

Comparison of the Protective Effect of Dapagliflozin and Empagliflozin on Cisplatin-Induced Ovarian Toxicity in Female Rats

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ABSTRACT

Background: Cisplatin (CDDP) is an effective chemotherapeutic agent whose gonadotoxicity can lead to premature ovarian insufficiency through oxidative stress, inflammation, and apoptosis. Sodium-glucose cotransporter-2 (SGLT2) inhibitors exhibit cytoprotective effects, but their ovarian effects during chemotherapy remain poorly defined. **Methods:** Twenty-four female Wistar rats were randomized (n = 6/group) to Control (vehicle), Cisplatin (7 mg/kg, i.p., day 14), Cisplatin + dapagliflozin (DAPA; 0.9 mg/kg/day, p.o., days 1–14), or Cisplatin + empagliflozin (EMPA; 10 mg/kg/day, p.o., days 1–14). At 24 h post-cisplatin, serum estradiol (E2), progesterone, follicle-stimulating hormone (FSH), and Anti-Müllerian Hormone (AMH) were measured (ELISA). Ovarian glutathione (GSH) and malondialdehyde (MDA) were assayed, TNF- α and IL-6 mRNA were quantified by qRT-PCR, caspase-3 protein by Western blot, and histopathology by H&E. **Results:** Cisplatin decreased GSH, E2, AMH and progesterone and increased MDA, FSH, TNF- α , IL-6, and caspase-3, with marked histological injury. Both SGLT2 inhibitors improved biochemical, molecular, hormonal, and histological indices versus Cisplatin. DAPA partially restored antioxidant status and reduced inflammatory/apoptotic markers. EMPA produced greater normalization: GSH and MDA approached control values; progesterone returned to control; FSH fell more than with DAPA; E2 and AMH increased versus Cisplatin but remained below Control in both treatment groups; TNF- α declined more with EMPA, whereas IL-6 reductions were comparable; caspase-3 decreased to near-control with EMPA and decreased but remained elevated with DAPA ($p < 0.05$ for stated comparisons; one-way ANOVA with Tukey). **Conclusion:** Prophylactic SGLT2 inhibition mitigates cisplatin-induced ovarian toxicity, with empagliflozin showing broader and deeper improvements than dapagliflozin. These findings support SGLT2 inhibitors as candidate adjuncts to preserve ovarian function during cisplatin therapy and justify studies of dose-response, timing, fertility outcomes, mechanistic pathways, and antitumor safety.

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1. Introduction

Cancer is the second-most common cause of death amongst workers in developed countries after cardiovascular diseases. Over nine million new cancer cases were reported every year at the WHO, and 9.6 million people died from cancer in 2018 (AL-MASHHADANI et al., 2019). Cisplatin is an inorganic platinum-based antineoplastic drug derived from carpenteridine (cis-diamminedichloroplatinum II; CDDP) (Alkhazragy & Alshawi, 2023), with broad-spectrum antineoplastic activity against numerous animal and human tumors (Al-Majed et al., 2006). It continues to be one of the most potent cytotoxic agent's for testicular-Hodgkin lymphoma, head and neck cancer, ovarian, testicular, and lung tumors. First identified by the FDA as antiproliferative in the 1960s, cisplatin quickly became a standard treatment for germ-cell tumors and in 1978 was the first platinum-based compound to be approved for cancer treatment by the FDA (Kelland, 2007). Cisplatin's anticancer effects are mediated by several mechanisms, including: DNA damage, activation of apoptosis, and cell damage from oxidative stress and inflammation. The clinical usefulness, however, is limited by dose-related toxicities—including nephrotoxicity, hepatotoxicity, and cardiotoxicity—primarily due to oxidative stress and the reduction of natural antioxidant defenses like reduced glutathione and important antioxidant enzymes (Dasari & Tchounwou, 2014; Kart et al., 2010).

The implication for female reproductive function is the most significant of off-target toxicities. Cisplatin may also lead to POI, an age-related disorder characterized by the loss of ovarian function after 40, with increased gonadotropin levels,

especially FSH, and lower levels of estradiol E2. This leads to infertility and infertility (Van Dorp et al., 2018). Cisplatin affects ovarian reserve by causing death or rapid activation of primordial follicles, raising atresia rates of developing follicles, inducing vascular and stromal damage, and increasing inflammatory signaling in the ovarian microenvironment (Spears et al., 2019). This is increasing in the cases of POI due to chemotherapy among young adults and adolescents who have been diagnosed with cancer, and who crave a fecund fertility status (Gupta et al., 2020; Ugai et al., 2022). The traditional methods of egg induction, hormone therapy, oocyte/embryo cryopreservation, and in vitro fertilization require functioning ovaries and healthy oocytes first, but cytotoxic therapies could prevent either, reducing the efficacy and usefulness of these methods as well as burdening them financially and emotionally (Carson & Kallen, 2021; De Vos et al., 2010; Dyer & Patel, 2012). The presence of granulosa cells in the pre-/small antral follicles represents an indicator for ovarian reserve; chemotherapy, particularly cisplatin, consistently declines AMH levels and depletes AMH positive follicles, and therefore AMH is a reliable predictor of ovariantoxicity and late ovarian insufficiency (Brougham et al., 2012; Moolhuijsen & Visser, 2020). Thus, adjunctive interventions that prevent or mitigate gonadotoxicity and preserve reproductive potential and quality of life are urgently needed (Feng et al., 2024).

