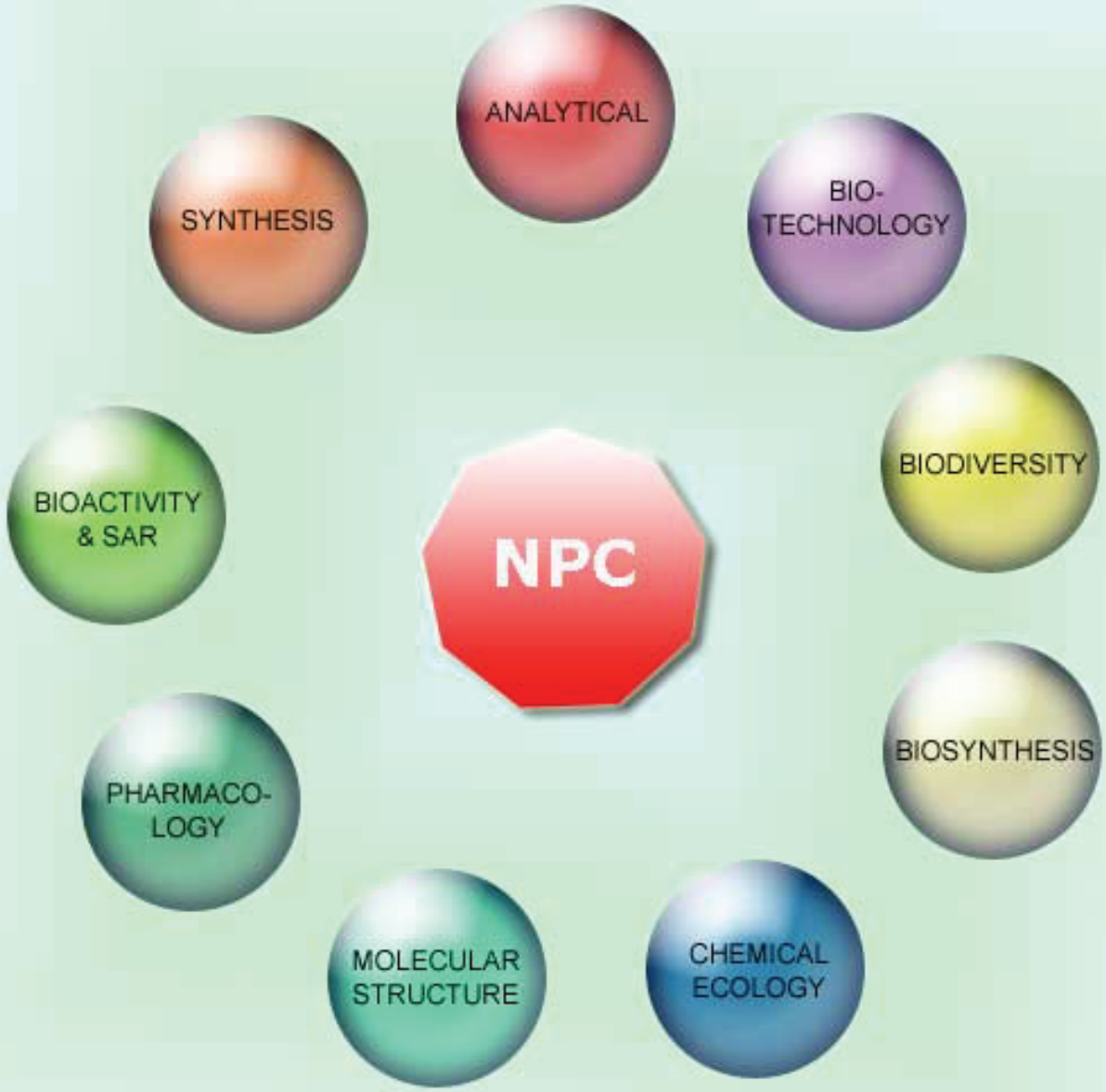
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Phytochemical Profile and Anti-lipase Activity of Balkan Endemic *Jurinea tzar-ferdinandii*

