Al-Rafidain J Med Sci. 2026;10(2):92-97.
DOI: https://doi.org/10.54133/ajms.v10i2.2691

AJMS

Online ISSN (3219-2789)

Research Article

Modulating Effects of Fimasartan and Omega-3 on Cisplatin-Induced Testicular Toxicity in Rats

Victoria Saad Kareem*[1], Ali Faris Hassan[2]

[1]*Marjan Teaching Hospital, Babylon, Iraq;* [2]*Department of Pharmacology and Toxicology, College of Pharmacy, University of Baghdad, Baghdad, Iraq*

Received: 3 January 2026; Revised: 26 March 2026; Accepted: 2 April 2026

Abstract

Background: Cisplatin is a widely used antineoplastic drug in different types of cancers (ovarian, testicular, and hematological) with several types of adverse effects, including testicular toxicity. Fimasartan is a newer angiotensin-receptor blocker (ARB) that has antioxidant and anti-inflammatory properties. Omega-3 is an unsaturated fatty acid that has antioxidant and anti-inflammatory effects. ***Objective***: to evaluate the protective effects of fimasartan alone or in combination with omega-3 against cisplatin testicular toxicity. ***Methods***: Thirty Wistar rats were divided into five groups: control group, cisplatin-treated group, fimasartan+cisplatin group, fimasartan+omega-3+cisplatin group, and omega-3+cisplatin group. Treatments were administered for 10 consecutive days. On day 10, a single intraperitoneal dose of cisplatin (7mg/kg) was given to induce testicular toxicity. On day 11, animals were sacrificed. Testicular tissue homogenates were used to measure malondialdehyde (MDA), reduced glutathione (GSH), and superoxide dismutase (SOD). Serum levels of testosterone and inhibin-B were measured using ELISA. Histopathological examination of the testes was also performed. ***Results***: Cisplatin administration significantly increased MDA levels and significantly decreased GSH, SOD, testosterone, and inhibin-B levels compared with the control group. Treatment with fimasartan alone or in combination with omega-3 significantly attenuated these alterations and improved histopathological changes in testicular tissue. ***Conclusions***: Fimasartan exerts protective effects against cisplatin-induced testicular toxicity through its antioxidant and reducing oxidative stress effects, and its combination with omega-3 enhances these protective effects.

Keywords: Antioxidant; Cisplatin; Fimasartan; Omega-3; Testicular toxicity.

تأثير الفيماسارتان وأوميغا-3 المضاد لتسمم خصية الجرذان الناتج عن السيسبلاتين

الخلاصة

الخلفية: السيزبلاتين على نطاق واسع كدواء مضاد للأورام في أنواع مختلفة من السرطان (المبيض، الخصية، الدم) مع العديد من الآثار الجانبية بما في ذلك سمية الخصية، أما الفيماسارتان فهو أحدث دواء من مثبطات مستقبلات الأنجيوتنسين II وله خصائص مضادة للأكسدة ومضادة للالتهابات، وأوميغا 3 هو حمض دهني متعدد غير مشبع وله تأثيرات مضادة للأكسدة ومضادة للالتهابات. **الهدف**: تقييم التأثيرات الوقائية للفيماسارتان وحده أو بالاشتراك مع أوميغا-3 ضد سمية السيسبلاتين على الخصيتين. **الطرائق**: تم تقسيم ثلاثين فأراً من سلالة ويستر إلى مجموعات مختلفة (مجموعة التحكم، مجموعة التحريض، مجموعة فيماسارتان، مجموعة أوميغا، مجموعة أوميغا + فيماسارتان). في نهاية التجربة، تم تضحية الحيوانات لقياس معايير مختلفة (الجلوتاثيون، مالوندیالدهید، سوبرأكسيد ديسميوتاز، التستوستيرون، مثبط بيتا) وإجراء اختبار نسيجي مرضي. **النتائج**: بعد إعطاء السيسبلاتين عن طريق الحقن داخل الصفاق للمجموعات المختلفة، لوحظ ارتفاع في مستوى مالوندیالدهید وانخفاض في (الجلوتاثيون، سوبرأكسيد ديسميوتاز، التستوستيرون، مثبط بيتا) وتغيرات نسيجية مرضية في مجموعة التحريض. وقد تم تخفيف هذه التأثيرات بإعطاء فيماسارتان وحده ومع أوميغا-3. **الاستنتاجات**: يتمتع فيماسارتان بتأثيرات وقائية ضد سمية السيسبلاتين على الخصيتين عن طريق تقليل الإجهاد التأكسدي، وبيروكسيد الدهون، وزيادة مضادات الأكسدة.