Other SGLT2-inhibitors, such as empagliflozin (EMPA) and dapagliflozin (DAPA), are antihyperglycemic drugs that block the SGLT2 pathway in the renal tubule and decrease glucose reabsorption (Padda et al., 2022). Originally approved for type 2 diabetes, they also reduce cardiovascular events in high-risk patients (Heerspink et al., 2016). Beyond glycemic control, SGLT2 inhibitors exhibit pleiotropic cytoprotective actions: attenuation of high-glucose-induced oxidative stress by limiting free-radical generation (Steven et al., 2017), suppression of pro-oxidant enzymes such as NOX4 (Terami et al., 2014), and upregulation of endogenous antioxidant systems including superoxide dismutases and glutathione peroxidases (Oshima et al., 2019; Osorio et al., 2012; Yaribeygi et al., 2019). They further exert anti-inflammatory effects, downregulating pro-inflammatory cytokines such as TNF- α and interleukin-6 and modulating associated signaling pathways (Han et al., 2017; Ojima et al., 2015; Tahara et al., 2014; Vallon et al., 2013). These properties have been validated across preclinical and clinical settings, where SGLT2 inhibition reduces oxidative stress and myocardial fibrosis (Li et al., 2019), improves renal outcomes in diabetic kidney disease via reduced reactive oxygen species production (Winiarska et al., 2021), and confers anti-apoptotic and anti-inflammatory benefits in diverse injury models (Faridvand et al., 2022). Empagliflozin has demonstrated cardio protection in both diabetic and non-diabetic populations, including mitigation of chemotherapy-related cardiotoxicity such as doxorubicin-induced injury (Guo & Javaheri, 2025; Koyani et al., 2020; Li et al., 2019; Verma et al., 2018). Systemic protective effects extend to models of inflammation, where DAPA lowers oxidative stress and apoptosis (Savran et al., 2025) and shields proximal tubular cells by reducing cytosolic and mitochondrial ROS (Zaibi et al., 2021).

In summary, this data suggest that SGLT2 inhibitors may mitigate ovarian injury induced by cisplatin by exploiting their antioxidant, anti-inflammatory, and anti-apoptotic effects. This study examined the protective effects of low-dose DAPA and EMPA on the ovary against acute ovarian injury induced by cisplatin in Wistar rats. We argued that they would decrease oxidative stress, lower inflammation, and prevent apoptosis while lowering ovarian histology and reproductive hormone levels.

2. Materials and Methods

2.1 Animals and Ethics

Adult female Wistar rats ($n = 24$; 160–200 g) were procured from the Animal House, College of Pharmacy, University of Baghdad. Animals were acclimatized for 2 weeks under standard conditions (20 ± 5 °C; 12/12 h light/dark cycle) with ad libitum access to commercial chow and water. All procedures were approved by the Animal Research Local Ethics Committee of the College of Pharmacy, University of Baghdad.

2.2 Experimental Design and Treatments

Rats were randomly allocated ($n = 6$ /group) to four groups: a Control group receiving vehicle (2% DMSO, 1 mL/kg/day, p.o.) for 14 days; a Cisplatin (Induction) group receiving the same vehicle regimen with a single cisplatin injection (7 mg/kg, i.p.) on day 14 (Caglayan et al., 2018); a Dapagliflozin (DAPA) group receiving dapagliflozin (0.9 mg/kg/day, p.o.) (Paget & Barnes, 1964) for 14 days with cisplatin (7 mg/kg, i.p.) on day 14; and an Empagliflozin (EMPA) group receiving empagliflozin (10 mg/kg/day, p.o.) (Farrokh-Eslamlou et al., 2024) for 14 days with cisplatin (7 mg/kg, i.p.) on day 14. Where applicable, vehicle volume was matched across groups, and animals were selected to be at the same estrous-cycle phase at randomization.

2.3 Estrous Staging

The estrous phase was determined by vaginal cytology using standard saline lavage and light microscopy; only rats

in the same phase were enrolled/randomized.

2.4 Dose Rationale and Vehicle

2.4.1 Dapagliflozin Dose

The therapeutic dose of dapagliflozin for type 2 diabetes is 10 mg daily. Using the Paget and Barnes body surface area conversion, this corresponds to an approximate rat equivalent dose of 0.9 mg/kg/day, which was adopted in the present study (Paget & Barnes, 1964).

2.4.2 Empagliflozin Dose

In a cisplatin-induced nephrotoxicity model in Wistar rats, empagliflozin administered at 10 mg/kg/day (and 30 mg/kg/day) for 7 days significantly attenuated oxidative stress, inflammation, and histological injury. To minimize drug load while retaining efficacy, we adopted the 10 mg/kg/day regimen for the present study (Farrokh-Eslamlou et al., 2024).

2.4.3 Cisplatin Dose

In humans, cisplatin is administered intravenously or intra-arterially at 20–100 mg/m² in 21–28-day cycles, depending on malignancy type (Ibrahim et al., 2021). For this experiment, a single 7 mg/kg i.p. dose was selected specifically to induce ovarian/uterine toxicity in rats, consistent with the protocol of Caglayan et al. (2018).

2.4.4 Vehicle (DMSO) Justification

A 2% DMSO vehicle was used to dissolve SGLT2 inhibitors and was volume-matched in control groups. Prior rodent studies administering empagliflozin or dapagliflozin with DMSO reported no vehicle-related adverse effects, supporting its use at this concentration (Chen et al., 2023; Herat et al., 2020).

2.5 Sample Collection and Tissue Processing

Twenty-four hours after the final treatment (day 15), animals were euthanized by diethyl ether inhalation followed by cervical dislocation. Blood was obtained from the carotid artery into plain tubes, allowed to clot, and centrifuged; serum was used to quantify FSH, estradiol (E2), and progesterone by ELISA.

Both ovaries were excised, rinsed in cold PBS (pH 7.4), and processed as follows: one portion was reserved for oxidative stress assays (malondialdehyde [MDA], reduced glutathione [GSH]) by ELISA; a second portion was preserved for qRT-PCR analysis of IL-6 and TNF- α ; a third portion was prepared for Western blotting of caspase-3; and a fourth portion was fixed in 10% neutral buffered formalin for histopathology (H&E). Samples were stored at -20°C until analysis.

