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*Full Length Research*

# Ethanol extract of *Ficus exasperata* leaf and gallic acid ameliorate cisplatin-induced toxicity in Wistar rats

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**ABSTRACT:** Cisplatin (CP), a widely used platinum-based chemotherapeutic, is effective in cancer treatment but it is associated with significant multiple organ toxicity, particularly the liver, kidneys, gastrointestinal tract, and cardiovascular system. Oxidative stress is a major contributor to this toxicity. This study aimed to investigate the protective effects of *Ficus exasperata* (FE) extract and gallic acid (GA), both known for their antioxidant properties, against cisplatin-induced toxicity, oxidative stress, and organ damage in Wistar rats. Fifty male Wistar rats (162–266 g) were randomly assigned to five groups (A–E; n=10). Group A received distilled water only (control). Group B was administered cisplatin (10 mg/kg, intraperitoneally) on day 8. Groups C and D received 100 mg/kg and 200 mg/kg of *Ficus exasperata* extract orally for 8 days, respectively, followed by cisplatin administration on day 8. Group E received gallic acid (100 mg/kg orally) for 8 days and cisplatin on day 8. Blood pressure and ECG measurements were taken before sacrifice. Blood, liver, kidney, and heart samples were analyzed for oxidative stress markers, antioxidant enzyme activities, hematological, liver, and renal function indices. Cisplatin administration significantly elevated systolic blood pressure and markers of oxidative stress, while reducing antioxidant enzyme levels in cardiac and renal tissues. Treatment with FE and GA significantly reduced oxidative stress and restored antioxidant enzyme levels. The 200 mg/kg dose of *Ficus exasperata* showed the most pronounced protective effect. FE and GA exert protective effects against cisplatin-induced cardio-renal toxicity in rats, likely through antioxidant activity. The protective effect of *Ficus exasperata* appears dose-dependent.

**Keywords:** Antioxidant, cardio-renal toxicity, cisplatin, *Ficus exasperata*, gallic acid, oxidative stress, Wistar rats.

## INTRODUCTION

Medicinal plants are widely recognized as effective sources of therapeutic agents (Regginato *et al.,* 2021). Their usage in the treatment of various diseases in both humans and animals has been well documented (Akhtar and Swamy, 2018). Numerous plant species possess powerful medicinal and therapeutic properties. Herbal remedies are often considered safer and more beneficial alternatives to synthetic drugs for disease management (Bari *et al*., 2020). The growing prevalence of oxidative stress-related diseases has prompted researchers to explore the antioxidant potential of medicinal plants and their bioactive constituents (Wang *et al*., 2019). The global demand for plant-based remedies has increased due to their therapeutic potential (Afsar *et al*., 2015), and mounting evidence supports the use of medicinal plants in various therapeutic applications (Zhao *et al*., 2020). Many

plant-derived bioactive compounds are efficient scavengers of reactive oxygen species (ROS) (Alkreathy *et al*., 2014; Sahreen *et al*., 2017). Natural antioxidants serve as a defense mechanism against free radicals, which are known to cause long-term cellular damage. Extracts from medicinal plants have demonstrated significant protective effects against chemically induced oxidative damage (Bakr *et al*., 2019). Cisplatin, a potent chemotherapeutic agent, is limited in clinical use due to its severe toxicity. It induces oxidative stress and causes damage to multiple organ systems, including the kidneys, liver, ovaries, gastrointestinal tract, and cardiovascular system (Eslamifar *et al*., 2021). Therefore, the identification of therapeutic agents with strong antioxidant potential is essential to mitigate cisplatin-induced toxicity and preserve organ function.

Cisplatin, chemically known as cis-diamine-dichloro-platinum (II), is a widely used chemotherapeutic agent effective against a variety of tumors, including cancers of the head, neck, breast, colon, lung, liver, kidney, ovary, cervix, bladder, and testes. Notably, it has been shown to cure over 90% of testicular cancers (Wheate, 2010). Once inside the cell, it undergoes activation and forms highly reactive platinum complexes that bind to DNA. This binding interferes with DNA replication and transcription, ultimately triggering apoptosis. The majority of administered cisplatin is excreted via the kidneys, with only a small fraction converted into the active diaquo-platinum form that interacts with DNA (Wheate, 2010). Despite its efficacy, CP's clinical utility is significantly limited by intrinsic and acquired resistance mechanisms. These include reduced drug uptake, increased efflux, enhanced detoxification via thiol-containing biomolecules, and increased DNA repair capacity (Wheate, 2010).

Cisplatin is also associated with numerous adverse effects, including nausea, vomiting, nephrotoxicity, hepatotoxicity, neurotoxicity, ototoxicity, gastrotoxicity, allergic reactions, and alopecia. These toxicities result from its non-selective action on both cancerous and healthy cells (Florea and Büsselberg, 2011; Li *et al*., 2018). It preferentially accumulates in renal tissues, where it induces nephrotoxicity through tubular necrosis and the generation of reactive oxygen species (ROS) (Kumar *et al*., 2017). The degree of renal damage correlates with platinum concentrations in the kidneys (McSweeney *et al*., 2021). CP administration also lowers plasma antioxidant levels, indicating compromised antioxidant defense mechanisms (Nematbakhsh *et al*., 2017). Its toxicity involves oxidative stress, mitochondrial dysfunction, and ionic imbalance (Dugbartey *et al*., 2016). Elevated serum creatinine and urea levels, reduced renal cortical enzyme activity, and histopathological changes such as necrosis (Abdel-Gayoum and Ahmida, 2017) further characterize Nephrotoxicity. Additional effects include electrolyte imbalances (e.g., decreased potassium, calcium, and magnesium levels), as well as dyslipidemia. Age and pre-existing hypertension are recognized risk factors for cisplatin-induced renal damage (Prasaja *et al*., 2015). Other organ toxicities include neurotoxicity, cardiotoxicity, and ototoxicity (Katanić Stanković *et al*., 2023). Protective strategies under investigation include co-administration of agents such as hydrogen sulfide (Dugbartey *et al*., 2016). Emerging biomarkers like Kidney Injury Molecule-1 (KIM-1), Tissue Inhibitor of Metalloproteinase-1 (TIMP-1), and N-terminal pro-B type Natriuretic Peptide (NT-proBNP) may offer early detection and monitoring of cisplatin-induced organ damage (Dugbartey *et al*., 2016).