* ***Corresponding author***: Victoria S. Kareem. Marjan Teaching Hospital, Babylon, Iraq; Email: fiktoria.saad2200p@copharm.uobaghdad.edu.iq

Article citation: Kareem VS, Hassan AF. Modulating Effects of Fimasartan and Omega-3 on Cisplatin-Induced Testicular Toxicity in Rats. *Al-Rafidain J Med Sci.* 2026;10(2):92-97. doi: https://doi.org/10.54133/ajms.v10i2.2691

INTRODUCTION

The testes are one of the main structures of the male reproductive system. Testes are responsible for many physiological functions in males. These functions include production and maturation of sperm in a process called spermatogenesis, beside steroidogenesis, which includes production of diverse male sex hormones like testosterone (which is the main androgenic hormone) that is responsible for the development of males, bone synthesis, and mood [1]. Synthesis and release of male sex hormones (mainly testosterone) are controlled by anterior pituitary gland hormones follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH is the hormone that is responsible for spermatogenesis in the testis. Exposure to certain chemicals, heavy metals like lead, drugs like cyclophosphamide, and environmental factors like heat had a deleterious influence on testicular physiological functions [2]. These factors increase oxidative stress inside the testes, damage or disrupt the blood-testis barrier, directly damage germ cells, and/or interfere with hormonal regulation. All these effects refer to testicular toxicity. Testicular toxicity is a crucial and critical pathological condition because it

leads to infertility, hormonal imbalance, and/or testicular atrophy [3]. Chemotherapy is a type of antibiotic used for its cytotoxicity against cancer cells; it is used to cure the patients from cancer, prevent cancer cell division, or for palliative care. The most major problem with chemotherapeutic drugs is their selectivity, in which some healthy cells (not cancerous cells) are affected by their action in different organs, raising many adverse effects for cancer [4]. The testis is highly vulnerable to toxic insults of chemotherapy due to its high metabolic rate and richness in blood vessels, besides the presence of rapidly dividing germ cells that increase susceptibility to DNA damage [5,6]. Cisplatin is widely used and considered the gold standard in many types of solid tumors, including lung, breast, testicular, ovarian, and bladder cancers [7]. Cisplatin is a prodrug molecule after entry to cancer cells. It forms reactive platinum complexes, which create intra-strand and inter-strand cross-links by binding covalently to guanine bases in DNA. This in turn distorts the DNA helix, inhibiting replication and transcription, triggering DNA damage response, cell cycle arrest (G2/M), and ultimately apoptosis (programmed cell death) [8]. The cure rates of use of cisplatin (Cis)-based chemotherapy are higher, up to 90%, in most frequent malignant cancers. Testicular dysfunction and infertility associated with Cis therapy are of particular concern, especially for young men of reproductive age [9]. Cisplatin has a direct effect on mitochondrial DNA (mtDNA); induced ROS generation occurs as a consequence of its mitochondrial effects [10]. Mitochondria are considered one of the most important endogenous sources of reactive oxygen species (ROS). As its main role is to produce cell energy by oxidative phosphorylation. Cisplatin has a direct effect on mtDNA; induced ROS generation occurs as a consequence of its mitochondrial effects [11]. Fimasartan, the ninth and most recent angiotensin II receptor blocker (ARB), was approved in 2010 for the treatment of hypertension [12, 13]. Fimasartan is a pyrimidin-4(3H)-one derivative of losartan in which the imidazole ring has been replaced with a change that provides higher potency and longer duration than losartan. Fimasartan exhibits slow dissociation and irreversible binding at the angiotensin II type 1 receptor, while losartan competes with angiotensin II, fimasartan acts more like a non-competitive, insurmountable antagonist. [14]. Renin-angiotensin system blockade has antihypertensive, antifibrotic, anti-inflammatory, and antioxidant effects [15]. The renin-angiotensin system (RAS) blockage with ARBs is highly effective in slowing the progression of kidney disease in humans and experimental animals [15]. Omega-3 fatty acids are long-chain polyunsaturated fatty acids. It's considered an essential fatty acid because of the inability of the human body to produce this fatty acid directly. Omega-3 has different bioactive families, which are necessary for the growth of the body; these fatty acids include eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and the less prevalent docosapentaenoic acid (DPA) [16]. EPA and DHA exhibited positive effects on multiple metabolic pathways, such as those involved in reducing serum triglycerides and glucose response, vascular endothelial function, platelet aggregation, regulation of the inflammatory response, and improvement of the myocardial, brain, and immune functions [17-19]. This study aims to evaluate the protective effects of fimasartan alone or in combination with omega-3 against cisplatin testicular toxicity.

