The Egyptian Journal of Hospital Medicine (July 2025) Vol. 100, Page 4231-4239

Dapagliflozin Exerts Renoprotective Effect by Activating the Nrf2/HO-1 Pathway in Glycerol-Induced Acute Kidney Injury

Amany Said Sallam[a*], **Asmaa A. Mohammed**[b]
[a] Department of Pharmacology and Toxicology, Faculty of Pharmacy,
Menoufia University, 32511 Shebin El-Kom, Menoufia, Egypt
[b] Department of Pharmacology and Toxicology, Faculty of Pharmacy (Girls), AL-Azhar University, Cairo, Egypt.
Corresponding author: Amany Said Sallam, **Mobile:** (+20) 01008663682, **Email:** Amany.said@phrm.menofia.edu.eg

ABSTRACT

Background: One serious clinical consequence of rhabdomyolysis is acute kidney injury (AKI). Dapagliflozin (Dapa) is a novel anti-diabetic drug for type 2 diabetes. Beyond its glucose-lowering action, evidence from both human and animal studies highlights its additional anti-inflammatory and antioxidative benefits.

Objective: This study aimed to demonstrate for the first time the effect of protection of Dapa via triggering the Nrf2/HO-1 pathway to counteract glycerol-induced AKI.

Materials and methods: Four groups of forty male Wistar rats were established (n = 10 each): (1) Normal control group (normal saline), (2) glycerol group (10 ml/kg, intramuscular), (3) glycerol + Dapa group (1 mg/kg, p.o.) and (4) Dapa (1 mg/kg, p.o.). After 7 days, Evaluations of renal function were conducted through the measurement of blood urea nitrogen (BUN) and serum creatinine levels (sCr). Oxidative stress markers, including malondialdehyde (MDA) and superoxide dismutase (SOD), were determined. Kidney injury molecule-1 (Kim-1), histopathological alterations, and inflammatory markers such as nuclear factor-κB (NF-κB) and tumor necrosis factor-α (TNF-α) were also evaluated. In addition, antioxidant defense mechanisms were investigated by assessing nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase-1 (HO-1) in kidneys.

Results: Pretreatment with Dapa improved kidney function by lowering sCr, BUN, and Kim-1 and reducing histopathological damage. It also suppressed glycerol-induced inflammation of TNF-α and NF-κB, while enhancing antioxidant defenses through Nrf2/HO-1 pathway activation.

Conclusion: Dapa pretreatment improved kidney function in a rat model of glycerol-induced rhabdomyolysis-associated renal damage by inhibiting the inflammatory response and lowering oxidative stress.

Keywords: AKI, Dapagliflozin, Nrf2, HO-1.

INTRODUCTION

Acute kidney injury (AKI) is a medical illness defined by an immediate and usually reversible loss in renal function. It is connected to an increase in mortality, prolonged hospitalization and rapid progression to chronic renal failure [(1)]. AKI is the most prevalent complication of rhabdomyolysis, a clinical illness that develops when the muscle tissue is damaged and discharges its contents into the bloodstream [(2)]. Trauma, illnesses, drug use, and excessive exercise are all potential causes. Furthermore, during wartime and natural calamities, rhabdomyolysis-induced myoglobinuric damage reached epidemic levels [(1)]. Rhabdomyolysis is clinically related with renal impairment in around 2–5% of individuals presenting to the emergency room [(3)]. Although the decline in kidney function can often be reversed in most patients who survive, the death rate associated with rhabdomyolysis AKI remains disturbingly high, and there are presently no effective medications available to prevent or manage AKI [(4)].

One well-established experimental model of rhabdomyolysis-induced AKI in rodents is a single glycerol injection administered intramuscularly. This model replicates human AKI by causing a significant drop affecting the glomerular filtration rate and renal blood flow [(2, 5)]. The pathogenic mechanisms involve renal ischemia, tubular toxicity due to myoglobin accumulation, and cytokine-mediated inflammatory responses following muscle injury [(3)]. Glycerol-induced AKI is brought on by myoglobin nephrotoxicity and renal ischemia. Despite the complexity and uncertainty of the pathophysiology of glycerol-induced AKI, lipid peroxidation, oxidative stress, apoptosis, endothelial dysfunction, and inflammatory mediators are all implicated [(2)].

In reaction to oxidative stress, Nrf2, a transcription factor, controls the production of cytoprotective enzymes that function as antioxidants [(6, 7)]. Among its downstream targets, HO-1 is critical for cellular defense. Nrf2 activation has been demonstrated to reduce myoglobinuric AKI, with HO-1 induction being essential for its renoprotective effects [(8)].

Dapa, an innovative treatment for type 2 diabetes mellitus is a selective sodium-glucose cotransporter 2 (SGLT2) inhibitor. Dapa promotes urinary glucose excretion, thereby improving glycemic control. Beyond glucose lowering, SGLT2 inhibition reduces glomerular hyperfiltration, tubular oxidative stress, and renal oxygen

Received: 30/04/2025
Accepted: 30/06/2025

consumption in diabetic kidneys [9]. Preclinical research findings have also demonstrated that Dapa does not induce hypoglycemia in rodents as reported in myocardial infarction. Recent clinical and experimental findings further suggest a renoprotective role of Dapa in AKI, particularly in patients with type 2 diabetes mellitus [10]. Also, large-scale clinical trials confirm that SGLT2 inhibitors not only improve glycemic control but also lower blood pressure and provide cardiovascular and renal benefits [11, 12].

