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SODIUM FUMARATE IN THE PREVENTION OF ISCHEMIA-REPERFUSION INJURY IN RENAL SURGERY: OUTCOMES AND PROSPECTS

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Objective: to review the current outcomes and future prospects of using sodium fumarate (SF) for the prevention of ischemia–reperfusion injury in renal surgery. **Materials and methods.** The drug used in the study was Konfumin, whose active ingredient is SF. The experimental sample consisted of 78 female Wistar rats. Renal warm ischemia (RWI) and reperfusion injury were modeled, involving either unilateral or bilateral kidney preservation. SF, administered as an infusion solution, was used to evaluate the effectiveness of infusion therapy in this renal injury model. It was administered as an intravenous infusion at doses of 1 mL/kg or 2 mL/kg. The infusion protocol included five administrations: one day prior to warm ischemia, on the day of the procedure, and over the subsequent three days. Clinical observation was then carried out. **Results.** Experimental therapy with SF led to a marked reduction in inflammation in the ischemic kidneys of rats, as evidenced by significant improvements in key markers of nephron function. The treatment also contributed to favorable pathomorphological changes associated with acute ischemia–reperfusion injury (IRI). Data from experimental models involving warm ischemia and reperfusion of a single kidney, as well as models with an intact contralateral kidney, demonstrated that SF, administered intravenously at doses ranging from 1 to 2.5 mL/kg, exerted a nephroprotective effect. This protective effect was reflected in the positive remodeling of ischemic renal infarction and its consequences, involving improvements across vascular, glomerular, tubular, and interstitial components of the renal parenchyma. **Conclusion.** SF, administered intravenously at doses of 1–2.5 mL/kg, demonstrated a clear nephroprotective effect. This was evidenced by favorable pathomorphological changes in ischemic renal infarction and its sequelae.

Keywords: sodium fumarate, intravenous infusion, ischemia-reperfusion, renal surgery, nephrectomy, RWI modeling.

INTRODUCTION

Ischemia and subsequent reperfusion of the organ activate pathological processes, notably the excessive production of reactive oxygen species and development of oxidative stress, leading to structural and functional tissue damage [1, 2]. In experimental nephrology, modeling various kidney pathologies is widely used to evaluate the efficacy of infusion drugs. The primary strategy for preventing post-ischemic kidney injury involves administration of pharmacological agents with anti-ischemic and antihypoxic properties [3]. One such agent is sodium fumarate (SF) [4]. In our study, we used the drug Konfumin, whose active ingredient is SF.

SF was selected for investigation because it is an effective antihypoxant. Exogenous fumarate is chemically identical to endogenous fumarate, making it indistinguishable when assessing intracellular substrate content. Its antihypoxic activity is mediated through participation in reversible oxidation–reduction reactions within the Krebs cycle, which facilitate adenosine triphosphate (ATP) synthesis essential for sustaining cellular function during hypoxia. Under oxygen deficiency, the pool of oxidation substrates, including fumarate ions, becomes depleted. Exogenous administration of Konfumin replenishes this pool, enhancing the reserve capacity of tissue respiratory systems and enabling continued ATP synthesis despite hypoxic conditions. This mechanism underlies the antihypoxic action of Konfumin.

Maintaining oxidative metabolism in tissues during oxygen deficiency prevents the formation and accumulation of under-oxidized metabolic products, thereby reducing acidosis. By promoting metabolic alkalization, Konfumin mitigates or eliminates acidosis through chemical neutralization of acidic metabolites.

The drug's positive effect on oxidative metabolism improves the functional state of vital organs, including

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the heart, under hypoxic conditions. It supports myocardial contractility and exerts a cardiotonic effect. Furthermore, Konfumin reduces the concentration of lipid peroxidation products in the blood, demonstrating its antioxidant properties. These characteristics form the rationale for selecting Konfumin as a preventive agent against reperfusion syndrome.