METHODS

Materials and chemical reagents

Fimasartan was purchased from MedChemExpress, USA. Cisplatin was obtained from Accord Healthcare, UK. Omega-3 was purchased from Nutrient Life, USA. Commercial ELISA kits for the determination of reduced glutathione (GSH), malondialdehyde (MDA), superoxide dismutase (SOD), testosterone, and inhibin-B were obtained from Elabscience, USA.

Study design and setting

In the present study, 30 Wistar albino rats were obtained from the animal house at the College of Pharmacy/University of Baghdad. The rats were between 8 and 10 weeks old and weighed between 100 and 125 grams. Prior to treatment, the animals were subjected to a two-week acclimatization period in the laboratory. Complimentary water and a regular food plan were given. The temperature was meticulously regulated at 25 ± 5ºC, while the environment was upheld with 12-hour alternating periods of light and darkness and suitable levels of humidity. The study methods and ethics were granted approval by the Research Ethics Committee of the College of Pharmacy at the University of Baghdad (REC02205111A on 3/4/2025).

Experimental procedures

The rats are randomly allocated into 5 groups of 6 animals as follows: Group I: Animals were orally administered a suspension of carboxymethylcellulose (CMC) (0.4 ml/day) by rats' oral gavage for 10 successive days. Group II: Animals were orally administered a suspension of 0.4 ml/day CMC by rats' oral gavage for 10 successive days; then on day 10, the animals were injected intraperitoneally (I.P.) with a single dose of 7 mg/kg cisplatin [20]. Group III: Animals were orally-received fimasartan at a dose of 10 mg/kg/day for 10 successive days; and, on day 10, the animals were I.P. injected with a single dose of 7 mg/kg cisplatin [21]. Group IV: Animals were orally receiving fimasartan at a dose of 10 mg/kg/day. + omega-3 at a dose of 400 mg/kg/day for 10 successive days, and on day 10, the animals were I.P. injected with a single dose of 7 mg/kg cisplatin. Group V: Animals received omega-3 orally at a dose of 400 mg/kg B.W. [22] for 10 successive

days; and on day 10, the animals were injected (I.P.) with a single dose of 7 mg/kg cisplatin. On day 11, animals were anesthetized using diethyl ether and then killed by cervical dislocation to ensure death before tissue collection. Blood samples were collected, and the right testis was removed for histopathological analysis, while the left was for tissue homogenization. Enzyme-Linked Immunosorbent Assay (ELISA) tests were used to measure testosterone and inhibin-B hormone levels in serum, while MDA, GSH, and SOD were measured in testicular tissue homogenate, and a histopathology study was done.

Statistical analysis

Data were expressed as mean ± standard deviation (SD). Statistical analysis was performed using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test for multiple comparisons. p-values < 0.05 were considered statistically significant.

RESULTS

As shown in Table 1, the cisplatin-treated group (group II) exhibited a significant decrease in antioxidant biomarkers, including reduced glutathione (GSH) and superoxide dismutase (SOD) ($p< 0.05$), compared to the control group (group I).

Table 1: Effects of Fimasartan and/or Omega 3 on different antioxidant parameters in cisplatin induce testicular toxicity

Animal group	GSH (mg/L)	SOD (ng/ml)	MDA (ng/ml)
Group I(control)	27.40±2.66^{a}	1.99±0.63^{a}	213.5±2.49^{a}
Group II (cisplatin)	6.39±1.33^{b}	0.36±0.08^{b}	714.6±212.7^{b}
Group III (fimasartan)	15.12±3.37^{c}	1.23±0.12^{c}	248.5±18.57^{ab}
Group IV(fimasartan+omega-3)	21.07±3.44^{ad}	1.46±0.25^{ac}	265.3±41.20^{ab}
Group V(omega-3)	20.26±2.72^{ad}	1.50±0.55^{ac}	200.8±4.03^{c}

Data is express as mean±SD, number of animals in each group=6. GSH: reduced glutathione, SOD: superoxide dismutase, MDA: malondialdehyde. Different superscripts (a,b,c,d) represent significant differences.

