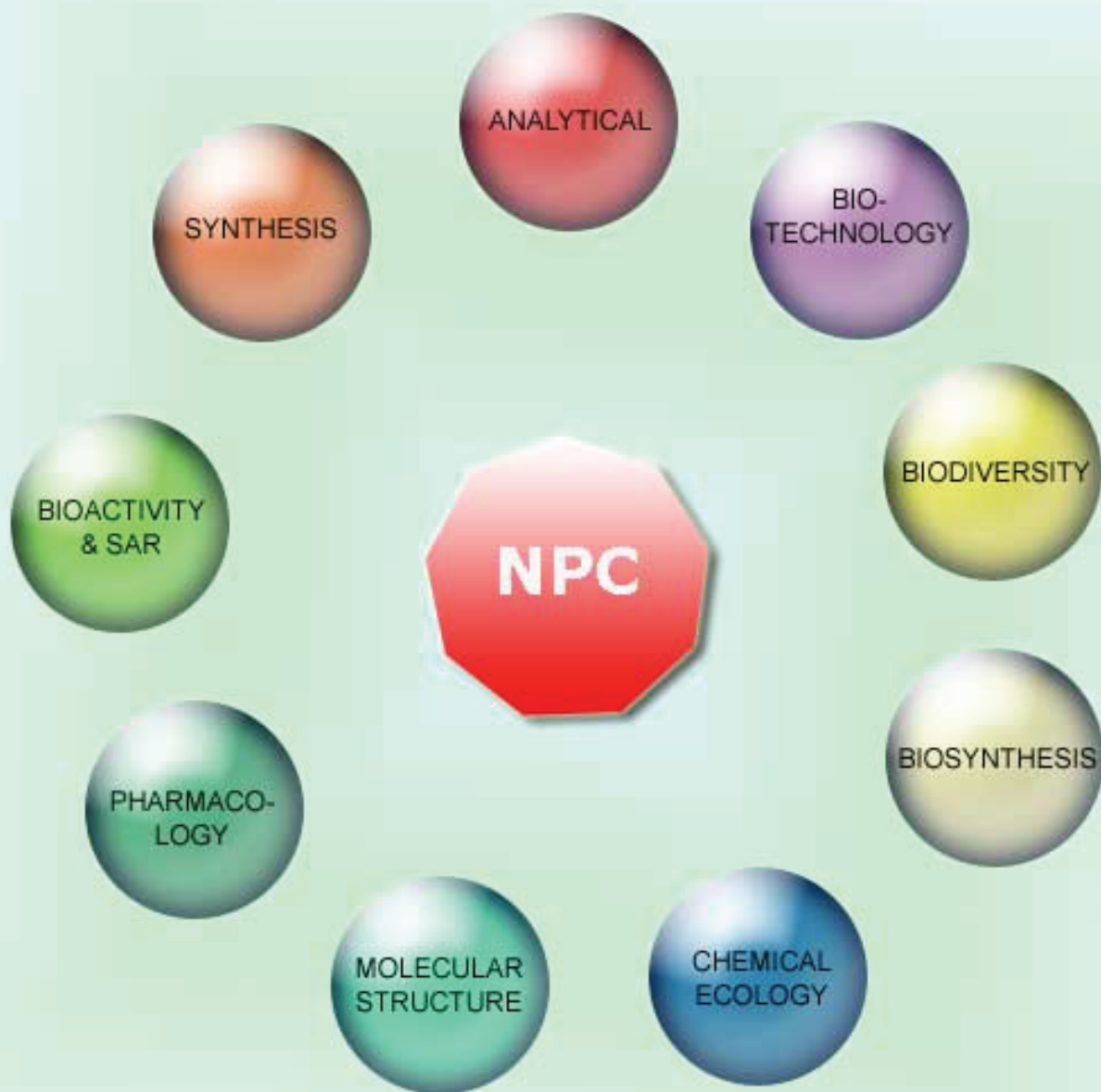


NATURAL PRODUCT COMMUNICATIONS

An International Journal for Communications and Reviews Covering all
Aspects of Natural Products Research



Volume 13. Issue 11. Pages 1419-1568. 2018
ISSN 1934-578X (printed); ISSN 1555-9475 (online)
www.naturalproduct.us

EDITOR-IN-CHIEF**DR. PAWAN K AGRAWAL**

Natural Product Inc.
7963, Anderson Park Lane,
Westerville, Ohio 43081, USA
agrawal@naturalproduct.us

EDITORS**PROFESSOR MAURIZIO BRUNO**

Department STEBICEF,
University of Palermo, Viale delle Scienze,
Parco d'Orleans II - 90128 Palermo, Italy
maurizio.bruno@unipa.it

PROFESSOR CARMEN MARTIN-CORDERO

Department of Pharmacology, Faculty of Pharmacy,
University of Seville, Seville, Spain
carmenmc@us.es

PROFESSOR VLADIMIR I. KALININ

G.B. Elyakov Pacific Institute of Bioorganic Chemistry,
Far Eastern Branch, Russian Academy of Sciences,
Pr. 100-letya Vladivostoka 159, 690022,
Vladivostok, Russian Federation
kalininv@piboc.dvo.ru

PROFESSOR YOSHIHIRO MIMAKI

School of Pharmacy,
Tokyo University of Pharmacy and Life Sciences,
Horinouchi 1432-1, Hachioji, Tokyo 192-0392, Japan
mimakiy@ps.toyaku.ac.jp

PROFESSOR STEPHEN G. PYNE

Department of Chemistry, University of Wollongong,
Wollongong, New South Wales, 2522, Australia
spyne@uow.edu.au

PROFESSOR MANFRED G. REINECKE

Department of Chemistry, Texas Christian University,
Forts Worth, TX 76129, USA
m.reinecke@tcu.edu

PROFESSOR WILLIAM N. SETZER

Department of Chemistry, The University of Alabama in Huntsville,
Huntsville, AL 35809, USA
wsetzer@chemistry.uah.edu

