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Protective Effects of 2-Aminoethoxydiphenyl Borate on Cisplatin-Induced Hepatorenal Toxicity in Rats

Sıçanlarda Sisplatin Kaynaklı Hepatorenal Toksisiteye Karşı 2-Aminoetoksidifenil Boratın Koruyucu Etkileri

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Abstract: Cisplatin is a platinum-based chemotherapeutic widely used for solid tumors; however, its clinical utility is limited by dose-dependent hepatotoxicity and nephrotoxicity driven by oxidative stress and disrupted intracellular Ca^{2+} homeostasis. 2-Aminoethoxydiphenyl borate (2-APB), a boron-containing IP_3 receptor antagonist, may exert cytoprotective effects via modulation of calcium signaling. This study investigated the prophylactic potential of 2-APB against cisplatin-induced hepatorenal toxicity in rats using biochemical and histopathological endpoints. Forty male Sprague-Dawley rats were randomized into five groups (n=8). Hepatorenal injury was induced by weekly intraperitoneal cisplatin (3 mg/kg) for five weeks. 2-APB (2, 4, or 8 mg/kg, i.p.) was administered concomitantly. Serum TNF-α and LDH levels, oxidative stress markers (MDA, GSH), and histopathological alterations (H&E scoring; Masson's trichrome for fibrosis) were evaluated. Cisplatin significantly increased TNF-α and LDH levels and caused marked tubular necrosis in the kidney and hepatocellular degeneration. Treatment with 2-APB at 2 and 4 mg/kg significantly attenuated biochemical alterations and improved histopathological injury scores. In contrast, 8 mg/kg provided limited protection. Although cisplatin elevated GSH levels, 2-APB reduced this compensatory increase, suggesting mitigation of oxidative stress–related adaptive responses. Moderate doses of 2-APB (2–4 mg/kg) effectively protect against cisplatin-induced hepatorenal toxicity, whereas loss of efficacy at 8 mg/kg indicates a biphasic dose-response, potentially due to excessive Ca^{2+} signaling disruption. These findings support 2-APB as a dose-dependent adjunctive therapeutic candidate.
Keywords: 2-Aminoethoxydiphenyl borate, cisplatin, hepatotoxicity, nephrotoxicity, oxidative stress.

Özet: Sisplatin, solid tümörlerin tedavisinde yaygın olarak kullanılan platin bazlı bir kemoterapötiktir; ancak klinik kullanımı, oksidatif stres ve hücre içi Ca^{2+} homeostazındaki bozulma ile ilişkili doz bağımlı hepatotoksisite ve nefrotoksisite nedeniyle sınırlanmaktadır. Bor içeren bir IP_3 reseptör antagonisti olan 2-Aminoetoksidifenil borat (2-APB), kalsiyum sinyalizasyonunun modülasyonu yoluyla sitoprotektif etki gösterebilir. Bu çalışmada, 2-APB'nin sisplatin kaynaklı hepatorenal toksisiteye karşı profilaktik etkisi biyokimyasal ve histopatolojik parametreler kullanılarak sıçan modelinde araştırıldı. Kırk erkek Sprague-Dawley sıçan beş gruba randomize edildi (n=8). Hepatorenal hasar, beş hafta boyunca haftalık intraperitoneal sisplatin (3 mg/kg) uygulanarak oluşturuldu. 2-APB (2, 4 veya 8 mg/kg, i.p.) eş zamanlı olarak verildi. Serum TNF-α ve LDH düzeyleri, oksidatif stres belirteçleri (MDA, GSH) ve histopatolojik değişiklikler (H&E yarı kantitatif skorlaması; fibrozis için Masson trikrom boyaması) değerlendirildi. Sisplatin uygulaması TNF-α ve LDH düzeylerini anlamlı şekilde artırdı; böbrekte belirgin tübüler nekroz ve karaciğerde hepatoselüler dejenerasyon oluşturdu. 2-APB'nin 2 ve 4 mg/kg dozları biyokimyasal değişiklikleri anlamlı düzeyde azalttı ve histopatolojik hasar skorlarını iyileştirdi. Buna karşın 8 mg/kg dozunda koruyucu etki sınırlı kaldı. Sisplatin GSH düzeylerini artırırken, 2-APB bu kompansatuvar artışı azaltarak oksidatif stresle ilişkili adaptif yanıtın hafifletildiğini düşündürdü. Sonuç olarak, 2-APB'nin 2–4 mg/kg dozları sisplatin kaynaklı hepatorenal toksisiteye karşı etkilidir; 8 mg/kg'da etkinliğin azalması bifazik doz-yanıt ilişkisine işaret etmektedir. Bulgular, 2-APB'nin doz bağımlı bir adjuvan terapötik aday olabileceğini göstermektedir.
Anahtar Kelimeler: 2-Aminoetoksidifenil borat, sisplatin, hepatotoksisite, nefrotoksisite, oksidatif stres.

