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Research Article

Modeling of cisplatin-induced acute kidney injury and its correction using polydatin

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Abstract

Introduction: Cisplatin is a key drug used for anticancer therapy. However, its use is often accompanied by the development of acute kidney injury. **The aim of this study** was to develop an optimal model of cisplatin-induced kidney injury in rats and use it to study the nephroprotective properties of polydatin.

Materials and Methods. The experiment was performed in 100 male Wistar rats. To test the cisplatin-induced acute kidney injury model, seven groups (n=10) were formed. Animals were administered cisplatin intraperitoneally at doses of 1 mg/kg, 5 mg/kg, 10 mg/kg, and 20 mg/kg once or twice on days 1 and 8. Nephrotoxicity was corrected using polydatin at doses of 4 mg/kg and 12 mg/kg. Alpha-tocopherol acetate at a dose of 75 mg/kg was used as a reference drug. The test drug and the reference drug were administered intragastrically daily for 14 days. Nephroprotection was assessed based on the following parameters: creatinine, urea, potassium and sodium ions in the blood serum, glomerular filtration rate, fractional sodium extraction, and renal parenchyma microcirculation.

Results and Discussion. The optimal model of cisplatin-induced acute kidney injury was the one in which cisplatin was administered at a dose of 5 mg/kg on days 1 and 8 of the experiment. This was evidenced by an increase in creatinine level to 124.0 ± 8.6 μmol/L and urea to 20.3 ± 1.2 mmol/L, a decrease in glomerular filtration rate to 0.08 ± 0.01 mL/min and a 2-fold deterioration in microcirculation. Other models were significantly inferior in representativeness. Polydatin demonstrated dose-dependent nephroprotective properties, which was confirmed by improvement in laboratory and instrumental parameters.

Conclusions. The use of cisplatin at a dose of 5 mg/kg intraperitoneally on days 1 and 8 results in optimal modeling of cisplatin-induced acute kidney injury in rats in the experiment. The potential of intragastric use of polydatin for nephroprotection in cisplatin-induced acute kidney injury has been proven in dosages of 4 mg/kg and 12 mg/kg per day for 14 days.

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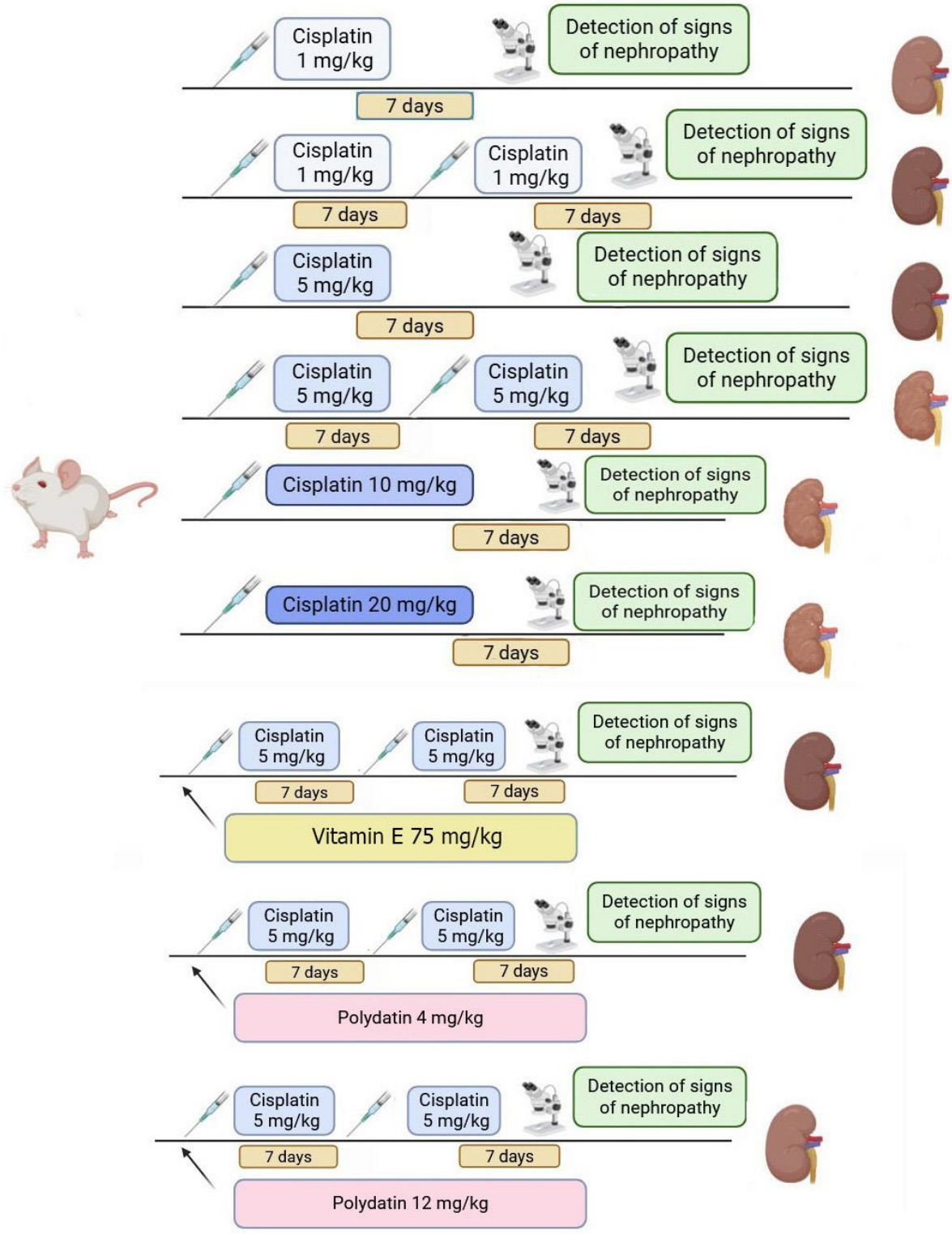
Graphical Abstract



