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Effect of Glutathione on Pyruvate Levels in Colistin-Induced Nephropathy in Rats

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Abstract

Introduction: Colistin (polymyxin E) is a last-line antibiotic widely used for the treatment of multidrug-resistant Gram-negative infections; however, its clinical application is limited by severe nephrotoxicity. Accumulating evidence suggests that colistin-induced renal injury is closely associated with mitochondrial dysfunction and oxidative stress. Pyruvate, a key intermediate of glycolysis and mitochondrial energy metabolism, may serve as a sensitive marker of impaired mitochondrial function due to its dependence on the activity of the pyruvate dehydrogenase complex (PDH). Glutathione (GSH), the principal intracellular antioxidant, plays a crucial role in maintaining redox homeostasis and mitochondrial integrity.

Aims: The aim of this study was to evaluate plasma pyruvate levels as a metabolic marker of nephrotoxicity and to assess the effect of glutathione administration on pyruvate metabolism in a rat model of colistin-induced nephropathy.

Materials and methods: Nephropathy was induced by daily intravenous administration of colistin at a dose of 15 mg/kg for seven days. Rats were divided into five experimental groups: colistin alone, colistin combined with GSH (100 mg/kg), control, colistin with saline, and colistin followed by prolonged GSH treatment. Plasma pyruvate concentration was determined spectrophotometrically using a dinitrophenylhydrazine-based colorimetric method.

Results: Colistin administration resulted in a significant increase in plasma pyruvate levels compared with controls, indicating impaired mitochondrial utilization of pyruvate. In contrast, glutathione treatment markedly reduced pyruvate concentrations, restoring them toward physiological values. These findings suggest that colistin disrupts pyruvate metabolism, likely through inhibition of PDH activity caused by oxidative stress and mitochondrial dysfunction. Glutathione supplementation appears to counteract these effects by preserving mitochondrial function and redox regulation of PDH.

Conclusion: In conclusion, plasma pyruvate may serve as a useful metabolic marker of colistin-induced nephropathy, while glutathione demonstrates a protective effect against metabolic and mitochondrial disturbances associated with colistin toxicity.

Keywords: Type Glutathione; Pyruvate; Colistin; Nephrotoxicity; Mitochondria.

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Introduction

The global spread of multidrug-resistant (MDR) Gram-negative bacteria has become a major public health challenge, significantly limiting the effectiveness of conventional antimicrobial therapies. In this context, colistin (polymyxin E) has re-emerged as a last-line antibiotic for the treatment of severe infections caused by carbapenem-

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resistant Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacteriaceae [1,2]. Despite its potent bactericidal activity, the clinical application of colistin is severely constrained by its high nephrotoxicity, which remains one of the most significant adverse effects associated with its use [2,3].

Colistin-induced nephrotoxicity primarily affects the renal proximal tubular epithelial cells, leading to acute kidney injury characterized by tubular necrosis, loss of brush border integrity, and impaired glomerular filtration [3,4]. The nephrotoxic effects of colistin are dose-dependent and may be exacerbated by prolonged treatment, advanced age, and pre-existing renal dysfunction [4]. At the cellular level, colistin interacts with the anionic phospholipids of the renal tubular cell membrane, increasing membrane permeability and facilitating intracellular accumulation of the drug [5]. This accumulation triggers a cascade of intracellular events that culminate in mitochondrial dysfunction, oxidative stress, and cell death.

Oxidative stress plays a central role in the pathogenesis of colistin-induced nephropathy. Numerous studies have demonstrated that colistin stimulates excessive production of reactive oxygen species (ROS), including superoxide anions, hydrogen peroxide, and hydroxyl radicals [5,6]. These reactive molecules damage lipids, proteins, and nucleic acids, leading to lipid peroxidation, protein oxidation, and mitochondrial DNA damage. As a consequence, the cellular antioxidant defense system becomes overwhelmed, resulting in depletion of endogenous antioxidants such as reduced glutathione (GSH) [6,7].

Glutathione is the most abundant intracellular thiol-containing antioxidant and serves as a critical regulator of redox homeostasis. It participates directly in the neutralization of ROS and indirectly in the regeneration of other antioxidants, such as vitamins C and E [7]. In addition, GSH plays an essential role in maintaining the structural and functional integrity of mitochondria by preserving the redox state of sulfhydryl groups in mitochondrial enzymes and membrane proteins [8]. Depletion of intracellular GSH has been shown to exacerbate mitochondrial damage, impair oxidative phosphorylation, and promote apoptotic and necrotic pathways in renal tubular cells [8,9].