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Phytochemical study of the Balkan endemic *J. tzar-ferdinandii* Davidov allowed the identification of twenty-two components. β-Amyrin, lupeol, taraxasterol and ψ-taraxasterol and their 3-*O*-acetates and 3-*O*-palmitates were identified by GC/MS. Six closely related sesquiterpene lactones and four flavones were isolated from the chloroform extract using column chromatography, and their structural identification was performed by spectral analyses. All isolated compounds are described for the first time in *Jurinea* species. The inhibitory potential of the total chloroform extract, fractions containing triterpenes, flavonoids and sesquiterpene lactones as well as individual compounds against a bacterial lipase from *Candida rugosa* (CRL) and a lipase from porcine pancrease (PPL) was evaluated. The half maximal inhibitory constants (IC_{50}) for the two enzymes were in the range of 28-150 μg/mL. The strongest inhibitory activity was found for the total chloroform extract (29±1 μg/mL and 39±1 μg/mL for CRL and PPL, respectively.). Among the individual compounds, onopordopicrin was found to be the most potent inhibitor for CRL and PPL with IC_{50} values of 32±1 μg/mL and 36±1 μg/mL, respectively.

Keywords: *Jurinea tzar-ferdinandii*, Asteraceae, Sesquiterpene lactones, Flavonoids, Triterpenoids, Lipase inhibitors.

The genus *Jurinea* Cass. (Asteraceae) comprising about 250 species is widespread in Southwest and Central Asia, the Mediterranean and the Balkan regions of Europe [1]. This genus is represented by 10 taxa in Bulgaria, five of them are local or Balkan endemics [2,3]. The phytochemical studies on genus *Jurinea* are limited and only a few species have been investigated so far. The literature survey revealed that *Jurinea* species are rich in sesquiterpene lactones, of which germacranolides are the most characteristic for this genus [4]. In addition, the pentacyclic triterpenes were found in the roots of *J. albicaulis* L. [5a] and in the fruits of *J. anatolica* Boiss. and *J. consanguinea* DC [5b]. Further, arctigenin and arctiin, have been isolated from the fruits of *J. mollis*. This aglycone-glycoside pair is dibenzylbutyrolactone lignans is reported to exhibit antioxidant, antiproliferative, antiviral, neuroprotective and colitis inhibitory properties [6]. Recently, the total phenolic and flavonoid contents in *J. consanguinea* DC and *J. dolomianea* Bioss extracts have been reported in relation to their antioxidant capacity [7,8]. The isolation of individual phenolic components from *Jurinea* species has not been described so far. These classes of natural products possess wide variety of biological and pharmacological activities such as antiviral, antibacterial, antifungal, hepatoprotective, cardiovascular, antiinflammatory, antiatherosclerotic, gastroprotective, etc. [9-12].

Enzyme inhibition is one of the most successful strategies for the regulation of some serious metabolic disorders and/or is able to alleviate effectively acute symptoms of some diseases and improve conditions. For example, drugs based on pancreatic lipase inhibitors are the only alternative for long-term treatment of obesity, a serious disease associated with a vast number of chronic diseases and disabilities like dyslipidemia, fatty liver disease, osteoarthritis, hypertension, type 2 diabetes, gastrointestinal cancers, coronary artery disease, heart failure, and stroke [13, 14].

At the same time, in recent years *Candida rugosa* has been recognized as an emerging fungal pathogen, which affects immunocompromized patients, patients receiving antibiotics or some patients exposed to invasive medical procedures [15]. *Candida rugosa* strains are refractory to antifungal therapy and the inhibition of *Candida rugosa* lipase and other proteolitic enzymes can affect microbial fitness and virulence and thus to assist in the treatment of the disease [16].

Up to date various plants have been screened for their anti-lipase activity and representatives of different chemical classes (saponins, polyphenols, flavonoids, di- and triterpenoids) and it was reported that many of them are potent lipase inhibitors [17-19]. However, only few of them are implemented in the practice due to their high cytoxicity or lack of enzyme selectivity. Yet, novel lipase inhibitors are of current research interest and can be a basis for development of high-added-value products such as food additives, nutraceuticals, and pharmaceuticals.

