National Journal of Physiology, Pharmacy and Pharmacology

RESEARCH ARTICLE

The influence of carrageenan on markers of endogenous intoxication in rats

Mariya Marushchak[1], Inna Krynytska[2], Oksana Kopanytsia[1], Larysa Tupol[3], Iryna Savchenko[4], Lyudmyla Mazur[5]

[1]Department of Functional Diagnostics and Clinical Pathophysiology, I. Horbachevsky Ternopil State Medical University, Ternopil, Ukraine, [2]Department of Clinical-Laboratory Diagnostics, I. Horbachevsky Ternopil State Medical University, Ternopil, Ukraine, [3]Department of Histology and Embryology, I. Horbachevsky Ternopil State Medical University, Ternopil, Ukraine, [4]Department of Internal Medicine, I. Horbachevsky Ternopil State Medical University, Ternopil, Ukraine, [5]Department of Clinical Immunology, Allergology and General Patient Care, I. Horbachevsky Ternopil State Medical University, Ternopil, Ukraine

Correspondence to: Mariya Marushchak, E-mail: marushchak@tdmu.edu.ua

Received: May 15, 2017; **Accepted:** August 17, 2017

ABSTRACT

Background: The growth of the world population and the need to increase food production led to the widespread use of food additives. One of such additives is carrageenan. Potentially negative health effects of carrageenans prompt us to question safety of their widespread use. **Aims and Objectives:** In this study, we defined the effect of carrageenan (E407) consumption on the main markers of endogenous intoxication in rats. **Materials and Methods:** Experimental studies were conducted on 72 non-linear, female, white rats weighing 150-180 g. The experimental animals had free access to 0.5% carrageenan solution in drinking water. Control group of animals received pure water. Syndrome of endogenous intoxication was evaluated using measurements of low, medium, and high molecular weight substances in blood plasma, red blood cell suspension, and urine. **Results:** Our results indicate shift of the markers of intoxication syndrome toward mainly catabolic substances. The results obtained after 1 week of the experiment correspond with phase of partial compensation, characterized by increased concentrations of low and middle molecular weight substances in red blood cells and plasma. After 2 weeks and up to 1 month of the experiment, the predominantly catabolic markers of endogenous intoxication continue to increase in erythrocytes and plasma, indicating a shift to the phase of partial decompensation to systems and organs of detoxification. **Conclusion:** The consumption of carrageenan with drinking water in concentration of 0.5% was associated with the development of excessive levels of low and middle molecular weight substances with reduced ability of kidneys to excrete toxic products.

KEY WORDS: Carrageenan; Endogenous Intoxication; Rats

INTRODUCTION

The growth of the world population and the need to increase food production led to the widespread use of food additives. An increase of food additives usage is related to the civilization progress, changes in the traditional lifestyle and nutrition.[1-3] Among the reasons for using food additives are the need for long-distance transportation, long-term storage, and cost reduction, as well as improvements in taste, color, and appearance of the products, especially those marketed as low calorie or diet. One of such additives is carrageenan. Carrageenan has no nutritional value and is used in food manufacturing for its gelling, thickening, and emulsifying properties. It is added to dairy and meat products, in particular to produce low-calorie foods, such as puddings, yogurt, jellies, and ice cream. Webber *et al.* stressed that 70-80% of commercially manufactured food in the world

Access this article online	
Website: www.njppp.com	Quick Response code
DOI: 10.5455/njppp.2017.7.0517017082017	

contain carrageenan.[4] Carrageenans are also used in the pharmaceutical, cosmetic, and textile industries.[5-7]

Carrageenan is a generic name for a family of gel-forming and viscosifying polysaccharides, which are obtained by extraction from certain species of red seaweeds. Sulfated polysaccharides from marine algae can have diverse biological activities including immunomodulatory, anticoagulant, antithrombotic, antiviral, and antitumor effect.[8] It was suggested that negatively charged molecules, including sulfated polysaccharides, can interact with the positive charges on virus or cell surface and thereby prevent penetration of the virus into the host cells.[9] However, carrageenan was reported to have no effect on virus attachment or penetration into host cells, rather it inhibited synthesis of viral proteins inside the cells. Moreover, carrageenan has been reported to have anti-HIV activity, but its strong anticoagulant activity is considered to be an adverse effect, preventing its use as therapy for HIV.[7]