The aim of this study is to evaluate the results and prospects of using SF for the prevention of ischemia-reperfusion injury (IRI) in kidney surgery.

Objective: to evaluate the results and prospects of using SF for the prevention of IRI in renal surgery.

MATERIALS AND METHODS

Study substance

The drug used was Konfumin, whose active ingredient is SF [5].

Sample characteristics

The study was conducted on 78 female Wistar rats. The animals were allocated into groups according to the extent of surgical intervention (right nephrectomy or no nephrectomy), duration of renal warm ischemia (45 minutes or 60 minutes), and administered SF dose (1 mL/kg or 2 mL/kg). At baseline, the rats were 6–8 weeks old and weighed 180–200 g. All animals were obtained from the laboratory animal breeding facility of the Kurchatov Institute – Rappolovo laboratory animal nursery, in Leningrad Oblast.

Study design: the experimental design is shown in Table 1.

Modeling methods

Renal warm ischemia (RWI) modeling and reperfusion injury were performed with either both kidneys or only one kidney preserved. RWI duration was set at either 45 or 60 minutes, depending on the experimental model. To evaluate the efficacy of the infusion drug in the induced kidney pathology, SF (solution for infusion) was administered at doses of 1 mL/kg or 2 mL/kg. Injections were given once daily for a total of 5 administrations – one day prior to warm ischemia, on the day of the procedure, and on the following 3 days.

Table 1

Study Design

Group	Sex	Sample size	Experimental procedure	Drug administration method and dose	Measured parameters
Intact	Female	6	None	None	Body weight, clinical condition, urine volume, density, protein content, creatinine levels, leukocyte and erythrocyte counts; blood urea, serum creatinine, lactate levels
RWI1	Female	6	Right nephrectomy followed by 45 minutes of renal ischemia and reperfusion	None	
RWI2	Female	6	Right nephrectomy followed by 60 minutes of renal ischemia and reperfusion	None	
RWI3	Female	6	Right nephrectomy with intravenous infusion of drug 1, followed by 45 minutes of renal ischemia and reperfusion	IV, 1.0 mL/kg sodium fumarate	
RWI4	Female	6	Right nephrectomy with intravenous infusion of drug 1, followed by 60 minutes of renal ischemia and reperfusion	IV, 1.0 mL/kg sodium fumarate	
RWI5	Female	6	Right nephrectomy with intravenous infusion of drug 2, followed by 45 minutes of renal ischemia and reperfusion	IV, 2.5 mL/kg sodium fumarate	
RWI6	Female	6	Right nephrectomy with intravenous infusion of drug 2, followed by 60 minutes of renal ischemia and reperfusion	IV, 2.5 mL/kg sodium fumarate	
RWI7	Female	6	Intravenous infusion of drug 1, followed by 45 minutes of renal ischemia and reperfusion	IV, 1.0 mL/kg sodium fumarate	
RWI8	Female	6	Intravenous infusion of drug 1, followed by 60 minutes of renal ischemia and reperfusion	IV, 1.0 mL/kg sodium fumarate	
RWI9	Female	6	Intravenous infusion of drug 2, followed by 45 minutes of renal ischemia and reperfusion	IV, 2.5 mL/kg sodium fumarate	
RWI10	Female	6	Intravenous infusion of drug 2, followed by 60 minutes of renal ischemia and reperfusion	IV, 2.5 mL/kg sodium fumarate	
RWI11	Female	6	Renal ischemia for 45 minutes followed by reperfusion	None	
RWI12	Female	6	Renal ischemia for 60 minutes followed by reperfusion	None	

Abbreviations: RWI, renal warm ischemia; IV, intravenous.

In some groups, a unilateral nephrectomy was performed to simulate acute kidney injury in a manner closely resembling clinical manifestations. RWI modeling, followed by reperfusion, was carried out two weeks after nephrectomy. At the end of the experiment, the rats were euthanized by decapitation under light anesthesia with diethyl ether.