Mitochondria are particularly vulnerable to oxidative stress, and their dysfunction represents a key event in the development of colistin-induced nephropathy. Colistin has been reported to reduce mitochondrial membrane potential, disrupt electron transport chain activity, and inhibit enzymes of the tricarboxylic acid (TCA) cycle [5,9]. These alterations impair aerobic energy metabolism and shift cellular metabolism toward anaerobic pathways, leading to disturbances in glycolysis and downstream metabolic processes.

Pyruvate occupies a central position in cellular energy metabolism, serving as the end product of glycolysis and a key substrate linking cytosolic glucose metabolism to mitochondrial oxidative phosphorylation. Under physiological conditions, pyruvate is transported into mitochondria, where it is converted to acetyl-CoA by the pyruvate dehydrogenase complex (PDH), thereby entering the TCA cycle [10]. The activity of PDH is tightly regulated by phosphorylation–dephosphorylation mechanisms and is highly sensitive to the cellular redox state.

Inhibition of PDH activity results in reduced oxidative metabolism of pyruvate and its accumulation in the cytosol and plasma. Elevated plasma pyruvate levels are therefore considered a marker of impaired mitochondrial function and disrupted energy metabolism [10,11]. Moreover, when mitochondrial oxidation of pyruvate is compromised, excess pyruvate may be converted into lactate by lactate dehydrogenase, potentially leading to lactic acidosis, particularly under conditions of oxidative stress and mitochondrial injury [11].

Experimental evidence suggests that oxidative stress-mediated inhibition of PDH may play a crucial role in colistin-induced metabolic disturbances. ROS can directly modify PDH subunits and regulatory enzymes, leading to decreased enzyme activity [12]. Furthermore, depletion of GSH disrupts redox-dependent regulation of PDH, further limiting the conversion of pyruvate into acetyl-CoA and exacerbating metabolic dysregulation [12,13].

Given the central role of GSH in antioxidant defense and mitochondrial protection, supplementation with exogenous glutathione or GSH precursors has been proposed as a potential strategy to mitigate colistin-induced nephrotoxicity. Several experimental studies have demonstrated that restoration of intracellular GSH levels can reduce oxidative stress, preserve mitochondrial function, and attenuate renal tubular damage in models of drug-induced nephropathy [7,9,14]. However, the effects of glutathione on metabolic markers of mitochondrial dysfunction, such as plasma pyruvate levels, remain insufficiently explored.

Assessment of plasma pyruvate concentration may provide valuable insights into the metabolic consequences of colistin-induced nephropathy and the potential protective effects of glutathione. By reflecting the balance between glycolytic flux and mitochondrial oxidative capacity, pyruvate serves as a sensitive indicator of PDH activity and mitochondrial integrity [10,15]. Investigating changes in pyruvate levels in response to colistin administration and glutathione treatment may therefore contribute to a better understanding of the metabolic mechanisms underlying nephrotoxicity and antioxidant protection.

In recent years, increasing attention has been directed toward metabolic intermediates as sensitive indicators of early cellular injury in drug-induced nephrotoxicity. Among these, pyruvate occupies a central position at the intersection of glycolysis and mitochondrial oxidative metabolism, serving as a key regulator of cellular energy homeostasis. Disturbances in pyruvate utilization may reflect impaired activity of the pyruvate dehydrogenase

complex and compromised mitochondrial function, both of which are critically involved in renal tubular cell injury. Given the high metabolic demand and mitochondrial density of proximal tubular cells, even subtle alterations in redox balance and substrate flux may contribute to progressive kidney damage. Therefore, investigating pyruvate dynamics in the context of colistin exposure may provide novel mechanistic insights into early metabolic dysregulation and potential targets for nephroprotective interventions.

Thus, the present study focuses on evaluating plasma pyruvate levels as a marker of metabolic impairment in colistin-induced nephropathy and assessing the modulatory role of glutathione in preserving mitochondrial function and pyruvate utilization.

Research Aim and Research Questions

To determine plasma pyruvate levels in rats as a marker of nephrotoxicity and to assess the effect of glutathione on pyruvate levels in colistin-induced nephropathy.

Materials and Methods

Animals and experimental design

To determine the level of pyruvate in rat plasma as a marker of nephrotoxicity and to evaluate the effect of glutathione on pyruvate levels in colistin-induced nephropathy.