Ethics Committee Approval: The study was approved by the Ethics Committee of Eskişehir Osmangazi University HADYEK (decision date:24.07.2018, number:676).

Informed Consent: The authors declared that it was not considered necessary to obtain informed consent from patients because the study was based on retrospective data analysis.

Authorship Contributions: EE: Writing –review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. ÇÇÜ: Methodology, Investigation, Formal analysis, Data curation. NH: Methodology, Investigation, Formal analysis, Data curation KE: Supervision, Methodology, Conceptualization. NSA: Methodology, Investigation. OÖ: Methodology, Investigation,

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1. Introduction

Cisplatin is a platinum-based chemotherapeutic agent widely utilized in the treatment of various solid tumors, including testicular, ovarian, bladder, and lung cancers (1). Its effectiveness stems from its ability to form DNA cross-links, thereby disrupting DNA replication and transcription, which leads to apoptosis in rapidly dividing cancer cells (2). Nevertheless, the clinical application of cisplatin is substantially constrained by its dose-limiting adverse effects, most notably nephrotoxicity and hepatotoxicity (3). Nephrotoxicity is the most prominent and well-documented adverse effect of cisplatin therapy, occurring in approximately 20–30% of patients (4). Cisplatin preferentially accumulates in renal tubular epithelial cells, particularly in the proximal tubules, where it induces acute kidney injury (AKI) through a combination of mechanisms including DNA damage, oxidative stress, inflammation, and apoptosis. This nephrotoxicity is characterized by compromised renal function and disturbances in electrolyte homeostasis (5). While nephrotoxicity is widely recognized, cisplatin-induced hepatotoxicity is less frequently discussed but equally important. The liver, being a central organ in drug metabolism, is vulnerable to cisplatin-induced injury (6). The underlying mechanisms involve oxidative stress, mitochondrial dysfunction, and inflammatory responses, leading to hepatocyte apoptosis and necrosis. Understanding these pathways is crucial for developing strategies to mitigate liver damage in patients undergoing cisplatin chemotherapy (7). Boron-containing compounds have garnered significant attention in biomedical research due to their diverse pharmacological properties, including antioxidant, anti-inflammatory, and cytoprotective effects (8). Recent studies suggest that boron-containing compounds hold promise as potential therapeutic agents for organ toxicities, particularly those affecting the liver and kidney (9-11). 2-Aminoethoxydiphenyl borate (2-APB) is a derivative of boronic acid known chemically for its diphenyl-boron group, which confers unique pharmacological activity (12). It has emerged as a particularly interesting cytoprotective agent, primarily due to its distinct molecular mechanism: the modulation of intracellular calcium signaling. 2-APB is recognized as a specific, competitive antagonist of the inositol trisphosphate (IP_3) receptor, the primary channel responsible for releasing Ca^{2+} from the endoplasmic reticulum (ER) into the cytosol (13). Cisplatin-induced cellular injury is closely linked to ER stress and disrupted Ca^{2+} homeostasis, where excessive and prolonged elevation of cytosolic Ca^{2+} triggers mitochondrial dysfunction and ultimately apoptosis (14). By selectively blocking the IP_3 receptor, 2-APB is able to stabilize intracellular Ca^{2+} levels, thereby mitigating the excessive Ca^{2+} overload that drives cellular pathology (15). Beyond its role in calcium regulation, 2-APB also exhibits antioxidant and anti-inflammatory properties, offering multi-faceted protection against the complex array of mechanisms involved in cisplatin toxicity (16, 17). In various in vitro and in vivo models, 2-APB has demonstrated significant hepatoprotective and nephroprotective efficacy against damage induced by diverse toxins, supporting its broad cytoprotective potential (18-20).

