Cardenolide

Eckehard Cuny

327

On the Structure of (*R*)-2-Methylheptyl Isonicotinate: Evidence for the Structural Solution from Total Synthesis

Mangala Gowri Ponnappalli, Narayana Rao Gundaju, Harikiran Theerthala, Ramesh Bokam and Nageswara Rao Yalavarthi

335

A New Quinolone Alkaloid with Cytotoxic Activity from the Fruits of *Euodia Rutaecarpa*

Chen Ma, Xiao Liu, Yu Shan, Shu Xu, Xiu-li Su, Xu Feng and Qi-Zhi Wang

339

Two Nitrogen-containing Compounds from *Pseudostellaria heterophylla*

Xiang-Ming Liao, Xun He, Guo-Bo Xu, Zhen Wang, Jing Li, Huan-Yu Guan, Meng Zhou, Yong-Jun Li, Yong-Lin Wang, Li-She Gan and Shang-Gao Liao

343

Yohimbine-related Alkaloids from *Tabernaemontana corymbosa*

Alfarius Eko Nugroho, Miho Moue, Tadahihiro Sasaki, Osamu Shirota, A. Hamid. A. Hadi and Hiroshi Morita

347

Continued inside backcover