2.6 Chemicals and Supplies

Cisplatin (1 mg/mL) was obtained from Accord Healthcare Ltd., UK. Dapagliflozin was purchased from MACKLIN, China, and empagliflozin was obtained from the same supplier. Dimethyl sulfoxide (DMSO; 100%) was purchased from HiMedia, India. ELISA kits for progesterone, estradiol (E2), FSH, malondialdehyde (MDA), and glutathione (GSH) were obtained from Elabscience (Houston, TX, USA). The TransZol Up Plus RNA kit was purchased from TransGen Biotech (Beijing, China), and the EasyScript First-Strand cDNA Synthesis SuperMix was obtained from the same manufacturer. GoTaq qPCR Master Mix was purchased from Promega (Madison, WI, USA). Primers for TNF- α and IL-6 were obtained from Macrogen (Seoul, Korea). A chemiluminescent Western blot detection kit, SDS-PAGE gel kit, and anti-caspase-3 polyclonal antibody were purchased from Elabscience (Houston, TX, USA).

2.7 Hormone Assays

Serum levels of Anti-Mullerian Hormone (AMH), follicle-stimulating hormone (FSH), estradiol (E2), and progesterone were measured by ELISA using commercial kits according to the manufacturer's guidelines. FSH, E2, and Progesterone kits were acquired from (Elabscience, Houston, TX, USA), whereas the AMH kit was supplied by (ELK Biotechnology, Wuhan, China). Absorbance was recorded using a microplate reader (Micro Digital, Seoul, South Korea), and concentrations were calculated based on specific standard curves for each analyte.

2.8 Oxidative Stress Biomarkers

Ovarian tissues were homogenized in chilled PBS (pH 7.4) and centrifuged; supernatants were assessed for malondialdehyde (MDA) and reduced glutathione (GSH) using ELISA (Elabscience, Houston, TX, USA) following the manufacturer's instructions.

2.9 Quantitative Real-Time PCR

Approximately 50 mg of ovarian tissue from each rat was used for RNA extraction with TransZol Up Plus (TransGen Biotech, Beijing, China). The purity and concentration of RNA were evaluated using a microvolume spectrophotometer (MicroDigital, Seoul, South Korea). One to two micrograms of RNA were converted to cDNA utilizing the EasyScript First-Strand cDNA Synthesis SuperMix (TransGen Biotech, Beijing, China). qPCR was conducted with GoTaq qPCR Master Mix (Promega, Madison, WI, USA) on a CFX Opus 96 system (Bio-Rad, version 2.1). IL-6 and TNF- α were measured using gene-specific primers (Table 1), with GAPDH serving as the reference gene. Reactions were conducted in triplicate, and relative expression was determined using the $2^{-\Delta\Delta C_t}$ method with the Control group serving as the calibrator (Atshan & Zalzala, 2024b).

2.10 Western Blot Analysis

Proteins were extracted from ovarian tissue, and RIPA lysis buffer of PMSF, and sodium orthovanadate (Na₃VO₄) were added to the 0.3 g ovary:1 ml RIPA lysis buffer of 10 L of PMSF and 10 L of Na₃VO. The protein concentration was determined using a BCA Protein Assay Kit from Labscience, USA. Next, 10 L of protein samples were loaded per lane, separated by SDS-PAGE, and transferred to PVDF membranes (Rattanakorn & Putri, 2026).

The membranes were fixed at room temperature for 1 hour in 5% fat-free milk to inhibit their growth, then overnight at 4°C with antibodies against beta-actin and Caspase-3. Next, membranes were exposed to 1 hour at room temperature, with horseradish peroxidase conjugated secondary antibodies (Elabscience, 1:1000). Ultimately, ECL detection reagents from Labscience USA were utilized to detect signals of protein expression and images via the ChemiDoc MP Imaging System from Bio-Rad Laboratories, USA (Atshan & Zalzala, 2024a).

2.11 Histopathological Evaluations

Ovarian tissues were stored in 10% formaldehyde in a 10 mM phosphate buffer (pH 7.4) before histological analysis. Tissue slices were micrographed in 5-m H&E on glass slides. A microscope was used to examine irregular slices.

2.12 Statistical Analysis

Data are presented as mean $\pm$ SEM (n = 6/group). Group differences were assessed by one-way ANOVA with Tukey's post-hoc test (two-tailed, α = 0.05). qPCR analyses were performed on ΔC_t values; fold changes are shown as $2^{-\Delta\Delta C_t}$ relative to Control. Exact *p* values are reported where possible. Analyses were conducted in SPSS Statistics 28.0 (IBM, Chicago, IL, USA). Data were organized (and figures prepared) in Microsoft Excel 365. (Microsoft Corporation, Redmond, WA, USA).

Supplementary Table S1: qRT-PCR Primer Sequences (5'→3') and Amplicon Sizes for Rat TNF- α , IL-6, and GAPDH.

Primer	Sequence	Primer Sequence 5' - 3'	T _m (°C)	GC%
TNF- α	F	TTAAGTGTGTGCCCTGAGGT	60.7	48
	R	CCAAGAGCAGCCCAACAAATC	61.7	52
IL-6	F	GCCACTGCCTTCCTACTTC	63.7	60
	R	TCTGACAGTGCATCATCGCT	60	50
GAPDH (Reference Gene)	F	TGTGAACGGATTTGGCCGTA	61.6	50
	R	TCCCGTTGATGACCAGCTTC	62.9	55