In light of this compelling evidence concerning the central role of calcium dysregulation in cisplatin-induced injury, this study was designed to elucidate the potential protective role of 2-APB against cisplatin-induced hepatorenal toxicity in an experimental rat model. Accordingly, this study was designed to test the hypothesis that 2-APB through its modulation of Ca^{2+} signaling and associated antioxidant effects, will significantly ameliorate the functional, biochemical, and histopathological markers of organ damage.

2. Materials and Methods

2.1. Animals

Forty male Sprague-Dawley rats, approximately 8–10 weeks old (weighing 200–250 g), were utilized in this study. Only male rats were used to eliminate potential confounding variables arising from the female reproductive cycle and the fluctuation of estrogen levels, which can influence both hepatorenal toxicity in experimental models. The animals were housed under standard laboratory conditions, including a temperature-controlled environment and a 12-hour light/dark cycle, with ad libitum access to food and water. Prior to the initiation of experimental procedures, animals were acclimatized for one week. All experimental procedures were approved by the Animal Experiments Local Ethics Committee of Eskişehir Osmangazi University (Approval No: 2018/676) and conducted in accordance with institutional guidelines for the care and use of laboratory animals.

2.2 Drugs and chemicals

2-APB (2-Aminoethoxydiphenyl borate, Sigma-Aldrich, St. Louis, USA), Cisplatin (50 mg/100 mL,

Kocak Farma, Turkey), ketamine (Alfamine 10%, Alfasan International BV Netherlands), and xylazine (Xylazinbio 2%, Bioveta PLC, Czech Republic) were used in the study. 2-APB were dissolved in 5% DMSO and saline and administered via intraperitoneal (i.p.) injection. Biochemical analyses were performed using ELISA kits (YL Biotech Co. Ltd., Shanghai), following the manufacturer's instructions.

2.3. Induction of cisplatin-induced hepato- and nephrotoxicity

Rats received cisplatin (3 mg/kg i.p once a week for 5 weeks) (21).

2.4. Treatment groups

The animals were randomly assigned into five experimental groups (n = 8 per group) as follows:

(i) Control group – received intraperitoneal (i.p.) injections of 5% DMSO and saline once weekly for five consecutive weeks;

(ii) Cisplatin group – administered 3 mg/kg cisplatin (i.p.) once weekly for five weeks to induce hepato- and nephrotoxicity;

(iii) 2APB2 + Cisplatin group – received 2 mg/kg 2-APB (Sigma) and 3 mg/kg cisplatin (i.p.) once weekly for five weeks;

(iv) 2APB4 + Cisplatin group – administered 4 mg/kg 2-APB and 3 mg/kg cisplatin (i.p.) once weekly for five weeks;

(v) 2APB8 + Cisplatin group – received 8 mg/kg 2-APB along with 3 mg/kg cisplatin (i.p.) once weekly for five consecutive weeks.

On each experimental day, cisplatin was administered first via intraperitoneal injection. 2-APB was administered intraperitoneally 30 minutes following cisplatin injection. This regimen was repeated once weekly for five consecutive weeks. This protocol was designed to evaluate the prophylactic and protective capacity of 2-APB against ongoing, chronic cisplatin exposure. The final concentration of DMSO did not exceed 5% and has been previously shown to be non-toxic.