Animal observation

General clinical monitoring of experimental animals was performed for 14 days after nephrectomy and for 21 days following RWI. Animal survival was assessed for 21 days after RWI modeling. Complete blood counts, urinalysis, clinical and biochemical parameters in blood and urine, biomarker measurements, and histological examinations were carried out. The degree of tissue damage was evaluated using a semi-quantitative method based on the EGTI scale for acute cortical necrosis of the kidney.

Data analysis was performed using Prism 8.0 (GraphPad Software, Inc.). All experimental procedures were approved by the institutional bioethics committee (protocol BEK No. 28, dated October 7, 2024).

RESULTS

Assessment of physiological and biochemical parameters in rats after nephrectomy and warm ischemia

The nephrectomy model in rats was successfully implemented without complications. On the day following surgery and throughout the subsequent 14-day follow-up period, all animals demonstrated normal coat condition, color of visible mucous membranes, respiratory rate, heart rhythm, response to stimuli, skeletal muscle tone, and fecal consistency. One animal in the RWI5 group died on postoperative day 3.

Following RWI surgery with reperfusion, most rats exhibited normal coat condition, mucous membrane color, respiratory rate, heart rhythm, reaction to stimuli, skeletal muscle tone, and fecal consistency on postoperative day 1. By day 3 after RWI, one animal in each of the RWI2, RWI5, and RWI6 groups died. The main indicators from the general urinalysis performed on day 7 after the procedures are presented in Table 2.

As shown by the data, body weight gain in animals subjected to nephrectomy (NE) followed by 45 minutes of RWI did not differ significantly from that of intact controls, with a slight positive trend observed in all rats. Extending the RWI duration to 60 minutes resulted in a significant decrease in body weight on day 7 after RWI in animals that received the drug at doses of 1 mL/kg or 2.5 mL/kg.

On day 7 after 45 minutes of RWI, a significant decrease in creatinine levels was observed compared with intact rats. In treated animals, the protein–creatinine ratio remained elevated. At the same time point after 60 minutes of RWI, a decrease in creatinine was noted only in rats receiving the 1 mL/kg dose. Other parameters remained within normal limits. Creatinine clearance did not differ between groups at any time during the study.

The results of blood biochemical analysis and measurement of renal injury biomarker levels are presented in Table 3.

On day 7 after 45 minutes of RWI, no significant changes were observed in most of the studied parameters. However, a significant increase in blood urea was noted in rats receiving both doses of the drug, with higher values recorded in the 2.5 mL/kg group. This group also demonstrated reduced lactate levels compared to intact controls, although the changes remained within the physiological range.

Following 60 minutes of RWI, rats in the pathology control group showed a significant increase in blood urea and creatinine levels. Elevated blood urea concentrations were also observed in animals receiving infusion therapy with the drug. Lactate levels did not differ significantly among the experimental groups.

Analysis of kidney injury biomarkers revealed no significant changes in serum or urinary cystatin C (Cys-C) on days 7 and 21 in any of the experimental groups.

On day 3 after RWI of 45 or 60 minutes, blood lipocalin-2 (NGAL) levels in the experimental groups were significantly elevated compared with intact animals, showing a 9–22-fold increase. Urinary NGAL concen-