To date, no research studies have investigated the effect of Dapa on glycerol-induced AKI. We believe that Dapa may provide renoprotection against glycerol-induced AKI by reducing oxidative stress and inflammation. Therefore, this work aimed to pinpoint the fundamental mechanisms that underlie its renoprotective advantages, concentrating on the Nrf2/HO-1 signaling pathway.

MATERIALS AND METHODS

Chemicals: We purchased glycerol and Dapa from Sigma-Aldrich Chemical Co. in St. Louis, Missouri, USA. High analytical quality was exhibited by the other substances used in the experiment.

Animals: The experimental animals production unit (VACSERA) in Giza, Egypt, provided 40 healthy male Wistar rat weighed 200 ± 20 g for testing. They were held for 10 days in accordance with established laboratory protocols. The rats were kept in a standard arrangement, with a 12-hour cycle of day and night. Before beginning the experiment, the animals were given a week to adapt to ensure that they were healthy and free of illness.

Induction of AKI: Rats were given a 50% glycerol injection to cause AKI (10 mL/kg, single dose) into the animals' hind limbs after diluting it in saline (0.9% NaCl). Rats were deprived of water 24 hours before the glycerol injection, as previously described [13].

Experimental design: Forty male Wistar rats were randomly selected and divided into four equal groups. (n = 10 each) as follows:

Group 1 (Normal control): Rats obtained an intramuscular injection of physiological saline (0.9% NaCl), which served as the baseline for all subsequent comparisons.

Group 2 (Glycerol): Rats were administered an intramuscular injection of 50% glycerol (10 mL/kg).

Group 3 (Glycerol + Dapa): Rats were administered 1 mg/kg/day Dapa orally for seven days [14], followed by an intramuscular injection of 50% glycerol (10 mL/kg).

Group 4 (Dapa): Rats received 1 mg/kg/day Dapa orally for seven days [14].

After 24 hours of glycerol administration, all animals were sacrificed under mild halothane anesthesia. Blood samples were taken for serum separation using centrifugation. The kidneys were removed, cleaned in ice-cold saline to eliminate blood, and then divided into small parts. One piece was frozen at -80 °C for upcoming molecular and biochemical examinations. For histological analysis, the other part was kept in 10% neutral buffered formalin.

Colorimetric analysis: BUN, sCr, SOD, and MDA were tested calorimetrically using biodiagnostic kits from Biodiagnostic Company (Dokki, Giza, Egypt). All of the steps in the kits were carried out exactly as specified by the manufacturer.

ELISA technique: KIM-1, Nrf2, HO-1, TNF-α, and NF-κB were quantified utilizing commercially available ELISA kits, following manufacturer guidelines. The kits utilized were as follows: KIM-1 (Elabscience Biotechnology Inc., Cat. No. E-EL-R3019, Houston, TX, USA), Nrf2 (MyBioSource, Inc., Cat. No. MBS012148, San Diego, CA, USA), HO-1 (BioVision, Cat. No. E4525-100, Milpitas, CA, USA), TNF-α (MyBioSource, Inc., Cat. No. MBS2507393, San Diego, CA, USA), and NF-κB (Cloud-Clone Corp., Cat. No. SEB824Mu, Katy, TX, USA).

Histopathological examination: The kidney samples were preserved with 10% buffered formalin. Tissues were fixed in paraffin after conventional histological processing. Hematoxylin and eosin were used to stain the 3 μm thick sections that were sliced using a rotary microtome (Leica RM2155; Leica Microsystems, Wetzlar, Germany), put on slides, stained with hematoxylin and eosin, and subjected to light microscope examination (Olympus CX21, 40X, Tokyo, Japan).

Ethical approval: All experimental techniques and methodologies followed the guidelines outlined in the Guide for the Care and Use of Laboratory Animals. Menoufia University Faculty of Pharmacy Ethics Committee accepted the study with NO: MPIR24/05.

RESULTS

Dapagliflozin improved renal impairment induced by intramuscular injection of glycerol:

As illustrated in figure (1), glycerol administration significantly increased (A) sCr, (B) BUN, and (C) KIM-1 levels by 256%, 134%, and 114% respectively compared to the normal control group. Nevertheless, Dapa pretreatment (1 mg/kg) significantly reduced the amounts of sCr, BUN, and KIM-1 by 53%, 55%, and 68% respectively, relative to the glycerol group.

