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Research Article

Protective effect of Dapagliflozin against Amphotericin B-induced nephrotoxicity in an experimental rat model

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Abstract

Objective: Background: Amphotericin B deoxycholate (AmBD), a potent antifungal agent, is limited by significant nephrotoxicity. SGLT-2 inhibitors, such as dapagliflozin, exhibit renoprotective effects beyond glycemic control. This study aimed to investigate the potential protective effects of dapagliflozin against AmBD-induced nephrotoxicity in an experimental rat model.

Materials and Methods: Thirty-two Wistar albino rats were randomized into four groups (n=8): Control, AmBD (single 50 mg/kg i.p. dose), Dapagliflozin (10 mg/kg/day, gavage), and AmBD + Dapagliflozin. After seven days, serum levels of creatinine, BUN, oxidative stress markers (TOS, MDA, MPO), antioxidant enzymes (CAT, SOD, GPx), and apoptotic mediators (Bax, Bcl-2, Caspase-3) were analyzed. Renal tissues were evaluated for histopathological changes.

Results: AmBD administration induced significant acute kidney injury, characterized by elevated serum BUN and creatinine levels and severe histopathological damage, including tubular necrosis and dilatation. Co-administration of dapagliflozin significantly attenuated these functional and structural injuries, but its effect on systemic oxidative stress and apoptotic markers could not be demonstrated in this model.

Conclusion: Dapagliflozin partially prevented AmBD-induced elevations in BUN and creatinine and significantly ameliorated histopathological damage. However, no significant effect was observed on systemic oxidative stress or apoptotic markers in this model

Keywords: Dapagliflozin, Amphotericin B, nephrotoxicity, oxidative stress, SGLT-2 inhibitor, acute kidney injury.

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INTRODUCTION

Amphotericin B deoxycholate (AmBD) is a broad-spectrum antifungal agent regarded as the gold standard in the treatment of systemic fungal infections. Effective against numerous pathogenic fungi, particularly Aspergillus, Candida, and Cryptococcus species, AmBD is frequently used in the management of severe immunosuppressive conditions and life-threatening clinical scenarios such as febrile neutropenia (1). Despite its high efficacy, nephrotoxicity remains the major adverse effect limiting its therapeutic success (2). This toxicity is mainly characterized by oxidative stress, inflammation, apoptosis, and tubuloglomerular feedback dysfunction, especially in proximal tubular cells (3, 4). In vitro studies have reported transient or permanent impairment of renal function in approximately 80% of patients receiving AmBD therapy (2, 3, 5).

In recent years, sodium–glucose cotransporter-2 (SGLT-2) inhibitors have become widely used in the management of diabetes, not only providing glycemic control but also attracting attention for their notable cardio-renoprotective effects (6-9). SGLT-2 inhibitors such as dapagliflozin exert kidney-protective actions by reducing glomerular hyperfiltration, lowering intraglomerular pressure, and limiting tubulointerstitial injury (10, 11). Moreover, both experimental and clinical studies have demonstrated that these agents modulate oxidative stress, inflammatory, and apoptotic pathways (6, 10, 12-15).

However, data regarding the potential renoprotective effects of SGLT-2 inhibitors against potent nephrotoxic agents such as AmBD remain limited. Elucidating whether dapagliflozin can prevent or mitigate AmBD-induced acute kidney injury (AKI) would address an important clinical and pharmacological gap. The aim of this study was to evaluate the possible renal protective effects of the SGLT-2 inhibitor dapagliflozin against AmBD-induced nephrotoxicity in an experimental rat model, using both biochemical and histopathological assessments.

MATERIAL AND METHODS

2. 1. Experimental Rats

Thirty-two male Wistar albino rats (2 months old; 250–350 g) were obtained from the Experimental Animal Research Unit, Faculty of Medicine, Çukurova University (Adana, Türkiye). Rats were housed under controlled conditions (23 ± 2 °C; 60 ± 5% humidity; 12 h light/dark cycle) with free access to standard pellet chow (Feed Institution Standard Rat Diet) and tap water. After a one-week acclimatization period, animals were randomly divided into four groups (n = 8 per group). All experimental procedures complied with the Guide for the Care and Use of Laboratory Animals (16).