Several studies have reported that carrageenans have antiproliferative activity on cancer cell lines *in vitro*, as well as inhibitory activity on tumor growth in mice. In addition, they have antimetastatic activity by blocking the interactions between cancer cells and the basement membrane, inhibit tumor cell proliferation, and tumor cell adhesion to various substrates, but the exact mechanisms of these actions are not yet completely understood.[7] On the other hand, there is an evidence of oncogenic transformation of cells under the influence of carrageenan, while positive correlation was found between the use of products with this additive in the diet and an increased risk of breast carcinoma.[10]

Moreover, in experimental medicine, carrageenan is often used to model inflammatory processes. It is used in pathophysiology for modeling of peritonitis, pleurisy, arthritis, and carrageenan-induced edema of the limbs in rats.[11,12]

These indications of potentially negative health effects of carrageenans prompt us to question safety of their widespread use. There is lack of definitive data on long-term outcomes of carrageenan consumption by either healthy adults or by persons with preexisting diseases.

This article reports the effect of carrageenan (E407) consumption on the main markers of endogenous intoxication in rats.

MATERIALS AND METHODS

Experimental studies were conducted on 72 non-linear, female, white rats weighing 150-180 g, that were housed at 25 ± 3°C and humidity of 55 ± 2%, under a 12 h light and dark cycle. Water was available *ad libitum*. Our study and manipulations complied with the requirements of the Law of Ukraine "On the protection of animals against cruel treatment" (No. 1759-VI from 15.12.2009), and the international principles of the European convention for the protection of vertebrate animals used for experimental and other scientific purposes (https://rm.coe.int/CoERMPublicCommonSearch Services/DisplayDCTM Content?documentId= 090000168007a67b). The experimental study was approved by the Ethics Committee of I. Horbachevsky Ternopil State Medical University. The experimental animals had free access to 0.5% carrageenan solution (Sigma-Aldrich, USA) in drinking water. Control group of animals received pure water.

Laboratory animals were divided into four groups. Group 1 consisted of intact animals, Group 2 had access to carrageenan solution for 7 days, Group 3 had access to carrageenan solution for 14 days, and Group 4 had access to carrageenan solution for 30 days. Animal euthanasia was carried out by cardiac puncture under deep anesthesia, in accordance with the requirements of the Animal Care Committee.[13] Urine was extracted from the bladder by needle aspiration (No 147-TSMU/2016).

Syndrome of endogenous intoxication was evaluated using measurements of low and medium molecular weight substances in blood plasma, red blood cell suspension, and urine quantified by the extraction-spectrophotometric method.[14] High molecular weight substances of blood plasma, erythrocytes, and urine were precipitated in 15% solution of trichloroacetic acid. Trichloroacetic extracts of blood plasma and red blood cells were measured by spectrophotometer SF-200 at wavelengths of 242, 254, and 282 nm, trichloroacetic extracts of urine-at wavelengths of 236, 254, and 282 nm. The obtained data are expressed in standard units of optical density (U). Using the data, the following indices were calculated to evaluate the intensity of endogenous intoxication:[15]

1. Ct - total content of low and medium molecular weight substances in plasma:
   Ct = (E242+E254+E282)×40;
2. Cc - the value of catabolic pool of low and medium molecular weight substances in plasma:
   Cc = (E242+E254)×12;
3. Pc% - catabolic pool of plasma:
   Pc% = Cc/Ct×100%;
4. ICP - intensity of catabolic processes in plasma:
   ICP = (E242+E254)/(E254+E282);
5. K1 - distribution rate of low and medium molecular weight substances between blood plasma proteins and erythrocyte glycocalyx:
   K1 = (E242+E254+E282) of plasma/(E242+E254+E282) of erythrocytes;
6. K2 - elimination process condition, indicating the ability of kidneys to excrete endotoxemia products:
   K2 = (E236+E254+E282) of urine/([E242+E254+E282] of plasma+[E242+E254+E282] of erythrocytes).