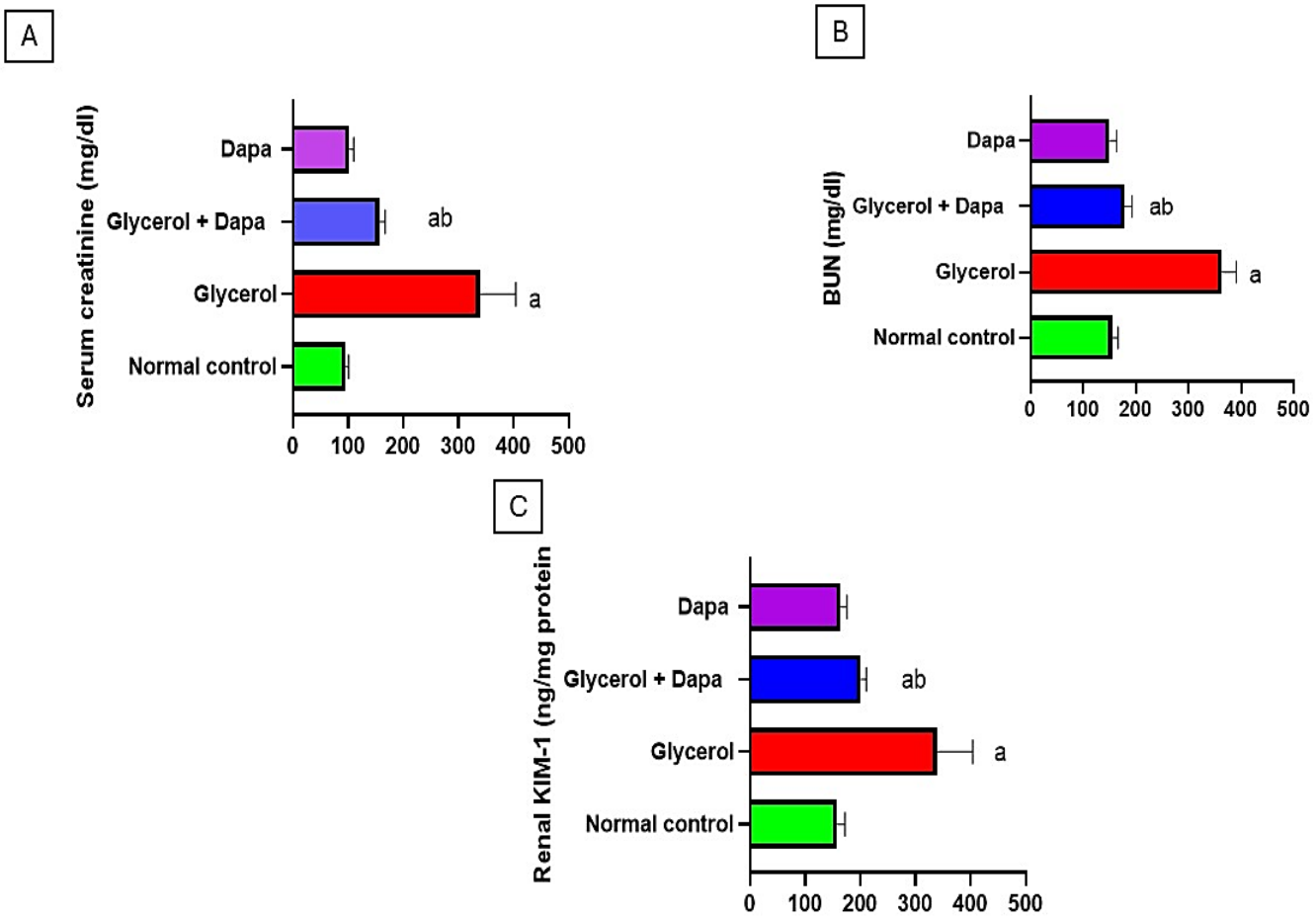

Figure (1): Effect of Dapa (1mg/kg) on (A) SCr, (B) BUN, and (C) KIM-1 levels induced by intramuscular glycerol injection. Values are expressed as means ± SD (n = 10). Statistical analysis was conducted using one-way ANOVA followed by Tukey's post-hoc test at $p < 0.05$. (a) Normal control. (b) Glycerol group. **ANOVA:** analysis of variance; **Scr:** serum creatinine, **Bun:** blood urea nitrogen; **Dapa:** dapagliflozin; **Gly:** glycerol; **KIM-1:** kidney injury molecule-1.

Dapagliflozin improves oxidative stress markers induced by intramuscular glycerol injection:
As demonstrated in figure (2) (C, D), glycerol administration significantly elevated renal lipid peroxidation, as evidenced by a 455.4% increase in MDA content, and significantly reduced renal SOD activity by 53.95%, indicating enhanced oxidative stress. However, using Dapa in pretreatment (1 mg/kg, p.o.) for seven days dramatically lowered MDA content. 50.95% and increased SOD activity by 125% compared to the glycerol group, demonstrating that Dapa effectively mitigated glycerol-induced oxidative stress.

Dapagliflozin improves the Nrf2/HO-1 pathway induced by intramuscular glycerol injection:
As depicted in figure (2) (A, B), Glycerol administered intramuscularly dramatically decreased kidney levels of Nrf2 and HO-1 by 57.96% and 50% respectively, in contrast to the normal control animals. Conversely, Dapa pretreatment (1 mg/kg, p.o.) for 7 days markedly upregulated renal Nrf2 and HO-1 contents by 99% and 99.49% respectively relative to the glycerol group. These results imply that Nrf2/HO-1 pathway activation might protect against oxidative stress-induced inflammatory kidney damage brought on by glycerol injection.