3. Results

3.1 Oxidative Stress Markers

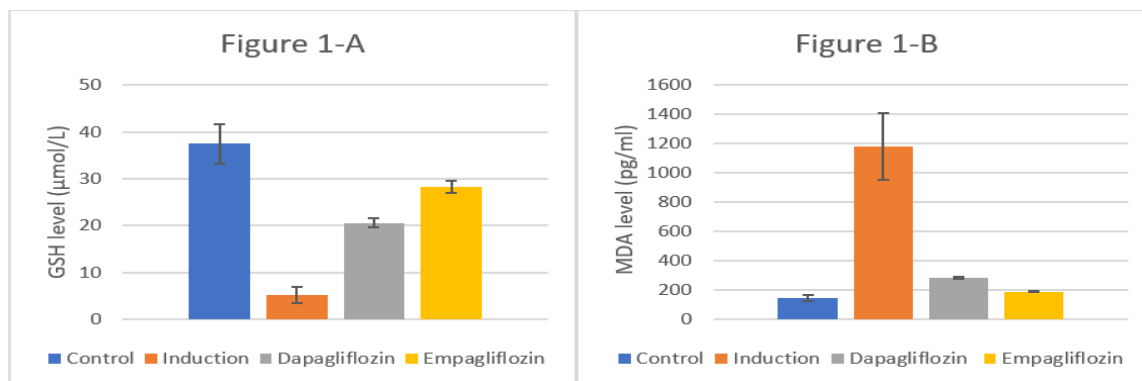
Relative to Control, the Cisplatin group showed decreased GSH and increased MDA (both *p* < 0.05). Dapagliflozin (DAPA) increased GSH vs Cisplatin (*p* < 0.05) but remained lower than Control (*p* < 0.05), and reduced MDA vs Cisplatin (*p* < 0.05) but remained higher than Control (*p* < 0.05).

Empagliflozin (EMPA) restored GSH to levels not significantly different from Control (*p* > 0.05) and reduced MDA to levels not significantly different from Control (*p* > 0.05); both outcomes were significant vs Cisplatin and vs DAPA (*p* < 0.05). See Fig. 1A–B and Table 1.

Table 1: The Effect of Dapagliflozin and Empagliflozin on Ovarian Oxidative Stress Parameters (GSH, MDA) in Cisplatin-Treated Rats

Parameter	Control Group	Induction Group	Dapagliflozin-treated Group	Empagliflozin-Treated Group
GSH level	37.505 ± 4.18	5.289 ± 1.706 *	20.612 ± 0.977 *#	28.25 ± 1.21 #~
MDA level	142.62 ± 22.46	1179.68 ± 225.97 *	281.47 ± 8.17 *#	187.45 ± 5.77 #~

- All Values are Expressed as Mean ± SEM. When (P < 0.05) it's Regarded Significant.
- * Indicates a Significant Difference from the Control Group, # Indicates a Significant Difference from the Induction Group, ~ Indicates a Significant Difference Between Treatment Groups.

**Figure 1:** Effect of Dapagliflozin and Empagliflozin on Ovarian Oxidative Stress (GSH, MDA) in Cisplatin-Treated Rats (A) GSH; (B) MDA.

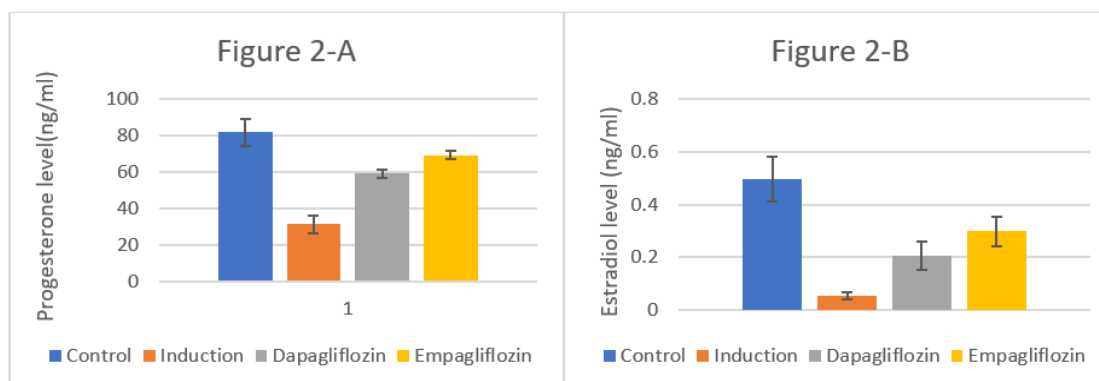
3.2 Hormones

Relative to Control, the Cisplatin group showed decreased progesterone, estradiol (E2), and AMH, and increased FSH (all $p < 0.05$). Dapagliflozin (DAPA) increased progesterone vs Cisplatin ($p < 0.05$). Still, it remained lower than Control ($p < 0.05$), whereas Empagliflozin (EMPA) increased progesterone to levels not significantly different from Control ($p > 0.05$) and higher than both Cisplatin and DAPA ($p < 0.05$). For E2 and AMH both DAPA and EMPA were higher than Cisplatin ($p < 0.05$) but remained lower than Control ($p < 0.05$), with no difference between DAPA and EMPA ($p > 0.05$). For FSH, both DAPA and EMPA were lower than Cisplatin ($p < 0.05$) but remained above Control ($p < 0.05$); EMPA was lower than DAPA ($p < 0.05$). Data are mean ± SEM ($n = 6/\text{group}$). See Fig. 2A–C and Table 2.

Table 2: The Effect of Dapagliflozin and Empagliflozin on Progesterone, Estradiol, FSH and AMH levels

Parameter	Control Group	Induction Group	Dapagliflozin-Treated Group	Empagliflozin-Treated Group
Progesterone	81.78 ± 7.47	31.36 ± 4.7 *	59.15 ± 2.17 *#	69.14 ± 2.2 ~#
Estradiol	0.497 ± 0.086	0.053 ± 0.011 *	0.205 ± 0.055 *#	0.299 ± 0.055 *#
FSH	12.92 ± 1.247	66.53 ± 7.68 *	40.304 ± 1.81 *#	28.37 ± 1.097 *#~
AMH	3.945 ± 0.15	1.46 ± 0.423 *	2.89 ± 0.17 *#	3.225 ± 0.25 *#

- All Values are Expressed as Mean ± SEM. When (P < 0.05) it's Regarded Significant.
- * Indicates a Significant Difference from the Control Group, # Indicates A Significant Difference from the Induction Group, ~ Indicates a Significant Difference Between Treatment Groups.