Chronic CP treatment has been shown to cause dose-dependent cardiovascular alterations, including changes in blood pressure, heart rate, and cardiac function (Herradón *et al*., 2017). The mechanisms underlying cisplatin-induced cardiotoxicity involve oxidative stress, disruption of ionic homeostasis, and impairment of cellular energy metabolism (Dugbartey *et al*., 2016). In isolated rat hearts, cisplatin has been observed to impair left ventricular pressure, reduce heart rate, and alter other cardiac parameters (Bukhari *et al*., 2022). Risk factors for developing left ventricular systolic dysfunction include individual genetic predisposition, concurrent use of other cardiotoxic agents, and prior exposure to anthracyclines or mediastinal radiation (Babbar *et al*., 2020). Potential protective strategies include the use of agents such as hydrogen sulfide (Dugbartey *et al*., 2016) and rutin trihydrate, both of which have demonstrated promise in attenuating cisplatin-induced cardiac dysfunction and histopathological damage (Bukhari *et al*., 2022). It can also induce hepatotoxicity through mechanisms involving oxidative stress and mitochondrial dysfunction. Studies have reported increased levels of liver enzymes, lipid peroxidation, and depletion of antioxidants such as glutathione following cisplatin treatment (Maheshwari *et al*., 2015). Mitochondrial injury, membrane rigidification, and apoptosis are key contributors to cisplatin-induced liver damage (Martins *et al*., 2008). Overexpression of cytochrome P450 2E1 (CYP2E1) further enhances hepatotoxicity by increasing the generation of ROS (Martins *et al*., 2008). Protective agents such as statins (e.g., simvastatin and rosuvastatin) and antioxidants like apocynin, a NADPH oxidase inhibitor, have demonstrated beneficial effects in reducing oxidative stress and preserving liver function in experimental models (Maheshwari *et al*., 2015).

Reactive oxygen species (ROS), including superoxide anions ($O_2^-$), hydrogen peroxide ($H_2O_2$), and hydroxyl radicals (•OH), are by-products of oxygen metabolism that can be generated endogenously through mitochondrial oxidative phosphorylation or exogenously through interaction with xenobiotics. Oxidative stress occurs when the production of ROS exceeds the capacity of the body's antioxidant defense mechanisms, leading to molecular damage (Ray *et al*., 2012). Excess ROS can cause protein denaturation, lipid peroxidation, and DNA damage, resulting in cellular injury, necrosis, or apoptosis—particularly in sensitive tissues such as the renal tubules

(Ratliff *et al*., 2016).

Gallic acid (GA), a trihydroxybenzoic acid widely distributed in fruits, teas, and wines, possesses strong antioxidant, anti-inflammatory, and antimicrobial properties (Liu *et al*., 2014). It protects biological tissues from oxidative stress-related damage by scavenging free radicals and modulating various cellular signaling pathways, including those involving inflammatory cytokines and antioxidant enzymes (Gao *et al*., 2019).

*Ficus exasperata* Vahl (family: Moraceae), commonly known as the sandpaper tree, is a tropical medicinal plant traditionally used to manage conditions such as arthritis, hypertension, infertility, gastric disturbances, and cancer (Faiyaz *et al*., 2012; Adekeye *et al*., 2020). It exhibits both antioxidant and antiproliferative effects, particularly in *in vitro* studies involving ovarian cancer cells (Akanni *et al*., 2014; Bator *et al*., 2017). Phytochemical analyses have identified numerous bioactive compounds in the leaves, bark, and fruits of *Ficus exasperata*, including cinnamoyl derivatives (e.g., caffeic acid, ferulic acid, sinapic acid), flavonoid O-glycosides (e.g., isoquercitrin, kaempferol), mono-C-glycosides (e.g., apigenin-8-C-glucoside), di-C-glycosides (e.g., luteolin-6,8-di-C-hexoside), and furanocoumarins such as bergapten and oxypeucedanin hydrate (Mouho *et al*., 2018; Mikail *et al*., 2019). Additionally, several organic acids, including oxalic, aconitic, citric, tartaric, malic, quinic, and fumaric acids, have been identified in *Ficus exasperata* extracts (Mouho *et al*., 2018).

Given the well-established antioxidant potentials of gallic acid and *Ficus exasperata*, the present study was designed to investigate their protective effects against cisplatin-induced oxidative stress and organ damage in Wistar rats.

## METHODOLOGY

### Experimental animals

Fifty male albino Wistar rats weighing between 162 and 226 g were procured from the Animal House of the Faculty of Veterinary Medicine, University of Ibadan. The animals were housed in well-ventilated cages under standard laboratory conditions, including a 12-hour light/dark cycle. They were allowed free access to standard pelleted feed and distilled water *ad libitum*. The animals were acclimatized for two weeks prior to the commencement of the experiment.

### Plant material and extraction

Fresh leaves of *Ficus exasperata* were collected, washed, and air-dried at room temperature. The dried leaves were pulverized into fine powder and defatted using *n*-hexane. The defatted plant material was subsequently extracted with ethanol by maceration for 72 hours. The extract was filtered and concentrated using a rotary evaporator. The final extract was stored at 4 °C until use.

### Experimental design and treatment protocol

The animals were randomly divided into five groups (A–E), with ten rats per group (n = 10). The treatment protocol was as follows:

- Group A (Control): Received distilled water orally for 8 consecutive days.
- Group B (Cisplatin-only): Received a single intraperitoneal injection of cisplatin (10 mg/kg) on day 8.
- Group C (Low-dose *Ficus exasperata*): Administered *Ficus exasperata* extract (100 mg/kg, orally) for 8 days, followed by cisplatin (10 mg/kg, i.p.) on day 8.
- Group D (High-dose *Ficus exasperata*): Administered *Ficus exasperata* extract (200 mg/kg, orally) for 8 days, followed by cisplatin (10 mg/kg, i.p.) on day 8.
- Group E (Gallic Acid): Administered gallic acid (100 mg/kg, orally) for 8 days, followed by cisplatin (10 mg/kg, i.p.) on day 8.

