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REVIEW PAPER

Drug-induced nephrotoxicity – a review of therapeutic activity of selenium and zinc in preclinical studies

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ABSTRACT

Introduction and aim. Certain drugs cause nephrotoxicity and renal dysfunction through induction of oxidative stress and activation of inflammatory and apoptotic signaling pathways within the renal tissue. To mitigate drug nephrotoxicity, the therapeutic potential of trace elements such as selenium (Se) and zinc (Zn) has been experimentally explored. The current knowledge and mechanisms are hereby summarized in this review.

Literature search. This narrative review was carried out through a critical assessment of relevant articles published in scientific databases like Google Scholar, PubMed, Scopus, and Web of Science.

Analysis of the literature. The antioxidant, antiapoptotic and anti-inflammatory properties of Se and Zn culminate in their therapeutic activity against drugs nephrotoxicity. The nephroprotective effect of Se and Zn has been characterized with suppression of renal oxidative stress (reduced malondialdehyde, protein cabonyl and elevated levels of superoxide dismutase, glutathione, glutathione peroxidase, catalase, total antioxidant capacity levels); upregulation of anti-apoptotic and anti-inflammatory markers (Bcl-2, heme oxygenase-1, factor related to nuclear factor erythroid 2; downregulation of pro-apoptotic and pro-inflammatory like inducible nitric oxide synthase, nitric oxide, tumor necrosis factor-α, interleukin-6, nuclear factor kappa light chain enhancer of activated B cells NF-κB, and Bax, leading to reparation of renal histomorphology and improved renal function (indicated by reduced serum creatinine, urea, BUN levels).

Conclusion. The therapeutic activity of Se and Zn against drugs nephrotoxicity underscores their potential role in the management of nephrotoxicity due to pharmacotherapy.

Keywords. drugs nephrotoxicity, selenium nephroprotection, zinc nephroprotection

Introduction

The kidney is a vital organ that performs several essential functions in the body, particularly related to maintaining body homeostasis.[1,2] In essence, it plays crucial role in maintaining the overall body health by removing toxic wastes and metabolites, regulating body fluid balance and osmolality, maintaining acid-base equilibrium, secreting hormones, and controlling the arterial pressure.[1,3,4] Due to its essential functions, the kidney is often exposed to and could bioaccumulate potential toxins (regarded as nephrotoxicants or nephrotoxins) which would in turn cause nephrotoxicity.[3,5] Nephrotoxicity thereby involves the degeneration of renal morphological components and loss of their functionality due to the toxic effects of nephrotoxins including chemotherapeutic agents.[2,6] Hence, the critical role of the kidney tissue in the removal of xenobiotics (including chemotherapeutic agents) from the body makes it prone to their toxic effects.

Drug-induced kidney toxicity has been characterized with renal histopathological changes such as ep-

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ithelial necrosis, glomerular congestion, interstitial edema and inflammation, tubular dilatation, which often lead to renal functional impairments and kidney failure.[7-9] The associated impairment of renal function has been further characterized by significant alteration of markers of renal function such as glomerular filtration rate, urine output, serum levels of electrolytes, and waste products of protein and muscle metabolism.[9,10] Essentially, nephrotoxicity is characterized with glomerular damage, inflammation, crystal nephropathy, renal tubular cell toxicity, rhabdomyolysis, and thrombotic microangiopathy.[11,12] As a risk factor of acute kidney injury and chronic kidney disease, nephrotoxicity poses great public health concern that requires effective therapeutic intervention.

Trace elements are essential elements that are required (in very low concentrations) to play an essential role in many physiological and metabolic processes of the body.[13] They have been shown to exhibit antioxidant, anti-inflammatory and anti-apoptotic effects which thereby underscore their therapeutic potential against various tissue pathologies.[14] Accordingly, the therapeutic potential of trace elements has been explored in preclinical studies to mitigate or ameliorate drug-induced nephrotoxicity.