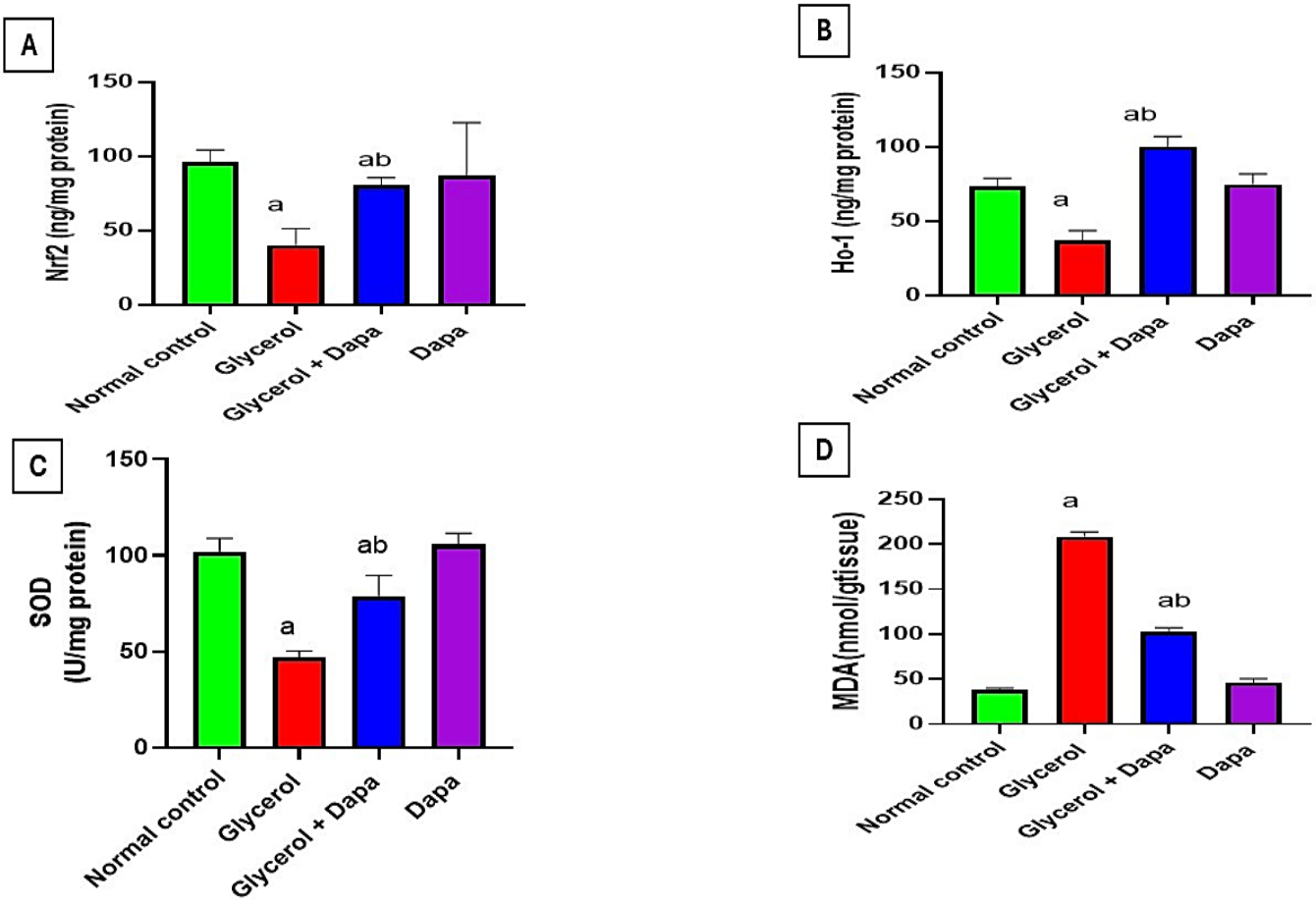

Figure (2): Effect of Dapa (1mg/kg) on renal (A) Nrf2, (B) HO-1, (C) SOD, and (D) MDA levels induced by intramuscular glycerol injection. The values are shown as means ± SD (n = 10). Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test at $p < 0.05$. (a) Normal control. (b) Glycerol group. ANOVA: analysis of variance; **Dapa:** dapagliflozin; **Nrf2:** Nuclear factor erythroid 2–related factor 2; **HO-1:** Heme oxygenase-1; **SOD:** Superoxide Dismutase; **MDA:** Malondialdehyde.

Dapagliflozin decreases NF-κB/TNF-α inflammatory markers induced by intramuscular glycerol injection:
As demonstrated in figure (3) (A, B), glycerol administered intramuscularly markedly raised kidney NF-κB and TNF-α levels by 77.67% and 251% respectively, compared to the normal control ones. However, pretreatment with Dapa (1 mg/kg, p.o.) for 7 days markedly reduced NF-κB and TNF-α contents by 55.9% and 70%, respectively, relative to the glycerol group.