Keywords

cisplatin; acute kidney injury; nephrotoxicity; microcirculation; polydatin

Introduction

More than 600,000 cases of cancer are diagnosed annually in the Russian Federation (Okladnikov and Nikitina 2023). Thanks to a well-developed system of screening and preventive medical examinations, early-stage cancer can be diagnosed in more than 50% of cases (Kaprin et al. 2024). However, despite all modern laboratory and imaging methods, in 18.9% of cases, cancer was first diagnosed when the disease was already at stage IV (Kaprin et al. 2024). According to current recommendations, drug-based antitumor therapy is the gold standard for all treatment of patients with advanced and metastatic cancer.

Cisplatin is one of the most commonly used chemotherapy drugs (Burnasheva et al. 2018). Cisplatin is a platinum derivative and is an alkylating agent (Fahmy et al. 2023). Like many other drugs, cisplatin is eliminated primarily by the kidneys. Cisplatin's antitumor and toxic effects are mediated by damage to mitochondrial and, to a lesser extent, nuclear DNA, which explains the high sensitivity of the renal proximal tubules, where mitochondrial density is highest (Miller et al. 2010). The subsequent decrease in ATP synthesis and cellular hypoxia, in turn, lead to the release of caspase 8 and 9 activation mediators, which act as initiators of programmed cell death. These events lead to the death of the proximal renal tubular epithelium, accompanied by apoptosis, the development of an inflammatory response in the parenchyma, and vascular damage, leading to renal ischemia (McSweeney et al. 2021). Cisplatin induces intracellular damage, leading to the release of DAMPs (damage-associated molecular patterns) – endogenous molecules that are ligands for toll-like receptors (McSweeney et al. 2021). Their activation, in turn, leads to the synthesis of chemokines and other cytokines, including TNF-α, a key inflammatory mediator. As a result, immune cells, particularly neutrophils and macrophages, are attracted to the damaged area, triggering a cascade of pathological inflammatory reactions (Veiga-Matos et al. 2020). Thus, the search for substances capable of reducing the intensity of pathological inflammatory reactions in the renal parenchyma against the background of cisplatin-induced acute kidney injury remains an extremely important task (Altındağ and Ergen 2023). Cisplatin is recommended for systemic therapy of a wide range of malignancies; however, it exhibits significant nephrotoxicity, which in some cases leads to dose reduction or even complete discontinuation of the drug (Luft 2021). Renal dysfunction significantly impairs the quality of life of cancer patients and can shorten their life expectancy. Despite all efforts, AKI develops in almost a third of patients after the first course of cisplatin-containing therapy and in some cases progresses to chronic renal failure (Latcha et al. 2016).