The aim of this study was to investigate chemical constituents of the unexplored Balkan endemic species *Jurinea tzar-ferdinandii* Davidov and to evaluate their anti-lipase properties against a pancreatic lipase and a bacterial lipase from *Candida rugosa.*

Aerial parts of *J. tzar-ferdinandii* were extracted successively with n-hexane and $CHCl_3$. n-Hexane extract was separated by CC on Silica gel and the obtained subfractions were analyzed by GC/MS. β-Amyrin (**1**), lupeol (**2**), taraxasterol (**3**) and ψ-taraxasterol (**4**), and the corresponding 3-*O*-acetates (**5 - 8**) and 3-*O*-palmitates (**9 - 12**) were identified by comparison their mass spectra with literature data [5, 20]. Further, CC and prep. TLC separation of the $CHCl_3$ extract afforded six closely related sesquiterpene lactones. Onopordopicrin (**13**) [21], onopordopicrin-4α,5β-epoxide (**14**) [22], 8-(4'-hydroxymethacryloyloxy)-15-oxohelianga-1(10),4,11 (13)-trien-6, 12-olide (**15**) [23], 8α-(4'-hydroxymethacryloyloxy)-4-epi-sonchucarpolide (**16**) [22, 24], 8α-(4'-hydroxymethacryloyloxy)-sonchucarpolide (**17**) [22], and 8α-(4'-hydroxymethacryloyloxy)-15-oxo-elema-1,3,11(13)- trien-12,6-olide (**18**) [25] were identified by comparison their NMR spectral data with those published in the literature. In addition, pectolinarigenin (**19**) [26], eupatilin (**20**) [27], jaceosidin (**21**) [28] and hispidulin (**22**) [29] were the flavonoids

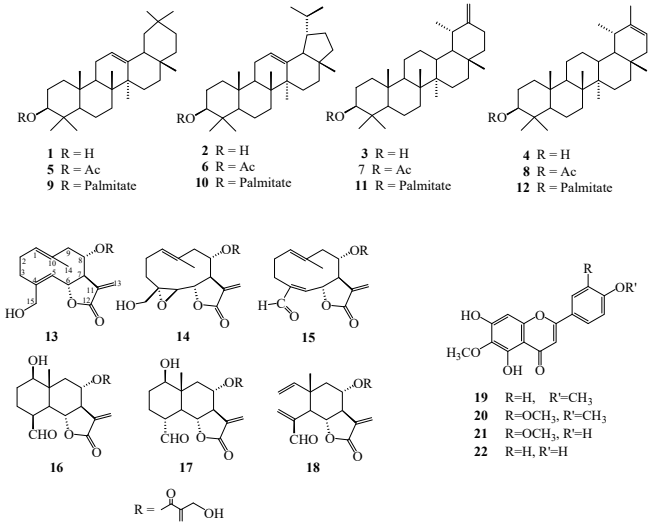


Figure 1: Structures of identified compounds.

identified by their ^{1}H NMR, MS and UV spectra using shift reagents for determination of OH and OMe positions in the structures.

The described sesquiterpene lactones are with germacrane, eudesmane and elemane carbon skeleton. All of them contained 4-hydroxymethacryloyl ester residue at C-8 and 12,6-*trans*-α-methylene-γ-lactone ring. The described above lactones were isolated for the first time from *Jurinea* species and the lack of any functional group at C-14 distinguishes them from the lactones found so far in the genus *Jurinea,* all of which contained oxygenated substituent at this position. The literature survey revealed that compounds **13**-**18** have been previously found in *Onopordon* и *Centaurea* genera [30, 31]. Further, all isolated flavonoids are 5,7-dihydroxy-6-methoxyflavones, differing in the substitution pattern of ring B: 4'-mono- (**19** and **22**) and 3',4'-disubstituted (**20** and **21**) with OH and/or OMe groups. It is worth to note, that the presence of flavonoids in *Jurinea* species is reported for the time now. Compounds **19 - 21** have been described as components in some *Centaurea* species [32], while only pectolinarigenin (**19**) and hispidulin (**22**) have been found in *Onopordon* plants [30]. *Onopordon* and *Centaurea* genera together with genus *Jurinea* belong to tribe Cardueae (Asteraceae). Thus, based on the structural type of the isolated lactones *J. tzar-ferdinandii* probably occupies an intermediate position and supported biogenetic relationship of genus *Jurinea* and the other two genera. The described flavonoids support partially this hypothesis, but further studies are needed, in order to understand their chemotaxonomical role in this case.