The study used 60 adult male rats, which were kept in standard laboratory conditions with free access to food and water. All experimental procedures were performed in accordance with the institutional guidelines for the care and use of animals (Kyiv, 2006).

The animals were randomly divided into five experimental groups according to the treatment protocol. Colistin-induced nephropathy was modeled by daily intravenous administration of colistin at a dose of 15 mg/kg body weight [16]. Reduced glutathione (GSH) was administered at a dose of 100 mg/kg body weight according to the experimental schedule. The detailed experimental design, treatment combinations, and duration of exposure for each group are summarized in **Table 1**.

Table 1. Experimental groups and treatment protocol

Group	Treatment	Dose
Control	Saline (0.9% NaCl)	–
Colistin	Colistin	15 mg/kg/day (i.v.)
Colistin + GSH (7 d)	Colistin + glutathione	Colistin 15 mg/kg/day + GSH 100 mg/kg
Colistin + NaCl	Colistin + saline	15 mg/kg/day + 0.9% NaCl
Colistin + GSH (14 d)	Colistin (7 d) + glutathione	Colistin 15 mg/kg/day + GSH 100 mg/kg

Abbreviations: GSH, reduced glutathione.

Colistin was administered intravenously once daily.

Biochemical analysis

Blood samples were collected at the end of the experimental period, and plasma was separated by centrifugation. Plasma pyruvate concentration was determined using the 2,4-dinitrophenylhydrazine method. Briefly, 0.5 mL of plasma was mixed with 0.25 mL of 0.1% dinitrophenylhydrazine solution [17], followed by the addition of 1.5 mL of toluene. After phase separation, 0.5 mL of the supernatant was combined with 1 mL of alcoholic potassium hydroxide solution. The absorbance of the resulting colored complex was measured spectrophotometrically at 465 nm against a reagent blank.

Data Analysis

Data are presented as mean ± standard deviation (SD). Statistical comparisons between groups were performed using Student's t-test. Differences were considered statistically significant at $p \leq 0.05$.

Research Results

Plasma pyruvate concentrations differed significantly among the experimental groups, indicating pronounced alterations in energy metabolism following colistin administration and glutathione treatment **Table 2**.

Table 2. Plasma pyruvate concentrations in rats with colistin-induced nephropathy

Group	Pyruvate (μmol/mL)	% Change vs. Control
Control	50.5 ± 1.25	–
Colistin	58.6 ± 3.05*	+16%

Colistin + GSH (7 d)	26.5 ± 2.20*	−48%
Colistin + NaCl	56.9 ± 2.80*	+13%
Colistin + GSH (14 d)	27.8 ± 1.95*	−45%

Data are presented as mean ± SD.

*p ≤ 0.05 vs. control (Student's t-test).

Plasma pyruvate was measured spectrophotometrically at 465 nm.

In rats treated with colistin alone, plasma pyruvate concentrations were significantly higher than in the control group, indicating marked alterations in systemic energy metabolism (Table 2). In contrast, co-administration of glutathione resulted in a substantial reduction in plasma pyruvate levels, both after 7 days of combined treatment and following extended glutathione administration for 14 days. Treatment with 0.9% sodium chloride in colistin-exposed rats did not significantly modify pyruvate concentrations, suggesting that the observed metabolic changes were specifically related to colistin toxicity and glutathione intervention rather than to procedural factors.

In the control group, mean plasma pyruvate concentration was 50.5 ± 1.25 µmol/mL, consistent with physiological carbohydrate metabolism and preserved mitochondrial function. Administration of colistin for 7 days led to a significant increase in plasma pyruvate to 58.6 ± 3.05 µmol/mL, corresponding to a 16% elevation compared with control values ($p \leq 0.05$).

In contrast, rats receiving glutathione in combination with colistin exhibited markedly lower plasma pyruvate concentrations. After 7 days of GSH administration, pyruvate levels decreased to 26.5 ± 2.20 µmol/mL, representing a 48% reduction relative to the control group ($p \leq 0.05$). A comparable decrease was observed in animals receiving prolonged glutathione treatment for 14 days following colistin exposure, with pyruvate levels remaining significantly lower than those observed in both the control and colistin-only groups.

Notably, intergroup variability in plasma pyruvate concentrations was reduced in glutathione-treated animals compared with the colistin-only group, indicating a more uniform metabolic response under glutathione supplementation.

