J Nephropharmacol. 2026; 15(1): e12805.

https://jnephropharmacology.com DOI: 10.34172/npj.2025.12805

Journal of Nephropharmacology

Potential of a palladium–Mexidol complex in normalization of liver tests as a dual organoprotective of hepato-renal function in a paracetamol-induced rat model

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ARTICLE INFO

Article Type:
Original

Article History:
Received: 10 Apr. 2025
Revised: 7 Jul. 2025
Accepted: 20 Jul. 2025
ePublished: 9 Aug. 2025

Keywords:
Palladium complexes
Mexidol
Acetaminophen
Paracetamol
Antioxidants
Liver function tests
Organoprotective
Hepatoprotective
Renal injury
Liver-kidney axis

ABSTRACT

Introduction: Paracetamol overdose is a primary cause of acute liver and renal damage due to oxidative stress and depletion of glutathione reserves. Palladium-Mexidol complexes have demonstrated significant antioxidant, membrane-protective, and cytoprotective properties.
Objectives: This study investigates the therapeutic potential of a palladium–Mexidol complex in this context.
Materials and Methods: This experimental animal study was conducted on 36 healthy white rats, randomly divided into four groups. The groups included a healthy control group, a paracetamol-induced hepatitis model group, a treatment group that received intraperitoneal palladium–Mexidol following hepatitis induction, and a post-treatment group assessed ten days after the final dose. Serum levels of hepatic and cellular injury markers, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), and alkaline phosphatase (ALP), were measured and compared between each pair of experimental groups
Results: The results indicated that the liver enzyme activities showed distinct changes across experimental groups, with healthy control rats maintaining normal levels of AST, ALT, ALP, GGT, LDH, and CPK. Paracetamol-induced hepatitis caused significant elevations in all these enzymes, reflecting liver injury. Treatment with palladium-Mexidol partially normalized enzyme levels, indicating initial recovery, and by the tenth-day post-treatment, further significant improvements were observed, with continued reductions in enzyme concentrations.
Conclusion: The result indicated the hepatoprotective efficacy of the palladium-Mexidol complex in mitigating paracetamol-induced liver toxicity, with progressive improvement observed by the tenth day post-treatment, indicating both immediate hepatoprotection and sustained liver recovery. We conclude that palladium-Mexidol complex is a promising hepatoprotective therapeutic approach that warrants further investigation and assessment of long-term safety profiles to advance its potential clinical applications.

Implication for health policy/practice/research/medical education:
In this experimental animal study, we found that the administration of the palladium-Mexidol complex has proven to be an effective strategy in shielding against liver toxicity induced by paracetamol. The study revealed that the complex not only provided immediate protection but also facilitated sustained recovery of the liver. Furthermore, the investigation tracked the liver's condition over a period of ten days, demonstrating progressive and continuous improvement throughout the observation period, highlighting the long-term benefits of the palladium-Mexidol complex in mitigating paracetamol-related liver damage.
Please cite this paper as: Mammadov FY, Polukhova SM, Amirgulu Abaszade Z, Alkishiev KS, Khidirova HF, Abbasova MR, Kazimli AV. Potential of a palladium–Mexidol complex in normalization of liver tests as a dual organoprotective of hepato-renal function in a paracetamol-induced rat model. J Nephropharmacol. 2026;15(1):e12805. DOI: 10.34172/npj.2025.12805.

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Original

Introduction

Paracetamol (acetaminophen) overdose represents the most common cause of acute liver failure in developed countries and continues to be a significant clinical challenge requiring comprehensive therapeutic interventions (1, 2). The hepatotoxic mechanism of paracetamol involves the formation of the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI) through cytochrome P450-mediated metabolism, which depletes cellular glutathione and forms protein adducts on mitochondrial proteins (1). This process leads to mitochondrial oxidative and nitrosative stress, accompanied by activation of c-Jun N-terminal kinase (JNK) and its translocation to mitochondria, ultimately resulting in mitochondrial membrane permeability transition and regulated necrosis (1,2). Studies have demonstrated that the severity of liver damage correlates with dose and duration of exposure, with animal models showing centrilobular necrosis and significant histological changes following paracetamol administration (3-5).