The average body weights of rats in each group and their and their respective treatments are as shown in Table 1.

## RESULTS

### Cardiac markers of oxidative stress

Cisplatin administration (Group B) significantly increased cardiac $H_2O_2$ and MDA levels, indicating elevated oxidative stress and lipid peroxidation. Co-treatment with *Ficus exasperata* (Groups C and D) and gallic acid (Group E) markedly reduced these markers (Table 2).

### Renal biomarkers of antioxidant defense mechanisms

Also, cisplatin significantly reduced the levels of key antioxidants and antioxidant enzymes (GSH, GPx, GST, SOD). However, co-treatment with FE and GA restored these antioxidants, especially in Group D, which exhibited the highest GSH and SOD levels, suggesting dose-dependent cardioprotective and antioxidant activity of FE (Table 3).

### Cardiac markers of oxidative stress

A significant increase in cardiac $H_2O_2$ and MDA levels was observed in the group given cisplatin alone when compared to the control, indicating oxidative stress and lipid peroxidation. Co-treatment with *Ficus exasperata* (Groups C and D) and gallic acid (Group E) markedly reduced these markers (Table 4).

### Renal biomarkers of antioxidant defense mechanisms

Cisplatin-induced nephrotoxicity and renal oxidative stress,

**Table 1.** Groups of rats, their average body weight and treatments given to each group.

| Group | Average body weight (g) | Treatment administered |
|---|---|---|
| A | 162 | Feed and distilled water only (Control) |
| B | 201 | Cisplatin (10 mg/kg, intraperitoneally) |
| C | 139 | Cisplatin (10 mg/kg, i.p.) + *Ficus exasperata* (100 mg/kg, oral) |
| **D** | **215** | Cisplatin (10 mg/kg, i.p.) + *Ficus exasperata* (200 mg/kg, oral) |
| **E** | **226** | Cisplatin (10 mg/kg, i.p.) + Gallic acid (100 mg/kg, oral) |

Group A (Control), Group B (Cisplatin-only (10 mg/kg, i.p), Group C Administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (100 mg/kg, orally. Group D: Administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (200 mg/kg, orally) Group E: Administered Cisplatin (10 mg/kg, i.p.) and Gallic acid (100 mg/kg, orally).

**Table 2.** Biochemical assay results of reactive oxygen species in heart tissue.

| Parameter | Group A | Group B | Group C | Group D | Group E |
|---|---|---|---|---|---|
| $H_2O_2$ | 42.01 ± 3.88 | $45.84 \pm 0.61^{cd}$ | $37.06 \pm 3.76^{b}$ | $36.55^{b} \pm 3.22^{a}$ | 41.28 ± 0.77 |
| MDA | 1.24 ± 1.17 | $2.63 \pm 0.25^{acde}$ | $0.26 \pm 0.04^{ab}$ | $0.60 \pm 0.10^{b}$ | $0.70 \pm 1.17^{b}$ |

Group A (Control), Group B (Cisplatin-only (10 mg/kg, i.p), Group C: Administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (100 mg/kg, orally. Group D: Administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (200 mg/kg, orally) Group E: Administered Cisplatin (10 mg/kg, i.p.) and Gallic acid (100 mg/kg, orally) . Values were expressed as mean±SD and significance was measured at $P<0.05$. Superscripts a, b, c,d, and e shows significance deference when the groups they denote and the groups A-E on which they appear were compared. Units of measurements: $H_2O_2$ (µmol/mg protein), MDA (µl/mg protein).

**Table 3.** Biochemical assay results of antioxidant enzymes in heart tissue.

| Parameter | Group A | Group B | Group C | Group D | Group E |
|---|---|---|---|---|---|
| GSH (µmol/g tissue) | $72.51 \pm 3.11^{d}$ | $68.94 \pm 2.17^{cde}$ | $74.85 \pm 2.59^{d}$ | $88.57 \pm 1.99^{ae}$ | 74.00 ± 0.56 |
| GPx (unit/mg protein) | 124.55 ± 27.31 | $68.67 \pm 1.29^{a}$ | $76.56 \pm 2.24^{a}$ | $80.06 \pm 4.30^{a}$ | $70.18 \pm 5.66^{a}$ |
| GST (µmol) | 2.27 ± 0.26 | $0.74 \pm 1.80^{a}$ | $0.99 \pm 0.10^{a}$ | $1.97 \pm 0.69^{acb}$ | $1.52 \pm 0.17^{ab}$ |
| SOD (unit/mg protein) | $9.48 \pm 2.60^{bc}$ | $5.62 \pm 0.93^{a}$ | $6.40 \pm 1.56^{ad}$ | $11.11 \pm 0.89^{bce}$ | $6.56 \pm 1.47^{d}$ |

Group A (Control), Group B (Cisplatin-only (10 mg/kg, i.p), Group C: Administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (100 mg/kg, orally. Group D: Administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (200 mg/kg, orally), Group E: Administered Cisplatin (10 mg/kg, i.p.) and Gallic acid (100 mg/kg, orally). Units of measurement: GSH (µmol/g tissue). Values were expressed as mean ± SD and significance was measured at $P<0.05$. Superscripts a, b, c,d, and e show significant difference when the groups they denote and the groups A-E on which they appear were compared.

as evident by the significant reduction in the antioxidant enzyme levels in Group B. FE and GA supplementation restored GSH, GPx, GST, and SOD levels toward normal, with Group D showing the most prominent improvement across all parameters (Table 5).

### Serum biomarkers of antioxidant defence mechanisms

Serum nitric oxide (NO) was significantly reduced in the cisplatin-only group, while MPO was elevated. Co-administration with FE or GA improved NO levels and reduced MPO activity, suggesting systemic antioxidant and anti-inflammatory effects, particularly in Group D (Table 6).

### Haematology parameters

Furthermore, cisplatin caused slight reductions in PCV, Hb, RBC, and platelet counts, with a rise in total WBC, eosinophils, and monocytes responses. These changes were mitigated in the treated groups, especially with higher FE dosage (Group D), which maintained hematological values close to normal (Table 7).

### Serum chemistry parameters

In addition, cisplatin induced hepatic and renal dysfunction, as shown by the significant elevation of AST, ALT, ALP, BUN, and creatinine in Group B. FE and GA treatments, particularly FE at 200 mg/kg (Group D), significantly improved these parameters, reflecting hepato-renal protection (Table 8).