Several Russian and international studies have already tested some models of cisplatin-induced acute kidney injury (Wadey et al. 2014; Kuwata et al. 2015; George et al. 2022; Sergeeva et al. 2024). Despite a large number of experimental models of cisplatin-induced acute kidney injury, it was not possible to develop an ideal, generally accepted method for reproducing this pathology in rats (Perse et al. 2018).

Currently, there are no effective drugs or treatments for cisplatin-induced acute kidney injury. In vitro and in vivo studies show that numerous natural compounds possess specific antioxidant, anti-inflammatory, and antiapoptotic properties that regulate the mechanisms of cisplatin-induced kidney injury (Holditch et al. 2019; Fang et al. 2021; Majee et al. 2023; Shcheblykina et al. 2024; Mamache et al. 2025). One such compound is polydatin, a stilbene derivative of resveratrol with improved bioavailability that has a complex cytoprotective effect (Karami et al. 2022; Gołąbek-Grenda et al. 2023). Vitamin E was chosen as the comparator drug because it has powerful antioxidant properties that help protect cells from free radical damage (Bratchikov et al. 2021). A number of studies have already examined the possible nephroprotective role of vitamin E in modeling cisplatin-induced acute kidney injury (Abo-Elmaaty et al. 2020).

Taking into account the above, **the aim of our study** was to develop an optimal model of cisplatin-induced acute kidney injury in rats in an experiment and then to study the nephroprotective properties of polydatin in a model of cisplatin-induced acute kidney injury.

Materials and Methods

Investigated compounds

The pathology was modeled using the drug cisplatin, concentrate for the preparation of an infusion solution (Pharmasyntez-Nord, Russia). Alpha-tocopherol acetate, an oral solution (oil) 100 mg/mL (Tula Pharmaceutical Factory LLC, Russia), and polydatin (Sigma Aldrich, China) were used as pharmacological agents. Animals received a polydatin suspension in 0.05% sodium carboxymethylcellulose solution for administration.

Animals

The experiment was performed in 100 white male Wistar rats weighing 250-300 g, which met all the necessary criteria and were kept in accordance with the current regulations. The study was conducted at the Research Institute of Pharmacology of Living Systems of Belgorod State National Research University in accordance with regulatory legal acts and guidelines governing the conduct of experimental research in the Russian Federation. The experimental protocols were approved by the local independent Ethical Committee of Belgorod State National Research University (Minutes № 01-10i/24 of 01 October 2024). The ethical principles of the treatment of laboratory animals meet requirements of the European Convention for the Protection of Vertical Animals Used for Experimental and Other Scientific Purposes. CETS N170.

Modeling of cisplatin-induced acute kidney injury

A nephrotoxicity study of cisplatin (Pharmasyntez-Nord, Russia) was conducted at doses of 1 mg/kg, 5 mg/kg, 10 mg/kg, and 20 mg/kg. The chosen doses were based on previously identified negative effects on renal parenchyma in rat models of kidney injury (Wadey et al. 2014; Kuwata et al. 2015; George et al. 2022; Sohn et al. 2013; Vinken et al. 2012). After randomization of animals by weight, the following experimental groups of 10 animals each were formed:

Group 1 – Intact animals

Group 2 – Cisplatin 1 mg/kg. Cisplatin was injected intraperitoneally once on the first day of the experiment. Evaluation of the quality of nephrotoxic effect on the 7th day after administration of cisplatin.

Group 3 – Cisplatin 1 mg/kg. Cisplatin was injected intraperitoneally twice on the first and eighth days of the experiment. Evaluation of the quality of nephrotoxic effect on the 14th day after the first administration of cisplatin.

Group 4 – Cisplatin 5 mg/kg (7 days). Cisplatin was injected intraperitoneally once on the first day of the experiment. Evaluation of the quality of nephrotoxic effect on the 7th day after administration of cisplatin.

Group 5 – Cisplatin 5 mg/kg. Cisplatin was injected intraperitoneally twice on the first and eighth days of the experiment. Evaluation of the quality of nephrotoxic effect on the 14th day after the first administration of cisplatin.

Group 6 – Cisplatin 10 mg/kg (7 days). Cisplatin was injected intraperitoneally once on the first day of the experiment. Evaluation of the quality of nephrotoxic effect on the 7th day after administration of cisplatin.