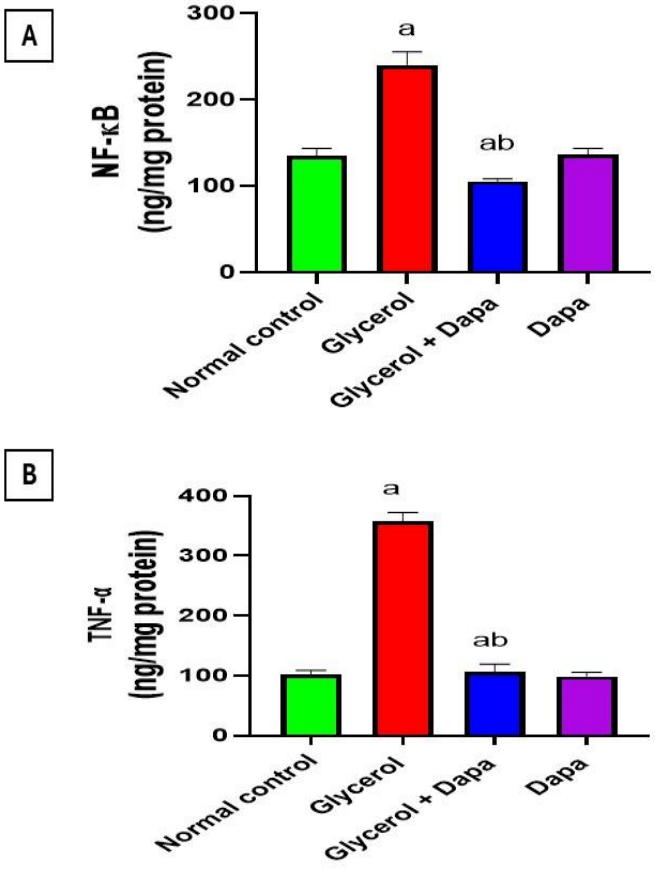

Figure (3): Effect of Dapa (1 mg/kg) on renal (A) NF-kB and (B) TNF-α levels by intramuscular glycerol injection**.** Values are shown as means ± SD (n = 6). Statistical analysis was conducted utilizing one-way ANOVA followed by Tukey's post-hoc test at $p < 0.05$. (a) Normal control. (b) Glycerol group. **ANOVA:** analysis of variance; **Dapa:** dapagliflozin; **NF-kB:** nuclear factor kappa B; **TNF-α:** tumor necrosis factor alpha.

Histopathological alterations in the kidney:

As shown in Figs. 4a–4d, renal tissues from the normal control and Dapa-treated groups (1 mg/kg, p.o., for 7 days) exhibited no histopathological alterations, displaying intact tubular epithelium, well-organized glomeruli, normal vasculature, and preserved interstitial tissue. In contrast, intramuscular injection of glycerol induced marked AKI, characterized by loss of cellular detail, disruption of tubular epithelial architecture in both the cortical and corticomedullary regions, and the presence of eosinophilic casts within the lumina of necrotic tubules. Notably, pretreatment with Dapa (1 mg/kg, p.o., for seven days before AKI introduction.) markedly improved renal histopathological changes compared to the glycerol group. These data are summarized in table (1).

Table (1): The protective effect of Dapa on histopathological analysis of renal tissues following glycerol-induced AKI

Histopathological lesions	Normal control	Glycerol	Glycerol + Dapa	Dapa
Inflammation	-	++	+	-
Congestion	-	++	+	-

++: moderate; **+:** mild; **-:** none; **Dapa:** dapagliflozin.

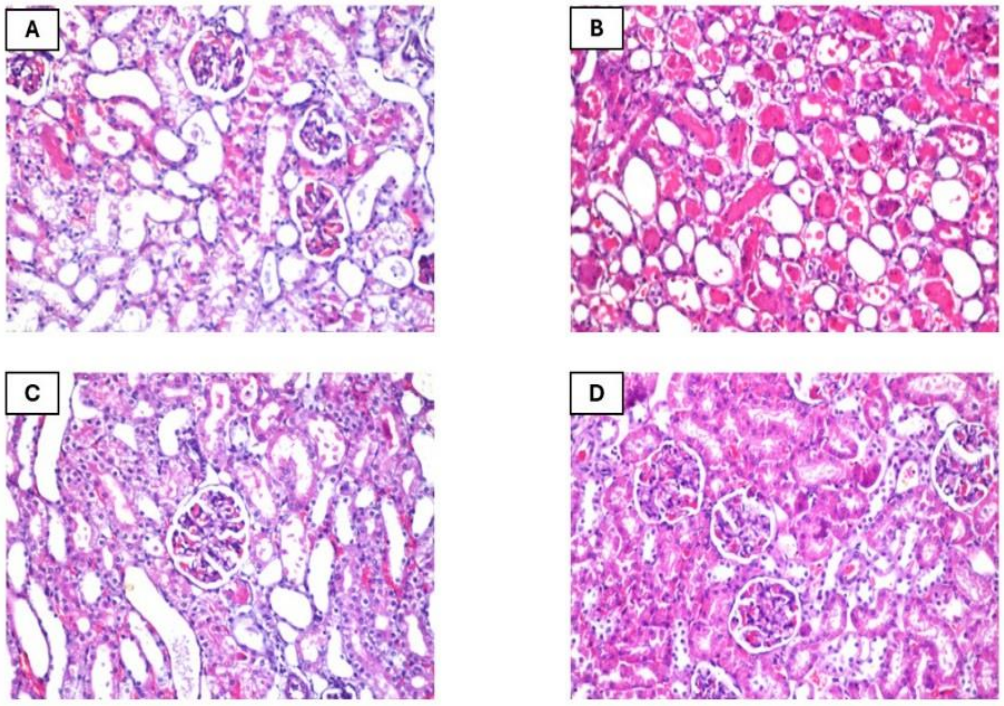

Figure (4 a, b, c & d**):** Photomicrographs illustrating the effect of dapagliflozin on renal tissue following glycerol-induced kidney damage in rats, stained with hematoxylin-eosin. (A) The normal control group displayed normal tubular epithelium, normally oriented cellular glomeruli, normal vasculature, and normal interstitial tissue. (B) Glycerol group: Loss of the cell detail and presence of the general architecture in the lining epithelium of the tubules at the cortex, as well as in the tubules at the corticomedullary junction. The corticomedullary junction showed also eosinophilic casts formation in the lumen of necrosed tubules. (C) Glycerol + Dapa group: improved renal histopathological damages induced by intramuscular injection of glycerol. (D) Dapa-treated group: There was no histopathological alteration in the glomeruli and tubules.