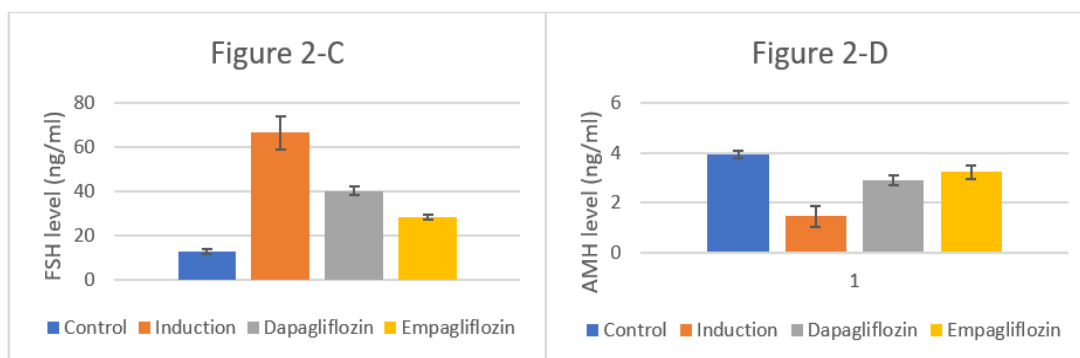


Figure 2: Effect of Dapagliflozin and Empagliflozin on Ovarian Hormones (Progesterone, Estradiol, FSH, AMH) in Cisplatin-Treated Rats (A) Progesterone; (B) Estradiol; (C) FSH; (D) AMH

3.3 Effects of Dapagliflozin and Empagliflozin on Inflammatory Gene Expression Markers

3.3.1 Effects of Dapagliflozin and Empagliflozin on TNF- α Gene Expression Level

TNF- α gene expression was significantly elevated in the induction group (Group II) compared to the control group (Group I), indicating an inflammatory response. Both Dapagliflozin (Group III) and Empagliflozin (Group IV) treatments significantly reduced TNF- α expression relative to the induction group, although levels remained significantly higher than in the control group. Notably, Empagliflozin-treated rats showed significantly lower TNF- α expression than those treated with Dapagliflozin, suggesting a stronger anti-inflammatory effect. Fig. 3A–B and Table 3.

3.3.2 Effects of Dapagliflozin and Empagliflozin on Interleukin-6 (IL-6) Gene Expression Level

IL-6 gene expression was significantly elevated in the induction group (Group II) compared to the control group (Group I), indicating heightened inflammatory activity. Treatment with Dapagliflozin (Group III) and Empagliflozin (Group IV) significantly reduced IL-6 expression levels relative to the induction group. However, both treatment groups maintained significantly higher expression levels than the control. No significant difference in IL-6 expression was observed between Groups III and IV, suggesting that both drugs exerted a comparable anti-inflammatory effect. Fig. 3A–B and Table 3.

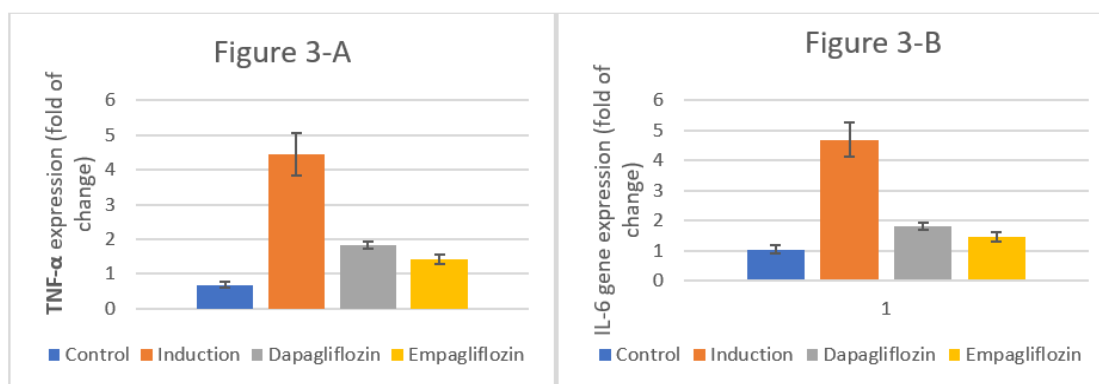


Figure 3: Effect of Dapagliflozin and Empagliflozin on Ovarian TNF- α , IL-6 Gene Expression Level in Cisplatin-Treated Rats (A) TNF- α ; (B) IL-6.

Table 3: The Effect of Dapagliflozin and Empagliflozin on TNF- α , IL-6 Gene Expression Level

Parameter	Control Group	Induction Group	Dapagliflozin-treated Group	Empagliflozin-Treated Group
TNF- α	0.686 $\pm$ 0.088 *	4.451 $\pm$ 0.619 *#	1.833 $\pm$ 0.112 *#	1.425 $\pm$ 0.137 *#~
IL-6	1.043 $\pm$ 0.13	4.69 $\pm$ 0.57 *	1.807 $\pm$ 0.132 *#	1.467 $\pm$ 0.162 *#

- All Values are Expressed as Mean $\pm$ SEM. When ($P < 0.05$) it's Regarded Significant.
- * Indicates A Significant Difference from the Control Group, # Indicates A Significant Difference from the Induction Group, ~ Indicates A Significant Difference Between Treatment Groups.