In contrast, a significant increase in malondialdehyde (MDA) levels was observed in the cisplatin group ($p< 0.05$). Treatment with fimasartan (group III) resulted in a significant elevation of GSH and SOD levels ($p< 0.05$), along with a significant reduction in MDA levels compared to the cisplatin group. Moreover, the combined treatment with fimasartan and omega-3 (group IV) demonstrated a more pronounced effect, with a highly significant increase in GSH and SOD levels ($p< 0.01$) and a significant decrease in MDA levels compared to the cisplatin group. As presented in Table 2, the cisplatin group (group II) showed a significant reduction ($p< 0.05$) in serum testosterone and inhibin-B levels compared to the control group.

Table 2: Effects of Fimasartan and/or Omega-3 on different male hormones in cisplatin induce testicular toxicity

Animal group	Testosterone (pg/ml)	Inhibin-b (pg/ml)
Group I(control)	3.43±0.88^{a}	300.8±58.42^{a}
Group II (cisplatin)	0.43±0.05^{b}	138.2±28.20^{b}
Group III (fimasartan)	1.47±0.14^{c}	286.7±49.50^{ac}
Group IV(fimasartan+omega-3)	2.68±0.44^{d}	288.5±41.85^{a}
Group V(omega-3)	2.29± 0.79^{d}	332.2±21.93^{a}

Data is express as mean±SD, number of animals in each group=6 Different superscripts (a,b,c,d) represent significant differences.

Treatment with fimasartan (group III) significantly increased both testosterone and inhibin-B levels ($p< 0.05$) relative to the cisplatin group. Notably, the combination therapy (group IV) produced a highly significant improvement ($p< 0.01$) in both parameters compared to the cisplatin group. In Figure 1a, the control group section of the testis (control group) shows a normal appearance with the shape and size of seminiferous tubules that are comprised of well-differentiated germinal cells (g), lumina (L), and interstitium (arrows). In Figure 1b, a section of testis (cisplatin) shows severe deterioration of seminiferous tubules that showed severe oligospermia (arrows) and apoptosis at the magnification metric (H&E stain, 100x). Figure 1c shows normal-sized seminiferous tubules with regular shape, normal spermatogenesis, and little oligospermia with necrosis of spermatocyte cells (black arrows) and normal interstitium (red arrow) (H&E stain, 100x). Figure 1d shows normal-sized seminiferous tubules with regular shapes, normal spermatogenesis, and few macrovacuoles within spermatocyte cells (arrows). Meanwhile, Figure 1e shows normal-sized seminiferous tubules with regular shapes, normal spermatogenesis, normal interstitium (red arrows), and few macrovacuoles within spermatocyte cells (m) (H&E stain, 100x).

DISCUSSION

The present findings are consistent with previous studies demonstrating the deleterious effects of cisplatin on testicular function. Cisplatin has been shown to induce DNA-adducts formation and excessive generation of reactive oxygen species (ROS), leading to mitochondrial oxidative stress and subsequent cellular damage [23]. This oxidative insult contributes to the destruction of both Leydig and Sertoli cells through activation of apoptotic pathways, particularly via caspase-dependent mechanisms [24,25], ultimately resulting in decreased levels of testosterone and inhibin-B [26]. Moreover, cisplatin has been reported to activate multiple signaling pathways, including mitogen-activated protein kinases (MAPK), nuclear factor kappa B (NF-κB), and inducible

nitric oxide synthase (iNOS), all of which play critical roles in the pathogenesis of testicular injury.