The results were analyzed using Statistica 6.0 software and presented as mean with standard deviations, and the minimum and maximum values of ranges. To evaluate the distribution of the character together by sampling data, we have used Lilliefors and Kolmogorov–Smirnov tests. Statistical significance was determined by the Student's *t*-test or non-parametric Mann–Whitney criterion. $P < 0.05$ was considered statistically significant.

RESULTS

Analysis of 242-282 nm range wavelength spectrograms for low and medium molecular weight substances in plasma and red blood cells glycocalyx indicates significant difference between experimental and control groups. In the range of 242 nm in plasma of portal vein and inferior vena cava of animals who consumed water with carrageenan, the values of extinction increased, peaking after 1 month of carrageenan usage. This indicates the high contents of catabolic substances in the blood of these rats (Figure 1).

In the ranges of 242 nm and 280 nm spectrograms of red blood cells showed displacement of spectral curves and higher optical density values. This suggests strain of detoxification reserves in the portal vein and inferior vena cava of the animals and increased content of catabolic substances (Figure 2).

These results demonstrate that most of low and medium molecular weight substances increased after 1 month of observation, mainly in the blood plasma.

The pool of low and medium molecular weight parameters form a marker group of the metabolic status of animals used to analyze the possible impact of the exposition to toxic substances. This is due to the fact that red blood cells bind and transport endogenous toxic components adsorbing them on their surface. We found increased the medium molecular weight fraction in red blood cells at 254 nm of vena portae and inferior vena cava after 1-week experiment, which then with further increased after 2 weeks. This increase was in comparison to control as well as to the 1st experimental group ($P < 0.05$). It should be noted that after 1 month of carrageenan consumption the average molecular weight content was higher than in control (in vena portae 40%, and inferior vena cava 43%) but did not significantly differ from that of the two research groups. We detected increase in the level medium molecular weight substances detected at 254 nm in portal vein plasma starting at the 1st week of the experiment, and after 2 weeks of carrageenan consumption, this marker not only in vena portae, but also inferior vena cava with an upward trend in the experimental Group 3 (Table 1).

The levels of substances detected at E_{280} increased in red blood cells and portal vein plasma of the 1st experimental group. After 2 weeks of the experiment, the medium molecular weight content at 280 nm in red blood cells of vena portae and inferior vena cava steadily increased up to 1 month of the experiment. In blood plasma of vena portae, this parameter remained practically unchanged during the study, while in the inferior vena cava, it was the highest at 2 weeks of the experiment. Low molecular weight substances content

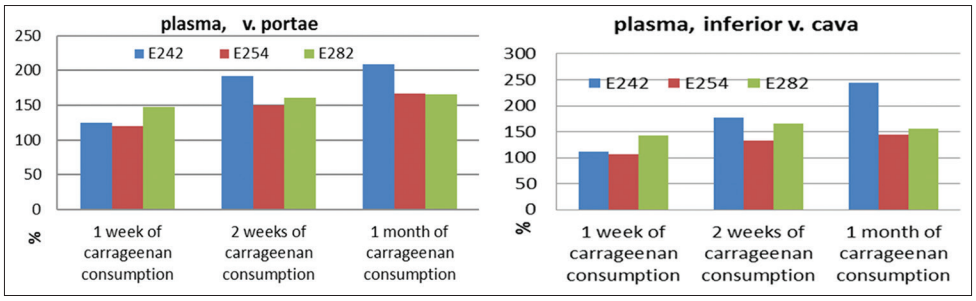

Figure 1: Change in low and middle molecular weight substances spectrograms at the wavelength range of 242-282 nm in plasma of rats that consumed water with carrageenan