3.4 Effects of Dapagliflozin and Empagliflozin on Caspase-3 Protein Expression Level

Caspase-3 protein levels were significantly higher in the induction group than in the control group as a consequence of increased apoptotic activity. Group III of dapolozin significantly decreased Caspase-3 expression compared with the induction group, but levels remained considerably higher than in controls. The Caspase-3 expression was significantly lower among group IV rats than in Group II and was similar to that of control rats, but no significant difference was observed. None of these variations was significant between Groups III and IV, suggesting both medications decreased apoptosis, although Empagliflozin showed a more extensive normalization than usual. Fig. 4A–B and Table 4.

Table 4: The effect of Dapagliflozin and Empagliflozin on Caspase-3 protein expression level

Parameter	Control Group	Induction Group	Dapagliflozin-Treated Group	Empagliflozin-Treated Group
Caspase-3	0.685 ± 0.106	1.906 ± 0.15 *	1.049 ± 0.128 *#	0.778 ± 0.142 #

- All Values are Expressed as Mean ± SEM. When (P < 0.05) it's Regarded Significant.
- * Indicates A Significant Difference from the Control Group, # Indicates A Significant Difference from the Induction Group.

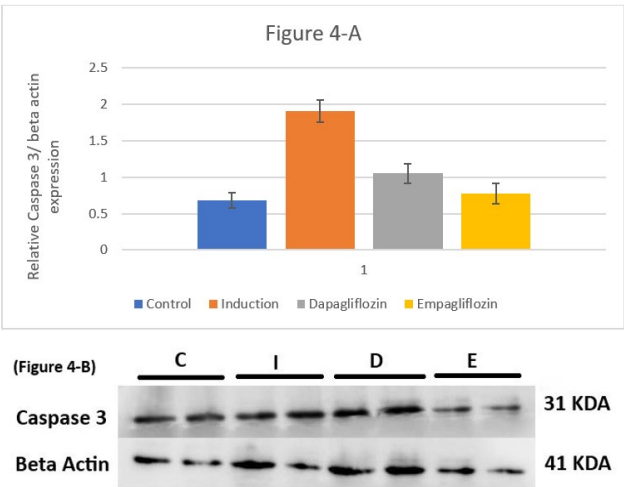
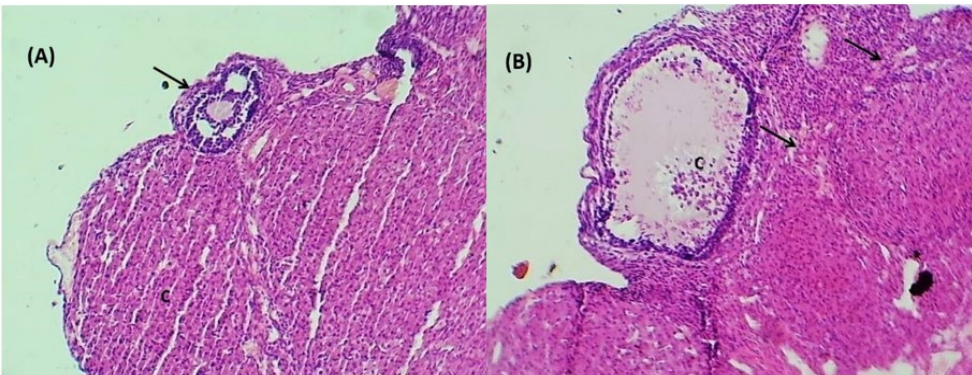


Figure 4: (A) Effect of Dapagliflozin and Empagliflozin on Caspase-3 Protein Expression Level in Cisplatin-Induced Ovarian Injury in Rats. (B) Western Blot Images of Caspase-3.

3.5 Histopathological Examination

Histological analysis of ovarian tissue revealed well-structured stromal cells and typical follicular structure in the control groups. Contrary to the induction group, these conditions, large ovarian atresia, interstitial swelling, bleeding, and infiltration of inflammatory cells indicate ovarian toxicity.

Dapagliflozin enhanced histopathology, produced fewer atretic follicles, slightly preserved follicular structure, and showed moderate degeneration. Empagliflozin treatment also provided better outcomes with nearly normal ovarian development, decreased inflammatory cytokine influx, and normalized follicles, supporting an even more convenient, preventative approach to cisplatin-induced histopathological harm.



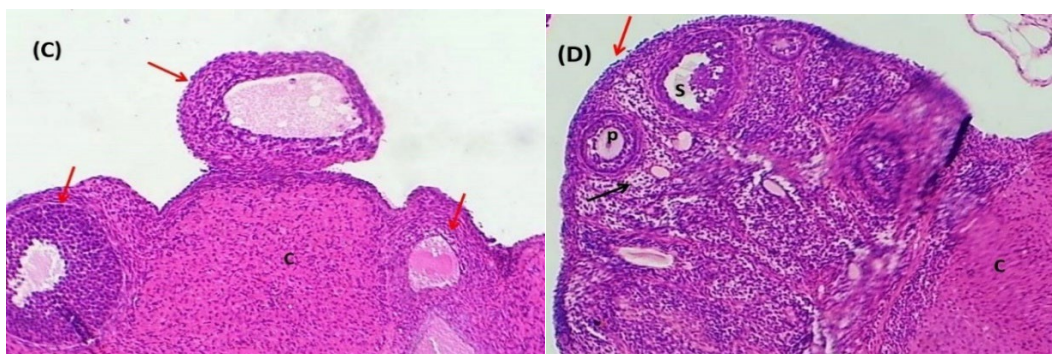


Figure 5: Effects of Dapagliflozin and Empagliflozin on Cisplatin-Induced Ovarian Injury in Rats. H&E-Stained Ovarian Sections (100× Magnification) (A) Control: Normal Follicles and Stroma. (B) Cisplatin (Induction): Follicular Atresia, Oocyte Degeneration, Granulosa-Cell Loss/Necrosis and Stromal Edema/Vascular Congestion. (C) Dapagliflozin (DAPA): Partial Preservation with Fewer Atretic Follicles and Reduced Edema/Congestion. (D) Empagliflozin (EMPA): Near-Normal Architecture with Preserved Follicles and Minimal Congestion.