Table 2

Results of general urine analysis on day 7

	Body weight (g)	Diuresis (mL/day/kg)	Urine protein (mg/dL)	Urine creatinine (mg/dL)	Protein/Creatinine ratio
Intact	217.4 ± 22.42	56.6 ± 33.0	23.6 ± 15.4	160.5 ± 76.8	0.139 ± 0.038
RWI1 / N + RWI 45 min	213.4 ± 7.35	93.7 ± 29.4	19.9 ± 9.2	87.2 ± 44.7	0.243 ± 0.126
RWI3 / N + RWI 45 min / SF, 1 mL/kg	198.4 ± 15.77	71.0 ± 35.5	33.6 ± 19.2	121.2 ± 56.9	0.285 ± 0.170
RWI5 / N + RWI 45 min / SF, 2.5 mL/kg	198.80 ± 16.43	106.9 ± 71.1	13.3 ± 12.4	93.4 ± 62.4	0.123 ± 0.044
RWI2 / N + RWI 60 min	193 ± 9.62	136.1 ± 62.9	24.3 ± 14.7	76.9 ± 64.2	0.446 ± 0.423
RWI4 / N + RWI 60 min / SF, 1 mL/kg	186.2 ± 11.47	139.3 ± 95.1	23.1 ± 14.2	72.6 ± 36.6	0.353 ± 0.192
RWI6 / N + RWI 60 min / SF, 2.5 mL/kg	1.81.6 ± 10.4	60.2 ± 25.9	28.5 ± 20.9	123.4 ± 74.8	0.220 ± 0.044

Abbreviations: RWI, renal warm ischemia; N, nephrectomy; SF, sodium fumarate.

tration after 45 minutes of RWI was also significantly higher than in intact controls; administration of the drug at both tested doses normalized this indicator.

RWI lasting 60 minutes resulted in a 2–3-fold increase in urinary NGAL in experimental animals compared with intact controls. Administration of SF at a dose of 2.5 mL/kg significantly reduced the elevated value compared with the pathology control group, although it remained higher than in intact animals.

On day 7 after 45 minutes of RWI, no significant differences in blood or urinary NGAL were observed between experimental groups. In contrast, at the same time point after 60 minutes of RWI, urinary NGAL concentrations in all experimental groups remained significantly elevated compared with intact controls – by approximately 4–6 times. In this case, therapy did not influence the changes in urinary NGAL levels.

On days 3 and 7 after RWI lasting 45 minutes, no significant changes were observed in blood MCP-1 levels in any of the experimental groups.

When ischemia time was extended to 60 minutes, a significant increase in blood MCP-1 was detected on day 3 in the pathology control group. SF therapy normalized this elevated parameter, with the higher dose of 2.5 mL/kg demonstrating greater efficacy. In treated rats, blood MCP-1 levels differed significantly from those in the pathology control group.

Urinary MCP-1 levels did not differ significantly among experimental groups overall. However, administration of SF at the maximum dose significantly reduced urinary MCP-1 levels in groups RWI5 and RWI6 compared with the pathology control. On day 7 after RWI, blood MCP-1 levels showed no significant differences between groups, while urinary MCP-1 was elevated in the pathology control group.

Assessment of physiological and biochemical indicators in rats after RWI

The main urinalysis parameters on day 7 after the procedures are presented in Table 4.

As can be seen from the data presented, therapy led to complete normalization of body weight by day 7. On day 3 after 45 minutes of RWI, rats in the pathology control group exhibited polyuria, decreased urine density, and reduced protein and creatinine levels. In rats treated with 1 mL/kg of the drug, urinary protein levels and diuresis returned to normal, while creatinine levels remained within the physiological range. In the group receiving 2.5 mL/kg, nearly all measured parameters matched those of healthy controls, except for creatinine, which remained elevated.

On day 7 after 45 minutes of RWI, only diuresis remained elevated in the pathology control group, whereas all urinary parameters in treated animals were within normal limits. Extending the RWI duration to 60 minutes led to increased diuresis and urinary pH, along with decreased creatinine levels. In treated animals, only the leukocyte count was elevated. Creatinine clearance