DISCUSSION

Rhabdomyolysis represents a pathological phenomenon distinguished by the release of intracellular components from muscle cells into the extracellular space. Myoglobin constitutes one of the most deleterious agents implicated in this pathological process [(15)]. Rhabdomyolysis-induced AKI resulting from a single intramuscular glycerol injection, administered bilaterally into the hind limbs, is a recognized and validated experimental model for investigating the underlying mechanisms of this condition and evaluating potential therapeutic agents [(16, 17).]

Coinciding with these data, intramuscular glycerol injection caused a severe decrease in renal function, as demonstrated by considerable increases in BUN and sCr. These findings suggest reduced renal excretory capacity and the development of AKI, which is supported by histological changes compared to the control group. Our findings are comparable with previous researches that describes glycerol-induced renal impairment and tissue damage [(18, 19)]. In our study, administration of Dapa (1 mg/kg, p.o., for 7 days) substantially reduced serum BUN and sCr, reflecting an improvement in renal function.

KIM-1, a type I membrane protein with both extracellular and cytoplasmic components, is typically found in small quantities in a healthy kidney. After kidney injury, the extracellular component quickly separates and enters the tubule lumens, and high amounts suggest renal tissue destruction [(20)]. KIM-1 is recognized as a highly specific, sensitive, and prognostic biomarker of AKI [(21)]. In the current study, Dapa significantly reduced KIM-1 levels, indicating a clear renoprotective effect. Since KIM-1 is a sensitive sign of proximal tubular damage, its reduction suggests that Dapa attenuates the progression of renal damage. Kidney damage progression, potentially through the suppression of inflammation and oxidative stress. These results are consistent with earlier studies highlighting the pivotal role of oxidative and inflammatory pathways in AKI pathogenesis [(22)].

Oxidative stress, predominantly instigated by reactive oxygen species (ROS), holds significant importance in the beginning and sustenance of glycerol-induced AKI [(4, 23)]. During RM development, muscle cells release massive

quantities of myoglobin. This myoglobin is transported *via* tubule cells' endocytosis and the glomerular filtration barrier. The hydroxyl radical is produced inside cells when ferrous myoglobin (Fe^2) oxidizes to ferric myoglobin (Fe^3), the most reactive type of ROS [(24)]. Redox cycling converts ferric myoglobin (Fe^3) to ferryl myoglobin (Fe^2), producing reactive species that raise membrane fatty acid lipid peroxidation and result in the production of MDA resulting in further harm to DNA and proteins [(15)].

Additionally, myoglobin itself possesses enzymatic activity that accelerates lipolysis and produces highly reactive chemicals known as isoprostanes. During rhabdomyolysis, these can raise the body's overall oxidative stress [(25)]. Myoglobin-derived lipid peroxidation and iron buildup can damage the kidneys by causing ferroptosis, during rhabdomyolysis.[(26)]. AKI induction in this investigation resulted in acute oxidative damage as seen by increased ROS production and lipid peroxidation via MDA levels, while the antioxidant marker SOD was reduced. By alleviating oxidative stress, Dapa decreases MDA levels and increases SOD levels. That is consistent with **Uchida *et al.*** [(27)] who showed that Dapa, an SGLT2 inhibitor protects against renal impairment by lowering the effects of oxidative stress.

Nrf2 is a key transcriptional modulator that controls both the induced and basal expression of a number of defense genes that encode antioxidant proteins and detoxifying enzymes, such as HO-1 [(28)]. In renal tissues, HO-1 is essential for the breakdown of accumulated myoglobin [(29)]. In this investigation, we discovered that HO-1 was markedly diminished in glycerol-induced AKI, suggesting that it was a factor that responded quickly to myoglobin in renal tissues. This aligns with previous research of **Chen *et al.*** [(30)]. According to the current study, rats treated with glycerol had significantly lower levels of Nrf2 and HO-1 than the normal control group. By contrast, Dapa significantly elevated the expression of Nrf2 and HO-1, which improved damage caused by free radicals to the kidneys. This result is in line with earlier studies showing how important the Nrf2/HO-1 pathway is for boosting antioxidant defense and preventing kidney damage brought on by oxidative stress [(31)]. Furthermore, this supports Dapa's role as a strong activator of antioxidant defense pathways by demonstrating that it reduces diabetic cardiomyopathy by upregulating Nrf2, which promotes glutathione synthesis and prevents cardiac ferroptosis [(32)].