Group 7 – Cisplatin 20 mg/kg (7 days). Cisplatin was injected intraperitoneally once on the first day of the experiment. Evaluation of the quality of nephrotoxic effect on the 7th day after administration of cisplatin.

Study of nephroprotective effect

After determining the optimal model for reproducing cisplatin-induced acute kidney injury, the following groups of 10 animals each were formed:

Group 8 – Cisplatin 5 mg/kg + vitamin E 75 mg/kg. Cisplatin was injected intraperitoneally twice on the first and eighth days of the experiment. Vitamin E was given daily intragastrically through a tube for 14 days. Evaluation of the quality of nephrotoxic effect on the 14th day after the first administration of cisplatin.

Group 9 – Cisplatin 5 mg/kg + polydatin 4 mg/kg. Cisplatin was injected intraperitoneally twice on the first and eighth days of the experiment. Polydatin was given daily intragastrically through a tube for 14 days. Evaluation of the quality of nephrotoxic effect on the 14th day after the first administration of cisplatin.

Group 10 – Cisplatin 5 mg/kg + polydatin 12 mg/kg. Cisplatin was injected intraperitoneally twice on the first and eighth days of the experiment. Polydatin was given daily intragastrically through a tube for 14 days. Evaluation of the quality of nephrotoxic effect on the 14th day after the first administration of cisplatin.

The study of the renoprotective properties of polydatin was carried out at doses of 4 mg/kg and 12 mg/kg. The studied dosages of polydatin were selected from the recommended dosages of resveratrol for human use – from 50 to 150 mg/day.

Alpha-tocopherol acetate was studied as a comparison drug. It was shown that daily oral administration of vitamin E at doses of 75 mg/kg or higher had contributed to the improvement of azotemia indices and normalization of the histological picture of the renal parenchyma (Darwish et al. 2017; Abdel-Rahman et al. 2022). It was also established that the maximum tolerable daily intake for humans is 1000 mg of vitamin E, which, taking into account the conversion factor for rats, is 79.6 mg/kg (Yasmin and Tang 2025). This fact justifies the choice of vitamin E at a dose of 75 mg/kg orally as the comparator drug in this study.

Evaluation of microcirculation in the renal parenchyma

Upon termination of the experiment, animals were anesthetized with chloral hydrate intraperitoneally at a dose of 300 mg/kg (Netrebenko 2023). After preliminary treatment of the surgical field, a midline laparotomy was performed, and the kidneys were isolated on both sides (Netrebenko et al. 2022). Renal cortex microcirculation was measured using a LAZMA ST laser diagnostic system (LAZMA Research and Production Enterprise, Russia), which includes a LAZMA-D peripheral blood flow, lymph flow, and tissue coenzyme analyzer. The peripheral sensor was applied to the mid-renal region, sparing the hilum.

Measurement of biochemical and functional parameters

Blood was drawn from the right ventricle intraoperatively for biochemical analysis. The concentrations of creatinine, urea, and the content of potassium and sodium ions were determined in the blood serum.

Urine was collected from rats for 12 hours prior to the end of the experiment.

Endogenous creatinine clearance (glomerular filtration rate) and fractional sodium excretion were calculated using standard formulas.

Statistical data processing

Descriptive statistics were applied to all the data: the data was tested for the normality of distribution. The type of distribution was determined using the Shapiro-Wilk's test. The mean value (M) and the standard error of the mean (m) were calculated in a normal distribution. Taking into account the normal distribution of the results, a parametric method (Student's t-test) was used to analyze the intergroup differences. All calculations were made using the Microsoft Excel 10.0 statistical software package (USA).

Results

Modeling of cisplatin-induced acute kidney injury

In a model of cisplatin-induced acute kidney injury, high doses of the drug – single administrations of 10 mg/kg and 20 mg/kg – resulted in high animal mortality, with mortality rates reaching 70% and 100% by day three of the experiment, respectively. Therefore, biopsy specimens were not collected. The results of cisplatin's nephrotoxic effect are presented in Figure 1. Single and double intraperitoneal administration of 1 mg/kg cisplatin did not cause statistically significant increases in serum creatinine and urea levels. Glomerular filtration rate, fractional sodium excretion, and renal parenchymal microcirculation remained close to those in the intact group, indicating the absence of significant nephrotoxicity from cisplatin at the studied dose.