PROFESSOR PING-JYUN SUNG

National Museum of Marine Biology and Aquarium
Checheng, Pingtung 944
Taiwan
pjsung@nmba.gov.tw

PROFESSOR YASUHIRO TEZUKA

Faculty of Pharmaceutical Sciences, Hokuriku University,
Ho-3 Kanagawa-machi, Kanazawa 920-1181, Japan
y-tezuka@hokuriku-u.ac.jp

PROFESSOR DAVID E. THURSTON

Institute of Pharmaceutical Science
Faculty of Life Sciences & Medicine
King's College London, Britannia House
7 Trinity Street, London SE1 1DB, UK
david.thurston@kcl.ac.uk

HONORARY EDITOR**PROFESSOR GERALD BLUNDEN**

The School of Pharmacy & Biomedical Sciences,
University of Portsmouth,
Portsmouth, PO1 2DT U.K.
axuf64@dsl.pipex.com

ADVISORY BOARD

Prof. Giovanni Appendino
Novara, Italy

Prof. Norbert Arnold
Halle, Germany

Prof. Yoshinori Asakawa
Tokushima, Japan

Prof. Vassaya Bankova
Sofia, Bulgaria

Prof. Roberto G. S. Berlinck
São Carlos, Brazil

Prof. Anna R. Bilia
Florence, Italy

Prof. Geoffrey Cordell
Chicago, IL, USA

Prof. Fatih Demirci
Eskişehir, Turkey

Prof. Francesco Epifano
Chieti Scalo, Italy

Prof. Ana Cristina Figueiredo
Lisbon, Portugal

Prof. Cristina Gracia-Viguera
Murcia, Spain

Dr. Christopher Gray
Saint John, NB, Canada

Prof. Dominique Guillaume
Reims, France

Prof. Duvvuru Gunasekar
Tirupati, India

Prof. Hisahiro Hagiwara
Niigata, Japan

Prof. Judith Hohmann
Szeged, Hungary

Prof. Tsukasa Iwashina
Tsukuba, Japan

Prof. Leopold Jirovetz
Vienna, Austria

Prof. Phan Van Kiem
Hanoi, Vietnam

Prof. Niel A. Koorbanally
Durban, South Africa

Prof. Chiaki Kuroda
Tokyo, Japan

Prof. Hartmut Laatsch
Gottingen, Germany

Prof. Marie Laccaille-Dubois
Dijon, France

Prof. Shoei-Sheng Lee
Taipei, Taiwan

Prof. M. Soledade C. Pedras
Saskatoon, Canada

Prof. Luc Pieters
Antwerp, Belgium

Prof. Peter Proksch
Düsseldorf, Germany

Prof. Phila Raharivelomanana
Tahiti, French Polynesia

Prof. Stefano Serra
Milano, Italy

Dr. Bikram Singh
Palampur, India

Prof. Marina Stefova
Skopje, Republic of Macedonia

Prof. Leandros A. Skaltsounis
Zografou, Greece

Prof. John L. Sorensen
Manitoba, Canada

Prof. Johannes van Staden
Scottsville, South Africa

Prof. Valentin Stonik
Vladivostok, Russia

Prof. Winston F. Tinto
Barbados, West Indies

Prof. Sylvia Urban
Melbourne, Australia

Prof. Karen Valant-Vetschera
Vienna, Austria

INFORMATION FOR AUTHORS

Full details of how to submit a manuscript for publication in Natural Product Communications are given in Information for Authors on our Web site <http://www.naturalproduct.us>.

Authors may reproduce/republish portions of their published contribution without seeking permission from NPC, provided that any such republication is accompanied by an acknowledgment (original citation)-Reproduced by permission of Natural Product Communications. Any unauthorized reproduction, transmission or storage may result in either civil or criminal liability.

The publication of each of the articles contained herein is protected by copyright. Except as allowed under national "fair use" laws, copying is not permitted by any means or for any purpose, such as for distribution to any third party (whether by sale, loan, gift, or otherwise); as agent (express or implied) of any third party; for purposes of advertising or promotion; or to create collective or derivative works. Such permission requests, or other inquiries, should be addressed to the Natural Product Inc. (NPI). A photocopy license is available from the NPI for institutional subscribers that need to make multiple copies of single articles for internal study or research purposes.

To Subscribe: Natural Product Communications is a journal published monthly. 2018 subscription price: US\$2,595 (Print, ISSN# 1934-578X); US\$2,595 (Web edition, ISSN# 1555-9475); US\$2,995 (Print + single site online); US\$595 (Personal online). Orders should be addressed to Subscription Department, Natural Product Communications, Natural Product Inc., 7963 Anderson Park Lane, Westerville, Ohio 43081, USA. Subscriptions are renewed on an annual basis. Claims for nonreceipt of issues will be honored if made within three months of publication of the issue. All issues are dispatched by airmail throughout the world, excluding the USA and Canada.

Polyphenol Compounds Melanin Prevented Hepatic Inflammation in Rats with Experimental Obesity

Natalia Belemets^a, Nazarii Kobylak^b, Tetyana Falalyeyeva^{a*}, Olena Kuryk^c, Oksana Sulaieva^d, Tetyana Vovk^a, Tetyana Beregova^a and Liudmila Ostapchenko^a

^aTaras Shevchenko National University of Kyiv, Volodymyrska Str., 64/13, Kyiv, 01601, Ukraine

^bDepartment of Endocrinology, Bogomolets National Medical University, 01610, Pushkinska 22a, Kyiv, Ukraine

^cScientific-Practical Center for Prophylactic and Clinical Medicine, Kyiv, Ukraine

^dLaboratory of Pathology "CSD Health Care", Kyiv, Ukraine

tfalalyeyeva@gmail.com

Received: August 17th, 2018; Accepted: September 21st, 2018

Melanin produced by yeast *Nadsoniella nigra* strain X-1 lead to significant reduction of steatosis, lobular inflammation and ballooning degeneration, according to NAFLD activity score (NAS), in liver of rats with monosodium glutamate (MSG) induced obesity. These histological changes were associated with substantial decrease of TNF- α expression in sinusoid cells that prevented NF- κ B activation in hepatocytes.