Along with causing direct oxidative stress, myoglobin-derived free radicals activate NF-κB, an important transcription factor that governs inflammatory reactions. NF-κB signaling pathway activation causes the release of proinflammatory cytokines, especially TNF-α, leading to increased renal inflammation and contributing to the pathophysiology of AKI [(33)]. Our investigation found significant rises in NF-κB and TNF-α levels in glycerol group. Pretreatment with Dapa improved the rhabdomyolysis-induced imbalance between Nrf2 and NF-κB by upregulating Nrf2 and HO-1 while suppressing the expression of NF-κB in the glycerol model. These findings suggest that Dapa mitigates inflammation primarily through inhibiting the signaling pathway of NF-κB. Coinciding with our results, **Abdollahi *et al.*** [(34)] showed how Dapa decreases inflammation by inhibiting LPS-induced TLR-4 expression and NF-κB activation in human endothelial cells.

CONCLUSION

Dapa significantly protects against glycerol-induced AKI by increasing antioxidant defenses, reducing oxidative stress, and inhibiting inflammatory responses. These findings highlight Dapa's therapeutic promise in the treatment of AKI and supply a solid framework for future clinical trials.

No funding.

No conflict of interest.

REFERENCES

1. **Al Asmari A, Al Sadoon K, Obaid AA, Yesunayagam D, Tariq M (2017):** Protective effect of quinacrine against glycerol-induced acute kidney injury in rats. BMC Nephrol, 18 (1): 41. https://doi.org/10.1186/s12882-017-0450-8.
2. **Nguyen M, Devarajan P (2008)** Biomarkers for the early detection of acute kidney injury. Pediatr Nephrol, 23 (12): 2151–7. https://doi.org/10.1007/s00467-007-0470-x.
3. **Rizk S, Abdel Moneim A, Abdel-Gaber R *et al.* (2023):** Nephroprotective Efficacy of Echinops spinosus against a Glycerol-Induced Acute Kidney Injury Model, 8(44):41865–75. https://doi.org/10.1021/acsomega.3c06792.
4. **Li Y, Xu B, An R *et al.* (2019):** Protective effect of anisodamine in rats with glycerol-induced acute kidney injury. BMC Nephrol., 20 (1): 1–14. https://doi.org/10.1186/s12882-019-1394-y.
5. **Reis N, Francescato H, de Almeida L *et al.* (2019):** Protective effect of calcitriol on rhabdomyolysis-induced acute kidney injury in rats. Sci Rep. ,9 (1):7090. https://doi.org/10.1038/s41598-019-43564-1.
6. **Rushmore T, Morton$ M, Pickett C (1991):** The antioxidant responsive element activation by oxidative stress and identification of the DNA consensus sequence required for functional activity. the journal of biological chemistry, 266 (18): 11632–9. https://doi.org/10.1016/S0021-9258(18)99004-6.

7. **Nguyen T, Sherratt P, Pickett C (2003):** Regulatory mechanisms controlling gene expression mediated by the antioxidant response element. Annu Rev Pharmacol Toxicol., 43: 233–60. https://doi.org/10.1146/annurev.pharmtox.43.100901.140229.
8. **Zhao W, Huang X, Zhang L *et al.* (2016):** Penehyclidine Hydrochloride Pretreatment Ameliorates Rhabdomyolysis-Induced AKI by Activating the Nrf2/HO-1 Pathway and Alleviating Endoplasmic Reticulum Stress in Rats. PLoS One, 11 (3): e0151158. https://doi.org/10.1371/journal.pone.0151158.
9. **Chang Y, Choi H, Jeong J *et al.* (2016):** Dapagliflozin, SGLT2 inhibitor, Attenuates renal ischemia-reperfusion injury. PLoS One, 11 (7): e0160478. https://doi.org/10.1371/journal.pone.0158810.
10. **Kim H, Won H, Park S *et al.* (2025):** Risk of acute kidney injury in dapagliflozin users with type 2 diabetes: A nationwide propensity score-matched cohort study in Korea. Pharmacotherapy, 45 (5): 282–90. https://doi.org/10.1002/phar.70015.
11. **Perkovic V, Jardine M, Neal B *et al.* (2019):** Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med., 380 (24): 2295–306.
12. **Neal B, Perkovic V, Mahaffey K *et al.* (2017):** Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med., 377 (7): 644–57. DOI: 10.1056/NEJMoa1611925.
13. **Kim J, Lee S, Jung M *et al.* (2010):** N-acetylcysteine attenuates glycerol-induced acute kidney injury by regulating MAPKs and Bcl-2 family proteins. Nephrol Dial Transplant., 25 (5): 1435–43. https://doi.org/10.1093/ndt/gfp659.
14. **Kabel A, Salama S (2021):** Effect of taxifolin/dapagliflozin combination on colistin-induced nephrotoxicity in rats. Hum Exp Toxicol., 40 (10): 1767–80. https://doi.org/10.1177/09603271211010906.
15. **Raslan N, Helal H, Balah A *et al.* (2025):** Wheatgrass ameliorates glycerol-induced nephrotoxicity via regulation of NF-kB p65/KIM-1/NGAL signaling pathway. Beni Suef Univ J Basic Appl Sci., 14 (1): 1–13. https://doi.org/10.1186/s43088-025-00677-z.
16. **Singh A, Muthuraman A, Jaggi A *et al.* (2012):** Animal models of acute renal failure. Pharmacol Rep., 64 (1): 31–44. https://doi.org/10.1016/S1734-1140(12)70728-4.
17. **Gois P, Canale D, Volpini R *et al.* (2016):** Allopurinol attenuates rhabdomyolysis-associated acute kidney injury: Renal and muscular protection. Free Radical Biology and Medicine,101:176–89. https://doi.org/10.1016/j.freeradbiomed.2016.10.012.
18. **Baghishani M, Mehri S, Aminifard T *et al.* (2025):** The protective properties of resveratrol against glycerol-induced acute kidney injury in rats. Avicenna J Phytomed., 15 (1): 860–73. doi: 10.22038/AJP.2024.24649.
19. **Kassab R, Elhenawy A, Abdulrahman T *et al.* (2023):** Modulation of inflammatory, oxidative, and apoptotic stresses mediates the renoprotective effect of daidzein against glycerol-induced acute kidney injury in rats. Environ Sci Pollut Res., 30 (56): 119016–33. https://doi.org/10.1007/s11356-023-30461-4.
20. **Karmakova T, Sergeeva N, Kanukoev K *et al.* (2021):** Kidney injury molecule 1 (KIM-1): A multifunctional glycoprotein and biological marker. Современные технологии в медицине, 13 (3): 64–80.
21. **Luft F (2021):** Biomarkers and predicting acute kidney injury. Acta Physiologica, 231(1): e13479. https://doi.org/10.1111/apha.13479.
22. **Ding T, Song M, Wang S *et al.* (2025):** Dapagliflozin has protective effects on palmitate-induced renal tubular epithelial cells by enhancing mitochondrial function and reducing oxidative stress. Journal of Diabetes and its Complications, 39 (2): 108930. https://doi.org/10.1016/j.jdiacomp.2024.108930.
23. **Guo S, Zhou H, Huang C *et al.* (2015):** Astaxanthin Attenuates Early Acute Kidney Injury Following Severe Burns in Rats by Ameliorating Oxidative Stress and Mitochondrial-Related Apoptosis. Marine Drugs, 13 (4): 2105–23. https://doi.org/10.3390/md13042105.
24. **Hebert J, Burfeind K, Malinoski D *et al.* (2022):** Molecular Mechanisms of Rhabdomyolysis-Induced Kidney Injury: From Bench to Bedside. Kidney Int Rep., 8 (1): 17–29.
25. **Oraby M, El-Yamany M, Safar M *et al.* (2019):** Dapagliflozin attenuates early markers of diabetic nephropathy in fructose-streptozotocin-induced diabetes in rats. Biomedicine and Pharmacotherapy, 109: 910–20. https://doi.org/10.1016/j.biopha.2018.10.100.
26. **Guerrero-Hue M, García-Caballero C, Palomino-Antolín A *et al.* (2019):** Curcumin reduces renal damage associated with rhabdomyolysis by decreasing ferroptosis-mediated cell death. FASEB J., 33 (8): 8961–75. https://doi.org/10.1096/fj.201900077R.
27. **Uchida A, Kidokoro K, Sogawa Y *et al.* (2019):** 5-Aminolevulinic acid exerts renoprotective effect