Aim

In this review, the aim was to elaborate on the therapeutic activity of trace elements, including selenium and zinc, against drug nephrotoxicity in preclinical studies. Furthermore, the associated mechanisms of therapeutic activity of the selected trace elements were highlighted.

Literature search

Published articles were sought in multiple scientific databases including Google Scholar, PubMed, Scopus, and Web of Science and assessed to select those that are relevant to the objective of the review. The search keywords included: 'drug nephrotoxicity', 'trace element nephroprotection', 'trace elements mitigate drug nephrotoxicity', 'antioxidants effect of trace elements'. The literature search was conducted between 1 April and 30 April 2025, and articles selected from preliminary search results were further critically evaluated to identify those that contain relevant findings on the therapeutic role of selenium and zinc against drug-induced nephrotoxicity in preclinical studies. The inclusion criteria included only articles that provided relevant findings, articles published in English and in peer-reviewed journals. Other non-compliant articles were excluded from the review.

Analysis of the literature

Induction of oxidative stress and activation of inflammatory and apoptotic signaling pathways within kidney tissue, following exposure to nephrotoxicants (including drugs), have been demonstrated as pivotal cellular mechanisms of the resulting nephrotoxicity.[18] Hence, the antioxidant, anti-inflammatory, and anti-apoptotic properties of selected trace elements (selenium and zinc) underscored the rationale for their therapeutic application to mitigate drug-induced nephrotoxicity in preclinical studies as presented in this review.

Drug-induced nephrotoxicity in preclinical studies

Nephrotoxicity due to drug administration occurs as an adverse effect of pharmacotherapy and commonly presents in the form of acute kidney injury, renal tubular disorders, glomerular damage, and nephrolithiasis and could lead to renal failure.[19] Although, the selected drugs under review have different structural conformation (Fig. 1), preclinical studies have demonstrated their relatively similar nephrotoxic mechanisms (Table 1).

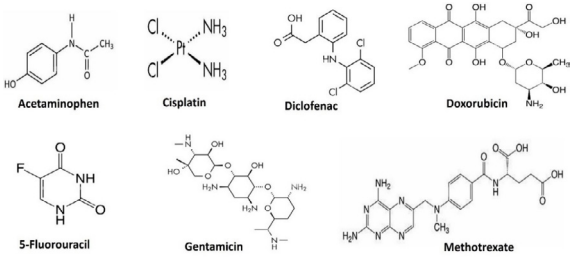

Fig. 1. Molecular structures of selected drugs that cause nephrotoxicity

Acetaminophen (or paracetamol) is a common analgesic and antipyretic agent that has been demonstrated to exhibit nephrotoxicity through the induction of endoplasmic reticulum (ER) stress and apoptosis within kidney tissue.[20] Acetaminophen-induced nephrotoxicity has been characterized by distortion of renal histomorphology, elevated levels of kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), serum blood urea nitrogen (BUN) and creatinine.[20,21] Acetaminophen exposure further caused upregulation of inducible nitric oxide synthase (iNOS), PERK, activating transcription factor 6 (ATF6), nuclear factor kappa-light chain-enhancer of activated B cells (NF-κB), p53, caspases 3 and downregulation of Bcl-2 and Bcl-xL expressions.[20] Acetaminophen-induced nephrotoxicity also caused decline of tissue antioxidant levels, including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), elevated levels of inflammatory markers (tumor necrosis factor-α (TNF-α), IL-1β, IL-33) and apoptotic marker (caspase-3).[21,22] Moreover, acetaminophen exposure caused increase in total oxidant status (TOS), and inhibition of nuclear factor erythroid-related factor 2 (Nrf2) signaling pathway.[22,23]