2.2. Experimental Design and Drug Administration

Treatment duration, administration routes, and dosing schedules were determined based on pharmacokinetic data and previous studies on AmBD- and dapagliflozin-induced nephrotoxicity in rats (2, 3). AmBD was administered intraperitoneally(ip) due to its poor oral bioavailability; this route provides consistent systemic exposure and reproducible nephrotoxicity in rodents (17). Dapagliflozin was administered orally by gavage to mimic the clinical route and ensure adequate gastrointestinal absorption (10, 13). Dapagliflozin (Forziga®, AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA) and AmBD (AmBD (Fungizone®, IV formulation, Bristol-Myers Squibb SA, France) were used in the study.

2.3. Experimental Groups

Rats were randomly divided into four groups (n = 8 per group) as follows:

1. Control group: Received isotonic saline (1 mL/kg, ip) once daily for 7 days.
2. Dapagliflozin group: Received dapagliflozin (10 mg/kg, oral gavage) once daily for 7 days.
3. AmBD group: Received a single ip dose of AmBD (50 mg/kg) on day 2 and isotonic saline on the remaining days.

4. AmBD + Dapagliflozin group: Received dapagliflozin (10 mg/kg, oral gavage) once daily for 7 days and a single ip dose of AmBD (50 mg/kg) on day 2.

2.4. Operation Procedures and Measurements

All procedures were conducted in accordance with the Guide for the Care and Use of Laboratory Animals (16). The experimental period lasted seven days. To minimize circadian variations, all treatments were administered between 09:00 and 10:00 a.m. Injections were performed twice daily at 12-hour intervals using insulin syringes inserted into the left lower abdominal quadrant; gentle aspiration was applied before each injection to prevent accidental intravenous administration.

On day 8, rats were anesthetized with ketamine (50 mg/kg, ip) and xylazine (10 mg/kg, i.p.). Blood samples were collected via intracardiac puncture, centrifuged at 3000 rpm for 10 min, and sera were stored at −80 °C until biochemical analysis. Animals were humanely euthanized by cervical dislocation under deep anesthesia, and both kidneys were harvested and fixed in 10% neutral-buffered formalin for histopathological examination.

Serum samples were thawed at room temperature before analysis. Oxidative stress markers—malondialdehyde (MDA), total oxidant status (TOS), and myeloperoxidase (MPO)—and antioxidant parameters—total antioxidant status (TAS), glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD)—were quantified. Pro-apoptotic proteins [Bcl-2-associated X protein (Bax) and Caspase-3 (Casp-3)], the anti-apoptotic protein Bcl-2, and renal function indicators (serum urea and creatinine) were also measured. All biochemical, immunohistochemical, and histopathological evaluations were performed by investigators blinded to group allocation to minimize observer bias.

2.5. Ethics Committee

The study was conducted at the Experimental Practice and Research Center of Çukurova University following approval from the Institutional Ethics Committee (Ethics Approval Date/No: July 20, 2023).

2.6. Biochemical Analyses

2.6.1. Determination of Serum Urea and Creatinine Concentrations

Serum urea and creatinine were analyzed colorimetrically with an autoanalyzer (Mindray BS-400, China) using commercial kits (Otto Scientific, Türkiye; Cat. No. OttoBC157 and OttoBC139, respectively). Results were expressed in mg/dL; blood urea nitrogen (BUN) was obtained by dividing urea values by 2.14.

2.6.2. Assessment of MDA and Catalase (CAT) Activities

Serum MDA was measured colorimetrically using a commercial kit (Otto Scientific, Cat. No. Otto1001) following Yoshioka et al (18). CAT activity was determined with a kit (Elabscience, USA; Cat. No. E-BC-K031-S) according to Aebi(19). Data were expressed as nmol/g for MDA and U/L for CAT.

2.6.3. Quantification of Bax, Bcl-2, and Casp-3 Levels

Casp-3 levels were quantified using an ELISA kit (Elabscience, USA; Cat. No. E-EL-R0160) following Engvall and Perlmann (20). Bax and Bcl-2 concentrations were determined with similar ELISA kits (BT-Lab, China; Cat. Nos. E0034Ra and E0037Ra). Absorbance was read at 450 nm using a microplate reader (BIO-TEK EL X 800), and results were expressed as ng/mL.