Mexidol (2-ethyl-6-methyl-3-hydroxypyridine succinate) is an established antioxidant and anti-ischemic agent with pronounced hepatoprotective properties that functions through multiple mechanisms (6,7). The compound exhibits direct antioxidant activity by inactivating free radicals and enhancing the activity of antioxidant enzymes such as glutathione peroxidase and superoxide dismutase (8,9). Studies have demonstrated that Mexidol pretreatment significantly reduces paracetamol-induced hepatotoxicity by inhibiting lipid peroxidation, normalizing enzyme markers of hepatocyte damage, and maintaining blood serum bilirubin levels (6,9). The succinate component of Mexidol provides additional cytoprotective effects by supporting adenosine triphosphate (ATP) synthesis through succinate dehydrogenase in mitochondrial enzyme complex II and activating specific succinate receptors (SUCNR1) that initiate metabolic cascades, enhancing tissue resistance to hypoxia (7,10). Palladium complexes have demonstrated significant biological activity in experimental models, with evidence indicating their capacity to interact with cellular antioxidant systems and modulate oxidative stress responses (11,12). The synthesis of palladium-Mexidol complexes represents a novel therapeutic approach that combines the antioxidant properties of Mexidol with the potential cytoprotective effects of palladium coordination compounds (13).

The concept of hepato-renal organoprotection has gained increasing recognition due to the intimate physiological and pathophysiological relationships between liver and kidney function (14). Hepatorenal syndrome, characterized by progressive kidney failure in patients with severe liver disease, represents a critical manifestation of this organ crosstalk and underscores the importance of dual organ protection strategies (15). The liver-kidney axis involves complex mechanisms, including circulatory dysfunction, activation of vasoconstrictor systems, and inflammatory responses that can simultaneously compromise both organs (14,16,17). Natural compounds and pharmaceutical agents with dual hepato-renal protective effects have shown promise in experimental models, with mechanisms involving antioxidant activity, anti-inflammatory properties, and preservation of cellular integrity in both organs (18). The palladium-Mexidol complex demonstrates potential for dual organ protection through its combined antioxidant and cytoprotective properties, with preliminary studies indicating protective effects against both hepatic and renal injury in experimental models (19). This dual organoprotective approach addresses the clinical need for therapeutic interventions that can simultaneously preserve liver and kidney function in conditions involving multi-organ toxicity, particularly in the context of drug-induced hepatotoxicity, where secondary renal complications may occur (14,20).

Objectives

This study aimed to evaluate the hepato-renal protective efficacy of a palladium-Mexidol complex in mitigating paracetamol-induced organ toxicity and normalizing liver function biomarkers in an experimental rat model. The objective directly targets the main therapeutic intervention, specifically the effect of palladium-Mexidol complex in liver function normalization, and its intended outcome of hepato-renal protection.

Materials and Methods

Study design and samples

This experimental animal study was conducted on 36 healthy adult white rats of both sexes, weighing between 200 and 250 g, which were bred and housed under standardized laboratory conditions at the Scientific Research Center vivarium of Azerbaijan Medical University. All experimental procedures were carried out following ethical guidelines and received prior approval from the Local Bioethics Committee, ensuring compliance with institutional and international standards for the care and use of laboratory animals.

Experimental design and grouping

The rats were randomly divided into four experimental groups to evaluate the effects of the palladium–Mexidol compound on paracetamol-induced hepatitis. Group 1, the control group (n = 6), consisted of intact rats that received no treatment or intervention. Group 2, the hepatitis model group (n = 10), received oral paracetamol to induce drug-induced liver injury. Group 3, the treatment group (n = 10), was subjected to the same hepatitis induction protocol as group 2, followed by intraperitoneal administration of a palladium–Mexidol compound at a dosage of 0.02 mg/kg once daily for three consecutive days. Group 4, the post-treatment group (n = 10), also underwent the same hepatitis induction and treatment regimen as group 3;

however, these animals were assessed 10 days after the final dose to investigate the persistence and potential long-term metabolic effects of the treatment.