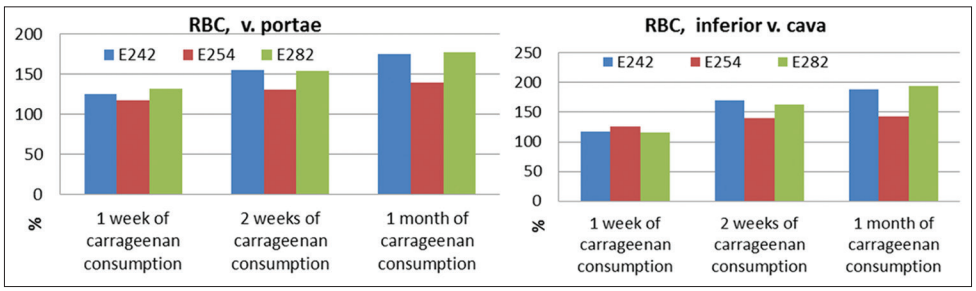

Figure 2: Spectrograms at the wavelength range of 242-282 nm of low and middle molecular weight substances in erythrocyte glycocalyx of rats that consumed water with carrageenan

Table 1: Low and medium molecular weight substances in erythrocyte glycocalyx, blood plasma, and urine of rats that consumed water with carrageenan and control group

Index	Control	1st experimental group (1 week of carrageenan consumption), U	2nd experimental group (2 weeks of carrageenan consumption), U	3rd experimental group (1 month of carrageenan consumption), U
Blood plasma				
E_{242}				
v. portae	0.12±0.01 (0.09;0.18)	0.15±0.01 (0.10;0.25)	0.23±0.01; (0.19;0.27) $P_{1,2}$<0.001	0.25±0.01 (0.22;0.30)
Inferior v. cava	0.09±0.01 (0.05;0.16)	0.10±0.01 (0.10;0.25)	0.16±0.01; (0.11;0.20) $P_{1,2}$<0.001	0.22±0.01 (0.18;0.26)
E_{254}				
v. portae	0.30±0.01 (0.22;0.37)	0.36±0.02 (0.27;0.42)	0.45±0.02; (0.34;0.53) $P_{1,2}$<0.001	0.50±0.02; (0.40;0.60) $P_{1,2}$<0.001
Inferior v. cava	0.27±0.02 (0.15;0.37)	0.29±0.01 (0.22;0.34)	0.36±0.01; (0.30;0.40) $P_{1,2}$<0.001	0.39±0.01; (0.34;0.45) $P_{1,2}$<0.001
E_{282}				
v. portae	0.23±0.02 (0.12;0.31)	0.34±0.02 (0.27;0.45) P_1<0.001	0.37±0.01; (0.29;0.45) P_1<0.001	0.38±0.01; (0.32;0.45) P_1<0.001; P_2=0.03
Inferior v. cava	0.23±0.01 (0.12;0.31)	0.33±0.01 (0.28;0.41) P_1<0.001	0.38±0.01; (0.29;0.45) P_1<0.001; P_2=0.01	0.36±0.01 (0.32;0.41) P_1<0.05
Red blood cell suspension				
E_{242}				
v. portae	0.20±0.01 (0.15;0.27)	0.25±0.01; (0.16;0.30) P_1=0.004	0.31±0.01; (0.24;0.35) $P_{1.2}$<0.001	0.35±0.01; (0.26;0.41) $P_{1,2}$<0.001; P3=0.01
Inferior v. cava	0.17±0.01 (0.11;0.25)	0.20±0.01 (0.14;0.24)	0.29±0.01; (0.23;0.32) $P_{1,2}$<0.001	0.32±0.01; (0.29;0.40) $P_{1,2}$<0.001; P_3=0.01
E_{254}				
v. portae	0.45±0.02 (0.32;0.51)	0.53±0.02; (0.42;0.59) P_1<0.001	0.59±0.01; (0.52;0.66) P_1<0.001; P_2=0.003	0.63±0.02; (0.54;0.76) $P_{1,2}$<0.001
Inferior v. cava	0.42±0.02 (0.32;0.51)	0.53±0.01; (0.45;0.60) P_1<0.001	0.59±0.01; (0.52;0.66) P_1<0.001; P_2=0.002	0.60±0.02; (0.48;0.66) $P_{1,2}$<0.001
E_{282}				
v. portae	0.22±0.01 (0.11;0.30)	0.29±0.02; (0.20;0.41) P_1<0.002	0.34±0.01; (0.25;0.40) P_1<0.001; P_2=0.01	0.39±0.01; (0.33;0.45) $P_{1,2}$<0.001; P_3=0.01
Inferior v. cava	0.19±0.02 (0.11;0.30)	0.22±0.01 (0.16;0.30)	0.31±0.02; (0.22;0.40) $P_{1,2}$<0.001	0.37±0.01; (0.33;0.42) $P_{1,2}$<0.001; P_3=0.002