Keywords: Polyphenols, Melanin, Obesity, Non-alcoholic fatty liver disease, Non-alcoholic steatohepatitis, Antioxidants.

Approximately 1.7 billion people in the world suffer from being overweight, most notably in developed countries. The number of which has more than doubled in children and quadrupled in adolescents in the past 30 years [1-3]. Obesity increase the risk for number of diseases, namely, cardiovascular diseases, type 2 diabetes, dyslipidemia, premature death, non-alcoholic fatty liver disease (NAFLD) as well as different types of cancer [4]. NAFLD is currently being in strict focus of the scientific community because of its increasing prevalence and complicated pathogenesis represented growing challenge in terms of prevention and treatment. The disorder has a prevalence of 15–20% in the general population and 76–90% in the obese [5]. NAFLD is currently a leading cause of chronic liver disease [6,7], which has resulted in significant health concerns such as morbidity, mortality, and liver transplants [8]. High clinical significance and complicated mechanisms of pathogenesis contributes to growing forces of scientist to fulfil the gaps in the understanding of NAFLD. However, currently the exact pathogenetic mechanisms involved in NAFLD, remain incompletely understood. Therapy is manly based on lifestyle modifications to achieve weight loss, health diet, and physical activity [9], on the use of omega-3 fatty acids to reduce hepatic fat accumulation [10-11]; antioxidants [12] and probiotics supplementation [13,14] for liver damage, and to treat the associated metabolic conditions to NAFLD. Despite of this a lot of obese people do not improve their health and the search of nontoxic anti-obesity drugs is still urgent.

Cell culture, animal, and limited human studies suggest that consumption of foods containing certain polyphenols or their corresponding supplements changes lipid and energy metabolism and may facilitate weight loss and prevent weight gain. [15, 16]. Evidence from pre-clinical and some clinical studies indicates that consumption of green and white teas containing catechins, fruits such as blueberries with anthocyanins, foods such as red grapes and wine with resveratrol, and spice like turmeric containing curcumin may provide several health benefits including improving blood glucose and lipid profiles, ameliorating insulin resistance, adiposity and obesity [17, 18]. Current knowledge suggests that the potential

complementary effect of these polyphenols may occur through several mechanisms: suppression of fat absorption from the gut, uptake of glucose by skeletal muscles, suppression of anabolic pathways, stimulation of catabolic pathways in adipose tissues, liver and other tissues, inhibition of angiogenesis in adipose tissues, inhibition of differentiation of pre-adipocytes to adipocytes, stimulation of apoptosis of mature adipocytes, and reduction of chronic inflammation associated with adiposity [15].

In the previous study, we have showed the effects of exogenously administered melanin produced by yeast *Nadsoniella nigra* strain X-1 on the obesity parameters of rats and the development of NAFLD/NASH. It was shown significant decrease of mass indexes and fat accumulation in visceral adipose tissue of treated rats that suggests preventive influence of melanin on obesity. Such impact may be one of the cause of the interruption of the NAFLD development confirmed by the histological analysis of liver. It was registered substantial reduction of steatosis, lobular inflammation and ballooning degeneration in liver tissue in 4-month MSG-rats treated with melanin. Melanin reduced the content of IL-1 in rat serum and restored the level of anti-inflammatory cytokines (IL-10, TGF- β) to the control values. [19]. The present study was performed to investigate the anti-inflammatory mechanism of melanin produced by yeast *Nadsoniella nigra* strain X-1 by the expression of tumor necrosis factor α (TNF- α) and nuclear factor kappa of activated B cells (NF- κ B) in rat liver with NAFLD/NASH.

In the control group, the structure of the hepatic lobule was normal, hepatic plates were arranged radially to the central vein. Hepatocytes demonstrated central round nuclei with nucleoli and oxyphilic cytoplasm. Sinusoids were arranged in regular pattern radially to the central vein. There were no any features of lobular inflammation or fibrosis.

MSG effects on proinflammatory pathways activation and NAFLD. In the MSG group, the structure of the hepatic lobules was different due to irregular distribution of hepatic plates and disarrangement of sinusoids. Hepatocytes varied in size and shape