### Electrocardiogram

Cisplatin exposure slightly altered heart rate and ECG

**Table 4.** Biochemical assay results of reactive oxygen species in kidney tissue.

| Parameter | Group A<br>(Control) | Group B<br>(Cisplatin 10 mg/kg) | Group C<br>(Cisplatin + FE 100 mg/kg) | Group D<br>(Cisplatin + FE 200 mg/kg) | Group E<br>(Cisplatin + GA 100 mg/kg) |
|---|---|---|---|---|---|
| $H_2O_2$ | 82.23 ± 12.01$^{ce}$ | 96.57 ± 10:33$^{cde}$ | 60.89 ± 5.43$^{b}$ | 52.68 ± 2.04$^{b}$ | 66.72 ± 4.85$^{b}$ |
| MDA | 2.99 ± 1.10 | 4.55 ± 1.97$^{cde}$ | 1.84 ± 0.53$^{b}$ | 1.47 ± 0.62$^{b}$ | 1.35 ± 0.52$^{b}$ |

Group A (Control), Group B (Cisplatin-only (10 mg/kg, i.p), Group C: Administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (100 mg/kg, orally. Group D: Administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (200 mg/kg, orally), Group E: Administered Cisplatin (10 mg/kg, i.p.) and Gallic acid (100 mg/kg, orally). Units of measurement: $H_2O_2$ (umol/mg protein), MDA (ul/mg protein). Values were expressed as mean±SD, and significance was measured at p<0.05. Superscripts a, b, c,d, and e show significant difference when the groups they denote and the groups A-E on which they appear were compared.

**Table 5.** Biochemical assay results of antioxidant enzymes in kidney tissue.

| Parameters | Group A | Group B | Group C | Group D | Group E |
|---|---|---|---|---|---|
| GSH | 115.58 ± 10.56 | 107.12 ± 3.22 | 117.79 ± 13.59 | 118.42 ± 7.62 | 118.54 ± 8.82 |
| GPx | 64.86 ± 15.76$^{be}$ | 35.80 ± 3.89$^{ac}$ | 57.72 ± 5.13$^{e}$ | 63.06 ± 7.52$^{e}$ | 37.51 ± 9.72$^{a}$ |
| GST | 26.07 ± 37.42$^{bcd}$ | 15.83 ± 32.20$^{ace}$ | 38.81 ± 18.51$^{de}$ | 50.54 ± 86.06$^{ace}$ | 16.48 ± 15.30 |
| SOD | 12.37 ± 3.12 | 7.22 ± 3.78$^{a}$ | 9.68 ± 1.20 | 10.40 ± 1.53 | 8.89 ± 1.20 |

Group A (Control), Group B (Cisplatin-only (10 mg/kg, i.p), Group C was administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (100 mg/kg, orally. Group D: Administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (200 mg/kg, orally). Group E: Administered Cisplatin (10 mg/kg, i.p.) and Gallic acid (100 mg/kg, orally). Units of Measurement: GSH (µmol/g tissue), GST (µmol-1-chloro-2,4-dimitrobenzene-GSH complex formed/min/mg/protein), SOD (units/mg protein). Values were expressed as mean±SD, and significance was measured at p<0.05. Superscripts a, b, c,d, and e show significant difference when the groups they denote and the groups A-E on which they appear were compared.

**Table 6.** Biochemical assay results in serum.

| Parameter | Group A | Group B | Group C | Group D | Group E |
|---|---|---|---|---|---|
| Nitric Oxide (NO) | 2.89 ± 1.32 | 1.82 ± 0.75$^{d}$ | 2.66 ± 0.30 | 3.29 ± 0.19 | 2.59 ± 0.32 |
| Myeloperoxidase (MPO) | 3.95 ± 1.32 | 5.79 ± 1.79 | 2.67 ± 2.44 | 2.50 ± 2.05 | 2.97 ± 2.14 |

Group A (Control), Group B (Cisplatin-only (10 mg/kg, i.p), Group C: Administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (100 mg/kg, orally. Group D: Administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (200 mg/kg, orally). Group E: Administered Cisplatin (10 mg/kg, i.p.) and Gallic acid (100 mg/kg, orally). Uits of measurement: Nitric Oxide (NO, µmol/mg protein), Myeloperoxidase (MPO, µmol/L). Values were expressed as mean ± SD, and significance was measured at p<0.05. Superscripts a, b, c,d, and e show significant difference when the groups they denote and the groups A-E on which they appear were compared.

**Table 7**. Hematological parameters.

| Parameter | A (Control) | B (Cisplatin) | C (FE 100 mg/kg) | D (FE 200 mg/kg) | E (GA 100 mg/kg) |
|---|---|---|---|---|---|
| PCV (%) | 54.00 ± 1.29 | 51.80 ± 3.73 | 52.80 ± 2.95 | 55.67 ± 2.52 | 53.33 ± 1.52 |
| Hb (g/dL) | 17.70 ± 0.90 | 16.80 ± 1.20 | 17.30 ± 1.00 | 17.30 ± 0.70 | 17.30 ± 0.40 |
| RBC (×$10^6$/uL) | 8.63 ± 0.11$^{de}$ | 8.27 ± 0.49 | 8.71 ± 0.12 | 8.76 ± 0.09$^{b}$ | 8.76 ± 0.12$^{b}$ |
| Platelets (×$10^9$/L) | 110.60 ± 8.44$^{d}$ | 110.60 ± 8.44$^{d}$ | 115.00 ± 7.75$^{d}$ | 130.33 ± 6.03 | 111.67 ± 7.37$^{abcd}$ |
| Lymphocytes (×$10^9$/L) | 75.40 ± 1.11 | 75.40 ± 1.14 | 61.00 ± 30.21 | 76.33 ± 2.08 | 73.33 ± 1.15 |
| Monocytes (×$10^9$/L) | 1.40 ± 0.54 | 1.80 ± 1.36 | 2.60 ± 2.51 | 2.33 ± 0.58 | 1.33 ± 0.56 |
| Eosinophils (×$10^9$/L) | 0.80 ± 0.84 | 1.80 ± 0.83 | 1.00 ± 0.72 | 0.67 ± 0.56 | 1.00 ± 0.00 |
| WBC (×$10^9$/L) | 2.77 ± 0.28 | 3.75 ± 0.74 | 3.18 ± 0.66 | 3.65 ± 0.51 | 3.15 ± 0.58 |
| Neutrophils (×$10^9$/L) | 22.40 ± 0.89 | 22.60 ± 2.88 | 23.00 ± 1.73 | 20.67 ± 2.52 | 24.33 ± 1.53 |