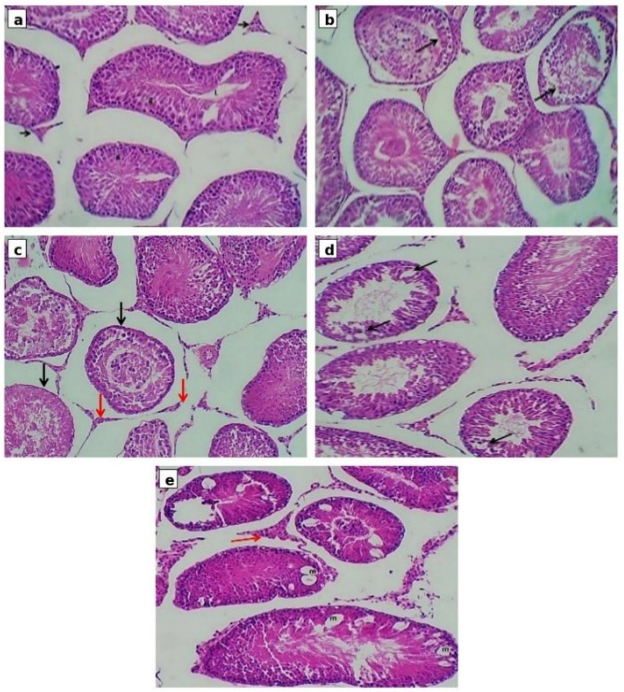

Figure 1: Histopathological image of rat testis, group I normal group (a), group II cisplatin group (b), group III fimasartan group+cisplatin (c), group IV, fimasartan+omega+cisplatin (d), group V omega group+cisplatin (e). Red arrow refers to interstitium, back arrow refers to spermatogenesis, except in group (b) indicated apoptosis.(Magnification 100X: H&E). Histopathological examination of testicular tissue (Figure 1) revealed normal architecture in the control group (Group I), characterized by well-organized seminiferous tubules containing differentiated germ cells, normal lumina, and intact interstitium. In contrast, the cisplatin group (Group II) showed marked degeneration of seminiferous tubules, severe oligospermia, and evident apoptotic changes (H&E stain, 100X). Treatment with fimasartan (Group III) showed partial restoration of testicular structure, with nearly normal seminiferous tubules, mild oligospermia, and some necrotic spermatocytes. The combined treatment group (Group IV) demonstrated substantial improvement, with preserved seminiferous tubule architecture and nearly normal spermatogenesis, although few cytoplasmic vacuoles were observed. Similarly, the omega-3-treated group (Group V) exhibited largely normal histological features with intact seminiferous tubules, normal spermatogenesis, and minimal vacuolization (H&E stain, 100X).

The activation of these pathways enhances inflammatory responses, characterized by elevated levels of pro-inflammatory cytokines such as IL-6, which further amplify oxidative stress and promote cell cycle arrest, thereby impairing spermatogenesis [27,28]. Under oxidative stress conditions, excessive ROS production leads to lipid peroxidation and protein damage, as evidenced by increased levels of malondialdehyde (MDA), a key marker of lipid peroxidation. Concurrently, antioxidant defense systems, including reduced glutathione (GSH) and superoxide dismutase (SOD), become depleted, exacerbating cellular injury [29]. Fimasartan, a blocker of angiotensin II receptors, has demonstrated potent antioxidants and anti-inflammatory properties in previous studies. It has been shown to attenuate oxidative stress and inflammation through upregulation of the Nrf2 signaling pathway, thereby enhancing endogenous antioxidant defenses [30]. Additionally, fimasartan reduces the expression of pro-inflammatory cytokines such as TNF-α and IL-6, while modulating apoptotic pathways by increasing anti-apoptotic Bcl-2 expression and decreasing pro-apoptotic markers including Bax and caspase-3 [31,32]. Given that cisplatin-induced toxicity is associated with elevated IL-6 levels and activation of downstream inflammatory cascades involving TNF-α and IL-1β [33–35], the inhibitory effects of fimasartan on these mediators contribute significantly to its protective role. Furthermore, fimasartan suppresses NF-κB activation, a key regulator of inflammatory responses and iNOS expression, thereby reducing inflammation and preventing apoptosis or necrosis in testicular tissue. These mechanisms collectively enhance cell viability and support testicular function. The activation of Nrf2 signaling is particularly important in preserving sperm quality and hormonal production, including testosterone and inhibin-B, while reducing oxidative stress by decreasing MDA levels and restoring antioxidant markers such as GSH and SOD [36]. Conversely, omega-3 fatty acids confer protective effects via various mechanisms. They are incorporated into cell membranes, improving membrane stability and maintaining tissue integrity while reducing lipid peroxidation and ROS generation [37]. Omega-3 also has anti-apoptotic effects by blocking NADPH oxidase (NOX), which helps cells stay alive and makes hormones like testosterone and inhibin-B [38]. In addition, omega-3 fatty acids enhance antioxidant defense systems by activating Nrf2 and upregulating downstream antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx). They also exert anti-inflammatory effects by increasing anti-inflammatory cytokines such as IL-10 and inhibiting NF-κB signaling and its downstream mediators, including IL-1β and TNF-α [39,40]. We used serum for hormone measurement because endocrine organs secrete into blood; it also gives us a clear picture of overall testicular function, spermatogenic activity, validated assay, and non-invasive method [41, 42], while tissue homogenate was used for GSH, MDA, and SOD for local tissue assessment. It provides an accurate view for oxidative damage, disease diagnosis (diabetic complication, mechanism of toxic agent, and assessment of reproductive toxicity), and therapeutic evaluation [43,44].