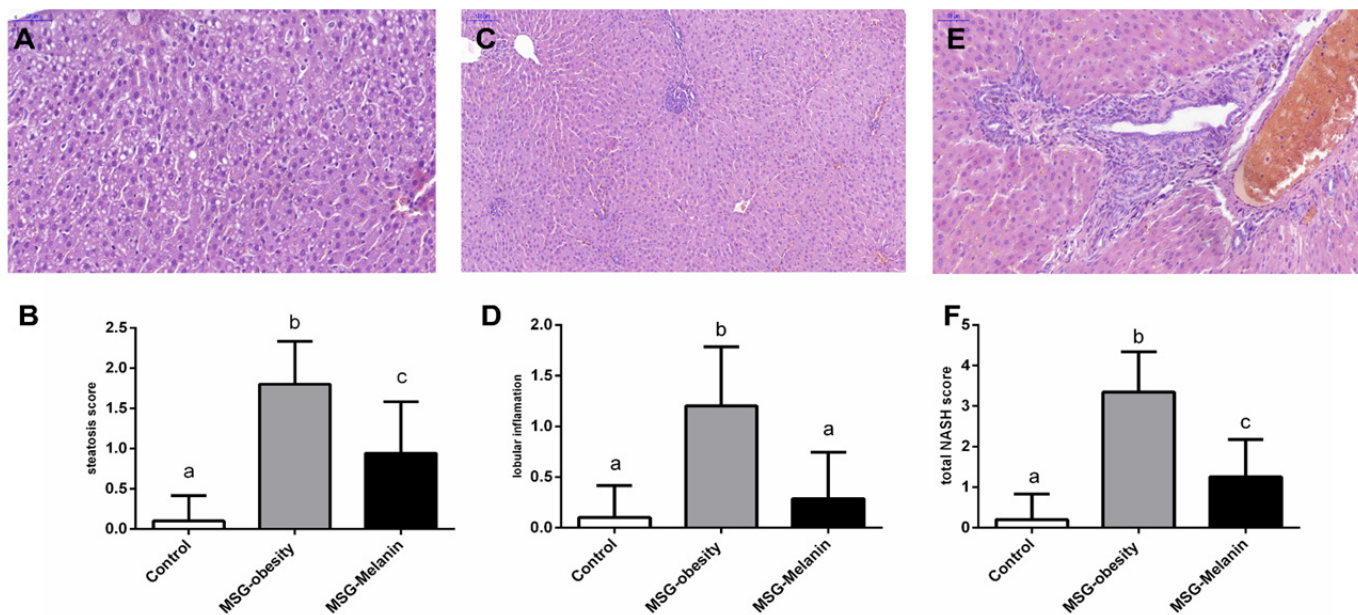


Figure 1: Histopathological changes in the liver of MSG animals, and attenuating effect of Melanin on NAFLD and NAS development. A, C, E – demonstrate steatosis, lobular inflammation and portal inflammation with fibrosis in MSG obese rats respectively. B – effect melanin on steatosis score, D – effect of Melanin on lobular inflammation score, F – effect of melanin on total NASH score. ^{a, b, c} Values at the same row with different superscript letters show significant differences at $p < 0.05$.

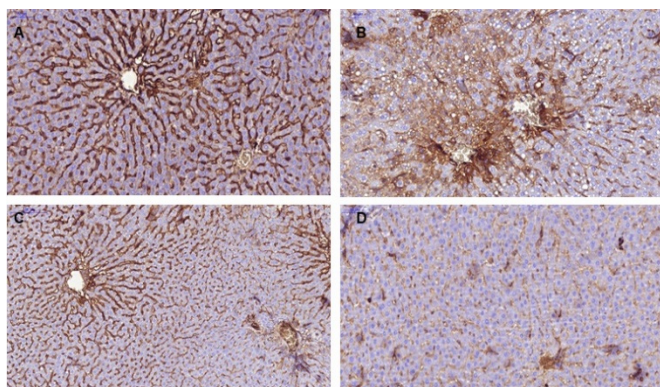


Figure 2: Number of CD68 positive cells (A and C) and TNF- α expression (B and D) in the liver of experimental rats. A – numerous CD68 cells in MSG group, B – high TNF- α expression in cells of sinusoids and hepatocytes of the liver in MSG group, C – CD68 cells in MSG + Melanin group, D – mild expression of TNF- α in the liver of MSG + Melanin group.

due to diffuse and numerous fat vacuoles of varying size (steatosis score was 1.8 ± 0.17). Number of hepatic cells contained large fat vacuoles (Figure 1). Most of fat-rich hepatocytes were located at the periphery of hepatic lobules. In some animals, hydropic degeneration and inflammatory cells infiltration were observed (lobular inflammation score = 1.20 ± 0.17). The total NASH score reached 3.33 ± 0.36 points. In addition to inflammation and ballooning degeneration the mild perivenular and perisinusoidal fibrosis associated with portal inflammation and fibrosis typical for NASH were found in 3 rats (33.3%). These changes were accompanied with increased number of macrophages in the liver.

Numerous CD68 positive cells covered almost the whole surface of sinusoidal capillaries that allowed to refer them to Kupffer cells. In addition, numerous CD68 positive cells were identified in periportal infiltrates. The very similar was the distribution of TNF- α positive cells. As macrophages and in particular Kupffer cells are considered demonstrate the role of TNF- α in NASH development. In addition, the moderate immunopositive reaction to TNF- α was found in some

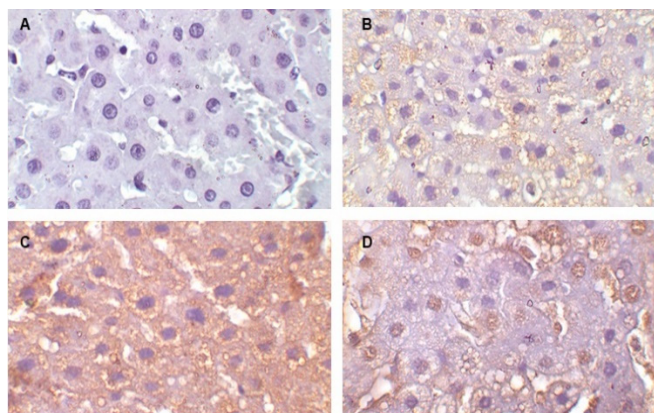


Figure 3: NF- κ B expression in healthy (A) and experimental rats with MSG-induced obesity (B-D). Steatosis development was associated with mild to strong cytoplasmic expression of NF- κ B. In addition, in about 40% of hepatocytes the nuclear expression of NF- κ B was found, that was accompanied with hepatic plates disarrangement and sinusoidal cells immunopositivity. Immunohistochemistry with using monoclonal antibodies against NF- κ B, $\times 400$.

to be the main source of TNF- α production, our findings could hepatocytes in rats with NASH (Figure 2). High TNF- α expression correlated with NF- κ B immunopositivity ($r=0.782$, $P < 0.001$). We found diffuse cytoplasmic reaction to NF- κ B in hepatocytes and sinusoid cells. In addition, severe steatosis and cell injury were accompanied with nuclear expression of NF- κ B in hepatocytes (Figure 3). Thus, neonatal MSG-induced obesity is associated with proinflammatory pathways activation in liver. The activation of NF- κ B signaling pathway may cause NAFLD due to TNF- α overexpression in Kupffer cells.

Melanin effects on NAFLD development in MSG-obese rats.