Paracetamol-induced hepatitis procedure

To assess the hepatoprotective potential of the palladium–Mexidol compound, a non-viral drug-induced hepatitis model was established using paracetamol, following protocols adapted from previous experimental studies (21). Paracetamol tablets were finely ground in a porcelain mortar, and a dose of 2500 mg/kg body weight was suspended in 20 mL of distilled water to form a homogenous mixture. This suspension was further diluted with an additional 30 mL of distilled water to facilitate enteral administration. Before dosing, anesthesia was induced via intraperitoneal injection of 0.5 mL of calypsol. Under anesthesia, a flexible gastric catheter was carefully inserted into the esophagus, and the prepared paracetamol suspension was slowly introduced into the stomach. This procedure was repeated on alternate days for a total of five administrations to induce cumulative hepatocellular injury. The successful induction of hepatitis was confirmed by marked elevations in serum liver enzyme biomarkers, indicating significant hepatic damage.

Administration of palladium–Mexidol compound

Following the induction of drug-induced hepatitis, the palladium–Mexidol compound was administered intraperitoneally to the designated treatment groups. After confirming the establishment of hepatic injury through repeated paracetamol administration, rats in group 3 (Treatment group) and group 4 (post-treatment group) received the palladium–Mexidol compound at a dose of 0.02 mg/kg body weight. The compound was prepared in sterile conditions and diluted in an appropriate volume of physiological saline to allow for accurate intraperitoneal injections based on each animal's weight. The injection was administered once daily for three consecutive days using a sterile insulin syringe with a fine-gauge needle, inserted into the lower right quadrant of the abdomen to avoid puncture of internal organs. Animals in group 3 were evaluated immediately after the treatment period to assess the therapeutic effects of the compound, while those in group 4 were monitored and sacrificed 10 days after the final dose to evaluate the persistence of metabolic and hepatoprotective effects.

Data collection and biochemical analysis

To evaluate hepatic function and the extent of hepatocellular injury, serum concentrations of key biochemical markers, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), and alkaline phosphatase (ALP), were quantitatively assessed. Blood samples were obtained from each animal via cardiac puncture under anesthesia to ensure both the accuracy of sampling and animal welfare. The enzyme levels in collected sera were determined using a BioSkreen MS-2000 fully automated biochemical analyzer (USA), employing standardized commercial reagent kits produced by Human GmbH (Germany), according to the manufacturers' protocols.

Outcomes

The primary outcome of this study is the comparative analysis of serum liver enzyme levels, specifically AST, ALT, ALP, CPK, LDH, and GGT, across four distinct experimental groups: healthy control rats, a paracetamol-induced hepatitis model group, a treatment group administered the palladium–Mexidol compound intraperitoneally following paracetamol-induced hepatitis (with assessment on the third day of treatment), and a post-treatment group subjected to the same hepatitis induction and treatment regimen but evaluated ten days after the final dose.

Statistical analysis

Statistical analysis was conducted using Statistical Package for Social Sciences (SPSS) version 27.0 (IBM Corp., USA). The Shapiro-Wilk test was applied to assess the normality of the data distribution. Given that the data did not meet the assumptions of normality, the non-parametric Mann–Whitney U test was employed to compare the serum levels of AST, ALT, ALP, CPK, LDH, and GGT between each pair of experimental groups. All tests were performed with a significance level set at $P < 0.05$.

Results

The results indicated that paracetamol administration induced a pronounced elevation in the average activities of all assessed hepatic enzymes when compared with untreated controls. Specifically, the paracetamol-induced group displayed markedly higher mean levels of AST and ALT, underscoring significant hepatocellular damage. Parallel rises in GGT and ALP suggested concomitant biliary involvement, while substantial increases in LDH and CPK further indicated widespread cellular leakage and metabolic distress (Table 1).

Palladium–Mexidol treatment in rats subjected to paracetamol-induced hepatitis led to a noticeable reduction in mean values of key liver enzymes when compared with the untreated paracetamol group. Specifically, the average activities of AST and ALT were lower in the treatment group, reflecting diminished hepatocellular damage. Additionally, the mean concentrations of GGT and ALP were reduced, indicating less pronounced biliary involvement. Markers of broader cell injury, such as LDH and CPK, also demonstrated lower mean levels following palladium–Mexidol administration, suggesting an overall attenuation of hepatic and systemic injury (Table 2).