Group A (Control), Group B (Cisplatin-only (10 mg/kg, i.p), Group C: Administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (100 mg/kg, orally. Group D: Administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (200 mg/kg, orally). Group E: Administered Cisplatin (10 mg/kg, i.p.) and Gallic acid (100 mg/kg, orally). Values were expressed as mean ± SD, and significance was measured at P<0.05. Superscripts a, b, c,d, and e show significant difference when the groups they denote and the groups A-E on which they appear were compared.

**Table 8.** Serum chemistry profile.

| Parameter | A | B | C | D | E |
|---|---|---|---|---|---|
| Total Protein (g/dL) | 8.40 ± 0.47 | 8.53 ± 0.68 | 8.80 ± 0.29 | 7.66 ± 0.77$^{c}$ | 8.08 ± 0.43 |
| Albumin (g/dL) | 3.30 ± 0.50 | 3.50 ± 0.50 | 3.02 ± 0.27 | 2.86 ± 0.59 | 3.14 ± 0.24 |
| Globulin (g/dL) | 5.10 ± 0.20 | 5.00 ± 0.48 | 4.86 ± 0.21 | 4.80 ± 0.41 | 4.94 ± 0.32 |
| A/G Ratio | 0.65 ± 0.12 | 0.73 ± 0.01 | 0.62 ± 0.07 | 0.59 ± 0.10 | 0.64 ± 0.06 |
| AST (units/L) | 46.80 ± 4.09$^{b}$ | 56.76 ± 5.25$^{acde}$ | 45.80 ± 1.64$^{b}$ | 44.20 ± 5.98$^{b}$ | 44.20 ± 1.48$^{b}$ |
| ALT (units/L) | 32.60 ± 2.41$^{b}$ | 38.30 ± 0.84$^{ade}$ | 34.20 ± 0.83 | 31.00 ± 4.42$^{b}$ | 33.00 ± 0.71$^{b}$ |
| ALP (units/L) | 114.20 ± 10.16 | 120.00 ± 12.52 | 109.20 ± 4.66 | 103.20 ± 18.47 | 122.80 ± 4.21 |
| BUN (mmol/dL) | 17.08 ± 0.72$^{b}$ | 23.55 ± 0.89$^{a}$ | 15.64 ± 2.44$^{b}$ | 17.28 ± 1.03$^{b}$ | 16.98 ± 0.55$^{b}$ |
| Creatinine (mg/dL) | 0.70 ± 0.07$^{b}$ | 1.21 ± 0.08$^{acde}$ | 0.64 ± 0.05$^{b}$ | 0.62 ± 0.11$^{b}$ | 0.66 ± 0.05$^{b}$ |

Group A (Control), Group B (Cisplatin-only (10 mg/kg, i.p), Group C: Administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (100 mg/kg, orally. Group D: Administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (200 mg/kg, orally). Group E: Administered Cisplatin (10 mg/kg, i.p.) and Gallic acid (100 mg/kg, orally). Values were expressed as mean±SD, and significance was measured at p<0.05. Superscripts a, b, c,d, and e show a significant difference when the groups they denote and the groups A-E on which they appear were compared.

**Table 9.** Electrocardiographic parameters.

| Parameter | A | B | C | D | E |
|---|---|---|---|---|---|
| Heart Rate (bpm) | 207.29 ± 20.48 | 203.50 ± 41.68 | 220.00 ± 44.55 | 241.00 ± 27.25 | 267.00 ± 70.56 |
| P wave (ms) | 19.25 ± 6.89 | 18.00 ± 11.28 | 14.75 ± 4.57 | 22.00 ± 6.58 | 26.25 ± 13.69 |
| PR interval (ms) | 37.00 ± 23.76 | 34.50 ± 24.15 | 37.50 ± 11.39 | 36.25 ± 16.50 | 52.00 ± 24.79 |
| QRS duration (ms) | 14.75 ± 1.26$^{bce}$ | 17.75 ± 1.26 | 18.00 ± 2.16$^{a}$ | 15.75 ± 1.71 | 18.50 ± 1.00$^{a}$ |
| QT interval (ms) | 109.50 ± 37.60 | 89.75 ± 12.57 | 108.29 ± 20.55 | 96.00 ± 11.17 | 99.50 ± 22.50 |
| RS amplitude (µV) | 200.75 ± 62.98 | 163.90 ± 21.50 | 208.00 ± 56.13 | 131.00 ± 17.45 | 184.25 ± 40.61 |

Group A (Control), Group B (Cisplatin-only (10 mg/kg, i.p), Group C: Administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (100 mg/kg, orally. Group D: Administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (200 mg/kg, orally). Group E: Administered Cisplatin (10 mg/kg, i.p.) and Gallic acid (100 mg/kg, orally). Values were expressed as mean±SD and significance was measured at P<0.05. Superscripts a, b, c,d, and e show significant difference when the groups they denote and the groups A-E on which they appear were compared.