The administration of melanin provided ameliorating effect on liver structure significantly decreasing the degree of steatosis and preventing injury of hepatocytes. We established substantial attenuation of lobular inflammation in MSG rats treated with melanin ($p < 0.001$). The degree of steatosis in the conditions of

melanin administration was lower by 59.4% ($p < 0.01$) as compared to MSG-group. It was also found significantly lower total NASH score ($p < 0.001$).

These histological changes were associated with substantial decrease of TNF- α expression in sinusoid cells that prevented NF- κ B activation in hepatocytes (table 1). Taking all together, these data confirmed the therapeutic impact of melanin on the MSG-induced NAFLD development.

Table 1: Impact of melanin on NF- κ B and TNF- α expression in the liver.

	MSG	MSG + Melanin	P-value
TNF- α score	7.2 \pm 0.4	1.2 \pm 0.1	< 0,001
NF- κ B score	3.5 \pm 0.3	1.6 \pm 0.1	< 0,001

NAFLD, which is a multi-factorial disorder associated with a variety of genetic and environmental contributory factors, is considered to be the most common cause of liver disease [20]. Whether the initial '2-hit hypothesis' or '3-hit hypothesis' is applied in determining the etiology, insulin resistance, oxidative stress and inflammatory cascades are believed to serve integral roles in the pathogenesis and progression [21]. The presence of steatosis induced by the over accumulation of free fatty acids and cholesterol is closely associated with chronic hepatic [19, 22], which is partly mediated by the activation of the inhibitor of the NF- κ B kinase subunit β /NF- κ B signaling pathway. In the present study, the results indicated that neonatal MSG-induced obesity is associated with proinflammatory pathways activation in liver. Histological analysis of liver micropreparations confirmed the development of NAFLD in rats. It was registered evidence of steatosis, lobular inflammation and ballooning degeneration in liver tissue in 4-month rats treated with MSG neonatally. We indicate the activation of NF- κ B signaling pathway which cause NAFLD due to TNF- α overexpression in liver Kupffer cells of 4-month MSG-rats. TNF- α is a major proinflammatory cytokine and plays an important role in the development of NAFLD. Thus, activated Kupffer cells can increase the production of TNF- α , which may be responsible for NAFLD. Current studies have exhibited that TNF- α inhibition could decrease the level of hepatic fatty storage in mice on high fat diet [23]. In this study, the effects of TNF- α were evaluated by immunohistochemistry in the damaged liver. The administration of melanin significantly decreased the degree of steatosis and prevented injury of hepatocytes. These histological changes were associated with substantial decrease of NF- κ B activation in hepatocytes. In conclusion melanin treatment up-regulated the expression of TNF- α , compared with the control group, and down-regulated the expression of TNF- α , compared with the MSG-NAFLD group.

Experimental

This study was carried out in strict accordance with the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health and the general ethical principles of animal experiments, approved by the First National Congress on Bioethics Ukraine (September 2001). The rats were kept in collective cages in controlled conditions of temperature (22 \pm 3 $^{\circ}$ C), light (12 h light/dark cycle) and relative humidity (60 \pm 5%). The animals were fed laboratory chow (PurinaW) and tap water ad libitum.

References

- [1] Ball K, Mishra G, Crawford D. (2002) Which aspects of socioeconomic status are related to obesity among men and women? *International journal of obesity and related metabolic disorders*, 26, 559–565.

There were 30 newborn Wistar male rats, divided into 3 groups: intact (n=10), MSG (n=10) and MSG + melanin treated (n=10). Newborns rats of intact group were administered with saline subcutaneously (s.c.) in the volume of 8 mL/g at 2nd, 4th, 6th, 8th and 10th postnatal days. Newborns rats of MSG-group and MSG + melanin group received a solution of MSG (4.0 mg/g of body weight) s.c. at 2nd, 4th, 6th, 8th and 10th days after birth [24–26]. Within 4 months after birth, rats had a normal diet. MSG + melanin group received aqueous solution of melanin in dose 1 mg/kg at volume 2.5 mL/kg per os (p.o.). Melanin was obtained from yeast-like fungi *Nadsoniella nigra* X1 strain from Ukrainian Antarctic station [27]. Melanin administration was started at the age of 4 weeks just after wean and continued for 3 months intermittently alternating two-week course of introduction with two-week course of break in dose 1 mg/kg dissolved in water (0.25 mL/100g) [19]. MSG-group respectively received 2.5 mL/kg of water (p.o.).

The impact of MSG on NAFLD development was assessed by histological evaluation of the liver. After excision it was fixed in 10% formalin, embedded in paraffin and cut into 4 μ m sections. The tissue sections were stained with hematoxylin and eosin. After that the histopathological changes in liver were observed and scored. Slides were evaluated histologically by 2 independent pathologists. NAFLD was interpreted according to widely recognized histopathological criteria: steatosis, lobular inflammation and ballooning degeneration of hepatocytes. The histological changes were assessed using NAS score:

- Steatosis was evaluated as 0 when <5% of cells demonstrated ectopic fat accumulation; 1 - if 5–33%; 2 when 34–66% and 3 if > 66% of cells were with fat droplets,
- Lobular inflammation was counted as following: 0 - none; 1 < 2 foci/20x field; 2 if 2–4 foci/20x field; 3 when > 4 foci/20x field)
- Ballooning degeneration of hepatocytes (0 - none; 1 - few; 2 - many)

As low-grade inflammation is one of the leading mechanisms of liver lesion in obesity, the proinflammatory activation of liver cells was analyzed by immunohistochemical assessment of CD68 cells, NF- κ B and TNF- α expression. CD68 cells number, NF- κ B subunits (p50 and p65) and TNF- α expression was detected in formalin-fixed paraffin-embedded tissue sections according to standard immunohistochemistry techniques. The percent of NF- κ B positive cells was semi-quantitatively scored on the basis of the percentage of positive cells as 0%=negative; 1–25% = 1+; 26–50% = 2+; and >50% = 3+. The intensity of NF- κ B and TNF- α expression was scored as weak (1+), moderate (2+) and strong (3+). The immunohistochemistry index of NF- κ B and TNF- α expression of each section was calculated as intensity multiplied by frequency and categorized as low (< 6) or high (> 6).