Table 1: Inhibitory activity of fractions and individual compounds against *C. rugosa* (CRL) and porcine pancreas (PPL) lipases.

Sample	CRL, IC_{50} [μg/mL]	PPL IC_{50} [μg/mL]
TrOH fraction	94±4	110±3
TrOAc fraction	119±3	148±5
TrOPal fraction	80 ±2	85±4
$CHCl_3$ extract	29±1	39±1
FL fraction	90±3	60±2
Onopordopicrin (13)	32±1	36±1
Pectolinarigenin (19)	111±3	126±5
Eupatilin (20)	91±3	85±3
Jaceosidin (21)	81±3	56±2
Orlistat (positive control)	27±1	11±0.4

Inhibitory activities of $CHCl_3$ extract**,** fractions containing triterpene alcohols (TrOH), triterpenyl acetates (TrOAc), triterpenyl palmitates (TrOPal) and flavonoids (FL) and individual compounds onopordopicrin (**13**) and flavonoids **19-21** were studied against a bacterial lipase from *Candida rugosa* (CRL) and a lipase from porcine pancreas (PPL) (Table 1). The estimated half maximal inhibitory constants (IC_{50}) for the two enzymes were in the range of 28-150 μg/mL. The total $CHCl_3$ extract, which contained sesquiterpene lactones and flavones was the most potent inhibitor for the two tested enzymes. Amongst the triterpenoids the strongest inhibitory activity was found for the fraction of the triterpenyl palmitates (TrOPal), which is probably due to their long-chain fatty acid substituents, which are able to accommodate efficiently in the substrate binding subside of the two lipases and thus, hinders the access of the substrate to the enzyme active side. Interestingly, the sesquiterpene lactone **13** possessed the lowest IC_{50} for the two enzymes (32±1 and 36±1 μg/mL, respectively) and was found to be the best inhibitor among individual compounds. Probably the lactone moiety of onopordopicrin interacts with the active sites PPL and CRL as it has been found for Orlistat, an irreversible inhibitor of lipases from *Candida sp.* and human pancreatic lipase [33, 34]. It has been established, that β-lactone ring in the tetrahydrolipstatin molecule is responsible for lipase inhibitory activity and its opening results in loss of activity [33, 34]. There is no information about the possible involvement of sesquiterpene γ-lactones on this matter so far. In fact, there is only one report on anti-lipase activity of sesquiterpene lactones [35].

Experimental

General: IR, Bruker Tensor 27 FT-IR spectrometer; NMR, Bruker Avance II+ 600 NMR spectrometer; CC, Sephadex LH20, Silica gel 60(230–400 mesh); TLC, Silica gel 60 F254 plates; TLC plates were visualized by spraying with: conc. H_2SO_4 followed by heating (150°C) for sesquiterpene lactones and NP/PEG reagent and UV visualization at 366 nm for flavonoids.

Gas Chromatography-Mass Spectrometry (GC/MS): The GC/MS analysis was performed on a gas chromatograph HP 6890 GC System Plus coupled to a mass selective detector HP 5973 MSD (Hewlett Packard, Palo Alto, CA). An ultra-inert fused silica capillary column DB-5ms UI (J&W Scientific, Folsom, CA) with 30 m column length, 0.25 mm i.d., 0.25 μm film thickness, was used. The oven temperature was programmed from 80°C to 300°C at a rate of 5°C /min and 20 min held at the final temperature was applied. Helium was used as a carrier gas at a constant flow rate of 0.8 ml/min. The split ratio was 1:50, the inlet temperature was set to 300°C and the transfer line temperature was 320°C. Mass selective detector operated in electron impact ionization (EI) mode at 70 eV electron energy, the ion source temperature was set to 230°C, and the quadrupole temperature was 150°C. The mass scan range was 45-700 amu. Instrument control and data collection were carried out using MSD Productivity ChemStation (E.02.02 SP2, Agilent Technologies).