**Table 10.** Blood pressure parameters.

| Parameter | Group A | Group B | Group C | Group D | Group E |
|---|---|---|---|---|---|
| Systolic BP (mmHg) | 110.92 ± 21.88$^{b}$ | 155.70 ± 23.33$^{acde}$ | 125.54 ± 13.77$^{b}$ | 118.17 ± 12.08$^{b}$ | 128.38 ± 16.97$^{b}$ |
| Diastolic BP (mmHg) | 80.67 ± 13.85 | 105.43 ±13.07$^{e}$ | 89.54 ± 12.31 | 81.65 ± 19.98 | 72.95 ± 15.10$^{b}$ |
| Mean Arterial Pressure (MAP, mmHg) | 88.58 ± 15.65$^{b}$ | 119.17 ± 16.64$^{a}$ | 101.13 ± 12.18 | 94.78 ± 16.85 | 90.61 ± 17.99 |

Group A (Control), Group B (Cisplatin-only (10 mg/kg, i.p), Group C: Administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (100 mg/kg, orally. Group D: Administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (200 mg/kg, orally). Group E: Administered Cisplatin (10 mg/kg, i.p.) and Gallic acid (100 mg/kg, orally). Values were expressed as mean±SD and significance was measured at P<0.05. Superscripts a, b, c,d, and e show significant difference when the groups they denote and the groups A-E on which they appear were compared.

waveforms, especially the QRS complex, which had a significant alteration. Groups C, D, and E exhibited improved cardiac electrical activity, with Group D showing the best stabilization of HR and QRS duration, suggesting cardioprotective effects (Table 9).

## Blood pressure measurement

Similarly, cisplatin significantly increased systolic, diastolic, and mean arterial pressures beyond normal values showing the development of hypertension. FE and GA treatments, however, reduced these values in their respective groups (Table 10).

## Histological findings of the kidney

Histological examination of the kidney tissues revealed varying degrees of pathological changes across the experimental groups. Plates A and C showed no significant lesions, with normal glomerular and tubular structures

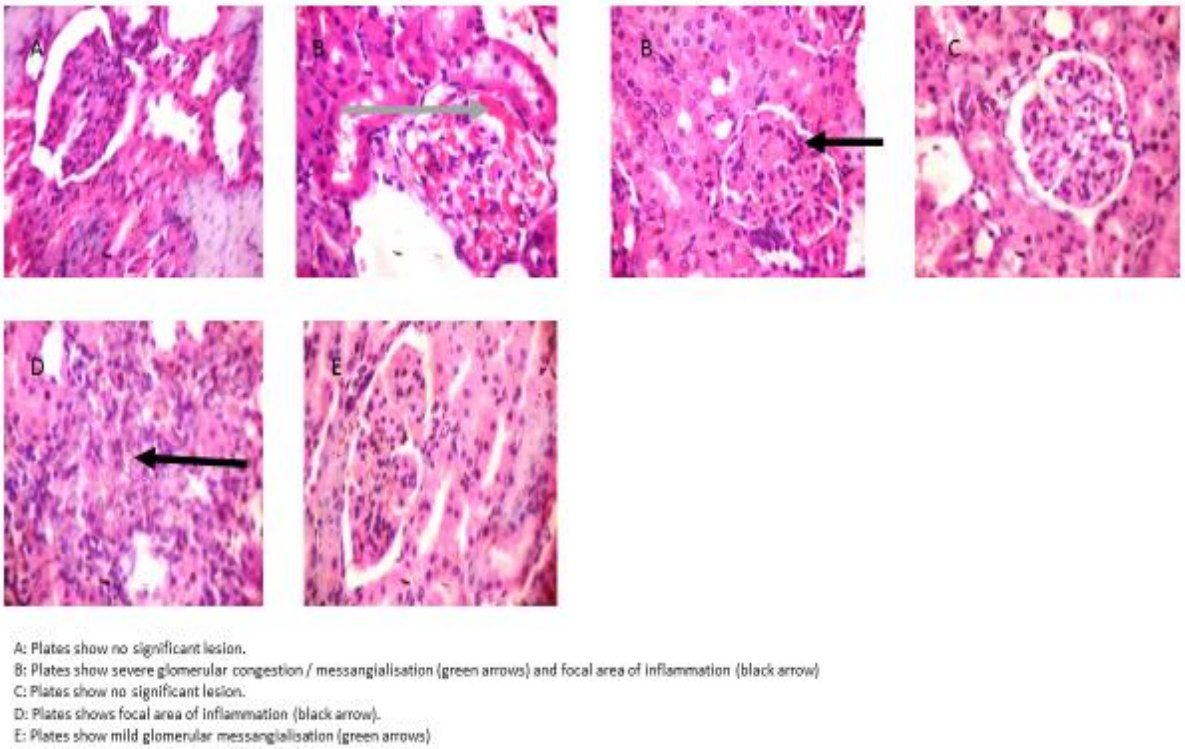


**Figure 1.** Histological findings of the kidney tissues of rats treated with cisplatin, *F. exasperate,* and Gallic. Group A (Control), Group B (Cisplatin-only (10 mg/kg, i.p), Group C: Administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (100 mg/kg, orally. Group D: Administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (200 mg/kg, orally). Group E: Administered Cisplatin (10 mg/kg, i.p.) and Gallic acid (100 mg/kg, orally).

preserved. In contrast, Plate B demonstrated severe glomerular congestion and mesangial expansion, as indicated by green arrows, alongside a focal area of inflammation (black arrow), suggesting marked glomerular injury. Plate D also revealed a localized inflammatory infiltrate (black arrow), while Plate E showed mild mesangial expansion (green arrows), indicative of early or resolving glomerular pathology (Figure 1).

### Histological findings of the heart

Examination of the heart tissues showed largely preserved myocardial architecture in most groups. Plates A, C, D, and E revealed no significant histological alterations, indicating normal cardiac muscle fibers. However, Plate B displayed a focal area of myocardial inflammation (black arrow), which could reflect a mild inflammatory or degenerative process affecting the myocardium (Figure 2).

### Histological findings of the liver

Histological evaluation of the liver, kidney, and heart tissues revealed varying degrees of lesions among the experimental groups. In the liver, Plates A and E showed no significant histological lesions, indicating preserved hepatic architecture. However, Plate B revealed focal portal congestion (green arrow) and mild disseminated infiltration of Zone B by inflammatory cells (black arrow), suggestive of an inflammatory response. Plate C showed focal portal congestion as indicated by the blue arrow, while Plate D also exhibited focal portal congestion (black arrow), reflecting mild hepatic vascular disturbances (Figure 3).

