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Short Communication

Pharmacological correction of post-contrast acute kidney injury with a functional product based on fermented grape juice

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Abstract

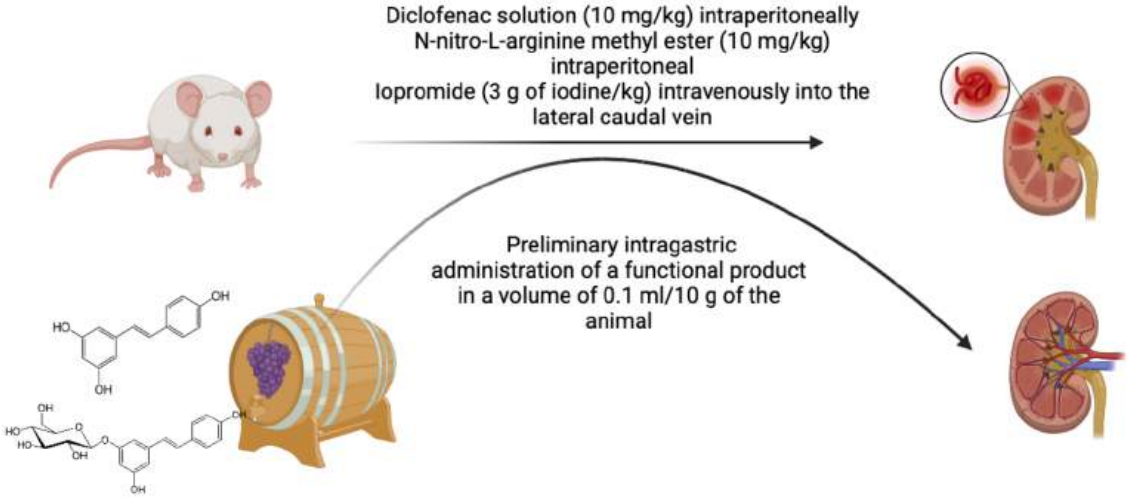
Introduction: Post-contrast acute kidney injury (PC-AKI) is a serious complication when taking iodine-containing radiopaque agents. The study is aimed at pharmacological correction of PK-AKI with a functional product obtained from fermented red grape berry juice with a high content of stilbenoids (trans-resveratrol and its glycoside polydatin).

Materials and Methods: The study was conducted on 36 male CD1 mice, 8-10 weeks old, weighing 25±3 g. The animals were divided into 3 groups (n=12): a group of intact animals; a group with PC-AKI modeling; and a group with PC-AKI modeling and preliminary intragastric administration of a functional product in a volume of 0.1 mL/10 g per animal. A morphological assessment of kidney changes was performed, as well as a blood test for creatinine, urea, and albumin.

Results: Preliminary administration of the functional product to mice led to a statistically significant decrease in creatinine and urea concentrations to 43.5±1.6 μmol/L and 34.5±1.4 μmol/L, respectively; the glomerular filtration rate increased to 66.2±4.1 μL/min and the urea/albumin ratio decreased to 1.9±0.03, with mortality also decreasing to 8.3%.

Conclusion: The preventive use of a functional product based on fermented red berry juice in an amount of 0.1 mL/kg of animal effectively reduces the severity of post-contrast acute kidney injury in a mouse model.

Graphical abstract



Keywords

resveratrol, polydatin, post-contrast acute kidney injury, radiopaque agent

Introduction

Post-contrast acute kidney injury (PC-AKI) is a serious complication associated with the use of iodine-containing contrast media (Lin et al. 2021). This pathology is most often found in patients with cardiac surgery. There are currently three main mechanisms in the development of PC-AKI: narrowing of the renal vessels and hypoxia of the renal medulla, direct toxic effect on tubular cells and formation of reactive oxygen species. The combination of these mechanisms results in apoptosis of epithelial and endothelial cells and a decrease in glomerular filtration rate (GFR) (Vlachopanos et al. 2019; Somkereki et al. 2024).