Furthermore, cisplatin is a common and effective anticancer drug which has been indicated to cause nephrotoxicity by induction of oxidative stress, in-

flammatory response and apoptosis of renal tubular cells.[24] Cellular mechanisms of cisplatin-induced nephrotoxicity included induction of oxidative stress, ER stress, mitochondrial dysfunction, DNA damage and stress responses such as inflammation, autophagy, cell cycle arrest, senescence, and apoptosis.[25] Additionally, exposure to cisplatin caused elevated levels of plasma renal markers including creatinine, urea uric acid and BUN, reduced levels of SOD, CAT, GPx and glutathione (GSH), renal histopathological changes including renal tubular cell death, vacuolization, vascular congestion.[26] Cisplatin-induced nephrotoxicity has been further characterized with increased levels of oxidative stress, inflammatory and apoptotic markers (MDA, NO, iNOS, TNF-α, NF-κB, IL-1β, caspase-3 and Bax).[27,28]

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID), commonly applied as analgesic or anti-inflammatory agent, and has been indicated to cause organ toxicity (like kidney) via increased generation of reactive oxygen species (ROS).[29] Diclofenac-mediated nephrotoxicity has been characterized with elevated levels of protein carbonyl (PC), urea, creatinine, uric acid, MDA, hydrogen peroxide, decreased antioxidant enzyme activities (SOD, CAT, GPx) and reduced antioxidant (GSH). 30, 31, Exposure to Diclofenac exposure further resulted in renal histopathological changes, reduced glomerular filtration rate, up-regulation of inflammatory and apoptotic factors including KIM-1, TNF-α, IL-6, IL-18, NF-κB, STAT3, Bax, p53, HIF-1α, caspase-3, and cyclooxygenase-2 (COX-2) while heme oxygenase-1 (HO-1), Nrf2, adenosine 5'-monophosphate-activated protein kinase (AMPK), and sirtuin-1 (SIRT-1) expressions were downregulated.[32-34]

Doxorubicin is an anthracycline anticancer drug which has been reported to cause a toxic effect on body tissue such as the kidney through ROS production, oxidative stress, apoptosis, inflammation and dysregulated autophagic flow, thereby limiting its clinical application.[35,36] Doxorubicin-induced nephrotoxicity was characterized by a marked decline of activities of antioxidant enzymes (SOD, CAT, GSH), elevated plasma levels of creatinine, urea, uric acid and renal MDA, cholesterol, calcium and sodium concentrations.[37] Moreover, doxorubicin exposure caused renal histopathological changes (including glomerular atrophy, tubular congestion and degeneration, inflammatory cell infiltrations), increased levels of BUN, NO, hydrogen peroxide (H_2O_2), upregulation of NF-κB, IL-1β, IL-6, caspase-3 and elevated apoptotic index.[38,39] Other mechanisms of doxorubicin-induced nephrotoxicity included decline in renal glutathione reductase (GR) activity and elevated levels of TNF- α and plasma neutrophil gelatinase-associated lipocalin (NGAL).[40]

Furthermore, the application of 5-fluorouracil as an anticancer drug has resulted into serious adverse effects, including hepatotoxicity and nephrotoxicity through induction of oxidative stress, inflammation and apoptosis.[41,42] 5-fluorouracil-induced nephrotoxicity has been characterized by renal histopathological changes (including tubular congestion, degeneration and atrophic glomeruli), marked increase in serum levels of uric acid, creatinine, urea, NO and MDA, decreased activity of antioxidant enzymes (CAT, SOD, GPx) and GSH level.[42,43] Other mechanisms of 5-fluorouracil-induced nephrotoxicity included up-regulation of lipocalin-2, KIM-1, increased levels of TNF-α, NF-κB and IL-6 linked with up-regulated expressions of ERK1 / 2 and VCAM-1, down-regulation of IL-10, Nrf2, HO-1, and FXR factors.[44,45] In addition, 5-fluorouracil administration further resulted in an increased Bax/Bcl-2 ratio, overexpression of iNOS and upregulation of caspase-3 within renal tissue.[46]