When modeling the pathology by intraperitoneal administration of cisplatin at a dose of 5 mg/kg, a set of changes corresponding to the current criteria for acute kidney injury KDIGO, 2012 was recorded (Fig. 1). As soon as seven days after a single administration, an increase in serum creatinine and urea levels was noted, whereas with double administration of cisplatin, the severity of azotemia increased significantly. Thus, by the fourteenth day, the creatinine level reached 124.0 ± 8.6 μmol/L, and urea – 20.3 ± 1.2 mmol/L. Functional impairments were also most pronounced against the background of double administration of cisplatin and were accompanied by a decrease in the glomerular filtration rate to 0.08 ± 0.01 mL/min, an increase in fractional excretion of sodium to 6.1 ± 0.36% and a decrease in microcirculation in the renal parenchyma to 13.4 ± 0.9 PU.

Thus, based on the obtained data, the following cisplatin administration regimens were selected to simulate the cisplatin-induced model of acute kidney injury: double intraperitoneal administration of cisplatin on the first and eighth days at a dosage of 5 mg/kg and subsequent assessment of nephroprotection 14 days after the first administration of the drug.

With the introduction of vitamin E, a moderate decrease in creatinine to 102.7 ± 5.0 μmol/L and urea to 18.4 ± 1.2 mmol/L was revealed. Daily oral administration of polydatin contributed to a decrease in nitrogen metabolism values: in the group of animals that were injected cisplatin at a dose of 5 mg/kg on the first and eighth days of the experiment together with polydatin at a dose of 4 mg/kg daily orally, the creatinine level was 101.8 ± 4.5 μmol/L, urea – 16.3 ± 1.3 mmol/L, and in the group of polydatin at a dose of 12 mg/kg/day, the creatinine level was 85.7 ± 4.6 μmol/L, urea – 12.3 ± 1.2 mmol/L (Fig. 2).

Nephroprotective effect of polydatin

To evaluate the nephroprotective activity of polydatin, its effects were compared with the reference drug, alpha-tocopherol acetate. The results are presented in Figure 2.