2.6.4. Determination of SOD, GPx, and MPO Activities

Serum SOD, GPx, and MPO activities were determined colorimetrically using commercial kits (Otto Scientific, Türkiye; Cat. Nos. Otto3047, Otto2085, and Otto3048) on a Mindray BS-400 autoanalyzer (Mindray, China). Analyses followed the methods of Marklund and Marklund, Paglia and Valentine, and Bradley et al. (21, 22). Results were expressed as U/mL for SOD and U/L for GPx and MPO.

2.7. Histopathological Examination of Renal Tissues

Renal tissues were fixed in 10% neutral-buffered formalin, dehydrated in ethanol, cleared with xylene, and embedded in paraffin. Sections (5 μm) were stained with hematoxylin–eosin (H&E) and periodic acid–Schiff (PAS) for morphological evaluation. Histopathological assessments were performed blindly by a pathologist using a light microscope (Olympus BX51, Olympus, Japan). Tubular necrosis, vacuolization, dilatation, atrophy, desquamation, mononuclear cell infiltration, cortical and medullary necrosis, inflammation, and hyaline cast formation were examined. Histopathological alterations were evaluated in a semi-quantitative manner using a scoring system, where the degree of renal damage was graded as (–) no damage, (+) mild, (++) moderate, or (+++) severe, according to the criteria established by Mozaffari(23).

2.8 Statistical Analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) software, version 27.0 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as numbers and percentages, while continuous variables were expressed as mean ± standard deviation (SD). Comparisons of categorical parameters were performed using the chi-square test, and post hoc pairwise group differences were analyzed with the Bonferroni-adjusted test.The Shapiro–Wilk test was applied to determine the normality of data distribution. For variables with normal distribution, one-way analysis of variance (ANOVA) was used, whereas the Kruskal–Wallis test was applied for data that did not follow a normal distribution. A p value of <0.05 was considered statistically significant.

RESULTS

The results for apoptotic mediators, oxidative stress parameters, and renal function tests are summarized in Table 1.

1. Renal Function Indicators

In the AmBD group, serum creatinine and BUN levels showed a significant increase compared to the control group ($p<0.001$). In the Dapagliflozin + AmBD group, these parameters were significantly lower than those in the AmBD group ($p < 0.01$), indicating that dapagliflozin partially prevented AmBD-induced renal dysfunction (Table 2).

2. Markers of Oxidative Stress, Antioxidant Defense, Apoptosis, and Inflammation

There were no statistically significant differences among the four rat groups in plasma levels of oxidative parameters (TOS, MPO, and MDA), antioxidant parameters (GPx, CAT, SOD, and TAS), pro-apoptotic markers (Bax and Casp-3), or the anti-apoptotic marker (Bcl-2) following AmBD administration and its co-administration with Dapagliflozin (Table 2).

3. Histopathological Findings

Renal histopathological evaluation under light microscopy revealed that rats in the AmBD group exhibited markedly more severe renal injury findings, including tubular dilatation ($p<0.001$), tubular vacuolization ($p<0.006$), hyaline cast formation ($p<0.045$), tubular necrosis ($p<0.002$), medullary hemorrhage ($p<0.002$), cortical necrotic areas ($p<0.033$), and tubular desquamation ($p<0.016$), compared with the control, dapagliflozin, and dapagliflozin + AmBD groups. Renal histopathological findings for each group are summarized in Table 2. The results of the kidney histopathological examination are presented in Figures 1-4.

DISCUSSION

Our findings demonstrated that AmBD induced significant histopathological renal damage in the experimental nephrotoxicity model, whereas concomitant administration of dapagliflozin ameliorated these injury findings. Consistent with previous studies (10, 24, 25) suggesting the renoprotective effects of SGLT-2 inhibitors against various nephrotoxic agents, co-treatment with

dapagliflozin also attenuated the AmBD-induced elevation in serum BUN and creatinine levels.

Feldman et al. (2) demonstrated that a single dose of 50 mg/kg ip AmBD was sufficient to induce nephrotoxicity. Similarly, Odabaşı et al. (5) reported that administration of 10 mg/kg ip AmBD for five consecutive days led to marked tubular apoptosis in rats. In our study, a single 50 mg/kg ip AmBD injection resulted in distinct tubular degeneration and interstitial inflammation, accompanied by significant increases in serum creatinine and BUN levels. Co-administration of AmBD with dapagliflozin prevented these increases and attenuated histopathological renal damage, demonstrating a pronounced renoprotective effect of dapagliflozin.