Table 3

Results of biochemical blood analysis and kidney damage biomarkers on day 7

	Urea (mmol/L)	Creatinine (mmol/L)	Lactate (mmol/L)
Intact	3.9 ± 0.5	65.4 ± 4.7	2.9 ± 0.4
RWI1 / N + RWI 45 min	6.2 ± 1.1	70.5 ± 2.7	2.7 ± 0.2
RWI3 / N + RWI 45 min / SF, 1 mL/kg	6.7 ± 1.2	68.6 ± 3.3	2.7 ± 0.4
RWI5 / N + RWI 45 min / SF, 2.5 mL/kg	9.3 ± 3.2	74.0 ± 13.0	2.1 ± 0.2
RWI2 / N + RWI 60 min	9.2 ± 5.0	92.3 ± 35.2	2.7 ± 0.3
RWI4 / N + RWI 60 min / SF, 1 mL/kg	15.4 ± 14.5	78.1 ± 31.3	2.2 ± 0.3
RWI6 / N + RWI 60 min / SF, 2.5 mL/kg	9.5 ± 4.4	63.2 ± 6.5	2.2 ± 0.2

Abbreviations: RWI, renal warm ischemia; N, nephrectomy; SF, sodium fumarate.

Table 4

Results of general urine analysis on day 7

	Body weight (g)	Diuresis (mL/day/kg)	Urine protein (mg/dL)	Urine creatinine (mg/dL)	Protein/Creatinine ratio
Intact	210.4 ± 18.46	43.6 ± 20.3	22.7 ± 9.4	153.2 ± 64.7	0.149 ± 0.014
RWI11 / 45 min	164.8 ± 16.2	120.7 ± 44.7	14.7 ± 5.9	74.9 ± 24	0.207 ± 0.114
RWI7 / RWI 45 min / SF, 1 mL/kg	186.9 ± 10.93	82 ± 22.5	10.0 ± 6.1	87.5 ± 26.4	0.106 ± 0.038
RWI9 / RWI 45 min / 60 min / SF, 1 mL/kg	184.6 ± 15.96	104.4 ± 67.4	18.1 ± 20.7	101.2 ± 104.0	0.162 ± 0.055
RWI12 / 60 min	161.1 ± 9.91	136.1 ± 62.9	22.7 ± 9.4	73.0 ± 23.3	0.244 ± 0.091
RWI8 / RWI 60 min / SF, 2.5 mL/kg	184.9 ± 16.49	139.3 ± 95.1	18.6 ± 11.1	163.8 ± 114.2	0.211 ± 0.132
RWI10 / RWI 45 min / SF, 2.5 mL/kg	187.2.6 ± 9.99	60.2 ± 25.9	37.2 ± 29.3	148 ± 53.9	0.185 ± 0.049

Abbreviations: RWI, renal warm ischemia; SF, sodium fumarate.

showed no significant differences between groups at any time point.

The results of biochemical blood analysis and kidney injury biomarker measurements are presented in Table 5.

On day 7 after 45 minutes of RWI, all parameters studied remained within normal limits. A slight decrease in lactate levels was observed in all rats after 60 minutes of RWI.

On day 7 following 60 minutes of RWI, a significant increase in Cys-C levels was detected in both blood and urine in all experimental groups, with values 4–5 times higher than those in intact controls. Administration of SF at a dose of 2.5 mL/kg had a positive effect, reducing Cys-C levels to values not significantly different from intact animals. Urinary Cys-C levels did not differ significantly among groups.

On day 3, all experimental groups exhibited a marked increase in blood NGAL concentrations after both 45 and 60 minutes of RWI, with values 50–90 times higher than those of intact controls. Urinary NGAL levels did not differ between groups. By days 7 and 21, NGAL concentrations in both blood and urine showed no significant differences among groups.

Calculation of the NGAL concentration index (CI) on day 3 after RWI revealed a significant decrease in all experimental groups compared with intact controls, except for the RWI11 pathology control group and the group receiving SF at a dose of 2.5 mL/kg. At later stages, no intergroup differences in CI were observed.

On day 7 after 45 minutes of RWI, MCP-1 levels in both blood and urine were elevated in the pathology control group and in animals receiving SF at a dose of 1 mL/kg. In contrast, rats treated with 2.5 mL/kg of the drug demonstrated MCP-1 levels within the normal range. A similar pattern was observed after 60 minutes of RWI, although in this case, therapy with 2.5 mL/kg reduced MCP-1 levels only in blood, while urinary levels remained pathologically high.