***Plant material*:** Wild growing *J. tzar-ferdinandii* was collected in full flowering stage in July 2016 from Chepan mountain in Bulgaria. The plant was identified by Prof. D. Dimitrov (National Museum of Natural History, Bulgarian Academy of Sciences, 1000 Sofia, Bulgaria). A voucher specimen (SOM 1356) has been deposited in the Herbarium of the Institute of Biodiversity and Ecosystem Research, BAS, Sofia, Bulgaria.

Extraction and isolation: Dried and powdered aerial parts of *J. tzar-ferdinandii* (25 g) were successively extracted with n-hexane and then with $CHCl_3$ (maceration at room temperature, 24 hours, two times). After filtration, the extracts were dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum at low temperature (40°C) to yield the crude extracts 0.24 g (n-hexane) and 1.5 g ($CHCl_3$). The hexane extract was separated by prep. TLC (Silica

gel, $CHCl_3$/hexane, 3:1) in 3 fractions (**A**, **B** and **C**), the composition of which was determined by GC/MS. β-Amyrin (**1**), lupeol (**2**), taraxasterol (**3**) and ψ-taraxasterol (**4**) were detected in Fr. **A**. Their 3-*O*-acetates (**5** - **8**) and 3-*O*-palmitates (**9** - **12**) were identified in Fr. **B** and Fr. **C**, respectively**.**

A portion of $CHCl_3$ extract (580 mg) was subjected to CC on Sephadex LH20 eluted with MeOH to give 3 fractions (S1 – S3). Fr. S1 (30.0 mg) contained triterpene derivatives identified in hexane extract described above as well as β-sitosterol detected by TLC and in the presence of authentic standard. Fr. S2 (450 mg) was separated by CC (Silica gel, $CHCl_3$/Acetone, 5:1 with increasing polarity to 0:1) in 12 subfractions (S2/1 – S2/12) combined according to their TLC profiles. From subfraction S2/4 (11.5 mg) by prep TLC (Silica gel, $CHCl_3$ / diethyl ether 1:1) was isolated 6.3 mg of compound **15**. Subfractions S2/7 (13.2mg), S2/8 (32.4 mg), S2/9 (15.5 mg) and S2/10 (16.0 mg) contained mainly one spot in their TLC (Silica gel, $CHCl_3$/Acetone, 4:1) and without additional purification was proved by ^{1}H-NMR spectroscopy the presence of compounds **18, 13**, **14**, and **15**, respectively. Prep TLC (Silica gel, $CHCl_3$/MeOH, 15:2) of S2/11 (38.4 mg) afforded 5.0 mg of compound **17**. Prep. TLC (Silica gel, $CHCl_3$/ MeOH, 20:1) of a portion of Fr. S3 (15 mg) afforded pectolinaragenin (**19**, 1.3 mg), eupatolin (**20**, 1.6 mg), jaceosidin (**21**, 4.6 mg) and hispidulin (**22**, 0.8 mg).