Chang et al. (13) reported that dapagliflozin reduced renal injury in a murine ischemia-reperfusion (IR) model by decreasing serum creatinine and BUN levels. Similarly, Değer et al. (10) demonstrated that dapagliflozin lowered TOS, MDA, and MPO levels while increasing TAS levels in a cyclosporine A-induced renal injury model, indicating enhanced antioxidant defense. These findings support the modulatory effect of dapagliflozin on oxidative stress and its potential renoprotective action through antioxidative mechanisms. In our study, adding dapagliflozin to AmBD treatment did not produce a statistically significant improvement in oxidative or antioxidant parameters compared to AmBD alone, a result that diverges from some literature findings. We propose several potential explanations for this outcome. The primary reason may be the unique pathophysiology of AmBD-induced nephrotoxicity, which is driven by direct tubular damage and vasoconstriction rather than being primarily an oxidative stress-mediated event like in cyclosporine A or ischemia-reperfusion models. Furthermore, our single measurement on day 8 may have missed the earlier, more acute phase of oxidative stress. Consequently, we hypothesize that the renoprotective action of dapagliflozin in this context is likely not through a direct, broad antioxidant effect. Instead, its benefits are more probably linked to alternative mechanisms, such as hemodynamic improvements (e.g., enhanced tubuloglomerular feedback, reduced glomerular pressure) or direct metabolic advantages for tubular cells. This highlights that the protective mechanisms of SGLT2 inhibitors are context-dependent and vary based on the specific type of renal injury. Future research is needed to clarify the precise role of dapagliflozin on oxidative pathways in this particular model.

Table 1. Renal function tests, oxidative stress markers, and apoptosis markers in experimental groups.

Parameters	Control	DAPA	AmBD	AmBD+DAPA	*p*
BUN	31.9±2.71[a]	40.8±16.7[a]	92.3±30.45[b]	37.28±5.36[a]	<0.001
Creatinine	0.75±0.03[a]	0.78±0.39[a]	1.89±0.22[b]	0.87±0.04[a]	<0.001
MDA	7.87±0.87	8.90±1.30	8.40±0.94	7.88±0.66	0.942
TOS	8.08±1.6 [a]	9.3±2.3 [a]	9.6±2.8 [a]	3.1±0.5[b]	0.050
MPO	57.9±3.4	66.5±3.8	62.3±5.5	62.1±2.8	0.069
GPx	501.3±48	543.4±78.9	609.5±14.3	549.9±56.9	0.081
CAT	40.5±3.9[a]	70.6±6.7[b]	43.2±3.1[a]	64.5±5.4[b]	0.001
SOD	282±18.1[a]	261.6±26.3[a]	325.2±15.4[b]	344.8±15.5[b]	0.016
TAS	1.52±0.05	1.52±0.04	1.49±0.09	1.48±0.10	0.847
BAX	8.81±0.37	8.42±0.33	9.75±0.44	8.86±0.26	0.166
Caspas-3	2.37±0.46	5.08±3.1	2.09±0.64	2.90±0.88	0.658
Bcl-2	6.92±0.35	6.89±0.36	7.50±0.39	7.14±0.39	0.353

Data are expressed as mean ± standard deviation. Different superscript letters (a, b) within the same row indicate a statistically significant difference between groups ($p < 0.05$). DAPA: Dapagliflozin, AmBD: Amphotericin B deoxycholate.