(*Contd...*)

Table 1:(*Continued*)

Index	Control	1st experimental group (1 week of carrageenan consumption), U	2nd experimental group (2 weeks of carrageenan consumption), U	3rd experimental group (1 month of carrageenan consumption), U
Urine				
E_{236}	0.48±0.02 (0.28;0.58)	0.49±0.02 (0.30;0.60)	0.48±0.01 (0.26;0.55)	0.47±0.01 (0.35;0.45)
E_{254}	0.44±0.02 (0.36;0.58)	0.45±0.01 (0.40;0.56)	0.43±0.01 (0.40;0.53)	0.42±0.01 (0.38;0.53)
E_{282}	0.40±0.03 (0.34;0.51)	0.42±0.02 (0.38;0.52)	0.38±0.02 (0.40;0.47)	0.40±0.01 (0.40;0.46)

P_1: Significant difference compared to the control group, P_2: Significant difference compared to the 1st experimental group, P_3: Significant difference compared to the 2nd experimental group

increased in red blood cells of vena portae after 1 week of the experiment, in red blood cells and plasma of vena portae and inferior vena cava after 2 weeks, and then remained virtually unchanged until the end of the experiment.

One of the most informative signs of adaptive reaction to stress exposition were the changes in marker K_1, which increased by 13% after 2 weeks and 1 month of the experiment in red blood cells of vena portae compared to the control values ($P < 0.05$). Against this background, values of K_2 marker, which is used for comprehensive assessment of endotoxemia on the body, showed gradual decline. This decline corresponded to the duration of carrageenan use and indicated the reduced ability of kidneys to excrete toxic products (Table 2).

DISCUSSION

Thus, the consumption of carrageenan with drinking water in concentration of 0.5% led to a statistically significant increase in endogenous intoxication, manifested by an increase in the content of low and medium molecular weight substances. This, obviously, suggests an increase in destructive processes, as well as inhibition of the detoxifying function of the body, which can lead to a violation of neutralization of endogenous toxins, and consequently, accumulation of intermediate metabolic products. Our results indicate shift of the markers of intoxication syndrome toward mainly catabolic substances. The results obtained after 1 week of the experiment correspond with the phase of partial compensation, characterized by increased concentrations of low and middle molecular weight substances in red blood cells and plasma. After 2 weeks and up to 1 month of the experiment, the predominantly catabolic markers of endogenous intoxication continue to increase in erythrocytes and plasma, indicating a shift to the phase of partial decompensation to systems and organs of detoxification.

In the modern literature, there is no reliable data on the effect of the systematic use of carrageenan on the body of an adult, on the child's organism, or on the fetus's organism with this supplement in the diet of a pregnant woman. In the clinic, the study of this issue is very problematic, so there is an urgent need to study the effect of carrageenan on metabolic indices in the experimental conditions.

The important role endogenous intoxication syndrome plays in the development of many diseases is being increasingly recognized. In short, endogenous intoxication occurs when damaging processes cause accumulation of intermediate and final products of normal metabolism and metabolic disorders in aberrant concentrations in body fluids and tissues.[16] These products have toxic effect and resulting in dysfunction of various organs and systems.[17] Concentration of low and middle molecular weight substances is an important and objective indicator of toxicity within the body systems, independent of the causes, and signs of the diseases. Concentration of low and middle molecular weight substances is thought to primarily reflect the extent of abnormal protein metabolism and correlate with main clinical and laboratory prognostic criteria for metabolic disorders.[18]

The entire range of low and middle molecular weight substances can be divided into two groups, catabolic and anabolic. According to Malakhova,[15] the catabolic group in the range of 242-258 nm provides the most information in assessing the extent of endogenous intoxication. The group includes products of protein molecules catabolism and low molecular weight metabolites such as urea, creatinine, uric acid, purine metabolism products, as well as nucleotides and their derivatives, nucleoprotein metabolites. A significant increase in the number of catabolic products is one of the stages in syndrome of endogenous intoxication. Anabolic group of the low and middle molecular weight substances is recorded in wavelength range of 258-298 nm. The group includes mainly fragments of protein molecules containing aromatic amino acids, metabolites of urea cycle, purine and pyrimidine, and their derivatives.