## DISCUSSION

Cancer management has advanced through various treatment options, including surgical intervention (Papavramidou *et al*., 2010), chemotherapy (Makovec, 2019), and radiotherapy. Despite their effectiveness, these modalities, particularly chemotherapy, are often associated with severe adverse effects and systemic toxicities. Chemotherapeutic agents, such as reducing agents or alkylating agents like cisplatin, are effective but pose significant risks. Cisplatin remains one of the most frequently used platinum-based chemotherapeutic agents due to its broad-spectrum efficacy against various cancers

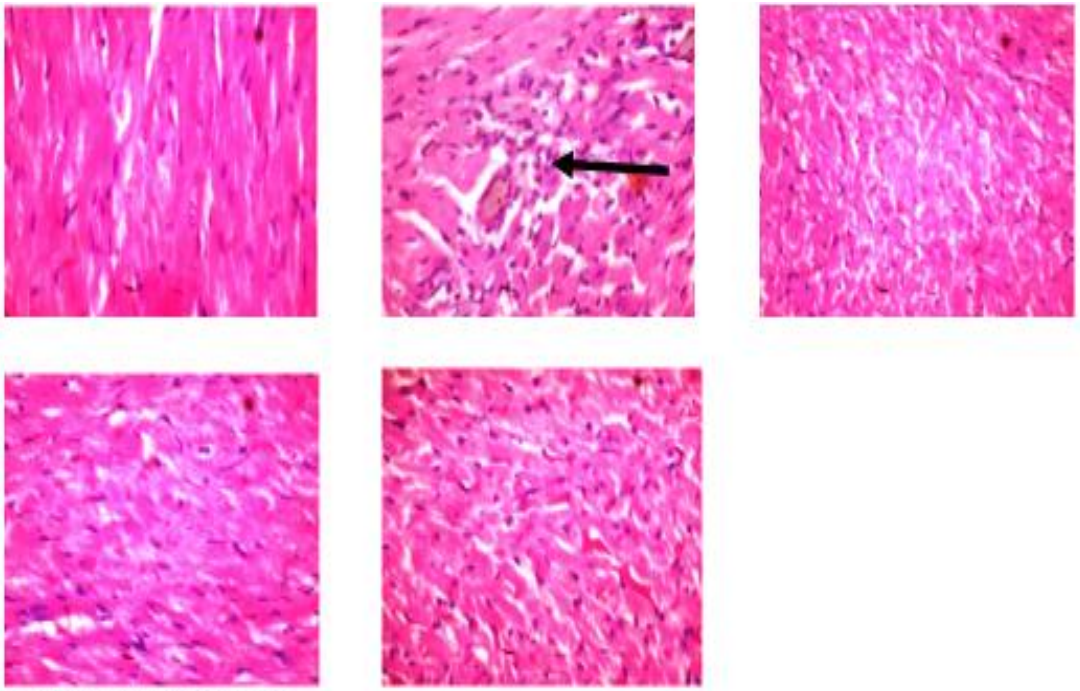


**Figure 2.** Histological findings of the heart tissues of rats treated with cispatin, *F. exasperate,* and gallic. Group A (Control), Group B (Cisplatin-only (10 mg/kg, i.p), Group C: Administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (100 mg/kg, orally. Group D: Administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (200 mg/kg, orally). Group E: Administered Cisplatin (10 mg/kg, i.p.) and Gallic acid (100 mg/kg, orally).

and sarcomas (Makovec, 2019). However, its clinical utility is limited by its dose-dependent toxicity, often affecting the kidneys, liver, gastrointestinal tract, cardiovascular system, and hematopoietic tissues (Dasari *et al*., 2022). The mechanism of this toxicity involves disruptions in calcium signaling, facilitated by copper transporters, leading to excessive generation of reactive oxygen species and oxidative stress (Lin *et al*., 2022).

This study was therefore designed to investigate potential strategies that could mitigate the toxicity of cisplatin and make it safer for clinical use. Our results demonstrated a significant increase in markers of oxidative stress, such as hydrogen peroxide ($H_2O_2$) and malondialdehyde (MDA) in the heart and kidney tissues of rats administered with cisplatin. These findings are consistent with the reports of Lin *et al*. (2022), who noted substantial elevations in oxidative stress biomarkers following cisplatin treatment. Co-treatment with *Ficus exasperata* (FE) extract and gallic acid led to a significant reduction in these markers, with the 200 mg/kg FE group showing the most pronounced improvement. In tandem, antioxidant enzyme levels (GSH, GPx, GST, and SOD) were significantly enhanced in the treated groups, particularly in groups C, D, and E, compared to the cisplatin-only group. These observations suggest that *Ficus exasperata* conferred substantial antioxidant protection in a dose-dependent manner.

These findings are in alignment with those of Oladele *et al*. (2017), who demonstrated the antioxidant potential of *Ficus exasperata* in ameliorating arsenate-induced oxidative stress. Similar antioxidant effects of gallic acid in mitigating chemotherapeutic toxicity have also been reported (Oyagbemi *et al*., 2016; Omobowale *et al*., 2018), supporting our current observations.

Furthermore, serum myeloperoxidase (MPO), a marker of inflammation, was elevated in cisplatin-treated rats and significantly reduced in the treated groups. Serum nitric oxide (NO) levels, which were suppressed in the cisplatin group, were restored in the medicated groups, further indicating improved vascular function and reduced oxidative burden. This agrees with Babatunde *et al*. (2022), who reported the ability of *Ficus exasperata* to restore NO levels and mitigate inflammatory damage.

Among the treatment groups, the 200 mg/kg FE group (Group D) consistently showed the lowest markers of oxidative stress and the highest antioxidant enzyme activity, followed by the 100 mg/kg FE (Group C) and gallic acid (Group E). This clearly suggests a dose-dependent