Lipase inhibition assay: The lipase activity was determined by monitoring the hydrolysis of a chromogenic substrate 4-nitrophenylpalmitate (4-NPP) (Sigma) spectrophotometrically at 410 nm. In the study lipase from porcine pancreas (PPL) (20.6 U/mg, olive oil as a substrate, 20% w/w protein content) (Fluka) and a lipase from *Candida rugosa* (CRL) (MW 64 kDa, 30 U/mg (olive oil as a substrate), 10 % (w/w) protein content) (Amano Pharmaceutical Co., Japan) were used. Tetrahydrolipstatin (Orlistat) was purchased from Sigma and was used as a positive control. Initially, stock solutions of the tested compounds (1.5 mg/mL) in DMSO were prepared. The substrate solution was prepared by dissolving 15 mg 4-NPP in 5 mL iso-propanol and then it was diluted to 50 mL with sodium-phosphate buffer (5 mM, pH 7.0). PPL (0.2 mg/mL) and CRL (0.05 mg/mL) were dissolved in sodium-phosphate buffer (5 mM, pH 7.0). In a typical reaction, to 1.8 mL of the substrate solution was added 0.5 mL of the studied compounds (various concentrations). The reaction started by adding 0.1 mL 0.2 mL PPL or CRL (stock solution). The temperature was maintained at 25^{o}C. The release of the 4-nitrophenol with the time was monitored. Lipase inhibition was calculated from the residual activity detected in the presence of the compound with respect to that of the sample without additive. IC_{50}, the concentration of the tested compound required to decrease the lipase activity by 50%, was determined graphically by a plot of percent of inhibitions versus log concentrations of the test sample. All experiments were done in triplicate the value reported referred to means. Standard deviation was determined by Microsoft Excel Program.

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Anti-Melanogenic Effect of Chestnut Spike Extract through Downregulation of Tyrosinase-Related Proteins and Activation of ERK 1/2
Jung-Hee Byeon, Md Badrul Alam, Ki-Chan Kim, Sangsun Heo, Ji-young Lim, Yoon-Gyung Kwon, Peijun Zhao, Yeong-Ho Cha, Hee-Jeong Choi and Sang-Han Lee **1023**

Analysis of the Volatile Components of *Pouteria sapota* (Sapote Mamey) Fruit by HS-SPME-GC-MS
Candelario Rodríguez, Armando A. Durant-Archibold, Ana Santana, Enrique Murillo and Carlos M. Franco Abuín **1027**

An Analysis of Volatile Components of the Liverworts *Dumortiera hirsuta subsp. hirsuta and Dumortiera hirsuta subsp. nepalensis* (Dumortieraceae) from Panama and Taxonomic Observations on the Species
Armando A. Durant-Archibold, Noris Salazar Allen, Anette Garrido, Jose Gudiño Ledezma and Mahabir P. Gupta **1031**

Terpenes and *n*-Alkanes in Needles of *Pinus cembra*
Biljana Nikolić, Marina Todosijević, Mihajlo Ratknić, Iris Đorđević, Jovana Stanković, Mirjana Cvetković, PetarD. Marin and Vele Tešević **1035**

Morphologic and Essential oil Profiles of Three Species from Asteraceae
Melda Dolarslan and Tugba Gurkok **1039**

Composition and Chemical Variability of Needle and Berry Oils from Corsican *Juniperus communis* var. *communis*
Joséphine Ottavioli, Ange Bighelli, Joseph Casanova and Félix Tomi **1043**

Antifungal and Insecticidal Properties of *Juniperus thurifera* Leaves
Meryem El Jemli, Naima Khattabi, Khadija Lachqer, Driss Touati, Yousra El Jemli, Ilias Marmouzi, El Mahdi Wakrim, Yahia Cherrah and Katim Alaoui **1047**

Antimicrobial Activity of two *Mentha* Species Essential Oil and its Dependence on Different Origin and Chemical Diversity
Mária Pľuchtová, Teresa Gervasi, Qada Benameur, Vito Pellizzeri, Daniela Gruľová, Luca Campone, Vincent Sedlák and Nicola Cicero **1051**

Seasonal Study of Methyleugenol Chemotype of *Ocimum campechianum* Essential Oil and Its Fungicidal and Antioxidant Activities
Pablo Luis B. Figueiredo, Sebastião G. Silva, Lidiane D. Nascimento, Alessandra R. Ramos, William N. Setzer, Joyce Kelly R. da Silva and Eloisa Helena A. Andrade **1055**

Evaluation of Antipneumonic Effect of Philippine Essential Oils Using Broth Microdilution Volatilization Method and Their Lung Fibroblasts Toxicity
Marketa Houdkova, Ivo Doskocil, Klara Urbanova, Ea Kristine Clarisse B. Tulin, Johana Rondevaldova, Anabella B. Tulin, Tomas Kudera, Edgardo E. Tulin, Vaclav Zeleny and Ladislav Kokoska **1059**