Thus, even the minimal intake of exogenous toxic substances, such as carrageenan in the blood, triggers endogenous intoxication. Metabolic products, which are usually removed

Table 2: Markers of endogenous intoxication in rats that consumed water with carrageenan and control group

Index	Control	1st experimental group (1 week of carrageenan consumption)	2nd experimental group (2 weeks of carrageenan consumption)	3rd experimental group (1 month of carrageenan consumption)
Ct				
v. portae	25.5±0.93	33.87±0.94; P_1<0.001	41.60±0.75; $P_{1,2}$<0.001	45.47±0.83; $P_{1,2}$<0.001; P_3=0.002
Inferior v. cava	23.13±1.13	28.83±0.82; P_1<0.001	36.07±0.76; $P_{1,2}$<0.001	38.73±0.66; $P_{1,2}$<0.001; P_3=0.01
Cc				
v. portae	4.95±0.19	6.13±0.14; P_1<0.001	8.07±0.20; $P_{1,2}$<0.001	9.03±0.21; $P_{1,2,3}$<0.001
Inferior v. cava	4.24±0.27	4.66±0.17	6.28±0.16; $P_{1,2}$<0.001	7.27±0.50; $P_{1,2,3}$<0.001
Pc%				
v. portae	19.49±0.56	18.16±0.42; P_1=0.04	19.41±0.30; P_2=0.01	19.86±0.22; P_2<0.001
Inferior v. cava	18.29±0.70	16.14±0.40; P_1<0.001	17.43±0.30; P_2=0.008	18.77±0.21; $P_{2,3}$<0.001
ICP				
v. portae	0.80±0.03	0.74±0.02	0.83±0.02; P_2<0.001	0.85±0.01; P_2<0.001
Inferior v. cava	0.72±0.03	0.63±0.02; P_1<0.001	0.71±0.02; P_2<0.001	0.81±0.02; $P_{1,2,3}$<0.001
K1				
v. portae	0.75±0.03	0.80±0.04	0.85±0.02; P_1<0.001	0.84±0.02; P_1<0.001
Inferior v. cava	0.74±0.03	0.76±0.02	0.76±0.02	0.75±0.02
K2				
v. portae	0.89±0.04	0.71±0.02; P_1<0.001	0.57±0.02; $P_{1,2}$<0.001	0.52±0.01; $P_{1,2}$<0.001; P3=0.01
Inferior v. cava	0.99±0.05	0.81±0.03; P_1<0.001	0.62±0.02; $P_{1,2}$<0.001	0.57±0.01; $P_{1,2,3}$<0.001

P_1: Significant difference compared to the control group, P_2: Significant difference compared to the 1st experimental group, P_3: Significant difference compared to the 2nd experimental group

from the body under normal metabolic processes, can cause intoxication if over-produced, if their elimination from the blood circulation is insufficiently effective, or if both of these events occur simultaneously.[18] We suggest that 1 month of 0.5% carrageenan consumption causes overproduction of toxic metabolites and disrupted elimination process condition resulting in endogenous intoxication syndrome.

There is original concept of endogenous intoxication: The occurrence of systemic inflammation (systemic inflammatory response syndrome).[19] Moreover, there are data that the activation of lipid peroxidation processes and reactive oxygen species are an important pathophysiological mechanisms for the development of endogenous intoxication.[20] Excessive lipoperoxidation is accompanied by the accumulation of peroxide oxidation products and the depletion of antioxidant system reserves, which causes hyperfermentemia and accumulation of toxic substances.