2.5. Histopathological examination

Tissue samples were collected from the left kidney and the median lobe of the liver immediately after animal sacrifice. All animals were sacrificed 24 hours after the final drug administration under ketamine (50 mg/kg) and xylazine (10 mg/kg) anesthesia. Kidney tissues were stained with hematoxylin-eosin, whereas liver tissues underwent staining with both hematoxylin-eosin and Masson's trichrome for histological assessment. Paraffin-embedded tissue sections, 5 μm thick, were prepared using a rotary microtome. For deparaffinization, sections were incubated overnight at 60°C, followed by two 30-minute treatments in fresh xylene. Subsequently, sections were rehydrated through a graded alcohol series descending from 95% to 60%, and rinsed under running water for 5 minutes. Sections were stained with hematoxylin for 3 minutes, then rinsed for 5 minutes to remove excess dye. This was followed by eosin staining for 30 seconds and a further 5-minute rinse. The sections were then dehydrated through ascending alcohol concentrations of 80% and 95%, air-dried, and cleared by immersion in xylene for 30 minutes with two changes of fresh xylene. Finally, the sections were mounted using Entellan. The sections were evaluated semiquantitatively under a light microscope (Olympus BX50) (22). Kidney injury score was assessed based on tubular necrosis, tubular vacuolar changes, hemorrhage, and tubular dilation, considering both severity and extent. Each section was scored on a scale of 0-4: (0: no damage, 1: minimal damage (≤5%), 2: moderate damage (5-25%), 3: extensive damage (25-75%), 4: severe damage (≥75)) (23).

2.6. Biochemical Assays

2.6.1. Measurement of TNF-α, MDA, GSH, and LDH levels

Blood samples were collected via cardiac puncture immediately after sacrifice, 24 hours following the final drug administration. Samples were centrifuged at 3000 rpm for 10 minutes at 4°C to obtain serum, which was stored at −80°C until biochemical analysis. TNF-α (tumor necrosis-alpha), MDA (malondialdehyde), GSH (glutathione), and LDH (lactate dehydrogenase) levels in blood samples measured by appropriate ELISA kits. Absorbance was measured based on the colorimetric method at 450 nm using a microplate reader (BioTek ELX800).

2.7. Statistical Analysis

All statistical evaluations were conducted using SPSS software (version 22.0; IBM Corp., Armonk, NY, USA). The normal distribution of the data was tested using the Shapiro–Wilk test. One-way ANOVA followed by Tukey’s multiple comparison test was employed to analyze the biochemical data that conformed to a normal distribution. For variables that did not conform to a normal

distribution, such as the kidney injury scores and other semi-quantitative histopathological scores, the Kruskal–Wallis test was applied. Results are expressed as mean± standard error of the mean (SEM), and statistical significance was set at $p < 0.05$.

3. Results

3.1. Effect of 2-APB on TNF-α, MDA, GSH, and LDH levels in cisplatin-treated animals

TNF-α level was examined, a significant increase was found in the cisplatin group compared to the control group ($p<0.001$, Figure 1) and 2-APB (2 and 4 mg/kg) administered with cisplatin decreased TNF-α level significantly ($p<0.01$, Figure 1). No statistically significant differences in MDA levels were observed among the groups (Figure 2). The cisplatin treatment caused a significant increase ($p<0.01$, Figure 3) in GSH level and 2-APB (2 and 4 mg/kg) administered with cisplatin decreased GSH level significantly ($p<0.01$, Figure 3). While a significant elevation of LDH levels ($p<0.05$) was observed in the cisplatin group compared to the control group, 2-APB (2 and 4 mg/kg) administered with cisplatin reduced LDH levels significantly in comparison with the cisplatin group ($p<0.05$, Figure 4).