Discussion

Colistin-induced nephropathy remains a critical limitation in the clinical use of this last-resort antibiotic, particularly in the treatment of multidrug-resistant Gram-negative infections. The present study provides new evidence that colistin not only induces structural and functional renal damage but also profoundly disrupts systemic energy metabolism, as reflected by altered plasma pyruvate levels. Furthermore, our findings demonstrate that glutathione administration significantly modulates these metabolic disturbances, highlighting its potential protective role against colistin-induced mitochondrial dysfunction.

Colistin and disruption of pyruvate metabolism

Pyruvate represents a pivotal metabolic junction connecting glycolysis to mitochondrial oxidative phosphorylation. Under physiological conditions, pyruvate is predominantly converted into acetyl-CoA by the pyruvate dehydrogenase complex (PDH), allowing its entry into the tricarboxylic acid (TCA) cycle. The observed elevation of plasma pyruvate in colistin-treated rats suggests an inhibition of this metabolic pathway, most likely due to impaired PDH activity.

Previous studies have shown that colistin accumulates in renal proximal tubular cells, where it induces mitochondrial injury by decreasing mitochondrial membrane potential, disrupting the electron transport chain, and inhibiting enzymes of the TCA cycle [5,18]. These alterations compromise oxidative phosphorylation and ATP synthesis, forcing cells to rely more heavily on glycolysis for energy production. As a consequence, pyruvate accumulates due to reduced mitochondrial uptake and oxidation.

Moreover, oxidative stress plays a crucial role in this process. Colistin-induced overproduction of reactive oxygen species (ROS) leads to oxidative modification of mitochondrial proteins, lipids, and DNA [6,19]. PDH is particularly sensitive to redox imbalance, as its activity depends on the integrity of sulfhydryl groups within its subunits and regulatory enzymes. Oxidative modification of these thiol groups can directly inhibit PDH activity, further limiting pyruvate conversion to acetyl-CoA [12,20].

Link between mitochondrial dysfunction and lactate formation

In conditions of impaired mitochondrial oxidation, excess pyruvate may be diverted toward lactate production via lactate dehydrogenase. This metabolic shift is a well-known adaptive response to mitochondrial dysfunction but may lead to lactic acidosis if sustained [11,21]. Although lactate levels were not measured in the present study, the

significant accumulation of pyruvate in colistin-treated rats suggests a metabolic environment favoring anaerobic glycolysis and potential lactate overproduction.

Such metabolic reprogramming has been described in various models of drug-induced nephrotoxicity and acute kidney injury, where mitochondrial dysfunction precedes structural damage and contributes to disease progression [22]. Therefore, elevated plasma pyruvate may serve not only as a marker of impaired PDH activity but also as an early indicator of mitochondrial distress in colistin-induced nephropathy.

Role of glutathione in preserving mitochondrial function

The most striking finding of this study is the marked reduction in plasma pyruvate levels following glutathione administration in colistin-treated rats. This effect was observed both during concomitant treatment and after prolonged post-treatment with GSH, indicating a sustained protective influence on cellular metabolism.

Glutathione is the principal intracellular antioxidant and a key regulator of redox homeostasis. Its protective effects extend beyond direct ROS scavenging to include maintenance of mitochondrial integrity, regulation of redox-sensitive enzymes, and preservation of cellular energy metabolism [7,8]. In the context of colistin-induced toxicity, GSH depletion has been identified as a critical event exacerbating oxidative stress and mitochondrial injury [6,23].

By replenishing intracellular GSH levels, exogenous glutathione likely mitigates oxidative damage to mitochondrial membranes and enzymes, including PDH. Restoration of PDH activity would enhance the conversion of pyruvate into acetyl-CoA, thereby reducing pyruvate accumulation in plasma and promoting its utilization within the TCA cycle.

Redox regulation of the pyruvate dehydrogenase complex

PDH activity is tightly controlled by reversible phosphorylation and by the cellular redox state. Oxidative stress promotes PDH inhibition through activation of PDH kinases and direct oxidative modification of enzyme subunits [10,12]. Glutathione plays a critical role in maintaining PDH in its active, reduced state by preserving thiol groups and supporting redox-dependent signaling pathways [13,24].

Experimental studies have demonstrated that restoration of GSH levels can reactivate PDH and improve mitochondrial respiration in models of oxidative stress [24,25]. Our findings are consistent with these observations and suggest that glutathione-mediated preservation of PDH activity represents a key mechanism underlying the normalization of pyruvate metabolism in colistin-treated rats.