Calculation of the MCP-1 CI on day 7 revealed significant differences only in animals receiving 1 mL/kg of the drug. After 45 minutes of RWI, this group showed a modest but significant increase in CI compared with intact controls. Treatment with 2.5 mL/kg was more effective, significantly reducing CI. Extending the duration of RWI to 60 minutes resulted in a significant increase in CI in rats treated with both doses compared to intact controls.

RWI of 45 or 60 minutes did not affect Stat3 levels in blood or urine at any point in the experiment, and no statistically significant differences were observed among groups.

DISCUSSION

As a result of the study on Wistar rats, experimental models of RWI and reperfusion injury of a single kidney were developed. In some animals, right-sided nephrectomy was performed, followed by warm ischemia of the remaining kidney for 45 or 60 minutes. In others, warm ischemia of the kidney was induced for the same durations without prior nephrectomy (NE).

For both NE and RWI models of varying duration (45 and 60 minutes), as well as for RWI-only models (45 and 60 minutes), organ injury biomarkers were assessed, and the therapeutic efficacy of SF (15% injectable solution) at doses of 1 and 2.5 mL/kg was evaluated.

Analysis of the results demonstrates that administration of SF after nephrectomy and warm ischemia exerts a positive effect on the functional state of kidneys in experimental animals. The most pronounced therapeutic benefit was observed with the 2.5 mL/kg dose. This was reflected in lower urine protein levels (13.3 ± 12.4 mg/dL) compared with the non-SF group (19.9 ± 9.2 mg/dL), as well as a more favorable protein/creatinine ratio (0.123 ± 0.044 *vs* 0.243 ± 0.126 in the non-SF group).

Serum urea and creatinine levels in the group receiving SF at a dose of 2.5 mL/kg (9.3 ± 3.2 mmol/L and 74.0 ± 13.0 mmol/L, respectively) indicated a lesser degree of impairment in renal nitrogen excretion compared with groups receiving a lower dose or no SF at all.

Additionally, blood lactate levels in all SF–treated groups remained within normal limits (2.1–2.7 mmol/L), suggesting that adequate energy metabolism was preserved. Thus, in the nephrectomy + warm ischemia model, a dose of 2.5 mL/kg provided the most favorable balance between reducing proteinuria and preserving renal function. This was evidenced by lower urine protein levels (13.3 ± 12.4 mg/dL *vs* 19.9 ± 9.2 mg/dL in untreated animals) and an improved protein/creatinine

Table 5

Results of biochemical blood analysis and kidney damage biomarkers on day 7

	Urea (mmol/L)	Creatinine (mmol/L)	Lactate (mmol/L)
Intact	4.3 ± 0.3	65.5 ± 1.9	3.3 ± 0.5
RWI11 / disease control 45 minutes	4.5 ± 0.9	63.4 ± 2.0	2.5 ± 0.3
RWI7 / RWI 45 min / SF, 1 mL/kg	4.9 ± 0.6	64.8 ± 1.1	2.6 ± 0.2
RWI9 / RWI 45 min / 60 min / SF, 1 mL/kg	5.6 ± 0.9	64.0 ± 3.2	2.5 ± 0.5
RWI12 / disease control 60 minutes	23.6 ± 24.1	65.5 ± 1.9	2.4 ± 0.4
RWI8 / RWI 60 min / SF, 2.5 mL/kg	4.7 ± 0.8	61.1 ± 4.0	2.6 ± 0.3
RWI10 / RWI 45 min / SF, 2.5 mL/kg	7.7 ± 2.3	75.1 ± 12.9	2.2 ± 0.2

ratio (0.123 ± 0.044 *vs* 0.243 ± 0.126). In contrast, in the warm ischemia–only model, the most pronounced therapeutic effect was observed at a dose of 1 mL/kg. This group demonstrated the lowest proteinuria (10.0 ± 6.1 mg/dL) and the most favorable protein/creatinine ratio (0.106 ± 0.038), which closely approximated values in intact animals (0.149 ± 0.014).