Statistical analysis performed by using SPSS-20 software. All data in this study were expressed as means \pm standard deviation (M \pm SD) or %. Data distribution was analyzed using the Kolmogorov-Smirnov normality test. Continuous variables with parametric distribution were analyzed using Analysis of Variance (ANOVA) and if the results were significant, a post-hoc Tukey's test was performed. For data with non-parametric distribution Kruskal-Wallis and post-hoc Dunn's test were conducted for multiple comparisons. The difference between groups was defined to be statistically significant when a p-value was less than 0.05.

- [2] Epstein LH, Gordy CC, Raynor HA, Beddome M, Kilanowski CK, Paluch R. (2001) Increasing fruit and vegetable intake and decreasing fat and sugar intake in families at risk for childhood obesity. *Obesity Research*, **9**, 171–178.
- [3] Kobylak N, Virchenko O, Falalyeyeva T. (2016) Pathophysiological role of host microbiota in the development of obesity. *Nutrition Journal*, **15**, 43.
- [4] Tsai AG, Williamson DF, Glick HA. (2011) Direct medical cost of overweight and obesity in the USA: a quantitative systematic review. *Obesity reviews: an official journal of the International Association for the Study of Obesity*, **12**, 50–61.
- [5] Angulo P, Lindor KD. (2002) Non-alcoholic fatty liver disease. *Journal of Gastroenterology and Hepatology*, **17**, 186–190.
- [6] Farrell GC, Larter CZ. (2006) Nonalcoholic fatty liver disease: from steatosis to cirrhosis. *Hepatology*, **43**, 99–112.
- [7] Kobylak N, Abenavoli L. (2014) The role of liver biopsy to assess non-alcoholic fatty liver disease. *Reviews on Recent Clinical Trials*, **9**, 159–169.
- [8] Musso G, Gambino R, Cassader M, Pagano G. (2011) Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. *Annals of Medicine*, **43**, 617–649.
- [9] Geffken DF, Cushman M, Burke GL, Polak JF, Sakkinen PA, Tracy RP. (2001) Association between physical activity and markers of inflammation in a healthy elderly population. *American journal of Epidemiology*, **153**, 242–250.
- [10] Kobylak, T. Falalyeyeva, P. Bodnar, T. Beregova, (2017) Probiotics supplemented with omega-3 fatty acids are more effective for hepatic steatosis reduction in an animal model of obesity. *Probiotics and Antimicrobial Proteins*, **9**, 123-130.
- [11] Kobylak N, Falalyeyeva T, Boyko N, Tsyryuk O, Beregova T, Ostapchenko L. (2018) Probiotics and nutraceuticals as a new frontier in obesity prevention and management. *Diabetes Research and Clinical Practice*, **141**, 190-199.
- [12] Abenavoli L, Milic N, Di Renzo L, Preveden T, Medić-Stojanoska M, De Lorenzo A. (2016) Metabolic aspects of adult patients with nonalcoholic fatty liver disease. *World Journal of Gastroenterology*, **22**, 7006-7016.
- [13] Kobylak N, Falalyeyeva T, Virchenko O, Mykhalchyshyn G, Bodnar P, Spivak M, Yankovsky D, Beregova T, Ostapchenko L. (2016) Comparative experimental investigation on the efficacy of mono- and multiprobiotic strains in non-alcoholic fatty liver disease prevention. *BMC Gastroenterology*, **16**, 34.
- [14] Kobylak N, Abenavoli L, Mykhalchyshyn G, Kononenko L, Boccutto L, Kyriienko D, Dynnyk O. (2018) A Multi-strain Probiotic Reduces the Fatty Liver Index, Cytokines and Aminotransferase levels in NAFLD Patients: Evidence from a Randomized Clinical Trial. *Journal of Gastrointestinal and Liver Diseases*, **27**, 41-49.
- [15] Mohsen M, Syeda H. (2010) Dietary Polyphenols and Obesity. *Nutrients*, **2**, 737-751.
- [16] Wang S, Moustaid-Moussa N, Chen L, Mo H, Shastri A, Su R, Bapat P, Kwun I, Shen C. (2014) Novel insights of dietary polyphenols and obesity. *The Journal of Nutritional Biochemistry*, **25**, 1–18.
- [17] Farhat G, Drummond S, Al Dujaili EAS. (2017) Polyphenols and Their Role in Obesity Management: A Systematic Review of Randomized Clinical Trials. *Phytotherapy Research*, **31**, 1005-1018.
- [18] Kalupahana NS, Moustaid-Moussa N, Claycombe KJ. (2012) Immunity as a link between obesity and insulin resistance. *Molecular aspects of medicine*, **33**, 26–34.
- [19] Belemets N, Kobylak N, Virchenko O, Falalyeyeva T, Tsyryuk O, Bodnar P, Savchuk O, Galenova T, Caprnda M, Rodrigo L, Skladany L, Delev D, Opatrilova R, Kruzliak P, Beregova T, Ostapchenko L. (2017) Effects of polyphenol compounds melanin on NAFLD/NASH prevention. *Biomedicine and Pharmacotherapy*, **88**, 267-276.
- [20] Petta S, Gastaldelli A, Rebelos E, Bugianesi E, Messa P, Miele L, Svegliati-Baroni G, Valenti L, Bonino F. (2016) Pathophysiology of non alcoholic fatty liver disease. *International Journal of Molecular Sciences*, **2016**, 17.
- [21] Lewis JR, Mohanty SR. (2010) Nonalcoholic fatty liver disease: A review and update. *Digestive Diseases and Sciences*, **55**, 560–578.
- [22] Cai D, Yuan M, Frantz DF, Melendez PA, Hansen L, Lee J, Shoelson SE. (2005) Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. *Nature Medicine*, **11**, 183–190.
- [23] Gao HY, Huang J, Wang HY, Du XW, Cheng SM, Han Y, Wang LF, Li GY, Wang JH. (2013) Protective effect of *Zhuyeqing liquor*, a Chinese traditional health liquor, on acute alcohol-induced liver injury in mice. *Journal of Inflammation*, **10**, 30.
- [24] Kobylak N, Abenavoli L, Falalyeyeva T, Beregova T. (2018) Efficacy of Probiotics and Smectite in Rats with Non-Alcoholic Fatty Liver Disease. *Annals of Hepatology*, **17**, 153-161.
- [25] Kobylak N, Falalyeyeva T, Beregova T, Spivak M. (2017) Probiotics for experimental obesity prevention: focus on strain dependence and viability of composition. *Endokrynologia Polska*, **68**, 659-667.
- [26] Kondro M, Mykhalchyshyn G, Bodnar P, Kobylak N, Falalyeyeva T. (2013) Metabolic profile and morpho-functional state of the liver in rats with glutamate-induced obesity. *Current Issues in Pharmacy and Medical Sciences*, **26**, 379-381.
- [27]Permyakova N, Zheltonozhskaya T, Beregova T, Klymchuk D, Falalyeyeva T. (2016) Micellar nanocarriers for anticancer drug melanin. *Molecular Crystals and Liquid Crystals*, **640**, 122-133.