4. Discussion

Cisplatin is widely used for solid tumors but is strongly gonadotoxic, precipitating premature ovarian insufficiency (POI) through cycle disruption, accelerated follicular apoptosis, and depletion of functional follicles (Borovskaya et al., 2004; Yucebilgin et al., 2004). In the present model, cisplatin reproduced hallmark features of ovarian injury—oxidative stress, inflammatory activation, apoptosis, endocrine dysregulation, and histoarchitectural damage—consistent with prior reports (Altuner et al., 2013; Caglayan et al., 2018; Ibrahim et al., 2021). Both dapagliflozin (DAPA) and empagliflozin (EMPA) ameliorated these changes, with EMPA generally showing greater normalization across several endpoints.

Oxidative stress is a principal driver of cisplatin reproductive toxicity, largely via excessive reactive oxygen species (ROS) that overwhelm antioxidant defenses (Altuner et al., 2013). Consistent with this mechanism and with prior ovarian injury models (Caglayan et al., 2018; Ibrahim et al., 2021).

A typical indicator of oxidative stress and the antioxidant state in cancer patients is the quantity of malondialdehyde (Abdul-Azeez & Mutlag, 2023), and glutathione levels, which serve as a free radical scavenger (Marouf et al., 2011), cisplatin in our model depleted reduced glutathione (GSH) and elevated malondialdehyde (MDA). Both DAPA and EMPA improved these indices, with EMPA yielding the greater normalization. These findings align with reports that DAPA activates Nrf2/HO-1 signaling and increases endogenous antioxidant enzymes (SOD, CAT, GPx) in cisplatin nephrotoxicity, concomitant with reductions in lipid peroxidation markers (e.g., 4-HNE, nitrites) (Satyam et al., 2025). Likewise, EMPA has been shown to activate Nrf2/ARE signaling in cardiac tissue and to upregulate Nrf2/HO-1 in mesothelial cells, thereby mitigating oxidative stress (Li et al., 2019; Shi et al., 2022). Although we did not directly assay Nrf2 in ovarian tissue, the observed redox recovery is compatible with these upstream pathways.

Additional support comes from Farrokh-Eslamlou et al. (2024), who demonstrated that EMPA ameliorates cisplatin nephrotoxicity by restoring antioxidant enzymes (CAT, SOD, GPx), lowering renal MDA, and suppressing inflammatory mediators (TNF- α , IL-1 β , myeloperoxidase). Given that ROS-induced lipid peroxidation produces reactive aldehydes such as MDA that damage membranes and cause cellular injury, the decrease in MDA observed in EMPA and DAPA is probably a result of ROS regulation. Collectively, these results suggest that SGLT2 inhibition provides ovarian antioxidant protection in line with repressed Nrf2-mediated signaling in all organ systems (Li et al., 2019; Satyam et al., 2025; Shi et al., 2022), while the present results extend this paradigm to the ovary in the context of cisplatin exposure.

5. Hormone Profile

In our model, reduced estradiol (E2), progesterone, and FSH were associated with hormonal changes induced by Cisplatin, which were interpreted as disrupting the hypothalamic-pituitary-gonadal axis. Ibrahim et al. (2021) reported higher levels of E2, lowered E2 and FSH, and increased progesterone levels in cisplatin-treated rats, which indicates ovarian impairment and weak feedback regulation.

Both SGLT2 inhibitors partially restored this profile, and empagliflozin was fully restored on several measures. Similarly, it has been shown that SGLT2 inhibition can modulate endocrine regulation, as evidenced by an experiment with dapagliflozin, which restored abnormal levels of estradiol and progesterone in ovarian conditions by increasing redox and inflammatory states associated with steroidogenesis (Chen et al., 2025). In addition, Abdelzاهر et al. (2023) reported that

empagliflozin lowered ovarian cancer risk by decreasing elevated FSH and LH and increasing AMH, as well as active antioxidant and anti-inflammatory effects. So, these observations are consistent with our conclusion that SGLT2 inhibition can maintain the stability of reproductive hormones by limiting oxidative and inflammatory stressors in the ovary, and that empagliflozin also exerted a much greater effect in this regard.

Cisplatin also significantly reduces AMH compared to controls, as has been demonstrated previously in studies in which cisplatin depletes AMH-positive follicles and reduces circulating AMH. Mechanistically, this results in follicle loss as well as atresia after oxidative stress, inflammation, as well as apoptosis (Li et al., 2013).

Both SGLT2 inhibitors reduced the AMH decrease: dapagliflozin and empagliflozin improved significantly with AMH inhibition but performed poorly without AMH, consistent with their anti-inflammatory/anti-oxidant effects across all endpoints of this study. Interesting, the difference in average AMH between empagliflozin and dapagliflozin was not statistically significant, even if the median AMH was higher than the average for dapagliflozin. These results are consistent with separate results of a model using non-cisplatin empagliflozin that restored AMH as well as significantly increased oxidative/inflammatory markers in ovarian tissues suggesting that empagliflozin may perform across classes as a mediator of follicular integrity (Abdelzaher et al., 2023).

In sum, our main hypothesis is supported by AMH levels, suggesting that inhibition of SGLT2 may explain the reduction in ovarian volume caused by cisplatin, perhaps through various antioxidant and anti-inflammatory mechanisms that maintain granulosa cell integrity.

6. Inflammation

The TNF- α is a major regulator with several effects on the inflammatory response, triggering the release of other cytokines and chemokines.

Plus, TNF- and IL-6 have been markedly increased in our model due to cisplatin-induced ovarian inflammation, suggesting that inflammatory signalling is implicated in follicular injury. These results are consistent with Dinc et al. (2023), who reported increased ovarian levels of NF- κ B, TNF- α , IL-1 β , and IL-6 in cisplatin-treated rats suggesting a marked inflammatory response.