Since there is currently no approved highly effective treatment for PC-AKI, prevention may be the best strategy to address this problem (Samadi et al. 2020). One of the promising pharmacological agents of the polyphenolic structure contained in grapes is stilbenoids such as trans-resveratrol and its glycoside polydatin, which has a higher bioavailability (Karami et al. 2022; Liu et al. 2022). Since the fermented juice of red grape berries, in addition to stilbenoids, contains a number of other polyphenolic compounds, including anthocyanides, catechins, proanthocyanidins, and other biologically active substances with endothelioprotective and antioxidant properties (Wang et al. 2019; Karami et al. 2022; Baxevanis and Kanellos 2024), the functional product we studied can be considered as one of the strategies for preventing PC-AKI.

The aim of the study was to evaluate the effectiveness of pharmacological correction of post-contrast acute kidney injury with a functional product based on fermented juice of red grape berries with a high content of stilbenoids.

Materials and Methods

Investigated compounds

A functional product based on fermented red grape berry juice containing ph-resveratrol and polydatin in concentrations of 4.5 mg/15 mL and 1.5 mg/15 mL, respectively, was used as a pharmacological agent (produced by the Research Institute of Pharmacology of Living Systems of National Research University ” Belgorod State University”); chromatograms of the studied compounds are shown in Figure 1a,b. Iopromide (Ultravist, Baer) was studied as an X–ray contrast agent.

Animals

The study was conducted on 36 male CD1 mice, 8-10 weeks old, weighing 25±3 g.

A model of post-contrast acute kidney injury (PC-AKI)

Sequentially, with an interval of 30 minutes, the animals were injected with diclofenac solution at a dose of 10 mg/kg intraperitoneally; endothelial NO synthase inhibitor – N–nitro-L-arginine methyl ester – at a dose of 10 mg/kg intraperitoneally and the iodine-containing radiopaque agent Ultravist (iopromide) at a dose of 3 g of iodine/kg