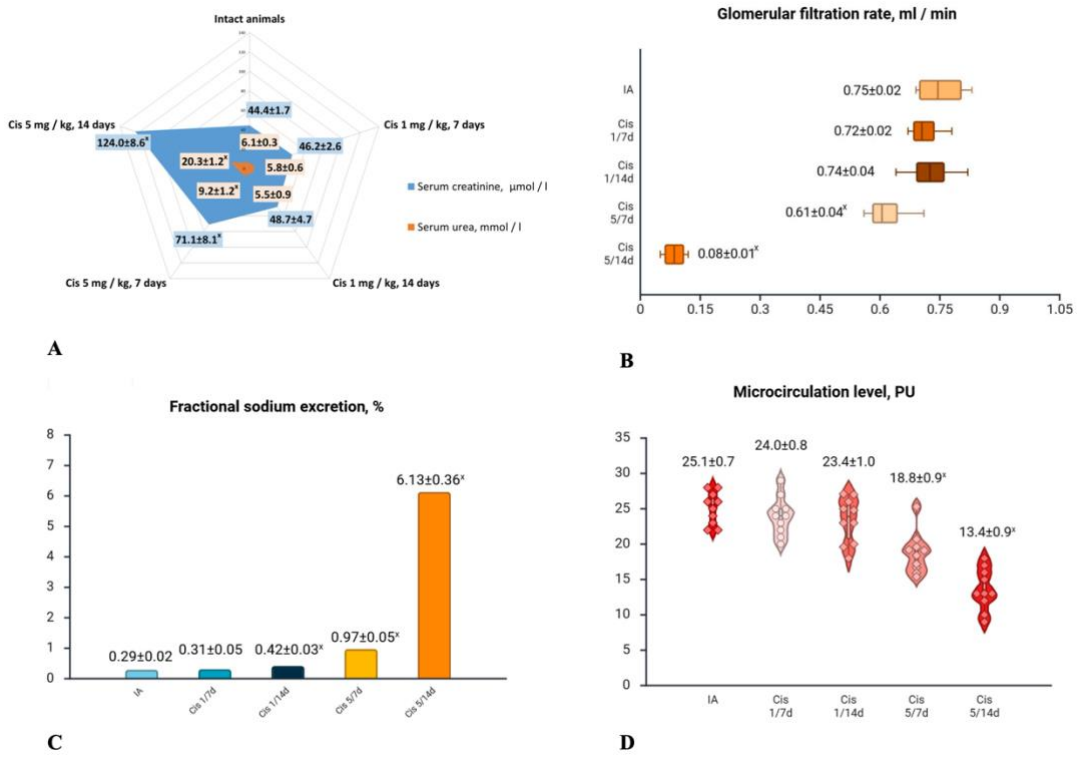


Figure 1. Results of the nephrotoxic effect in rats induced by cisplatin. A – concentration of creatinine and urea in blood serum; B – values of glomerular filtration rate; C – fractional excretion of sodium; D – the level of microcirculation in the renal parenchyma. ***Note:*** Group 1 – intact animals; Group 2 – a single intraperitoneal administration of cisplatin at a dose of 1 mg/kg; Group 3 – double intraperitoneal administration of cisplatin at a dose of 1 mg/kg; Group 4 – a single intraperitoneal administration of cisplatin at a dose of 5 mg/kg; Group 5 – double intraperitoneal administration of cisplatin at a dose of 5 mg/kg; ^{x} – $p < 0.05$ in comparison with the intact group of animals.

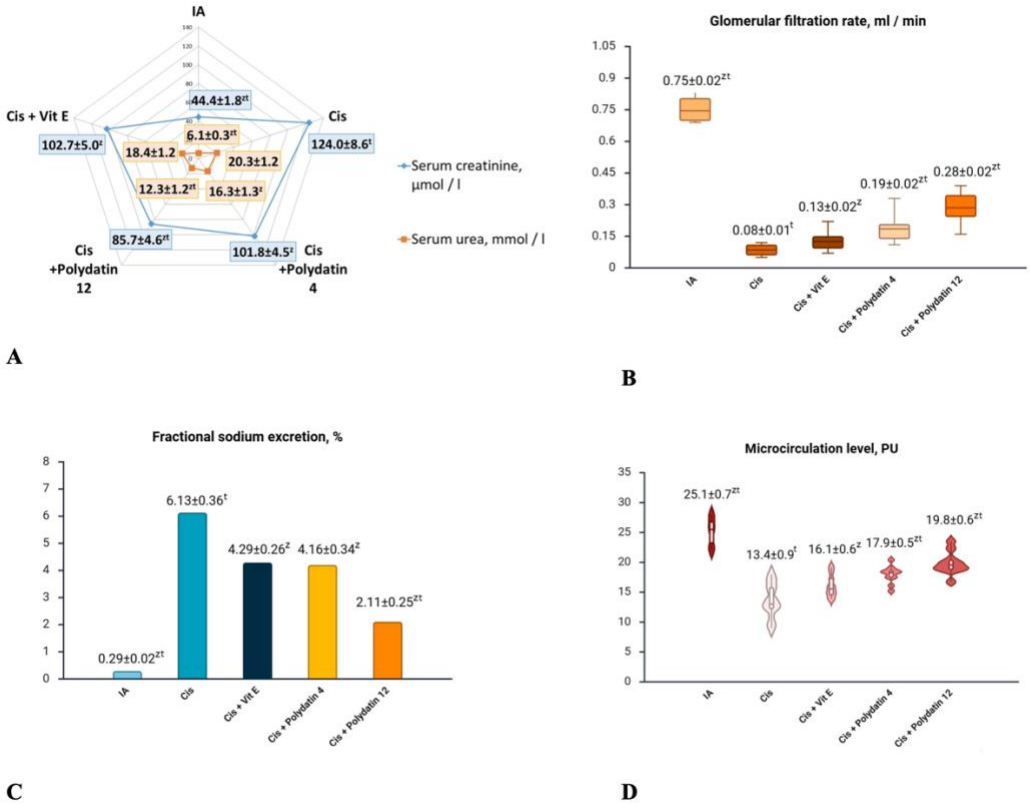


Figure 2. Results of the nephroprotective effect of polydatin in rats with cisplatin-induced acute kidney injury. A – concentration of creatinine and urea in blood serum; B – values of glomerular filtration rate; C – fractional excretion of sodium; D – the level of microcirculation in the renal parenchyma. ***Note:*** Group 1 – intact animals; Group 2 – a single intraperitoneal administration of cisplatin at a dose of 1 mg/kg; Group 3 – double intraperitoneal administration of cisplatin at a dose of 1 mg/kg; Group 4 – a single intraperitoneal administration of cisplatin at a dose of 5 mg/kg; Group 5 – double intraperitoneal administration of cisplatin at a dose of 5 mg/kg; ^{z} – $p < 0.05$ in comparison with the intact group of animals; ^{t} – $p < 0.05$ in comparison with a group of animals treated with vitamin E.