Ten days after paracetamol-induced hepatitis, the group receiving palladium–Mexidol treatment exhibited

Table 1. Changes in rats' liver enzyme concentration following paracetamol-induced hepatitis

Experimental group	Statistical parameters	Serum liver enzyme concentrations					
		AST (U/L)	ALT (U/L)	GGT (U/L)	LDH (U/L)	CPK (U/L)	ALP (U/L)
Group 1 (Control [No treatment])	Min	25	30	28	270	243	150
	Max	33	40	58	440	275	300
	Mean	29.4	35.2	43.2	368	260.4	234
	SEM	1.50	1.85	5.43	28.53	6.00	27.13
	SD	3.36	4.15	12.13	63.80	13.41	60.66
Group 2 (Paracetamol-induced hepatitis)	Min	39	48	64	540	448	400
	Max	70	73	110	800	565	600
	Mean	58.6	63.4	86.8	718	519	526
	SEM	5.34	4.56	8.98	47.79	23.33	37.89
	SD	11.95	10.19	20.08	106.86	52.17	84.73
P Value*		<0.001	<0.001	<0.01	<0.001	<0.001	<0.001

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT; Gamma-glutamyl transferase; LDH: Lactate dehydrogenase; CPK: Creatine phosphokinase; ALP: Alkaline phosphatase; Min: Minimum; Max: Maximum; SD: Standard deviation; SEM: Standard error of the mean. *Mann-Whitney U.

Table 2. Effect of palladium–Mexidol treatment on rats' liver enzyme levels in paracetamol-induced hepatitis

Experimental group	Statistical parameters	Serum liver enzyme concentrations					
		AST (U/L)	ALT (U/L)	GGT (U/L)	LDH (U/L)	CPK (U/L)	ALP (U/L)
Group 2 (Paracetamol-induced hepatitis)	Min	39	48	64	540	448	400
	Max	70	73	110	800	565	600
	Mean	58.6	63.4	86.8	718	519	526
	SEM	5.34	4.56	8.98	47.79	23.33	37.89
	SD	11.95	10.19	20.08	106.86	52.17	84.73
Group 3 (Palladium–Mexidol treatment)	Min	28	48	43	490	352	350
	Max	58	63	100	710	626	500
	Mean	47.2	55.6	71.4	636	483.4	446
	SEM	5.05	2.46	9.74	41.30	52.34	30.27
	SD	9.84	10.20	19.45	104.74	64.23	64.27
P Value*		<0.05	<0.01	<0.05	<0.01	>0.05	<0.01

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT; Gamma-glutamyl transferase; LDH: Lactate dehydrogenase; CPK: Creatine phosphokinase; ALP: Alkaline phosphatase; Min: Minimum; Max: Maximum; SD: Standard deviation; SEM: Standard error of the mean. *Mann-Whitney U.

substantially lower mean levels of all measured liver enzymes compared to the untreated paracetamol group. The decreases in mean AST and ALT indicate notable recovery from hepatocellular injury over the ten days. Similarly, mean values of GGT and ALP were reduced, signifying diminished biliary involvement. Furthermore, the average concentrations of LDH and CPK also declined, reflecting an overall attenuation of both hepatic and systemic cell damage (Table 3).

Liver enzyme activity measurements across the four experimental groups revealed distinct patterns. In the healthy control rats, AST, ALT, and ALP levels remained within the normal range. Following hepatitis induction by paracetamol, these enzyme concentrations increased markedly. Treatment with palladium-Mexidol resulted in a partial normalization of the enzyme levels. By the tenth day post-treatment, further significant improvements were observed (Figure 1).

In healthy control rats, the levels of GGT, LDH, and CPK remained within the normal range. However, following the induction of hepatitis using a paracetamol-induced model, all three parameters showed a significant increase. Treatment with palladium-Mexidol led to a partial reduction in these enzyme levels, indicating initial recovery. By the tenth day post-treatment, further improvements were evident, with the levels of GGT, LDH, and CPK continuing to decrease (Figure 2).