Serum urea and creatinine levels in the group receiving SF at a dose of 1 mL/kg (4.9 ± 0.6 mmol/L and 64.8 ± 1.1 mmol/L, respectively) demonstrated the least impairment of renal nitrogen excretion compared with groups receiving other doses or no SF at all. Blood lactate levels in all SF–treated groups remained within the physiological range (2.2–2.6 mmol/L), indicating preserved energy metabolism. Overall, a comprehensive analysis of clinical and biochemical parameters suggests that a dose of 1 mL/kg SF is optimal for correcting renal dysfunction after warm ischemia, offering the most favorable balance between reducing proteinuria and preserving renal function.

CONCLUSION

The effectiveness of SF infusion was assessed in experimental models of RWI and reperfusion injury. The results demonstrated a pronounced therapeutic effect in mitigating renal dysfunction following nephrectomy and warm ischemia in experimental animals.

A dose-dependent response was observed: after nephrectomy and warm ischemia, the optimal dose was 2.5 mL/kg. This was evidenced by a marked reduction in proteinuria (13.3 ± 12.4 mg/dL) and a more favorable protein-to-creatinine ratio (0.123 ± 0.044), along with lower serum urea and creatinine levels (9.3 ± 3.2 mmol/L and 74.0 ± 13.0 mmol/L, respectively) compared with the control group.

After warm ischemia without nephrectomy, the most effective dose was 1 mL/kg, which yielded the lowest proteinuria level (10.0 ± 6.1 mg/dL) and a protein-to-creatinine ratio (0.106 ± 0.038) closest to that of the intact group. Corresponding serum urea and creatinine levels were 4.9 ± 0.6 mmol/L and 64.8 ± 1.1 mmol/L, respectively. A key indicator of therapeutic efficacy was the normalization of blood lactate levels (2.1–2.7 mmol/L), reflecting the preservation of adequate energy metabolism.

Overall, SF shows a significant nephroprotective effect, with the optimal dose varying according to the type of injury: 2.5 mL/kg for combined nephrectomy and ischemia, and 1 mL/kg for isolated warm ischemia. These conclusions are supported by a comprehensive set of biochemical markers of kidney function.

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REFERENCES

1. *Plotnikov EY, Kazachenko AV, Vyssokikh MY, Vasileva AK, Tcvirkun DV, Isaev NK et al*. The role of mitochondria in oxidative and nitrosative stress during ischemia/reperfusion in the rat kidney. *Kidney Int*. 2007; 72 (12): 1493–1502.
2. *Goncharov RG, Rogov KA, Temnov AA, Novoselov VI, Sharapov MG*. Protective role of exogenous recombinant peroxiredoxin 6 under ischemia-reperfusion injury of kidney. *Cell Tissue Res*. 2019; 378 (2): 319–332.
3. *Grond J, van Goor H, Erkelens DW, Elema JD*. Glomerular sclerosis in Wistar rats: analysis of its variable occurrence after unilateral nephrectomy. *Br J Exp Pathol*. 1986 Aug; 67 (4): 473–479.
4. *Akinrinde AS, Oduwole O, Akinrinmade FJ, Bolaji-Alabi FB*. Nephroprotective effect of methanol extract of Moringa oleifera leaves on acute kidney injury induced by ischemia-reperfusion in rats. *Afr Health Sci*. 2020 Sep; 20 (3): 1382–1396.
5. *Khalid U et al*. Kidney ischaemia reperfusion injury in the rat: the EGTI scoring system as a valid and reliable tool for histological assessment. *J Histol Histopathol*. 2016; 3 (1): 1.

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