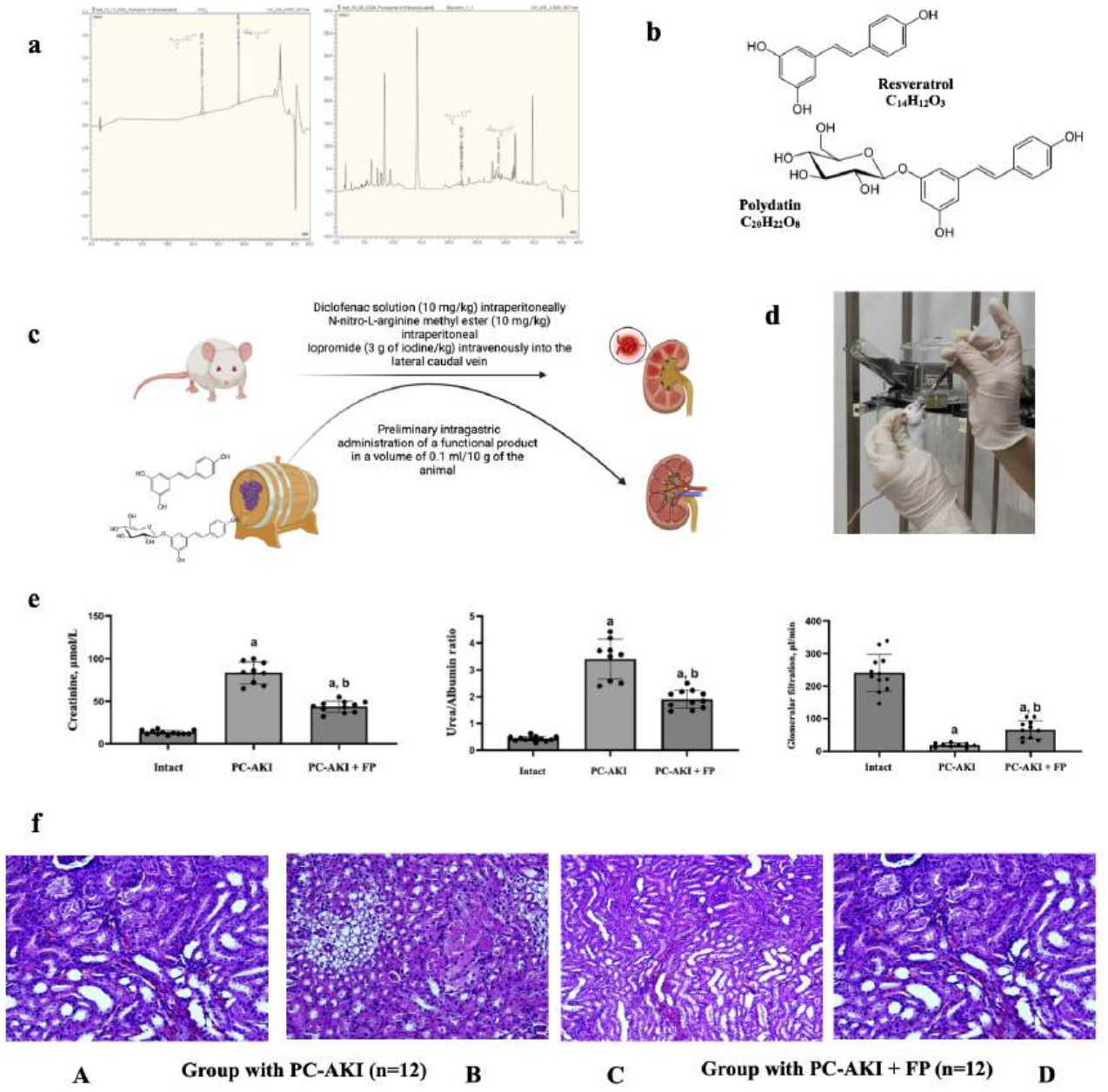


Figure 1. The results of pharmacological correction of post-contrast acute kidney injury with a functional product based on fermented grape juice. ***Note:*** **a** – Representative chromatograms of a solution of standard samples of polydatin and trans-resveratrol (left) and a functional product based on fermented juice of red grape berries (right). λ=307 nm; **b** – Structural formulas of trans-resveratrol and polydatin; **c** – The study is aimed at the pharmacological correction of post-contrast acute kidney injury in mice (PC–AKI) with a functional product based on fermented red grape berry juice with a high content of stilbens – trans-resveratrol and polydatin; **d** – Intragastric administration of a functional product to mice; **e** – The dynamics of serum creatinine, urea, and glomerular filtration rates in the study groups (n=12). The data are presented as an average ± standard deviation, a – $p<0.05$ in comparison with the group of intact animals; b – $p<0.05$ in comparison with the control group (PC-AKI). **f (A, B)** – Representative images of post–contrast acute kidney injury in mice caused by taking iopromide: A – focal tubular necrosis of the renal cortex at the border with the cerebral one in the histological preparation of the kidney of the group of simulated pathology. Hematoxylin+eosin, X200; B – the focus of balloon dystrophy of the epithelium of the convoluted tubules (left) and the focus of tubular necrosis (right) in the histological preparation of the kidney of the group of simulated pathology. Hematoxylin+eosin, X300. **f (C, D)** – representative images of kidneys in mice treated with iodopromide while taking a functional product: C – parenchyma of the kidney of a mouse treated with the studied wine material, the border of the cortical and medullary layers of the kidney. Hematoxylin+eosin, X200; D – granular dystrophy of the epithelium of the proximal convoluted tubules at the border of the renal cortex and medulla. Hematoxylin+eosin, X300. PC-AKI – post–contrast acute kidney injury; FP – functional product.

intravenously into the lateral caudal vein.

Research design

The animals were divided into 3 groups (n=12): a group of intact animals; a group with PC-AKI modeling; and a group with PC-AKI modeling and preliminary intragastric administration of a functional product in a volume of 0.1 mL/10 g of the animal (Fig. 1c, d).

Mice were placed in metabolic cells, and urine was collected 24 hours after pathology modeling; after 48 hours, blood samples were taken from the left ventricle of the heart under anesthesia for subsequent analysis of creatinine, urea and albumin concentrations; glomerular filtration rate was assessed by endogenous creatinine clearance; after 24 and 48 hours, the number of deaths was taken into account.

Histology

After euthanasia, the kidneys were opened and taken out, the samples were fixed in 10% formalin buffer, enclosed in paraffin blocks, and sections were made and stained with hematoxylin and eosin.