Discussion

Our results indicated that paracetamol administration in rats resulted in a significant increase in the mean levels of all major liver enzymes, indicating substantial hepatic injury, biliary involvement, and systemic cellular damage. However, treatment with palladium–Mexidol effectively reduced the mean concentrations of these enzymes, reflecting notable hepatoprotective effects and

Table 3. Changes in rats' liver enzyme concentration 10 days after paracetamol-induced hepatitis

Experimental group	Statistical parameters	Serum liver enzyme concentrations					
		AST (U/L)	ALT (U/L)	GGT (U/L)	LDH (U/L)	CPK (U/L)	ALP (U/L)
Group 2 (Paracetamol-induced hepatitis)	Min	39	48	64	540	448	400
	Max	70	73	110	800	565	600
	Mean	58.6	63.4	86.8	718	519	526
	SEM	5.34	4.56	8.98	47.79	23.33	37.89
	SD	11.95	10.19	20.08	106.86	52.17	84.73
Group 4 (Post-Treatment, Day 10)	Min	25	30	30	380	263	260
	Max	50	56	80	670	355	450
	Mean	36.4	42.6	59.4	550	305.4	382
	SEM	4.42	4.47	8.78	51.67	15.93	33.38
	SD	9.89	9.99	19.64	115.54	35.61	74.63
P Value*		< 0.05	< 0.05	< 0.05	<0.05	<0.05	<0.05

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT; Gamma-glutamyl transferase; LDH: Lactate dehydrogenase; CPK: Creatine phosphokinase; ALP: Alkaline phosphatase; Min: Minimum; Max: Maximum; SD: Standard deviation; SEM: Standard error of the mean.
*Mann-Whitney U.

Figure 1. Changes in liver enzyme activity following paracetamol-induced hepatitis and palladium–Mexidol treatment during the study period. AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; ALP, Alkaline phosphatase; Pd-Mexidol, Palladium–Mexidol treatment.