Study limitations

This study has some limitations. Sperm count and spermatogenesis parameters were not evaluated, as they are important indicators of reproductive function. In addition, only a single dose of fimasartan was tested, and future studies are recommended to include different doses and additional reproductive parameters.

Conclusion

Fimasartan provides significant protection against cisplatin-induced testicular toxicity through its antioxidant, reducing oxidative stress effects, and anti-apoptotic properties. The combination with omega-3 enhances these protective effects, suggesting a potential therapeutic strategy for reducing chemotherapy-induced reproductive toxicity.

Conflict of interests

The authors declared no conflict of interest.

Funding source

The authors did not receive any source of funds.

Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

REFERENCES

1. Li L, Lin W, Wang Z, Huang R, Xia H, Li Z, et al. Hormone regulation in testicular development and function. *Int J Mol Sci*. 2024;25(11):5805. doi: 10.3390/ijms2511580.
2. Antar SA, Halouani A, Gad C, Al-Karmalawy AA. An overview of the mechanisms of cadmium-induced toxicity in the male reproductive system. *Pharm Sci*. 2024;30:36–53. doi: 10.34172/PS.2023.10.
3. Bhardwaj JK, Panchal H, Saraf P. Cadmium as a testicular toxicant: A review. *J Appl Toxicol*. 2021;41:105–117. doi: 10.1002/jat.4052.
4. Almohammadi A, Alqarni A, Alraddadi R, Alzahrani F. Assessment of patients' knowledge in managing side effects of chemotherapy: Case of King Abdul-Aziz University Hospital. *J Cancer Educ*. 2020;35(2):334–338. doi: 10.1007/s13187-019-01605-4.
5. Alafifi S, Wahdan S, Elsherbiny D, Azab S. Doxorubicin-induced testicular toxicity: Possible underlying mechanisms and promising pharmacological treatments in experimental models. *Arch Pharm Sci Ain Shams Univ*. 2022;6(2):196–207. doi: 10.21608/aps.2022.155127.1098.
6. Howell SJ, Shalet SM. Testicular function following chemotherapy. *Hum Reprod Update*. 2001;7(4):363–369. doi: 10.1093/humupd/7.4.363.
7. Tchounwou PB, Dasari S, Noubissi FK, Ray P, Kumar S. Advances in our understanding of the molecular mechanisms of action of cisplatin in cancer therapy. *J Exp Pharmacol*. 2021;13:303–328. doi: 10.2147/JEP.S267383.
8. Abdel-Latif R, Fathy M, Anwar HA, Naseem M, Dandekar T, Othman EM. Cisplatin-induced reproductive toxicity and oxidative stress: Ameliorative effect of kinetin. *Antioxidants*. 2022;11(5):915. doi: 10.3390/antiox11050915.
9. Fuertes MA, Alonso C, Pérez JM. Biochemical modulation of cisplatin mechanisms of action: Enhancement of antitumor activity and circumvention of drug resistance. *Chem Rev*. 2003;103(3):645–662. doi: 10.1021/cr020010d.
10. Gandin V, Hoeschele JD, Margiotta N. Cisplatin in cancer therapy: Molecular mechanisms of action 3.0. *Int J Mol Sci*. 2023;24. doi: 10.3390/ijms24097917.
11. Marullo R, Werner E, Degtyareva N, Moore B, Altavilla G, Ramalingam SS, et al. Cisplatin induces a mitochondrial-ROS response that contributes to cytotoxicity. *PLoS One*. 2013;8(11):e81162. doi: 10.1371/journal.pone.0081162.
12. Lee HY, Oh BH. Fimasartan: A new angiotensin receptor blocker. *Drugs*. 2016;76(10):1015–1022. doi: 10.1007/s40265-016-0597-2.
13. Drugs C, Data A, Bv I. Fimasartan. *Am J Cardiovasc Drugs*. 2011;11(4):249–252. doi: 10.1007/s40265-016-0592-1.
14. Kim TW, Yoo BW, Lee JK, Kim JH, Lee KT, Chi YH, et al. Synthesis and antihypertensive activity of pyrimidin-4(3H)-one derivatives as losartan analogues for new angiotensin II receptor type 1 (AT1) antagonists. *Bioorg Med Chem Lett*. 2012;22(4):1649–1654. doi: 10.1016/j.bmcl.2011.12.116.