Accounts/Reviews

The Roles of Natural Compounds in Epigenetics
Yanhong Yang, Zuohua Chi, Ruiping Gao and Zili Lei **1067**

Secondary Metabolites, Dietary Fiber and Conjugated Fatty Acids as Functional Food Ingredients Against Overweight and Obesity
Kamila Kasprzak, Karolina Wojtunik-Kulesza, Tomasz Oniszczuk, Maciej Kuboń and Anna Oniszczuk **1073**

The Sulfated Polysaccharides of Brown Algae and Products of Their Enzymatic Transformation as Potential Vaccine Adjuvants
Tatyana A. Kuznetsova, Elena V. Persiyanova, Svetlana P. Ermakova, Maxim Yu. Khotimchenko and Natalya N. Besednova **1083**

Natural Product Communications
2018
Volume 13, Number 8

Contents

Original Paper ***Page***

Synthesis and Cytotoxic Evaluation of Artemisinin Derivatives Containing an Aminopropanol Group
Le Nhat Thuy Giang, Doan Duy Tien, Dang Thi Tuyet Anh, Nguyen Tien Dung, Ngo Hanh Thuong, Luc Quang Tan, Nguyen Ha Thanh, Le Thi Tu Anh, Nguyen Van Tuyen and Phan Van Kiem **919**

Biotransformation of Bicyclic Sesqui- and Diterpene 1,2-dials and Their Derivatives by the Fungus, *Aspergillus niger*
Yoshinori Asakawa, Masako Sekita and Toshihiro Hashimoto **923**

Synthesis of Ester-linked Taxol-oligosaccharide Conjugate and Its Drug Delivery System Using Bio-nanocapsules and Hybrid-bio-nanocapsules
Hiroki Hamada, Shouta Okada, Noriyoshi Masuoka, Yuya Fujitaka, Kei Shimoda, Shouta Doi and Katsuhiko Mikuni **933**

Monoaminergic Involvement in Decreased Locomotor Activity of Mice Treated with α and β-amyrin from *Protium heptaphyllum*
Gislei F. Aragão, Manoel O. de Moraes Filho, Paulo N. Bandeira, Antônio P. Frota Junior, Yasmin Ingrid S. de Oliveira, Claudina F. Alves Balacó and Maria Elisabete A. de Moraes **935**

Cytotoxic Evaluation of Compounds Isolated from the Aerial Parts of *Hedyotis pilulifera* and Methanol Extract of *Inonotus obliquus*
Hoai Thi Nguyen, Duc Viet Ho, Phu Dinh Quynh Nguyen, Hung Quoc Vo, Thao Thi Do and Ain Raal **939**

Production of the Anticancer Compound Withaferin A from Genetically Transformed Hairy Root Cultures of *Withania Somnifera*
Zeynab Yousefian, Behnaz Hosseini, Hassan Rezadoost, Javier Palazón and Mohammad Hossein Mirjalili **943**

New Oxygenated Steroid from the Marine-Derived Fungus *Aspergillus flavus*
Meng-Yue Yang, Jian-Kun Yang, Jin-Kai Yang, Lian-Dong Hu, Hua-Jie Zhu and Fei Cao **949**

Sulfated Glycosides from the Sea Cucumbers Block Ca^{2+} Flow in Murine Neuroblastoma Cells
Evgeny A. Pislyagin, Ekaterina S. Menchinskaya, Dmitry L. Aminin, Sergey A. Avilov and Alexandra S. Silchenko **953**

New Sesquiterpene Pyridine Alkaloids from *Hippocratea excelsa*
Megumi Furukawa, Masakatsu Furukawa, Mitsuko Makino, Taketo Uchiyama, Yasuo Fujimoto and Keiichi Matsuzaki **957**