Dapagliflozin and empagliflozin both induced significantly smaller reductions in TNF- and IL-6, and empagliflozin induced a further reduction. This pattern is consistent with the mechanical results reported by Shi et al. (2022) reported that empagliflozin induced inflammasome activation of NLRP3 and downregulated NF- κ B, thus inhibiting TNF- and IL-6 expression in endothelial cells, and Farrokh-Eslamlou et al. (2024) demonstrated dose-dependent reductions of TNF- α and IL-1 β with empagliflozin in a cisplatin-nephrotoxicity model. Other anti-inflammatory effects of dapagliflozin have been described: Chen et al. (2025) reported suppression of TNF- α , IL-6, and NF- κ B in experimental systems., and Li (2024) showed reduced expression of TNF- α and reduced NF- κ B stimulation of renal inflammation. Taken together, these data reveal novel anti-inflammatory effects of SGLT2 inhibition that may contribute to protection against cisplatin-induced cytokine-mediated ovarian damage.

7. Apoptosis

Caspases are crucial enzymes involved in programmed cell death, or apoptosis. Different stimuli like inflammation, oxidative stress, and other factors can trigger these significant apoptotic pathways (Mahmood & Kathem, 2023).

Our model showed that cisplatin activates the ovarian caspase-3, indicating that the inactive pathway is engaged. This is consistent with previous analyses of apoptosis induced by caspase and induced by cisplatin in ovarian tissue, such as Henkels and Turchi (1999) who identified both caspase-3-dependent and caspase-3-independent pathways for cisplatin-triggered apoptosis in ovarian cancer cell lines, affirming that caspase-3 plays a role in the execution phase of apoptosis in ovarian cells.

DAPA and empagliflozin, both of which decreased caspase-3 levels relative to cisplatin, with EMPA levels nearly returning to baseline, suggesting an anti-apoptotic effect. Another tissue providing mechanical support: Han et al. (2023) reported that DAPA decreased Bax and caspase-3, upregulated Bcl-2, and activated PI3K/Akt survival signalling, which was abolished by PI3K/Akt inhibition, thereby stabilising mitochondria and conferring cryoprotection. Topsakal et al. (2024) identified the effects of DAPA in female reproductive organs: it decreased oxidative stress and pro-inflammatory cytokines, downregulated caspase-3, and, as a result, preserved the histoarchitecture of ovarian, tubal, and uterine histology. Plus, in a chemically induced model of ovarian toxicity, Abdelzaher et al. (2023) found that EMPA mediates the Sirt-1/Hsp70/TNF- α /caspase-3 axis and notably reduces caspase-3 expression, suggesting direct anti-apoptotic effects in ovarian tissue. Together, these findings suggest that SGLT2 inhibition enhances mitochondrial pathway stabilization's enhancement of anti-apoptotic activity (Bax/Bcl-2 balance, PI3K/Akt) as well as inhibition of inflammatory mediators (e.g., Sirt-1/Hsp70/NF- κ B/TNF- α) consistent with the reduction of caspase-3 observed here and thus, contributes to improved ovarian histology among the two groups treated.

8. Histopathology

H&E demonstrates the differences between the groups. Control ovaries presented intact cytoarchitecture, with well-preserved cortical and medullary regions and distinct, normal granulosa and theca layers, along with intact follicles at multiple stages (primary to tertiary) and a normal corpus luteum structure.

In the cisplatin group, ovaries suffered severe degeneration: extensive follicular atresia, oocyte loss, granulosa cell necrosis, stromal disruption, and vascular congestion. These lesions do not appear to reflect the selective vulnerability of primordial oocytes to cisplatin, as reported by [Kerr et al. \(2012\)](#) and is consistent with germline-specific apoptosis as an effector of decreased lasting fertility.

DAPA maintained even slightly more stable ovarian function: there was a greater level of maintenance of the follicular structure and theca layers; there was better organization of granulosa; and stromal edema and vascular congestion were reduced with some oocyte lysis. These findings align with the reproductive tissue findings reported by [Topsakal et al. \(2024\)](#) where they found that DAPA restored the histological appearance and reversed epithelial disruption, stromal inflammation, and caspase-3-mediated apoptosis, with an estimated reduction in stromal inflammation.

The ovaries treated with empagliflozin (EMPA) showed normal layering for the first and second follicles, with minimal congestion of the cortical stroma, and both the germinal epithelium and corpus luteum was maintained. In the present study, [Abdelzاهر et al. \(2023\)](#) finding that EMPA reversed chemically induced ovarian damage while inhibiting caspase-3 expression suggests that EMPA has a direct tissue-protective effect.

Overall, our results support cisplatin as both a promising chemotherapeutic and an inert inducer of ovarian injury and thus represent a need for protection. SGLT2 inhibitor-induced, particularly empagliflozin-induced, oxidative, inflammatory, apoptotic, hormonal and histological diseases in this rat model were suppressed. Together, these data support the role of SGLT2 inhibitors as adjuvants to reduce chemotherapy-induced gonadotoxicity and warrant further investigation to establish dosing, timing, fertility outcomes, and pathway involvement.

9. Conclusion

This rat model was adversely impacted by oxidative, apoptotic, endocrine and histological ovarian injury caused by Cisplatin. These disturbances were greatly mitigated by dapagliflozin and empagliflozin, while empagliflozin maintained levels close to control for several endpoints (e.g., GSH, MDA, progesterone, caspase-3), with greater FSH lowering than dapagliflozin. Therefore, prophylactic SGLT2 inhibition is an attractive intervention to mitigate chemotherapy-associated gonadotoxicity. Future research should focus on dose-response and timing, follicle count and fertility outcome, and investigate upstream pathways (e.g., Nrf2, NF- κ B, Sirt-1), and evaluate potential effects on antitumor efficacy.

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