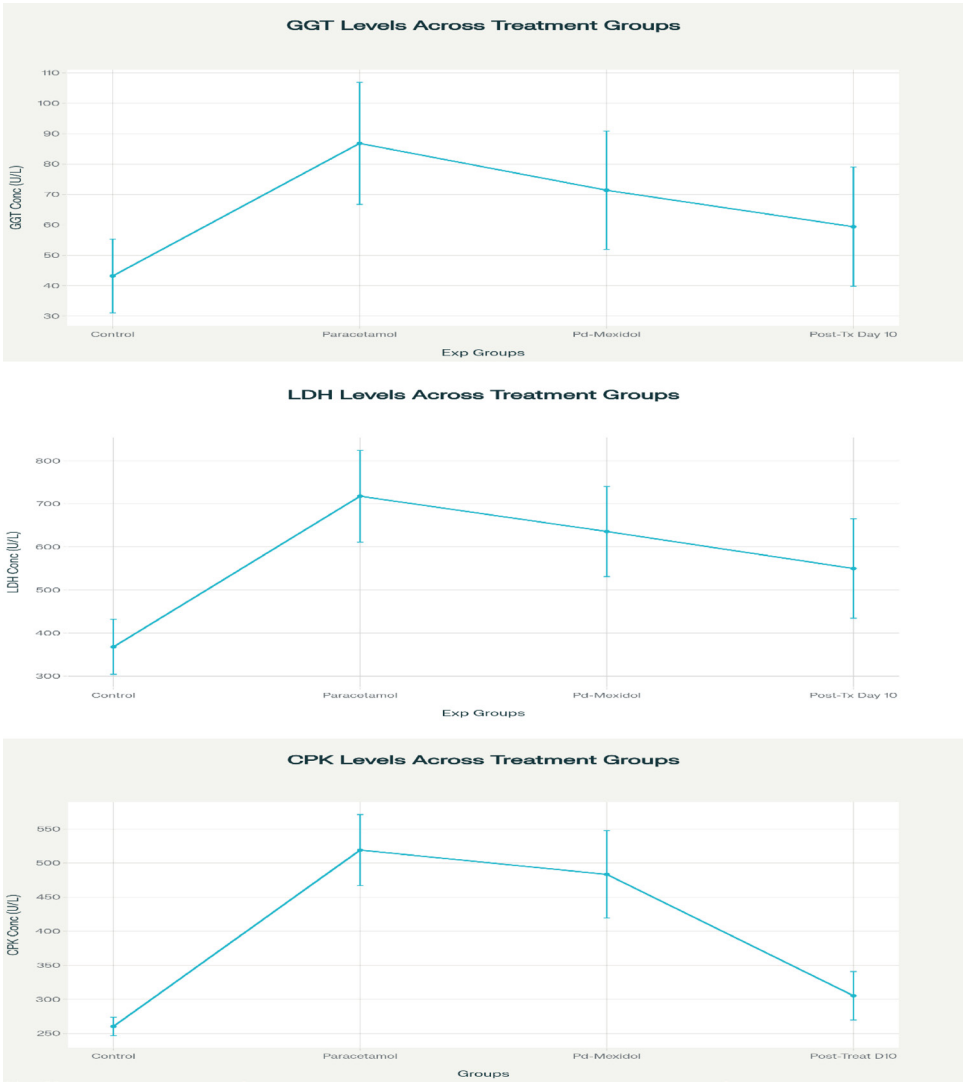

Figure 2. Changes in GGT, LDH, and CPK following paracetamol-induced hepatitis and palladium–Mexidol treatment during the study period. GGT, Gamma-glutamyl transferase; LDH, Lactate dehydrogenase; CPK, Creatine phosphokinase; Pd-Mexidol, Palladium–Mexidol treatment; EXP, Experimental.

less pronounced cellular and biliary injury. Importantly, this biochemical improvement was sustained over time, as evidenced by further reductions in liver enzyme means ten days post-intervention, suggesting significant recovery and attenuation of both hepatic and systemic damage following palladium–Mexidol treatment in paracetamol-induced hepatitis. The hepatoprotective effects of the palladium-Mexidol complex against paracetamol-induced hepatotoxicity align with numerous previous investigations that demonstrate the efficacy of various compounds in mitigating acetaminophen-induced liver injury. Studies have consistently shown that paracetamol administration results in a significant elevation of liver enzymes, including ALT, AST, and ALP, indicating substantial hepatocellular damage (22,23). Previous research on Mexidol has demonstrated its potent antioxidant and hepatoprotective properties, with studies showing significant reductions in plasma ALT and AST levels in animal models of liver injury (7,24). Similarly, palladium nanoparticles have demonstrated remarkable hepatoprotective activity, with one study reporting significant decreases in liver enzymes (ALT, AST, and ALP) and improvements in antioxidant parameters when used to treat acetaminophen-induced hepatotoxicity in rats (25). The sustained recovery observed in the current study over ten days post-intervention is particularly noteworthy, as most hepatoprotective studies typically evaluate short-term effects, with sustained liver enzyme normalization being reported in only select investigations involving direct-acting antivirals and other therapeutic interventions (26, 27).

The present findings represent a significant advancement in hepatoprotective therapeutics, as the combination of palladium and Mexidol appears to provide synergistic benefits that exceed those reported for individual compounds. The sustained biochemical improvement observed ten days post-intervention is particularly significant, as it suggests not merely acute protection

but genuine hepatic recovery and regeneration. This prolonged effect distinguishes the palladium-Mexidol complex from many conventional hepatoprotective agents, which often provide only transient protection. The mechanism likely involves multiple pathways, including enhanced antioxidant defense systems, as Mexidol is known to regulate antioxidant enzymes like catalase and glutathione peroxidase while reducing oxidative stress markers (7,24). The palladium component may contribute through its ability to scavenge reactive oxygen species and form protective complexes with toxic metabolites, as demonstrated in previous studies with palladium nanoparticles (25). The combination therapy approach mirrors successful strategies in other hepatoprotective interventions, where synergistic effects have been observed with natural compounds and metal complexes (28,29).