The inflammatory cascades activated by carrageenan exposure are mediated by reactive oxygen species and by activation of an innate immune pathway involving the toll-like receptor-4 and B-cell leukemia/lymphoma 10.[21-24] Changes in the intestinal wall in case of the carrageenan action on the mucous membrane of the intestine lead to the damage of the mucous membrane and violation of the barrier, motor, and nutritional functions of the intestine.[25] The permeability of the epithelial intestinal barrier is affected by a number of factors: Acute endotoxemia, oxidative stress, cellular hypoxia, suppression of metabolism, proinflammatory cytokines, bacterial toxins, parenteral nutrition, proteolytic enzymes, massive hemorrhage, etc.[26] The loss of the barrier function by the intestine causes

the translocation of bacteria and their endotoxins both into the abdominal cavity and into the general blood flow, followed by the development of endotoxicosis.[27] The main mechanisms which may be involved into bacterial translocation are disruption of immune response, change of the bacterial flora in the small intestine, and increased intestinal permeability. Moreover, intestinal mucosa is damaged by oxidative stress, which also increases its permeability. Endotoxemia may be caused either directly by the movement of bacteria through the intestinal mucosa or indirectly through the cytokine cascade stimulates vascular endothelial inducible nitric oxide synthase, which increases the production of NO.[28,29] Violation of the enterohepatic barrier as one of the pathological manifestations of enteric insufficiency leads to the emergence of an additional source of endotoxicosis, which closes the vicious circle and causes the occurrence of irreversible lesions of various organs and systems.[30]

Strengths and limitations: Experimental research designs are repeatable, and therefore, results can be checked and verified. Findings usually cannot be generalized to the study population or community because of small amount of animals in experimental groups.

CONCLUSION

Thus, our results indicate that consumption of carrageenan with drinking water in concentration of 0.5% was associated with significant increase in endogenous intoxication, manifested by increased levels of low and middle molecular weight substances with reduced ability of kidneys to excrete toxic products.