Gentamicin, an aminoglycoside antibiotic widely applied as antibiotic to treat Gram-negative bacterial infections, has been reported to exhibit nephrotoxicity due to induction of oxidative stress and activation of apoptotic and inflammatory signaling pathways.[47] Exposure to gentamicin in preclinical studies resulted in renal histopathology (such as tubular necrosis and tubulointerstitial inflammation), decreased renal antioxidant enzymes (SOD, GSH, CAT), elevated TOS, oxidative stress index (OSI) MDA, iNOS, NO, TNF-α levels.[47-49] Other mechanisms of gentamicin-induced nephrotoxicity included up-regulation of NF-κB p65, IL-1β, IL-6, IL-18, p38-MAPK, NGAL, KIM-1, caspase-9, caspase-3 and Bax while Bcl-2, HO-1 and Nrf2 were downregulated within kidney tissue.[47,50,51]

Methotrexate is an effective anticancer and immunosuppressive drug that exhibits characteristic adverse effect including nephrotoxicity due to associated oxidative damage and inflammatory responses in renal tissue.[52] Methotrexate-induced nephrotoxicity has been characterized by marked distortion of renal histoarchitecture, elevated serum creatinine, BUN, reduced renal CAT, glutathione-S-transferase (GST), GSH, and increased levels of NO, IL-1β, TNF-α.[53,54] In preclinical studies, exposure to methotrexate exposure further resulted in impaired mitochondrial biogenesis, reduced SOD and increased MDA levels, upregulation of TLR-4, TNF-α, NF-κB. IL-6, caspase-3, Bax, beclin-1, LC-3, and down-regulation of Bcl-2, Nrf2, HO-1.[52,55,56]

Some other chemotherapeutic agents that exhibit nephrotoxicity essentially through the aforementioned mechanisms include cyclophosphamide (an alkylating anticancer drug), vancomycin (a glycopeptide antibiotic drug), tenofovir/lamivudine/efavirenz (a combination antiretroviral drug) and cyclosporine A (an immunosuppressive agent).[57-60]

Table 1. General profile of selected drugs and mechanisms of nephrotoxicity in preclinical studies