Overall, the palladium-Mexidol complex demonstrates exceptional hepatoprotective efficacy against paracetamol-induced liver injury, with sustained recovery extending beyond the typical observation periods reported in most hepatoprotective studies. The significant and prolonged reduction in liver enzymes, coupled with evidence of continued improvement ten days post-treatment, suggests that this novel complex may represent a paradigm shift in hepatoprotective therapeutics. While these results are promising and align with previous studies on individual components, the specific combination of palladium and Mexidol appears to offer unique advantages in terms of sustained recovery and comprehensive hepatic protection. However, further investigation is warranted to fully elucidate the molecular mechanisms underlying this sustained hepatoprotective effect, establish optimal dosing regimens, and evaluate long-term safety profiles. Additionally, comparative studies with established hepatoprotective agents and eventual clinical trials will be essential to validate the therapeutic potential of this novel palladium-Mexidol complex for clinical application in drug-induced liver injury.

Conclusion

This study successfully demonstrated the hepatoprotective efficacy of the palladium-Mexidol complex in mitigating paracetamol-induced liver toxicity. The results established that paracetamol administration caused significant elevation in all measured liver enzymes, including AST, ALT, ALP, GGT, LDH, and CPK, confirming the induction of hepatotoxicity in the experimental model. The therapeutic intervention with palladium-Mexidol complex effectively countered these pathological changes, as evidenced by the partial normalization of enzyme levels following treatment. Notably, the progressive improvement observed by the tenth day post-treatment suggests that the palladium-Mexidol complex not only provides immediate hepatoprotection but also facilitates sustained liver recovery. The findings support the dual organoprotective potential of the palladium-Mexidol complex, as the normalization of liver function biomarkers indicates effective mitigation of paracetamol-induced organ toxicity. The time-dependent improvement pattern observed in the treatment group demonstrates the compound's ability to promote hepatic regeneration and restore normal liver function. These results validate the therapeutic rationale for combining palladium with Mexidol, likely leveraging the antioxidant and membrane-protective properties of Mexidol alongside the organoprotective effects of palladium complexes. The study's outcomes contribute valuable insights into the development of novel hepatoprotective agents for drug-induced liver injury, particularly in the context of paracetamol toxicity, which remains a significant clinical challenge. The palladium-Mexidol complex represents a promising therapeutic approach that warrants further investigation, including dose-response studies, mechanistic evaluations, and assessment of long-term safety profiles to advance its potential clinical applications.

Limitations of the study

While the current study provides valuable insights into the potential hepato-renal protective effects of the palladium–Mexidol complex in a paracetamol-induced injury model, several limitations should be acknowledged. Firstly, the small sample size (n = 36) may limit the generalizability and statistical power of the findings. Secondly, the use of a single animal model (healthy adult rats) under controlled laboratory conditions may not fully replicate the complexity of paracetamol-induced toxicity or treatment responses in humans, thereby limiting translational applicability. Additionally, the relatively short duration of treatment and follow-up (three days of administration and a maximum of ten days post-treatment observation) prevents a comprehensive assessment of the long-term safety, efficacy, and possible cumulative toxicity of the compound.

Acknowledgments

The authors gratefully acknowledge the Azerbaijan Medical University, Baku, Azerbaijan, for providing the rats and facilities essential to this study.

Authors' contribution

Conceptualization: Fuad Yusir Mammadov and Shahzada Musa Polukhova.
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Project management: Zumrud Amirgulu Abaszade.

Resources: All authors.
Supervision: All authors.
Validation: Hijran Faramaz Khidirova and Hijran Faramaz Khidirova.
Writing–original draft: All authors.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare no conflict of interest.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of generative artificial intelligence (AI) and AI-assisted technologies in the writing process

While preparing this work, the authors utilized AI (Perplexity and Grammarly) to refine grammar points and language style. Subsequently, they thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

The research and the protocol of this study followed the guidelines of animal studies and were approved by the Scientific Research Center of the Azerbaijan Medical University, Baku, Azerbaijan. Experimental procedures were approved by the Local Bioethics Committee and conducted under the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986). We also followed the guidelines related to animal experiments, approved by the United States National Institutes of Health (NIH, 1978). Besides, the authors have ultimately observed ethical issues (including plagiarism, data fabrication, and double publication).

Funding/Support

The authors did not receive any source of funding.

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