Synthesis and Biological Activity of Novel Comenic Acid Derivatives Containing Isoxazole and Isothiazole Moieties Alexey V. Kletskov, Vladimir I. Potkin, Irina A. Kolesnik, Sergey K. Petkevich, Anastasia V. Kvachonak, Margarita O. Dosina, Diana O. Loiko, Maria V. Larchenko, Svetlana G. Pashkevich and Vladimir A. Kulchitsky	1507
Characterization and Quantitation of Polyphenolic Compounds in <i>Senna gardneri</i> and <i>S. georgica</i> from the Northeast of Brazil Irvila Ricarte de O. Maia, Maria Teresa Salles Trevisan, Maria Goretti de V. Silva, Andrea Breuer and Robert W. Owen	1511
Identification of 6,7-Dimethoxychromone as a Potent Allelochemical from <i>Jatropha podagrica</i> Sutjaritpan Boonmee, Arihiro Iwasaki, Kiyotake Suenaga and Hisashi Kato-Noguchi	1515
Identification and Quantification of Human Neutrophil Elastase Inhibitory Caffeoylquinic Acids in the Leaves of <i>Aster koraiensis</i> Ik-Soo Lee, Chan-Sik Kim and Jin Sook Kim	1519
Antitumor Effects of Nordihydroguaiaretic Acid (NDGA) in Bladder T24 Cancer Cells are Related to Increase in ROS Production and Mitochondrial Leak Respiration Gustavo Ignacio Vázquez-Cervantes, Karla Villaseñor-Aguayo, Jacqueline Hernández-Damiána, Omar Emiliano Aparicio-Trejoa, Omar Noel Medina-Campos, Rebeca López-Marureb and José Pedraza-Chaverria	1523
Effect of Precursor and Phytohormones on Podophyllotoxin Production in <i>Juniperus virginiana</i> Suspension Cultures Marie Kašparová, Pavla Pilařová, Lenka Tůmová and Tomáš Siatka	1527
Effect of Resveratrol Dimers and Tetramers Isolated from Vitaceous and Dipterocarpaceous Plants on Human SIRT1 Enzyme Activity Kiyomi Hikita, Norikazu Seto, Yusuke Takahashi, Ayako Nishigaki, Yuya Suzuki, Tomiyasu Murata, Arthorn Loisuangsin, Nanik Siti Aminah, Yoshiaki Takaya, Masatake Niwa and Norio Kaneda	1531
A Concise Asymmetric Synthesis of the Macrolide Antibiotic (-)-A26771B and Evaluation of its Antibacterial Activity and Some of its Precursors Sucheta Chatterjee, Mahesh Subramanian, Anubha Sharma and Subrata Chattopadhyay	1535
Screening of Chemical Composition, <i>in vitro</i> Antioxidant, α-Amylase and α-Glucosidase Inhibitory Activities of the Leaf Essential Oils of <i>Cinnamomum wightii</i> from Different Populations Venkatraman Sriramavaratharajan and Ramar Murugan	1539

Accounts/Reviews

Potential Phytopharmacy and Food Applications of <i>Capsicum</i> spp.: A Comprehensive Review Bahare Salehi, Alan Javier Hernández-Álvarez, María del Mar Contreras, Miquel Martorell, Karina Ramírez-Alarcón, Guiomar Melgar-Lalanne, Karl R. Matthews, Mehdi Sharifi-Rad, William N. Setzer, Muhammad Nadeem, Zubaida Yousaf and Javad Sharifi-Rad	1543
A Review of Common Medicinal Plants in Chin State, Myanmar Zaw Min Thu, Mya Mu Aye, Hnin Thanda Aung, Myint Myint Sein and Giovanni Vidari	1557