Table 2. A comparison of renal histopathology across the studied rat groups

Parameters	Category	Control	DAPA	AmBD	AmBD+DAPA	*p*
Tubular dilatation	Normal	8 (100)	8(100)	3(37.5)	2(25)	<0.001
	Light	-	-	2(25)	6(75)	
	Moderate	-	-	2(25)	-	
	Severe	-	-	1(12.5)	-	
Tubular vacuolization	Normal	8(100)	6(75)	4(50)	-	<0.006
	Light	-	2(25)	1(12.5)	4(50)	
	Moderate	-	-	2(25)	4(50)	
	Severe	-	-	1(12.5)	-	
Hyaline cast	Normal	1(12.5)	-	-	-	<0.045
	Light	7(87.5)	8(100)	5(62.5)	8(100)	
	Moderate	-	-	3(37.5)	-	
	Severe	-	-	-	-	
Tubular necrosis	Normal	8(100)	7(87.5)	4(50)	1(12.5)	
	Light	-	1(12.5)	-	5(62.5)	<0.002
	Moderate	-	-	3(37.5)	2(25)	
	Severe	-	-	1(12.5	-	
	Normal	8(100)	7(87.5)	5(62.5)	7(87.5)	<0.564
Tubular atrophy	Light		1(12.5)	1(12.5)	1(12.5)	
	Moderate	-	-	1(12.5)	-	
	Severe	-	-	1(12.5)	-	
Interstitial edema	Normal	8(100)	8(100)	5(62.5)	4(50)	<0.054
	Light	-	-	2(25)	4(50)	
	Moderate	-	-	1(12.5)	-	
	Severe	-	-	-	-	
Tubular inflammation	Normal	8 (100)	7 (87.5)	5(62.5)	8(100)	<0.077
	Light	-	1(12.5)	3(37.5)	-	
	Moderate	-	-	-	-	
	Severe	-	-	-	-	
Mononuclear cells in the medulla	Normal	8(100)	7(87.5)	4(50)	5(62.5)	<0.088
	Light	-	1(12.5)	2(25)	3(37.5)	
	Moderate	-	-	2(25)	-	
	Severe	-	-		-	
Medullary hemorrhage	Normal	8 (100)	8 (100)	4(50)	4(50)	<0.002
	Light	-	-	1(12.5)	4(50)	
	Moderate	-	-	3(37.5)	-	
	Severe	-	-	-	-	
Necrotic area in cortex	Normal	8(100)	8 (100)	4(50)	8(100)	<0.033
	Light	-	-	3(37.5)	-	
	Moderate	-	-	1(12.5)	-	
	Severe	-	-	-	-	
Tubular desquamation	Normal	8 (100)	8 (100)	4(50)	3(37.5)	<0.016
	Light	-	-	3(37.5)	5(62.5)	
	Moderate	-	-	1(12.5)	-	
	Severe	-	-	-	-	

Values are presented as n (%). DAPA: Dapagliflozin. AmBD: Amphotericin B deoxycholate

When the association between dapagliflozin and apoptosis was examined, Chang et al. (13) demonstrated in an ischemia-reperfusion (IR) mouse model that dapagliflozin attenuated renal injury and improved kidney function. They reported that dapagliflozin reduced renal Bax expression and tubular damage in the hypoxic proximal tubular cells of IR-injured mice. Moreover, the Bax/Bcl-2 ratio, a well-established indicator of apoptotic signaling, was markedly increased in hypoxic proximal tubular cells and was significantly reduced following dapagliflozin treatment. In contrast to reports suggesting anti-apoptotic benefits, our study found no significant impact of dapagliflozin on the measured apoptotic markers. This discrepancy may be explained by several factors. First, our single-timepoint measurement might have missed the transient peak of apoptotic activity, a process known to be highly dynamic (26). Second, the analytical methods may have lacked the sensitivity to detect subtle changes, particularly in distinguishing between active and inactive forms of proteins like casp-3(27). Finally, the dosage or duration of dapagliflozin treatment may have been insufficient to provoke a measurable apoptotic response in our specific model. Thus, while dapagliflozin may have anti-apoptotic potential in other contexts, our findings suggest its influence is limited under these experimental conditions. Future studies using multiple time points and more sensitive assays are needed to fully clarify its role.

Odabaşı et al. (5) observed tubular cell necrosis, cell loss, accumulation of proteinaceous material within the tubular lumen, cellular degeneration, and inflammatory cell infiltration in renal tissues

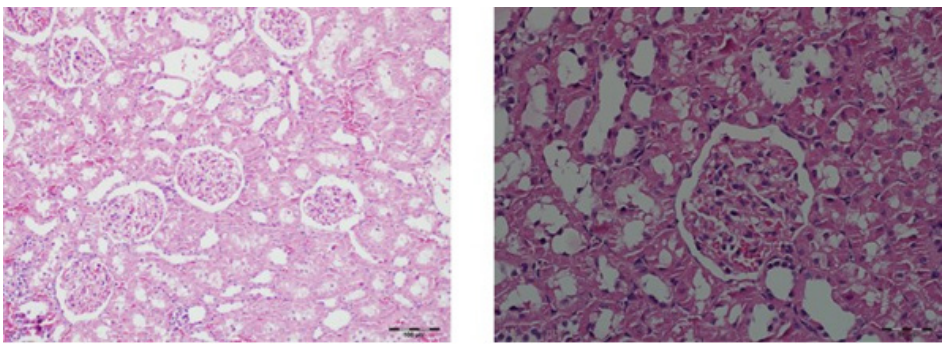

Figure 1. Histological appearance of the kidney tissue from the control group. Glomeruli, proximal, and distal tubules with normal morphology are observed in the cortical and medullary regions (Hematoxylin and Eosin (H&E), ×40).