Statistical analysis

The data obtained was subjected to statistical analysis using IBM SPSS Statistics 26 and Microsoft Excel 2010 software and expressed as average values ± standard deviation. To determine the significance of the differences, the Student's t-test was used, $p<0.05$. An ANOVA test was used to compare the data between the groups.

Results and Discussion

The results of pharmacological correction of PK-AKI with a functional product based on fermented juice of red grape berries are shown in Figure 1e.

Modeling of PK-AKI resulted in a statistically significant increase in creatinine and urea from 13.5±0.2 μmol/L and 8.35±0.1 μmol/L to 83.5±3.3 μmol/L and 52.7±2.3 μmol/L, respectively. At the same time, there was a decrease in the glomerular filtration rate by more than 12 times from 241.1±8.2 to 18.7±0.1 μL/min.

The urea/albumin ratio, on the contrary, increased significantly from 0.43±0.01 to 3.4±0.07. There was also a fairly high mortality rate (25%).

Pre-administration of the functional product to mice resulted in a statistically significant decrease in creatinine and urea concentrations to 43.5±1.6 μmol/L and 34.5±1.4 μmol/L, respectively. The improvement in the functional state of the kidneys was also indicated by an increase in the glomerular filtration rate to 66.2±4.1 μL/min and a decrease in the urea/albumin ratio to 1.9±0.03. Mortality also decreased significantly in this group of laboratory animals and amounted to 8.3%.

The obtained results were confirmed by morphological examination (Fig. 1f). Histological preparations of the kidneys of the group of simulated pathology were marked by pronounced pathological changes in the parenchyma of the cortical layer at the border with the cerebral one: focal necrosis of the epithelium of the proximal and distal convoluted tubules (Fig. 1f A), as well as their pronounced dystrophic changes in the type of granular and balloon dystrophy (Fig. 1f B). In addition, changes in the nuclei by the type of karyopycnosis, karyorexis and karyolysis, as well as cytoplasmic fragmentation, were detected in the foci of dystrophies.

In the kidney preparations of mice treated with the functional product under study, the preservation of renal histoarchitectonics without signs of tubular necrosis was microscopically determined (Fig. 1f C). However, it is worth noting that foci of a rather pronounced granular dystrophy of the epithelium of the proximal convoluted tubules were noted on the border of the cortical and medulla of the kidneys, and eosinophilic cylinders were found in their lumens. In addition, multiple small extravasal accumulations of red blood cells were detected in the same area (Fig. 1f D).

The positive pharmacological effects of a functional nutrition product with a high content of stilbenoids against the background of PK-AKI with iopromide are due to their nephroprotective properties, the realization of which may be associated with anti-inflammatory, antioxidant and endothelioprotective effects (Vlachopanos et al. 2019; Karami et al. 2022; Liu et al. 2022).

In addition, stilbenoids are able to activate SIRT1, one of the enzymes that deacetylate histones. In acute kidney injury, activation of this enzyme leads to a decrease in fibrosis, inhibition of oxidative stress, apoptosis and inflammation, induction of autophagy, regulation of the cell cycle, improvement of mitochondrial function, maintaining the number of peroxisomes and catalase activity (Raji-Amirhasani et al. 2021).

Conclusion

Thus, the preventive use of a functional product based on fermented red grape berry juice containing trans-resveratrol and polydatin in concentrations of 4.5 mg/15 mL and 1.5 mg/15 mL, respectively, in an amount of 0.1 mL/kg of animal, according to a set of morphofunctional criteria, effectively reduces the severity of post-contrast acute kidney injury caused by intravenous administration iopromide in a dose of 3 g of iodine/kg.

Ethical statement

The study was approved by the local Ethics Committee of Belgorod State National Research University (Minutes No. 52 dated December 21, 2024). The ethical principles of handling laboratory mice were observed in accordance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Purposes and Directive 2010/63 EU and other regulatory legal acts regulating preclinical research in the Russian.

Conflict of interest

The authors declare the absence of a conflict of interests.

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Data availability

All of the data that support the findings of this study are available in the main text.

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All the authors reviewed and edited the manuscript.