Natural Product Communications

2018

Volume 13, Number 11

Contents

<u>Original Paper</u>	<u>Page</u>
Sesquiterpenes Isolated from <i>Aspergillus fumigatus</i>, an Endophytic Fungus from <i>Ligusticum wallichii</i> Xiao-Hua Li, Han-Wen Hu, Lu Tan, Wen-Lin Wu, Zhi-Xing Cao, Yu-Cheng Gu, Yun Deng and Da-le Guo	1419
Kojic Acid Derivatives and Sesquiterpenes from the <i>Aspergillus flavus</i> GZWMJZ-288, A Fungal Endophyte of <i>Garcinia multiflora</i> Yanchao Xu, Liping Wang, Qianyu Gong, Guoliang Zhu, Chunmao Yuan, Mingxing Zuo, Qing Rao, Weiming Zhu and Xiaojiang Hao	1421
A New Taxane Diterpenoid and a New Neolignan from <i>Taxus baccata</i> Xiaoyun Lei, Shuai Huang, Hu Xiao, Feng Gao and Xianli Zhou	1425
Diterpenoid Alkaloids from <i>Delphinium aemulans</i> Nurfida Ablajan, Bo Zhao, Wenjuan Xue, Zukela Ruzi, Jianguy Zhao and Haji Akber Aisa	1429
Trinulactones A–D, New Dinorserterpenoids from <i>Streptomyces</i> sp. S006 Feifei Wei, Wen Li, Rentai Song and Yuemao Shen	1433
Grapefruit Seed Extract Inhibits the Formation of Amyloid-like Fibrils by Trypsin in Aqueous Ethanol Phanindra Babu Kasi, Attila Borics, Mónika Varga, Gábor Endre, Kinga Molnár, Lajos László and Márta Kotormán	1437
Lanostane-type Triterpenoids from <i>Ganoderma lucidum</i> and <i>G. multipileum</i> Fruiting Bodies Pham Thanh Binh, Nguyen Phuong Thao, Nguyen Thi Luyen, Duong Thu Trang, Phung Thi Xuan Binh, Nguyen Phuong Dai Nguyen, Nguyen Tuan Hiep, Nguyen Hai Dang, Tran Manh Tri and Nguyen Tien Dat	1441
Cytotoxic Effects of Cucurbitacin I and <i>Ecballium elaterium</i> on Breast Cancer Cells Kadir Yılmaz, Fuat Karakuş, Ergül Eyol, Emir Tosun, İsmet Yılmaz and Songül Ünüvar	1445
Anti-HIV-1 Activities and Chemical Constituents from Leaves and Twigs of <i>Santisia pagetii</i> (Bignoniaceae) Suphitcha Limjiasahapong, Patoomratana Tuchinda, Vichai Reutrakul, Manat Pohmakotr, Radeekorn Akkarawongsapat, Jitra Limthongkul, Chanita Napaswad and Narong Nuntasana	1449
Two New Oleanane-type Saponins from <i>Hydrocotyle multifida</i> Mayra Rengifo Carrillo, Anne-Claire Mitaine-Offer, Thomas Paululat, Laurent Pouységu, Stéphane Quideau, Luis Rojas, Carmelo Rosquete Porcar and Marie-Aleth Lacaille-Dubois	1453
Two New Steroidal Alkaloid Saponins from the Whole Plants of <i>Solanum nigrum</i> Bui Huu Tai, Vu Van Doan, Pham Hai Yen, Nguyen Xuan Nhiem, Nguyen Thi Cuc, Do Thi Trang, Dan Thi Thuy Hang, Duong Thi Dung, Duong Thi Hai Yen, Tran Hong Quang, Nguyen Hai Dang, Nguyen Thi Mai, Chau Van Minh and Phan Van Kiem	1457
Competitive Inhibition of Mammalian Hyaluronidase by Tomato Saponin, Esculeoside A Jian-Rong Zhou, Souta Kimura, Toshihiro Nohara and Kazumi Yokomizo	1461
Application of Racemization Process to Dynamic Resolution of (<i>RS</i>)-Phenylephrine to (<i>R</i>)-Phenylephrine β-D-Glucoside by <i>Nicotiana tabacum</i> Glucosyltransferase Yuya Fujitaka, Daisuke Uesugi, Hatsuyuki Hamada, Hiroki Hamada, Kei Shimoda, Masayoshi Yanagi, Manami Inoue and Shin-ichi Ozaki	1465
Cytotoxic Activity of Alkaloids from the Fruits of <i>Piper nigrum</i> Quynh Mai Thi Ngo, Thao Quyen Cao, Le Son Hoang, Manh Tuan Ha, Mi Hee Woo and Byung Sun Min	1467
A New Oxoaporphine Alkaloid from the Root of <i>Dasymaschalon glaucum</i> Weerachai Silprakob, Nuntaporn Sukhamsri, Chutima Kuhakarn, Sakchai Hongthong, Surawat Jariyawat, Kanoknetr Suksen, Radeekorn Akkarawongsapat, Jitra Limthongkul, Narong Nantasaen and Vichai Reutrakul	1471
Boldine Does Not Modify Gender Specific Wound Healing in Zucker Diabetic Rats Renata Köhlerová, Eva Čermáková and Milena Hajzlerová	1475
Phytochemical Analysis and Antimicrobial Efficacy of <i>Macleaya cordata</i> against Extensively Drug-Resistant <i>Staphylococcus aureus</i> Manead Khin, Alan M. Jones, Nadja B. Cech and Lindsay K. Caesar	1479
Polyphenol Compounds Melanin Prevented Hepatic Inflammation in Rats with Experimental Obesity Natalia Belemets, Nazarii Kobylak, Tetyana Falalyeyeva, Olena Kuryk, Oksana Sulaieva, Tetyana Vovk, Tetyana Beregova and Liudmila Ostapchenko	1485
Antioxidant and α-Glucosidase Inhibitory Activities of Fisetin Yike Yue, Yongsheng Chen, Sheng Geng, Guizhao Liang and Benguo Liu	1489
Simultaneous Quantification of Two Flavonoids in <i>Morus alba</i> by High Performance Liquid Chromatography Coupled with Photodiode Array Detector Chang-Seob Seo and Hyeun-Kyoo Shin	1493
Chemical Composition and Cytotoxicity of <i>Garcinia rubro-echinata</i>, a Western Ghats Endemic Species Lekshmi N. Menon, Ganapathy Sindhu, Kozhiparambil G. Raghu and Koranappallil B. Rameshkumar	1497
Antioxidant and Anti-inflammatory Activities of Cynaroside from <i>Elsholtzia bodinieri</i> Ying Zou, Min Zhang, Tingrui Zhang, Junwen Wu, Jun Wang, Kehai Liu and Nannan Zhan	1501
Phenolic Constituents from <i>Xyloselinum leonidii</i> Nguyen Phuong Hanh, Nguyen Sinh Khang, Chu Thi Thu Ha, Nguyen Quoc Binh and Nguyen Tien Dat	1505

Continued inside backcover