Selected drugs (Applications)	Molecular formula/weight	Experimental model	Dosage/ Route of administration	Mechanisms of nephrotoxicity	References
Acetaminophen (Analgesic, antipyretic agent)	$C_8H_9NO_2$/ 151.16 g/mol	Experimental rats (Wistar, Sprague Dawley)	- 2 g/kg single dose/ oral - 500 mg/kg single dose, intraperitoneal (ip)	renal histopathological changes - elevated levels of markers of oxidative stress, pro-inflammatory and apoptotic factors. - decreased renal function - reduced renal antioxidant levels - downregulation of anti-apoptotic factors	Coban et al.[20] Aktas et al.[21] Ozatik et al.[22] Shi et al.[23]
Cisplatin (Anticancer agent)	$Pt(NH_3)_2Cl_2$/ 300.10 g/mol	Experimental rats (Wistar, Sprague Dawley)	- 7 mg/kg single dose/ ip - 5 mg/kg single dose / ip	- decline of renal function; - reduced activities of renal antioxidants - distortion of renal histomorphology - increased levels of oxidative stress markers - increased expressions of pro-inflammatory and apoptotic factors	Tang et al.[25] El-Rhman et al.[26] Shinde et al.[27] Qi et al.[28]
Diclofenac (Analgesic, antipyretic agent)	$C_{14}H_{11}Cl_2NO_2$/ 296.15 g/mol	Experimental rats (Wistar, Sprague Dawley)	- 50 mg/kg daily for 7 days / ip. - 150 mg/kg daily for 6 days / ip	- decreased renal function - increased levels of oxidative stress markers - decreased activities of renal antioxidants - increased levels of pro-inflammatory markers - upregulation of pro-apoptotic factors - downregulation of anti-inflammatory factors	Moradi et al.[30] Karimi-Matloub et al.[31] Alorabi et al.[32] Comez et al.[33] Mansoure et al.[34]
Doxorubicin (Anticancer agent)	$C_{27}H_{29}NO_{11}$/ 543.52 g/mol	Experimental rats (Wistar, Sprague Dawley)	- 15 mg/kg single dose/ i.p. - 20 mg/kg single dose/ i.p. - 3 mg/kg daily for 6 weeks / ip.	- decrease in levels of renal antioxidants and reduced renal function - increased levels of oxidative stress markers - prominent renal histopathological changes - upregulation of pro-inflammatory and apoptotic signaling	Ikewuchi et al.[36] Afsar et al.[37] Altinkaynak et al.[38] Hekmat et al.[39] Al Suleimani et al.[40]
5-Fluorouracil (Anticancer agent)	$C_4H_3FN_2O_2$/ 130.08 g/mol	Experimental rats (Wistar, Sprague Dawley)	- 150 mg/kg single dose (day 8) / ip.	- renal histopathological changes - decreased renal function and activity of renal antioxidants - up-regulation of pro-inflammatory and apoptotic factors - downregulation of anti-inflammatory factors	Famurewa et al.[41] Mansoori et al.[42] El-Gendy et al.[43] Althagafy et al.[44] Albadrani et al.[45] Al-Ghamdi et al.[46]
Gentamicin (Antibiotic agent)	$C_{21}H_{43}N_5O_7$/ 477.60 g/mol	Experimental rats (Wistar, Sprague Dawley)	- 100 mg/kg daily for 8 days / ip - 100 mg/kg daily from day 8-14 of the 15-day study / ip	- renal histopathological changes - decreased activities of renal antioxidants - elevated levels of oxidative stress markers - up-regulation of inflammoapoptotic factors - down-regulation of anti-apoptotic signaling	Akila et al.[47] Abukhalil et al.[48] Saeedavi et al.[49] Dik et al.[50] Nadeem et al.[51]
Methotrexate (Anticancer or antirheumatic agent)	$C_{20}H_{22}N_8O_5$/ 454.44 g/mol	Experimental rats (Wistar, Sprague Dawley)	- 20 mg/kg single dose/ i.p.	- distortion of renal histoarchitecture - elevated serum creatinine, BUN levels - reduced levels of renal antioxidants - upregulation of inflammatory and apoptotic factors - down-regulation of anti-apoptotic expressions	Mishriki et al.[53] Morsy et al.[54] Wasfey et al.[55] Kandemir et al.[56]

Therapeutic activity of selenium against drug-induced nephrotoxicity

Selenium (Se) is a trace element vital to human health in trace amounts but could exhibit an adverse effect at high concentration.[61,62] Deficiency of Se has been associated with increased susceptibility of the body to various pathologies.[63] Its important role in body antioxidant defense system, metabolic homeostasis, and immune functions underscores its therapeutic potential, which has been widely harnessed to mitigate tissues' toxicity, including the kidney. In a previous study, intraperitoneal (ip) exposure of Se (0.5 or 1 mg/kg) mitigated cyclophosphamide-induced nephrotoxicity and reversed associated mechanisms via increased total antioxidant capacity (TAC), reduced TOS, OSI, serum creatinine and reparation of renal histomorphology.[57] The oral administration of Se (0.1 mg/kg for 90 days) further caused a protective effect against tenofovir/lamivudine/efavirenz-induced nephrotoxicity, characterized with elevation of renal antioxidant levels (GSH, SOD, GPx, CAT) levels, reduction of the level of MDA, improved renal function (marked by reduced serum creatinine, uric acid, urea) and amelioration of renal histopathological changes.[58]