15. Nephrology U, Ospedaliera A, Riuniti O, Diseases R. The role of renin-angiotensin-aldosterone system in the progression of chronic kidney disease. *Kidney Int*. 2005;68:57–65. doi: 10.1111/j.1523-1755.2005.09911.x.
16. Afroze S, Janakiraman AK, Gunasekaran B, Djearamane S, Wong LS. Potentials of omega-3 fatty acids as therapeutic drugs and its obstacles in the pathway: A critical review. *J Pharm Pharmacogn Res*. 2024;12:120–145. doi: 10.56499/jppres23.1689_12.1.120.
17. Gareri P. Omega-3 long-chain polyunsaturated fatty acids in the elderly: A review. *OBM Geriatr*. 2022;6(2):1–28. doi: 10.21926/obm.geriatr.2202180.
18. Hathaway D, Pandav K, Patel M, Riva-Moscoso A, Singh BM, Patel A, et al. Omega-3 acids and COVID-19: A comprehensive review. *Infect Chemother*. 2020;52:478–495. doi: 10.3947/ic.2020.52.4.478.
19. O'Connell TD, Mason RP, Budoff MJ, Navar AM, Shearer GC. Mechanistic insights into cardiovascular protection for omega-3 fatty acids and their bioactive lipid metabolites. *Eur Heart J Suppl*. 2020;22:J3–J20. doi: 10.1093/eurheartj/suaa115.
20. Ateşşahin A, Karahan I, Türk G, Gür S, Yilmaz S, Çeribaşi AO. Protective role of lycopene on cisplatin-induced changes in sperm characteristics, testicular damage and oxidative stress in rats. *Reprod Toxicol*. 2006;21(1):42–47. doi: 10.1016/j.reprotox.2005.06.001.
21. Chang SA, Lim BK, Lee YJ, Hong MK, Choi JO, Jeon ES. A novel angiotensin type I receptor antagonist, fimasartan, prevents doxorubicin-induced cardiotoxicity in rats. *J Korean Med Sci*. 2015;30(5):559–568. doi: 10.3346/jkms.2015.30.5.559.
22. Awad MM, Abd-Ellatif RN, Ibrahim S, Abd Elmaaboud MA, El-Shaer RA. Role of heme oxygenase (HO)-1 enzyme in the protective and therapeutic effect of omega-3 fatty acids on cisplatin-induced hepatic and renal toxicity in rats. *Suez Canal Univ Med J*. 2023;26(1):17–39. doi: 10.21608/scumj.2023.283960.
23. Wang L, He Y, Li Y, Pei C, Olatunji OJ, Tang J, et al. Protective effects of nucleosides-rich extract from Cordyceps cicadae against cisplatin-induced testicular damage. *Chem Biodivers*. 2020;17(11). doi: 10.1002/cbdv.202000462.
24. Park HJ, Kim JS, Lee R, Song H. Cisplatin induces apoptosis in mouse neonatal testes organ culture. *Int J Mol Sci*. 2022;23(21). doi: 10.3390/ijms232113408.
25. Pogach LM, Gould S, Fshuang P. Characterization of cis-platinum-induced Sertoli cell dysfunction in rodents. *Toxicol Appl Pharmacol*. 1989;98:350–365. doi: 10.1016/0041-008X(89)90239-1.
26. Stewart J, Turner KJ. Inhibin B as a potential biomarker of testicular toxicity. *Cancer Biomark*. 2005;1:75–91. doi: 10.3233/CBM-2005-1109.
27. Soni KK, Zhang LT, You JH, Lee SW, Kim CY, Cui WS, et al. The effects of MOTILIPERM on cisplatin-induced testicular toxicity in Sprague-Dawley rats. *Cancer Cell Int*. 2015;15:121. doi: 10.1186/s12935-015-0269-6.
28. Ferreiro ME, Amarilla MS, Glienke L, Méndez CS, González C, Jacobo PV, et al. Inflammatory mediators TNFα and nitric oxide arrest spermatogonia GC-1 cell cycle. *Reprod Biol*. 2019;19(4):329–339. doi: 10.1016/j.repbio.2019.10.002.
29. Brozovic A, Ambriović-Ristov A, Osmak M. Relationship between cisplatin-induced ROS, glutathione and BCL-2 and resistance to cisplatin. *Crit Rev Toxicol*. 2010;40:347–359. doi: 10.3109/10408441003601836.
30. Kim S, Kim SJ, Yoon HE, Chung S, Choi BS, Park CW, et al. Fimasartan protects against renal inflammation and fibrosis in mice with unilateral ureteral obstruction: The possible role of