3.2. Effect of 2-APB on cisplatin-induced hepatotoxicity in liver tissues

In the control group, normal morphological structure was observed. In the cisplatin group, there was disruption of the hepatocyte cord structure, vacuolization and pyknosis in hepatocytes, increased sinusoidal dilation, as well as hemorrhage and edema in the sinusoidal areas and central vein. In the 2-APB (4 mg/kg) administered with cisplatin group, a significant reduction in sinusoidal hemorrhage was observed compared to the cisplatin group group. Similar findings were observed in all other treatment groups at levels comparable to those in the cisplatin group (Figure 5 and Figure 6).

3.3. Effect of 2-APB on cisplatin-induced nephrotoxicity in kidney tissues

Histological evaluation of the kidneys revealed that the control group exhibited normal morphological structure. In the cisplatin group, focal vacuolization and hemorrhage were observed in the tubular epithelial cells. In the 2-APB (4 and 8 mg/kg) administered with cisplatin groups, widespread hemorrhage, vacuolization of tubular epithelial cells, luminal shedding, tubular necrosis, and inflammatory cell infiltration were observed at similar levels. However, in the 2-APB (4 mg/kg) administered with cisplatin group, relatively less hemorrhage and vacuolization were detected compared to the other groups (Figure 7). According to the kidney damage scoring, severe damage was observed in the cisplatin group, while damage was present in other groups as well, but particularly in the APB (4 and 8 mg/kg) administered with cisplatin groups the damage was less compared to the cisplatin group (Figure 8).

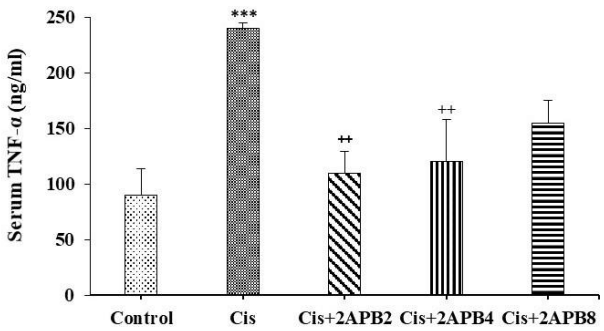

Figure 1. Effect of 2-APB (2, 4, and 8 mg/kg) on TNF-α levels (***P < 0.001 vs. Control; $^{++}$P < 0.01 vs. Cis). All data represent the mean ± SEM. (Cis, Cisplatin; 2APB, 2-APB). One-way ANOVA *post hoc* Tukey's test. n= 8 rats per group.

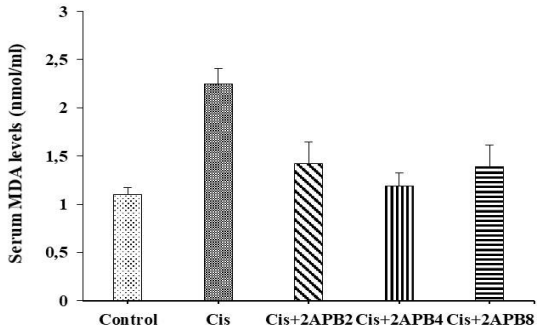

Figure 2. Effect of 2-APB (2, 4, and 8 mg/kg) on MDA levels. All data represent the mean ± SEM. (Cis, Cisplatin; 2APB, 2-APB). One-way ANOVA *post hoc* Tukey's test. n= 8 rats per group.

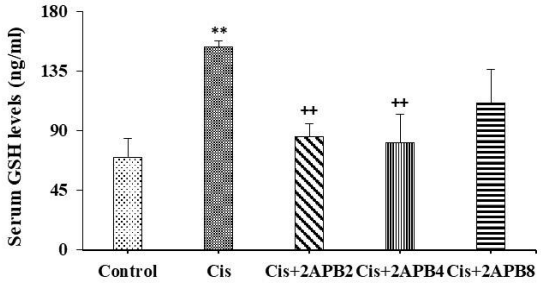

Figure 3. Effect of 2-APB (2, 4, and 8 mg/kg) on GSH levels (**P < 0.01 vs. Control; $^{++}$P < 0.01 vs. Cis). All data represent the mean ± SEM. (Cis, Cisplatin; 2APB, 2-APB). One-way ANOVA *post hoc* Tukey's test. n= 8 rats per group.