Furthermore, exposure to Se nanoparticles (0.5, 1 and 2 mg/kg) demonstrated a protective effect against vancomycin nephrotoxicity through a significant decrease in the levels of MDA, iNOS, NO, TNF-α, and KIM-1, increased Bcl-2 and reduced Bax, caspase-3, caspase-9.59 Furthermore, daily ip administration of Se (1 mg/kg for 8 days) mitigated gentamicin-induced nephrotoxicity, indicated by reduced serum levels of renal function markers (urea, creatinine), reduced levels of MDA and PC levels, and amelioration of renal histopathological changes.[64] Furthermore, administration of Se (1.5 mg/kg/day for 5 days, ip) demonstrated protective effect (in combination exposure with vitamin E) against cisplatin nephrotoxicity, characterized with decrease of plasma levels of MDA, urea, creatinine, elevated levels of GSH, GPx, CAT and reparation of renal histopathological changes (Fig. 2).[65]

Therapeutic activity of zinc against drug-induced nephrotoxicity

Zinc (Zn) is an important trace element that participates in several physiological and biochemical processes of the body.[66] It further participates in the body's antioxidant system, promotes vitamin D, down-regulates prostaglandin synthesis, and enhance immune responses of the body.[67,68] Essentially, the antioxidant and anti-inflammatory effects of Zn have been explored to mitigate drug-induced nephrotoxicity. In a previous study, the mitigation of cisplatin-induced nephrotoxicity was demonstrated by Zn administration (6 mg/kg, ip) and further characterized by reduced serum urea, creatinine, MDA, TNF-α levels, down-regulation of renal Bax and heat shock proteins.[69] The protective effect of Zn administration (25 and 50 mg/kg) has been further demonstrated against gentamicin-induced nephrotoxicity and characterized with restoration of renal function indicated by decreased serum urea, creatinine.[70]

Furthermore, the therapeutic activity of Zn supplementation (10 mg/kg/day for 10 days), based on its antioxidant potential, has been demonstrated against cyclosporine A-induced nephrotoxicity in the experimental model and indicated by reduced serum levels of creatinine, BUN and kidney tissue damage score.[71] Furthermore, Zinc oxide nanoparticles (ZnONPs) have demonstrated a therapeutic effect against doxorubicin-induced nephrotoxicity indicated by elevated levels of renal antioxidants (SOD, GPx, CAT), decline in MDA levels, downregulation of inflammatory markers (IL-6, NF-κB), improved renal function and improved renal histomorphology.[72] Additionally, pretreatment with ZnONPs (5 mg/kg ip) exhibited protective effect against cisplatin nephrotoxicity as demonstrated by reduced serum levels of renal function markers (creatinine, BUN), elevated levels of renal antioxidants (SOD, CAT, GR), reduction of renal MDA level, upregulation of anti-inflammatory markers (HO-1 and Nrf2), downregulation of apoptotic factor (Bax) within the kidney tissue.[73]

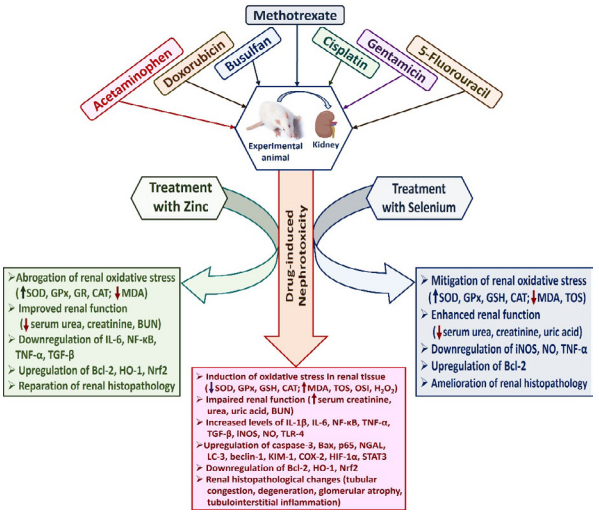

Fig. 2. Schematic summary of mechanisms of drug-induced nephrotoxicity and therapeutic activity of selenium and zinc

Safety concerns and dose-response considerations

Recent studies have reported some concerns regarding selenium exposure at high dosage levels that include adverse metabolic effects of selenoproteins and their potential to stimulate tumor formation.[74] Similarly, reports have associated excess zinc exposure with clinical symptoms such as anemia, neutropenia, while the deficiency also poses significant health risks.[75] Therefore, the dosage and duration of exposure to these trace elements require strict regulation both in health and disease.