Flavonoids from *Milletia leucantha* and Their Cytotoxicity
Uraiwan Sriphana, Chavi Yenjai, Siriporn Tungnoi, Jongjai Srirapa and Auemporn Junsongduang **961**

Inhibitory Effect of Pelargonidin on Secretory Group IIA Phospholipase A2
In-Chul Lee and Jong-Sup Bae **963**

Skin Anti-aging Assays of Proanthocyanidin Rich Red Rice Extract, Oryzanol and Other Phenolic Compounds
Supachai Yodkeeree, Pilaiporn Thippraphan, Wanisa Punfa, Jatupol Srisomboon and Pornngarm Limtrakul (Dejkriengkraikul) **967**

Identification of Plant Origin of Propolis from Thailand Stingless Bees by Comparative Analysis
Eriko Ishizu, Sari Honda, Boonyadist Vongsak and Shigenori Kumazawa **973**

Leaves of *Eugenia brasiliensis* Used as a Folk Medicine Contain Cyclooxygenase Enzyme and Lipid Peroxidation Inhibitory Compounds
Alessandra C. Dametto, Nivaldo Boralle, Chuan-Rui Zhang, Dulce H. S. Silva and Muraleedharan G. Nair **977**

Difficulties to Determine the Absolute Configuration of Guaiaretic Acid
Alfredo R. Ortega, Eleuterio Burgueño-Tapia and Pedro Joseph-Nathan **981**

Comparison of Chemical Constituents in Magnoliae Officinalis Cortex Processed by "Sweating" and "Non Sweating" based on Ultra Fast Liquid Chromatography-Triple Quadrupole-Time of Flight Mass Spectrometry and Gas Chromatography-Triple Quadrupole Mass Spectrometry Combined with Multivariate Statistical Analysis
Hui Zhao, Ying Yan, Cheng-cheng Wang, Li-si Zou, Xun-hong Liu, Shu-yu Chen and Jing-jing Shi **987**

Potent α-Glucosidase Inhibitors from the Roots of *Aruncus sylvester*
Zhang-Peng Li, Meng Que, Wen-Yuan Gao and Yan-Fang Su **993**

Cytotoxic Compounds from the Seeds of *Sophora alopecuroides*
Ping Song, Hao Chen, Yanzhang Wen, Yibing Lv, Shihao Deng and Xinzhou Yang **997**

Antibacterial and Antibiofilm Effects of *Zanthoxylum bungeanum* Leaves against *Staphylococcus aureus*
Shi-Yuan Chang, Kai Xiao, Jia-Qi Zhang, Kai Zhong, Elena Grosu, Zhen Gao, Yan-Ping Wu and Hong Gao **1001**

Evaluation of Anti-glycation Activities of Phlorotannins in Human and Bovine Serum Albumin-glyceraldehyde Models
Shingo Sugiura, Ryosuke Taniguchi, Yoshihiko Nishioka, Ryota Iwase, Reiji Tanaka, Hideo Miyake, Tetsushi Mori, Mitsuyoshi Ueda and Toshiyuki Shibata **1007**

Stereoselective Total Synthesis of 1,4-Dideoxy-1,4-imino-L-ribitol by an Intramolecular Ring Opening of Epoxide with a Tethered Amide
Dhudmal Chaya N, Dhanraj O Biradar, Maddipatla V. Satyanarayana and Basi V Subba Reddy **1011**

Impact of Melittin on Microalgae Cell Wall: A Monolayer Study
Magda Vargas-Perez, Gerardo Sierra-García, Hugo Luna Olvera, Abelardo Chavez-Montes and Azucena Gonzalez-Horta **1013**

Phytochemical Profile and Anti-lipase Activity of Balkan Endemic *Jurinea tzar-ferdinandii*
Antoaneta Trendafilova, Milka Todorova, Nikolina Kutova and Maya Guncheva **1017**

The *Chaenomeles sinensis* Extract has the Potential to Exhibit Antioxidant Activity or Attenuate Liver Damage
Young-Ji Choi, Young-Moo Choo, Seung-Il Jeong, Kang-Yeol Yu and Jiyoung Kim **1021**

Continued inside backcover