Nrf2. *Int J Med Sci*. 2015;12(11):891–904. doi: 10.7150/ijms.13187.
31. Roberts AW. Therapeutic development and current uses of BCL-2 inhibition. *Hematology Am Soc Hematol Educ Program*. 2020;2020(1):1–9. doi: 10.1182/hematology.2020000154.
32. Abbas W, Altemimi M, Qassam H, Hameed AA, Zigam Q, Abbas L, et al. Fimasartan ameliorates renal ischemia reperfusion injury via modulation of oxidative stress, inflammatory and apoptotic cascades in a rat model. *J Med Life*. 2022;15(2):241–251. doi: 10.25122/jml-2021-0154.
33. Li W, Khor TO, Xu C, Shen G, Jeong WS, Yu S, et al. Activation of Nrf2-antioxidant signaling attenuates NF-κB inflammatory response and elicits apoptosis. *Biochem Pharmacol*. 2008;76(11):1485–1499. doi: 10.1016/j.bcp.2008.07.029.
34. Cho JH, Choi SY, Ryu HM, Oh EJ, Yook JM, Ahn JS, et al. Fimasartan attenuates renal ischemia-reperfusion injury by modulating inflammation-related apoptosis. *Korean J Physiol Pharmacol*. 2018;22(6):661–670. doi: 10.4196/kjpp.2018.22.6.661.
35. Chung S, Yoon HE, Kim SJ, Koh ES, Hong YA, et al. Oleanolic acid attenuates renal fibrosis in mice with unilateral ureteral obstruction via facilitating nuclear translocation of Nrf2. *Nutr Metab*. 2014;11:2. doi: 10.1186/1743-7075-11-2
36. Ryu S, Shin JS, Cho YW, Kim HK, Paik SH, Lee JH, et al. Fimasartan, an anti-hypertension drug, suppressed inducible nitric oxide synthase expression via NF-κB and AP-1 inactivation. *Biol Pharm Bull*. 2013;36:467–474. doi: 10.1248/bpb.b12-00859.
37. Alramadneh T, Abu-Harirah HA, Saleh IA, Athamneh RY, Abusalah M, Okla MK, et al. Protective effects of omega-3 fatty acids against cisplatin-induced hepatocellular damage and oxidative stress in rats. *Res Square*. 2023. doi: 10.21203/rs.3.rs-3645657/v1.
38. Al-Attar AM, Al-Rethea HA. Chemoprotective effect of omega-3 fatty acids on thioacetamide-induced hepatic fibrosis in male rats. *Saudi J Biol Sci*. 2017;24(4):956–965. doi: 10.1016/j.sjbs.2016.01.029.
39. Adeyemi WJ, Olayaki LA. Diclofenac-induced hepatotoxicity: Low dose of omega-3 fatty acids have more protective effects. *Toxicol Rep*. 2018;5:90–95. doi: 10.1016/j.toxrep.2017.12.002.
40. Eraky SM, Abo El-Magd NF. Omega-3 fatty acids protect against acetaminophen-induced hepatic and renal toxicity in rats through HO-1–Nrf2–BACH1 pathway. *Arch Biochem Biophys*. 2020;686:108387. doi: 10.1016/j.abb.2020.10838740.
41. Kelsey TW, Miles A, Mitchell RT, Anderson RA, Wallace WH. A normative model of serum inhibin B in young males. *PloS One*. 2016;11(4):e0153843. doi: 10.1371/journal.pone.0153843.
42. Guzelce EC, Galbiati F, Goldman AL, Gattu AK, Basaria S, Bhasin S. Accurate measurement of total and free testosterone levels for the diagnosis of androgen disorders. *Best Pract Res Clin Endocrinol Metab*. 2022;36(4):101683. doi: 10.1016/j.beem.2022.101683.
43. Didžiapetrienė J, Kazbarienė B, Tikuišis R, Dulskas A, Dabkevičienė D, Lukosevičienė V, et al. Oxidant/antioxidant status of breast cancer patients in pre-and post-operative periods. *Medicina*. 2020;56(2):70. doi: 10.3390/medicina56020070.
44. Cheng SB, Liu HT, Chen SY, Lin PT, Lai CY, Huang YC. Changes of oxidative stress, glutathione, and its dependent antioxidant enzyme activities in patients with hepatocellular carcinoma before and after tumor resection. *PloS One*. 2017;12(1):e0170016. doi: 10.1371/journal.pone.0170016.