Polydatin at a dose of 4 mg/kg improved renal function. Moreover, administration of polydatin at a dose of 12 mg/kg resulted in more significant improvements: glomerular filtration rate increased to 0.28 ± 0.02 mL/min, while fractional excretion of sodium decreased to 2.11 ± 0.25%, significantly different from the results in the group of rats treated with vitamin E. Polydatin also provided more pronounced restoration of microcirculatory processes. The most significant increase in microcirculation was observed with polydatin at a dose of 12 mg/kg, reaching 19.8 ± 0.6 PU, statistically significantly exceeding the values in the untreated group and animals treated with vitamin E. These results demonstrate the pronounced nephroprotective potential of polydatin in the setting of cisplatin-induced kidney injury.

Discussion

The development of acute kidney injury during the use of cisplatin for cancer treatment remains a very dangerous and common complication and requires special attention. The pathogenesis of cisplatin-induced nephrotoxicity includes damage to the proximal tubular epithelium, the development of oxidative stress, activation of proinflammatory signaling cascades, mitochondrial dysfunction, endothelial damage, and disturbances in the renal microcirculation.

Currently, a significant number of experimental models of cisplatin-induced acute kidney injury have been proposed, but a universal and accepted protocol for reproducing this pathology in rats has not been developed. It was shown that administration of 1.0 mg/kg cisplatin after 5 days resulted in significant variability in proximal tubular necrosis: from minimal in some animals, where only a few necrotic tubular epithelial cells were present, to severe, when numerous cells were affected in all tubules. Meanwhile, 2.5 mg/kg cisplatin demonstrated a high incidence of severe proximal tubular necrosis in all cases (Wadey et al. 2014). Because the study neither determined blood urea levels and microcirculation parameters, nor calculated the glomerular filtration rate, this model cannot be considered optimal. With the introduction of cisplatin at a dosage of 20 mg/kg, a significant increase in the level of creatinine and urea in the blood plasma was already noted on the 3rd day, an increase in calbindin and Kim-1 in the urine was detected; however, due to the high risk of developing general toxicity, the maximum observation period for animals was 4 days (George et al. 2022). Kuwata et al. (2015) found that the use of cisplatin at a dosage of 5 mg/kg leads to a significant increase in the level of creatinine and urea in the blood plasma in rats 5 days after administration, but these indicators were almost completely restored after 12 days, and re-administration of cisplatin was not performed. Despite a large number of experimental models of cisplatin-induced acute kidney injury, it was not possible to develop an ideal, generally accepted method for reproducing this pathology in rats (Perse et al. 2018).

In this study, we compared different modes of modeling cisplatin-induced acute kidney injury in rats. It was found that administration of 1 mg/kg cisplatin did not result in significant renal functional impairment. This may be due to the fact that low doses of cisplatin do not lead to the accumulation of high levels of reactive oxygen species and do not activate the proinflammatory mechanisms underlying nephron damage (Perše and Večerić-Haler 2018; Wadey et al. 2014). Administration of 5 mg/kg cisplatin resulted in a complex of hemodynamic and functional impairments corresponding to the KDIGO criteria for acute kidney injury. Particularly pronounced changes were observed with double administration of cisplatin, indicating the cumulative nature of the drug's nephrotoxic effect. An increase in fractional sodium excretion indicates impaired tubular sodium reabsorption due to damage to the proximal tubular epithelium and is one of the key pathogenetic features of nephrotoxicity (Milleret et al. 2010; Holditch et al. 2019). A decrease in microcirculation, revealed in the pathology model, reflects the deterioration of intrarenal hemodynamics and the development of hypoxic damage to nephrons. Cisplatin is known to induce endothelial dysfunction, vasoconstriction, and ischemic damage to renal tissue, which aggravates the course of the pathological process (dos Santos et al. 2012). It has now been established that one of the leading mechanisms in the development of cisplatin-induced nephrotoxicity is the activation of the NF-κB signaling pathway and subsequent hyperproduction of proinflammatory cytokines, including TNF-α, IL-1β, and IL-6, which leads to increased infiltration, damage to cell membranes, impaired mitochondrial function, and the induction of apoptosis in tubular epithelial cells (Jiang and Dong 2008; Ozkok and Edelstein 2014). The present study demonstrated that administration of cisplatin at a dose of 5 mg/kg ensures the development of a reproducible set of functional disorders with acceptable animal survival, which allows us to consider this regimen as a promising experimental model for studying nephroprotective compounds.