Conclusion

Exposure to certain drugs mainly results into nephrotoxicity through induction of oxidative stress and activation of inflammatory and apoptotic signaling pathways within the renal tissue. On the other hand, trace elements such as Selenium and zinc have demonstrated therapeutic activity against drug nephrotoxicity in preclinical studies based on their antioxidant, antiapoptotic, and anti-inflammato-

Table 3. General Profile and therapeutic mechanisms of selected trace elements against drugs nephrotoxicity in preclinical studies

Trace element (symbol/atomic number/mass)	Sources	Biological functions	Experimental model	Treatment regimen	Therapeutic mechanisms against drug-induced nephrotoxicity	References
Selenium (Se/34/76.96 u)	Garlic, nuts, cabbage, rice, potatoes, oats, fishes, eggs, meats, lentils	- Formation of key enzymes, proteins (selenoproteins) - Antioxidant, anti-cancer, anti-inflammatory effect - Immune booster	Experimental rats (Wistar, Sprague Dawley)	- 0.1 mg/kg for 90 days/oral - 1.5 mg/kg/ daily for 5 days/ip	- elevated renal GSH, SOD, GPx, and CAT levels - reduced serum levels of urea, creatinine, and uric acid - decreased levels of TOS, OSI, MDA, PC, - Down-regulation of iNOS, NO, TNF-α and up-regulation of Bcl-2 expressions - amelioration of renal histopathology	Gunes et al.[57] Adikwu et al.[58] Mehanna et al.[59] Bai et al.[61] Genchi et al.[62] Randjelovic et al.[64] Aksoy et al.[65]
Zinc (Zn/30/65.41 u)	Oysters, pork, fish, liver, meat, wheat, mollusks, dairy products, oats, dried peas, nuts, cheese	- Gene regulation - Enzyme cofactor - Wound repair, hair growth - Development of muscle, bone, and cartilage	Experimental rats (Wistar, Sprague Dawley)	- 10 mg/kg/daily for 10 days/oral - 5 mg/kg single dose /ip - 6 mg/kg single dose/ip	- increased renal SOD, GPx, GR, CAT levels - decrease in serum levels of urea, creatinine, BUN - decreased MDA levels - downregulation of IL-6, NF-κB, TNF-α, TGF-β and upregulation of Bcl-2, HO-1, Nrf2 expressions - amelioration of renal histopathology	Al-Fartusie et al.[66] Lahhoba et al.[68] Kone et al.[70] Choopani et al.[71] Elgohary et al.[72] Barakat et al.[73]

ry properties. The efficacy of Selenium and Zinc as mitigants of drug nephrotoxicity thereby underscores their potential role in the management of nephrotoxicity that occurs during pharmacotherapy.

Declarations

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Author contributions
Conceptualization, D.R.O. and F.C.E.; Methodology, D.R.O.; Software, F.C.E.; Validation, D.R.O. and F.C.E.; Formal Analysis, D.R.O.; Investigation, F.C.E.; Resources, D.R.O.; Data Curation, D.R.O.; Writing – Original Draft Preparation, F.C.E.; Writing – Review & Editing, D.R.O; Supervision, D.R.O.

Conflicts of interest
The authors declare that they have no competing interests.

Data availability
The data supporting the findings of this review study have been included in the article.

Ethics approval
Not applicable.

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