REFERENCES

1. Stoma M, Ślaska-Grzywna B, Żukiewicz-Sobczak WA, Kostecka M, Bojanowska M, Dudziak A, *et al.* Food allergies in rural areas. Postepy Dermatol Alergol 2016;33:281-5.
2. El Khoury D, Goff HD, Berengut S, Kubant R, Anderson GH. Effect of sodium alginate addition to chocolate milk on glycemia, insulin, appetite and food intake in healthy adult men. Eur J Clin Nutr 2014;68:613-8.
3. Patel NM, Joshi KJ, Kumar P, Purani SK, Kartha GP. Knowledge, attitude and practice (KAP) regarding carbonated drinks among medical students of C.U.Shah. Medical college and hospital of Surendranagar district. Int J Med Sci Public Health 2017;6:38-41.
4. Webber V, de Carvalho SM, Ogliari PJ, Hayashi L, Barreto PL. Optimization of extraction of carrageenan. Ciênc Tecnol Aliment 2012;32:812-8.
5. Campo VL, Kawano DF, da Silva JD, Carvalho I. Carrageenans: Biological properties, chemical modifications and structural analysis – A review. Carbohydr Polym 2009;77:167-80.
6. Imeson AP, Phillips GO, Williams PA. Handbook of Hydrocolloids. Cambridge: Wood Head Publishing Limited; 2000.
7. Necas J, Bartosikova L. Carrageenan: A review. Vet Med 2013;58:187-205.
8. de Jesus Raposo MF, de Morais AM, de Morais RM. Marine polysaccharides from algae with potential biomedical applications. Mar Drugs 2015;13:2967-3028.
9. Cunha L, Grenha A. Sulfated seaweed polysaccharides as multifunctional materials in drug delivery applications. Mar Drugs 2016;14:42.
10. Tobacman JK, Wallace RB, Zimmerman MB. Consumption of carrageenan and other water-soluble polymers used as food additives and incidence of mammary carcinoma. Med Hypotheses 2001;56:589-98.
11. Morris CJ. Carrageenan-induced paw edema in the rat and mouse. Methods Mol Biol 2003;225:115-21.
12. Kim KS, Kim MH, Yeom M, Choi HM, Yang HI, Yoo MC, *et al.* Arthritic disease is more severe in older rats in a kaolin/carrageenan-induced arthritis model. Rheumatol Int 2012;32:3875-9.
13. Reznikov O. General thical principles of experiments on animals. Endocrynology 2003;8:142-5.
14. Urakova TY, Lysenkova NS. Endogenous intoxication and adaptive possibilities of obese patients. Int J Fundam Investig 2009;5:39-45.
15. Malakhova MY. Endogenous intoxication as reflection of compensatory reconstruction of metabolic processes in organism. Eff Ther 2000;4:3-14.
16. Koryakina EV, Belova SV. Molecules of medium mass as an integral measure of metabolic disorders (literature review). Clin Lab Diagn 2004;2:3-8.
17. Kopytova TV, Dmitriyeva ON, Khimkina LN, Panteleyeva GA. Oxidative modification of proteins and oligopeptides in patients with chronic dermatoses with the syndrome of endogenous intoxication. Fundam Investig 2009;6:25-9.
18. Cavrilov VB, Bidula MM, Furmanchuk DA, Konev SV, Aleynikova OV. Assessment intoxication of organism by an imbalance between accumulation and binding of toxins in the blood plasma. Clin Lab Diagn 1999;2:13-7.
19. Bone RS. Toward a theory regarding the pathogenesis of the systemic inflammatory response syndrome: What we do and not know about cytokine regulation. Crit Care Med 1996;241:163-72.
20. Paneok OS, Kostiv MO. Processes of peroxide lipid oxidation and endogenous intoxication in pregnant women with thyropaatia. Exp Clin Physiol Biochem 2012;1:97-101.
21. Borthakur A, Bhattacharyya S, Dudeja PK, Tobacman JK. Carrageenan induces interleukin-8 production through distinct BCL-10 pathway in normal human intestinal epithelial cells. Am J Physiol Gastrointest Liver Physiol 2007;292:G829-38.
22. Bhattacharyya S, Gill R, Chen ML, Zhang F, Linhardt RJ, Dudeja PK, *et al.* Toll-like receptor 4 mediates induction of the bcl10-NFkappaB-interleukin-8 inflammatory pathway by carrageenan in human intestinal epithelial cells. J Biol Chem 2008;283:10550-8.
23. Bhattacharyya S, Dudeja PK, Tobacman JK. Carrageenan-induced NFkappaB activation depends on distinct pathways mediated by reactive oxygen species and hsp27 or by bcl10. Biochim Biophys Acta 2008;1780:973-82.
24. Bhattacharyya S, Borthakur A, Tyagi S, Gill R, Dudeja PK, Tobacman JK. BCL10 is required for NFκB nuclear translocation by both canonical and non-canonical pathways and for NIK phosphorylation. J Biol Chem 2010;285:522-30.
25. Moyana TN, Lalonde MBA. Carrageenan-induced intestinal

injury in the Rat – A model for inflammatory bowel disease. Ann Clin Lab Sci 2012;20:420-6.
26. Tretyakov EV, Varganov EV, Nifontova EE. A modern view of intestinal bacterial translocation as the main cause of purulent-septic complications in destructive pancreatitis. Success Mod Natural Sci 2013;9:78-8027.
27. Krivoruchko IA, Zhukov VI, Ivanova SE, Povelichenko MS, Moiseenko AS. The condition of the liver monooxygenase system in rats with ischemia/reperfusion of the small intestine. Kharkov Surg Sch 2012;6:36-9.
28. Garbuzenko DV. The role of intestine micro flora in the development of portal hypertension in hepatic cirrhosis. Clin Med 2007;8:15-9.
29. Krynytska IY, Marushchak MI, Klishch IM, Birchenko IV. Molecular mechanisms of hepatopulmonary syndrome. J Physiol 2017;63:90-102.
30. Guo ZZ, Wang P, Yi ZH, Huang ZY, Tang CW. The crosstalk between gut inflammation and gastrointestinal disorders during acute pancreatitis. Curr Pharm Des 2014;20:1051-62.

How to cite this article: Marushchak M, Krynytska I, Kopanytsia O, Tupol L, Savchenko I, Mazur L. The influence of carrageenan on markers of endogenous intoxication in rats. Natl J Physiol Pharm Pharmacol 2018;8(3):412-419.

Source of Support: Nil, **Conflict of Interest:** None declared.