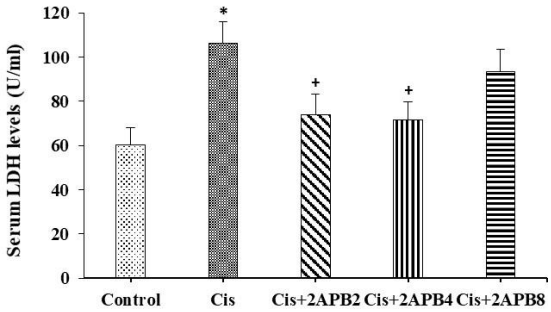

Figure 4. Effect of 2-APB (2, 4, and 8 mg/kg) on LDH levels (*P < 0.05 vs. Control; $^{+}$P < 0.05 vs. Cis). All data represent the mean ± SEM. (Cis, Cisplatin; 2APB, 2-APB). One-way ANOVA *post hoc* Tukey's test. n= 8 rats per group.

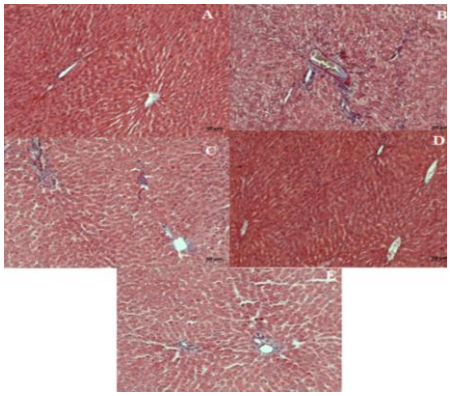

Figure 5. Effect of 2-APB (2, 4, and 8 mg/kg) on cisplatin-induced hepatotoxicity in liver tissues sections stained with Mason trichrome. (A) Control group, (B) Cisplatin group, (C) 2-APB (2 mg/kg) group, (D) 2-APB (4 mg/kg) group, (E) 2-APB (8 mg/kg) group. The scale represents 50 µm.

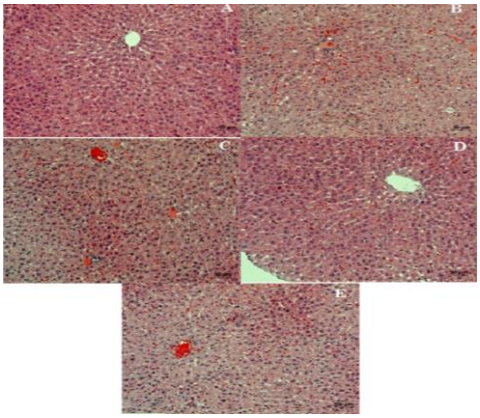

Figure 6. Effect of 2-APB (2, 4, and 8 mg/kg) on cisplatin-induced hepatotoxicity in liver tissues sections stained with hematoxylin-eosin. (A) Control group, (B) Cisplatin group, (C) 2-APB (2 mg/kg) group, (D) 2-APB (4 mg/kg) group, (E) 2-APB (8 mg/kg) group. The scale represents 50 µm.

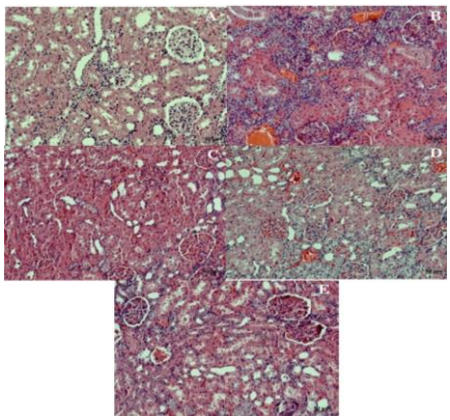

Figure 7. Effect of 2-APB (2, 4, and 8 mg/kg) on cisplatin-induced nephrotoxicity in kidney tissues sections stained with hematoxylin-eosin. (A) Control group, (B) Cisplatin group, (C) 2-APB (2 mg/kg) group, (D) 2-APB (4 mg/kg) group, (E) 2-APB (8 mg/kg) group. The scale represents 50 µm.