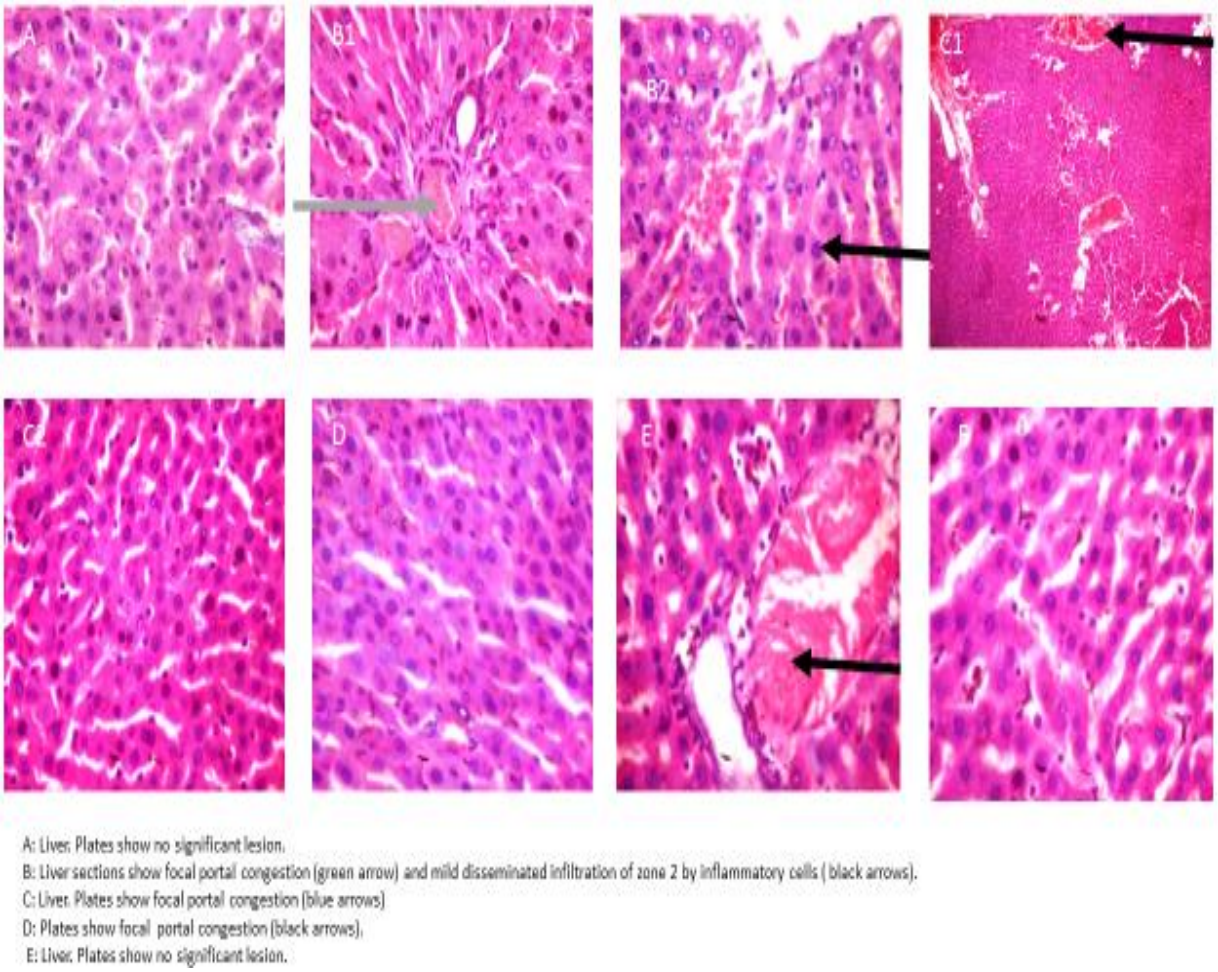


**Figure 3.** Histological findings of the kidney tissues of rats treated with cispatin, *F. exasperate,* and gallic. Group A (Control), Group B (Cisplatin-only (10 mg/kg, i.p), Group C: Administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (100 mg/kg, orally. Group D: Administered Cisplatin (10 mg/kg, i.p.) and *Ficus exasperata* extract (200 mg/kg, orally). Group E: Administered Cisplatin (10 mg/kg, i.p.) and Gallic acid (100 mg/kg, orally).

antioxidant activity of *Ficus exasperata*, corroborating previous studies (Karale *et al.*, 2017).

Cisplatin-induced elevations in serum ALT, AST, ALP, creatinine, and total bilirubin levels confirmed liver and kidney dysfunction. However, co-treatment with FE extract or gallic acid ameliorated these biochemical alterations, suggesting hepatoprotective and nephroprotective effects. These findings are supported by similar reports on the protective effects of plant extracts in drug-induced organ damage (Adetuyi *et al*., 2022).

While cisplatin administration caused only mild reductions in hematological parameters such as hemoglobin, RBC, PCV, and platelets, these values were slightly improved in the treated groups. An increase in white blood cells, especially in the cisplatin group, suggests an inflammatory response, which was normalized in the FE and GA treated groups. These observations are in line with the findings of Bagavan *et al*. (2011) and Karale *et al*. (2017), which collectively reported that phytochemical-rich plant extracts can preserve hematopoiesis and reduce leukocytosis during chemotherapeutic stress.

Additionally, cisplatin-treated rats exhibited elevated systolic and diastolic blood pressures, indicative of cardiovascular strain. Treatment with FE and gallic acid significantly reduced blood pressure levels, particularly in the 200 mg/kg FE group. This finding is consistent with the study by Ajeigbe *et al*. (2021), which showed that *Ficus* species can modulate blood pressure through antioxidant pathways and inhibition of enzymes such as arginase and angiotensin-converting enzyme.

Taken together, our results demonstrate that *Ficus exasperata* extract at 200 mg/kg confers the greatest protection against cisplatin-induced oxidative damage, outperforming both the lower dose of FE and gallic acid. The dose-dependent nature of its protective effect suggests that optimization of dosing could enhance its therapeutic utility.

## Conclusion

This study investigated the ameliorative potential of ethanol extract of *Ficus exasperata* and gallic acid on cisplatin-induced cardio-renal oxidative stress in Wistar rats. Cisplatin administration led to significant oxidative damage, characterized by increased markers of oxidative stress and reduced levels of endogenous antioxidants. Treatment with *Ficus exasperata* and gallic acid effectively reversed these changes, improving antioxidant enzyme activity and mitigating tissue damage.

The findings show that the 200 mg/kg dose of *Ficus exasperata* extract provided superior protection compared to both the 100 mg/kg dose and gallic acid, suggesting a dose-dependent effect. These results underscore the potential of *Ficus exasperata* as a natural chemoprotective agent capable of reducing cisplatin-induced toxicity. Future studies should explore its bioactive constituents, long-term safety, and mechanisms of action, with a view toward its potential clinical application in oncology supportive care.

## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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