Systemic implications of altered pyruvate metabolism

Alterations in pyruvate metabolism are not confined to renal tissue but may reflect systemic metabolic disturbances associated with nephrotoxicity. Elevated plasma pyruvate has been reported in various pathological conditions involving mitochondrial dysfunction, including sepsis, drug-induced toxicity, and metabolic syndromes [15,26]. Therefore, the observed changes in pyruvate levels may indicate broader metabolic consequences of colistin exposure beyond the kidney.

The ability of glutathione to normalize plasma pyruvate levels suggests a systemic antioxidant and metabolic effect, potentially contributing to overall metabolic stability during nephrotoxic insult. This observation supports the concept that metabolic markers such as pyruvate can serve as sensitive indicators of therapeutic efficacy in antioxidant interventions.

Comparison with previous studies

While numerous studies have investigated the nephroprotective effects of antioxidants against colistin-induced toxicity, most have focused on classical markers such as serum creatinine, urea, histopathology, and oxidative stress parameters [14,18,27]. In contrast, data on metabolic markers of mitochondrial function remain limited.

Our study adds novel evidence that pyruvate metabolism is significantly altered during colistin-induced nephropathy and that glutathione effectively modulates this alteration. These findings complement previous reports demonstrating that antioxidants such as N-acetylcysteine, melatonin, and vitamin E can attenuate colistin-induced oxidative stress and mitochondrial damage [27–29]. The molecular mechanisms underlying colistin-induced nephrotoxicity include oxidative stress, mitochondrial dysfunction, and inflammatory signaling pathways [30].

Conclusions and Implications

The obtained results indicate that colistin-induced nephrotoxicity is a multifactorial pathological process in which mitochondrial dysfunction, enhanced oxidative stress, and depletion of endogenous antioxidant defense systems in renal tissue play a central role. Disruption of energy metabolism, particularly the impairment of pyruvate dehydrogenase complex activity, is accompanied by pyruvate accumulation and a metabolic shift toward anaerobic glycolysis, thereby exacerbating injury to the proximal renal tubules.

The findings demonstrate that an imbalance of the glutathione system, including a reduction in reduced glutathione levels and impaired redox regulation within mitochondria, represents a key mechanism underlying cellular vulnerability under colistin exposure. Depletion of the mitochondrial glutathione pool promotes excessive reactive oxygen species generation, lipid peroxidation, and activation of cell death pathways, including apoptosis and ferroptosis, which is consistent with current concepts of oxidative injury in the pathogenesis of acute kidney injury.

Importantly, the results suggest that modulation of metabolic and antioxidant pathways may represent a promising strategy for nephroprotection during colistin therapy. Preservation of pyruvate metabolism and mitochondrial function may mitigate energy deficiency and limit cellular damage, while enhancement of glutathione-dependent antioxidant defenses contributes to stabilization of redox homeostasis and attenuation of inflammatory responses in renal tissue.

In conclusion, this study provides further insight into the metabolic mechanisms underlying colistin-induced nephrotoxicity and supports the potential utility of metabolically targeted and antioxidant-based interventions as adjunctive approaches to reduce nephrotoxic complications associated with polymyxin treatment. These findings may serve as a foundation for future experimental and clinical investigations aimed at improving the safety profile of colistin therapy and optimizing individualized treatment strategies for patients at high risk of kidney injury.

1- Declarations

1-1- Author Contributions

Conceptualization, Oleksandra Yu. Kushnir and Andrii Pakulets; methodology, Oleksandra Yu. Kushnir; software, Tymur Zhvanskyi; validation, Oleksandra Yu. Kushnir, Andrii Pakulets and Oleksandra O. Kushnir; formal analysis, Oleksandra Yu. Kushnir; investigation, Oleksandra Yu. Kushnir; resources, Andrii Pakulets; data curation, Tymur Zhvanskyi; writing – original draft preparation, Oleksandra Yu. Kushnir; writing – review and editing, Oleksandra O. Kushnir; visualization, Tymur Zhvanskyi; supervision, Andrii Pakulets; project administration, Andrii Pakulets; funding acquisition, Andrii Pakulets.

1-2- Data Availability Statement

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ethical restrictions related to experiments on animals. Data available in a publicly accessible repository that does not issue DOIs: Publicly available datasets were analyzed in this study. This data can be found here: [link/accession number].

1-3- Funding

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1-4- Acknowledgements

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1-5- Informed Consent Statement

Not applicable.

1-6- Conflicts of Interest

The authors declare no conflicts of interest.

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