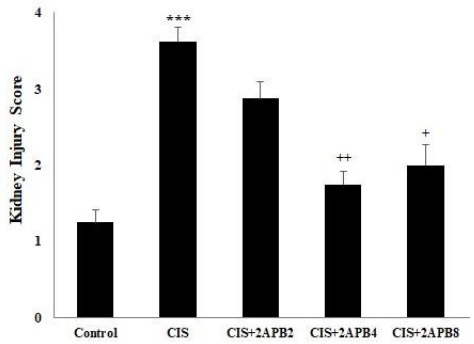

Figure 8. Effect of 2-APB (2, 4, and 8 mg/kg) on kidney injury (***P < 0.001 vs. Control; $^{+}$P < 0.05, $^{++}$P < 0.01 vs. Cis). All data represent the mean ± SEM. (Cis, Cisplatin; 2APB, 2-APB). Kruskal-Wallis test. n= 8 rats per group.

4. Discussion

The present study investigated the potential protective effects of 2-APB against cisplatin-induced toxicity, particularly focusing on oxidative stress markers, hepatotoxicity, and nephrotoxicity in experimental models. Our results demonstrate that 2-APB exerts significant modulatory effects on inflammatory and oxidative stress markers, as well as histopathological changes in liver and kidney tissues.

Cisplatin is known to induce systemic inflammation and oxidative stress, contributing to organ toxicity (24). Our findings align with previous studies, showing a significant increase in TNF-α levels in the cisplatin-treated group compared to controls, which is indicative of an enhanced inflammatory response. The administration of 2-APB at both 2 mg/kg and 4 mg/kg significantly attenuated TNF-α levels, suggesting that 2-APB may mitigate inflammation through its modulatory effects on cytokine release (25).

Interestingly, while previous studies have reported elevated MDA levels following cisplatin treatment due to increased lipid peroxidation (26), no significant changes in MDA levels were observed across treatment groups in our study. This discrepancy might be attributed to variations in experimental conditions, dosing, or species-specific responses. However, we found a significant increase in GSH levels in the cisplatin group, possibly as a compensatory mechanism against oxidative stress, which was subsequently reduced with 2-APB administration. These results suggest that 2-APB may modulate redox homeostasis, preventing excessive GSH accumulation that could indicate cellular distress (27). Additionally, the observed increase in LDH levels in the cisplatin-treated group, indicative of cellular injury, was significantly reduced with 2-APB treatment, further supporting its cytoprotective role (28) A notable observation in our study was the redox marker profile: while MDA levels remained unchanged, GSH levels significantly increased in the cisplatin group. This finding is complex, as MDA is a key indicator of lipid peroxidation, and its lack of change contrasts with many acute cisplatin models (29). This discrepancy might stem from the chronic, low-dose regimen (five weeks) used, allowing for adaptive mechanisms rather than a severe acute peroxidation burst. More importantly, the significant elevation of GSH in the cisplatin-only group strongly suggests a robust compensatory up-regulation of GSH synthesis (GSH synthetase) indicating that the cells are under severe oxidative pressure but are effectively mounting a defense, temporarily masking the expected GSH depletion typical of early-stage toxicity (30). This compensatory rise in GSH was significantly attenuated by 2-APB administration, suggesting that 2-APB successfully reduced the underlying oxidative stress trigger, thereby negating the need for excessive GSH overproduction. The precise timing of sample collection (at the end of five weeks) may capture this adaptive phase, unlike studies focusing on acute toxicity (31).