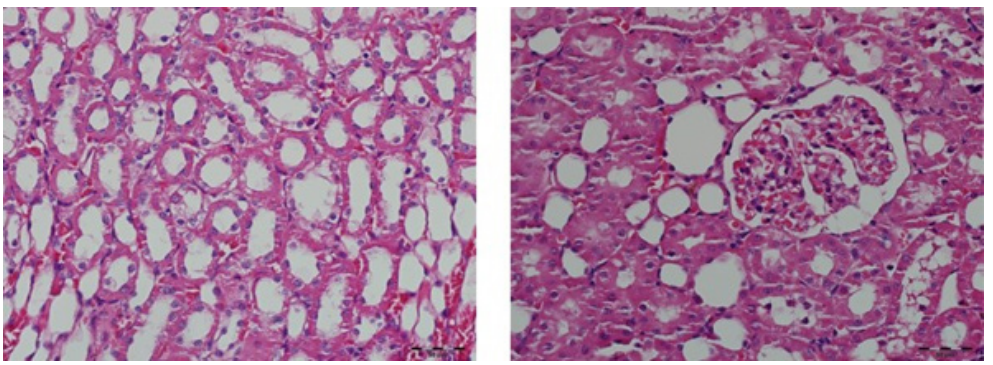

Figure 2. Histology of kidney tissue from the Dapagliflozin-only group. The renal architecture is largely preserved in the cortical and medullary regions, with the exception of mild tubular vacuolization (H&E, ×40).

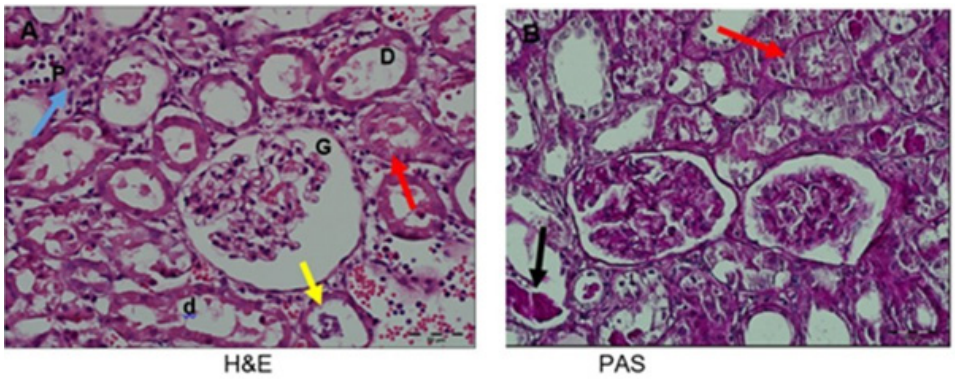

Figure 3. Histopathological findings of severe renal damage observed in the Amphotericin B (AmBD) group.(A) The medullary region displays widespread tubular necrosis (red arrows), tubular dilatation (d), and exfoliation of epithelial cells into the tubular lumen (yellow arrows). Other prominent changes include glomerular damage (G), hyaline material accumulation (black arrows), and dense cellular infiltration (blue arrows) (H&E, ×100). (B) PAS staining shows an irregular reaction in both cortical and medullary regions (PAS, ×100).