The use of the natural phytoalexin polydatin holds great promise in developing a comprehensive nephroprotective model capable of protecting the renal parenchyma from the

destructive effects of cisplatin on various nephron components. Polydatin's cytoprotective effect is based on its ability to inhibit oxidative stress and inflammation. Considering the mechanism of acute kidney injury caused by the toxic effects of cisplatin, it can be hypothesized that polydatin administration resulted in a reduction in the severity of pathological inflammation: the concentration of proinflammatory cytokines IL-1β, IL-6, and TNF-α decreased. This contributed to the normalization of metabolic processes, with a decrease in azotemia and an improvement in microcirculation in the renal parenchyma.

Similar mechanisms of the protective effect of polydatin have already been identified and clearly demonstrated in a model of non-alcoholic steatohepatitis and hepatofibrosis in mice (Li et al. 2018). It was demonstrated that activation of NF-κB signaling led to increased liver tissue infiltration by CD-68 positive cells, which reflects an increase in the number of macrophages. Increased levels of IL-1β, IL-6, and TNF-α mRNA were observed in hepatocytes, which apparently led to the progression of nonalcoholic steatohepatitis with subsequent hepatocyte fibrosis.

Similar trends were revealed when studying the possible protective role of polydatin in infectious pneumonia caused by Mycoplasma pneumoniae. The results showed that polydatin treatment suppressed mycoplasma-induced lung injury in mice by suppressing the expression of inflammatory factors and inhibiting the development of pulmonary fibrosis. Meanwhile, polydatin treatment inhibited activation of the NLRP3 inflammasome and nuclear factor κB (NF-κB) pathway. Overexpression of NLRP3 reversed the protective effect of polydatin against mycoplasma-induced injury in BEAS-2B cells. Taken together, these results indicate that polydatin treatment suppressed the inflammatory response and the development of pulmonary fibrosis by inhibiting the NLRP3 inflammasome and NF-κB pathway after mycoplasma infection (Tang et al. 2019). However, these changes require further experimental study in the pathology of cisplatin-induced acute kidney injury. It should be noted that due to its powerful antioxidant and anti-inflammatory properties, polydatin has great potential as an adjunct to standard antitumor drug therapy.

Conclusion

The results of the study revealed that the optimal model for cisplatin-induced acute kidney injury in rats is the one in which cisplatin is administered intraperitoneally at a dose of 5 mg/kg twice on days 1 and 8 of the experiment, with animals observed for 14 days. Cisplatin administration using this method resulted in a significant increase in serum creatinine and urea levels, a decrease in glomerular filtration rate, and an increase in fractional sodium excretion. This, coupled with a significant decrease of renal parenchymal microcirculation level, most closely corresponds to the current KDIGO criteria for acute kidney injury. This method can serve as a basis for studying the nephroprotective properties of new drugs in modeling cisplatin-induced kidney injury. Polydatin administered intragastrically at a dose of 12 mg/kg for 14 days demonstrated dose-dependent nephroprotective properties, which was confirmed by a decrease in azotemia indices, an improvement in the glomerular filtration rate and fractional sodium excretion, as well as an increase in the level of microcirculation in the renal parenchyma when modeling cisplatin-induced acute kidney injury.

Additional Information

Conflict of interest

The authors declare that they have no conflicts of interest.

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Ethics statement

The animal protocols employed were approved by the Animal Care and Use Committee of the E.D. Goldberg Research Institute of Pharmacology and Regenerative Medicine, Tomsk National Research Medical Center (Minutes № 01-10i/24 of 01 October 2024).

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