via Nrf2 activation in murine rhabdomyolysis-induced acute kidney injury. Nephrology, 24 (1): 28–38. https://doi.org/10.1111/nep.13189.

28. **Nguyen T, Nioi P, Pickett C (2009):** The Nrf2-antioxidant response element signaling pathway and its activation by oxidative stress. Journal of biological chemistry, 284 (20): 13291-13295.
29. **Shin S, Chung S, Kim S *et al.* (2016):** Effect of Sodium-Glucose Co-Transporter 2 Inhibitor, Dapagliflozin, on Renal Renin-Angiotensin System in an Animal Model of Type 2 Diabetes. PLoS One, 11 (11): e0165703.. https://doi.org/10.1371/journal.pone. 0165703.
30. **Chen X, Wang T, Gao Y *et al.* (2025):** Dapagliflozin attenuates diabetic cardiomyopathy via NRF2 protein upregulation-driven glutathione synthesis to inhibit myocardial ferroptosis. Life Sci., 378: 123819. https://doi.org/10.1016/j.lfs.2025.123819.
31. **Uddin M, Kim E, Hannan M *et al.* (2021):** Pharmacotherapy against oxidative stress in chronic kidney disease: Promising small molecule natural products targeting nrf2-ho-1 signaling. Antioxidants, 10(2): 258. https://doi.org/10.3390/antiox10020258
32. **Maurea N, Canale M, Bisceglia I *et al.* (2023):** Dapagliflozin Reduces Myocardial and Renal NF-kB Expression in Preclinical Models Exposed to Doxorubicin Through Myd-88 and NLRP3 Pathways: An Hystological Study. Circulation, 148: A15030-A15030. https://doi.org/10.1161/circ.148.suppl_1.15030.
33. **Hassan N, Kamel G, Fayed H *et al.* (2025):** Dapagliflozin alleviates thioacetamide induced-liver fibrosis in rats via controlling the Nrf2/HO-1 and TLR4/TGF-β1/PI3K signaling pathways. Immunopharmacol Immunotoxicol., 47 (3): 392–405. https://doi.org/10.1080/08923973.2025.2496661.
34. **Abdollahi E, Keyhanfar F, Delbandi A *et al.* (2022):** Dapagliflozin exerts anti-inflammatory effects via inhibition of LPS-induced TLR-4 overexpression and NF-κB activation in human endothelial cells and differentiated macrophages. European journal of pharmacology, 918: 174715. https://doi.org/10.1016/j.ejphar.2021.174715.