Cisplatin-induced hepatotoxicity is characterized by histopathological alterations, including vacuolization, pyknosis, sinusoidal dilation, and hemorrhage (32). Our histological findings corroborate these known effects, as the cisplatin group exhibited severe hepatocyte damage. However, the administration of 2-APB, particularly at 4 mg/kg, significantly reduced sinusoidal hemorrhage and structural disorganization, indicating a protective effect on hepatic tissue. These results align with previous reports suggesting that 2-APB may exert hepatoprotective effects by modulating calcium signaling and reducing oxidative damage. The exact mechanism remains to be elucidated, but it is plausible that 2-APB exerts its protective effect by inhibiting calcium overload-induced cell damage, which is a known contributor to cisplatin hepatotoxicity (33).

Nephrotoxicity is a major dose-limiting side effect of cisplatin, often leading to acute kidney injury due to oxidative stress, apoptosis, and inflammation (34). In our study, cisplatin administration resulted in significant renal damage, characterized by hemorrhage, vacuolization, tubular necrosis, and inflammatory cell infiltration. Notably, treatment with 2-APB at 4 mg/kg and 8 mg/kg mitigated these pathological alterations, albeit damage was still present in treated groups. The relatively lower extent of hemorrhage and vacuolization observed in the 4 mg/kg 2-APB group suggests a dose-dependent renoprotective effect. Importantly, although the repeated low-dose cisplatin regimen is frequently used in chronic toxicity and neuropathy models, our findings clearly demonstrate that this administration protocol also results in significant biochemical and histopathological hepatorenal injury.

A crucial, yet unexpected, finding was the failure of the highest dose of 2-APB (8 mg/kg) to provide protection, which was clearly observed with 2 mg/kg and 4 mg/kg doses in both biochemical and histopathological analyses. This phenomenon is characteristic of a biphasic or hormetic dose-response, where a compound is beneficial at low/moderate concentrations but loses efficacy or becomes detrimental at higher concentrations. The primary mechanism of 2-APB is the antagonism of the IP_3 receptor and the resultant stabilization of intracellular Ca^{2+} levels[33]. While moderate inhibition prevents the cytotoxic Ca^{2+} overload induced by cisplatin, excessive IP_3 receptor blockade at 8 mg/kg may profoundly disrupt the fundamental Ca^{2+} signaling necessary for normal cellular function and adaptation to stress, potentially leading to a mild pro-toxic or pro-apoptotic effect. Furthermore, high concentrations of 2-APB may engage secondary molecular targets beyond IP3 receptors, such as the inhibition of store-operated Ca^{2+} (SOCE) or non-specific membrane effects (35), which could contribute to a negative shift in the benefit profile at suprapharmacological doses. This observation underscores the necessity of precise dose optimization for 2-APB in translational applications.

The established clinical strategy for mitigating cisplatin-induced nephrotoxicity relies heavily on hyperhydration and the use of the thiol compound Amifostine (36). However, Amifostine presents several practical drawbacks: it requires intravenous administration, carries a high cost, and is associated with significant side effects like hypotension and nausea (37). Our finding that the boron-containing compound, 2-APB, provides robust hepatorenal protection at optimal doses is thus highly relevant. As a small, potentially orally available molecule, 2-APB offers significant advantages in ease of application and patient compliance compared to Amifostine. Mechanistically, 2-APB offers a novel approach by modulating the critical Ca^{2+} signaling pathway, which contrasts with the broad free-radical scavenging mechanism of Amifostine. While further toxicological and preclinical studies are required to confirm its safety and efficacy, 2-APB represents a promising candidate for an adjunctive oral therapeutic agent to enhance the therapeutic index of cisplatin chemotherapy.

5. Conclusion

Taken together, the findings of this study underscore the potential protective role of 2-APB in mitigating cisplatin-induced toxicity in rats, particularly through the reduction of inflammatory responses, oxidative stress, and histopathological alterations in hepatic and renal tissues. The observed decreases in TNF-α, LDH, and GSH levels, alongside notable histological improvements, support the potential utility of 2-APB as an adjunctive therapeutic agent to counteract cisplatin-associated organ damage. Further mechanistic and dose-optimization studies are warranted before clinical translation.

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