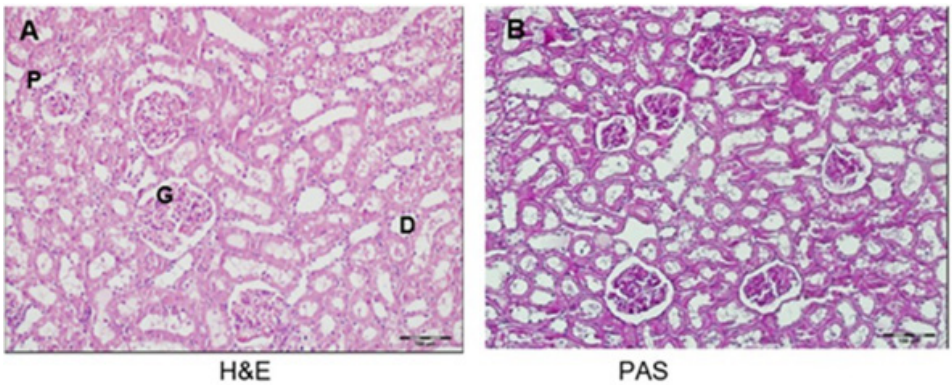

Figure 4. Renal histology of the group co-administered with Dapagliflozin and Amphotericin B (AmBD). (A) A marked attenuation of damage is evident compared to the AmBD group. In the cortical region, glomeruli (G), proximal (P), and distal (D) tubules exhibit a near-normal morphology. While partial tubular necrosis and desquamation persist in the medullary region, the number of dilated tubules is reduced. Mild vacuolization is present in some proximal tubules (H&E, ×40). (B) PAS staining shows a largely regular pattern (PAS, ×40).

of rats treated with AmBD. Similarly, Değer et al. (10) reported that dapagliflozin treatment markedly improved cyclosporine A induced renal histopathological injury. In the study by Chang et al. (13), histological evaluation of IR models demonstrated that dapagliflozin attenuated renal damage characterized by loss of brush border, vacuolization, and desquamation of tubular epithelial cells following IR injury. Consistent with these findings, in our study, renal tissues of rats treated with AmBD showed histopathological alterations such as tubular dilatation, tubular vacuolization, hyaline casts, tubular necrosis, medullary hemorrhage, cortical necrotic areas, and tubular desquamation. The severity of these lesions was significantly higher in the AmBD group compared with the other groups. In contrast, the administration of dapagliflozin with AmBD markedly ameliorated indicators of renal injury, such as tubular dilatation, vacuolization, medullary hemorrhage, and tubular necrosis. These results suggest a protective role for dapagliflozin against AmBD-associated renal injury.

This study has several limitations. First, due to limited data in nephrotoxic rat models, we referenced studies in mice, and species-specific differences in physiology and metabolism warrant caution in interpretation. Second, our study protocol, including the co-administration timing and the

short 8-day duration, may not have captured the optimal therapeutic window for dapagliflozin or its potential long-term effects. Additionally, the absence of blood glucose monitoring is a shortcoming, given that the mechanism of SGLT-2 inhibitors involves glucosuria. Another limitation is that measurements were performed only in serum, which may not fully reflect local renal oxidative stress; different results might have been obtained if tissue-level biomarkers had been assessed. Furthermore, the study did not include urinary biomarkers such as NGAL or KIM-1 in addition to serum markers, which might have provided a more sensitive and earlier indication of kidney injury. Most importantly, these findings are derived from an animal model, and their direct extrapolation to human clinical practice is not warranted.

In conclusion, dapagliflozin was found to attenuate AmBD-induced renal injury. However, further experimental and clinical studies are required to clarify the effects of dapagliflozin on nephrotoxic processes and to determine its potential clinical implications.

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Peer-Review

Double blind both externally and Internally Peer Reviewed

Conflict of Interest

The authors declare that they have no conflict of interest regarding content of this article.

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Ethical Declaration

The study was conducted at the Experimental Practice and Research Center of Çukurova University following approval from the Institutional Ethics Committee (Ethics Approval Date/No: July 20, 2023).

Authorship Contributions

Concept: EA, BK, ST, CA, KEA, GG, TSE BM, Design: EA, BK, ST, CA, KEA, GG, TSE BM, Supervising: EA, BK, ST, CA, KEA, GG, TSE BM, Financing and equipment: EA, BK, ST, CA, KEA, GG, TSE BM, Data collection and entry: EA, BK, ST, CA, KEA, GG, TSE BM, Analysis and interpretation: EA, BK, ST, CA, KEA, GG, TSE BM, Literature search: EA, BK, ST, CA, KEA, GG, TSE BM, Writing: EA, BK, ST, CA, KEA, GG, TSE BM, Critical review: EA, BK, ST, CA, KEA, GG, TSE BM

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