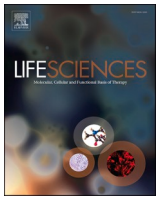
Cytoprotective remedies for ameliorating nephrotoxicity induced by renal oxidative stress

Life Sciences 318 (2023) 121466

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie



Review article

Cytoprotective remedies for ameliorating nephrotoxicity induced by renal oxidative stress

Ranmali Ranasinghe *, Michael Mathai, Anthony Zulli

Institute for Health and Sport, College of Health and Medicine, Victoria University, Melbourne, Victoria, Australia

ARTICLE INFO

Keywords:
Renal oxidative stress
Nephrotoxicity
Sources of oxidative stress
Mitigating oxidative stress
Antioxidant compounds
Mechanisms of oxidative stress

ABSTRACT

Aims: Nephrotoxicity is the hallmark of anti-neoplastic drug metabolism that causes oxidative stress. External chemical agents and prescription drugs release copious amounts of free radicals originating from molecular oxidation and unless sustainably scavenged, they stimulate membrane lipid peroxidation and disruption of the host antioxidant mechanisms. This review aims to provide a comprehensive collection of potential cytoprotective remedies in surmounting the most difficult aspect of cancer therapy as well as preventing renal oxidative stress by other means.

Materials and methods: Over 400 published research and review articles spanning several decades were scrutinised to obtain the relevant data which is presented in 3 categories; sources, mechanisms, and mitigation of renal oxidative stress.

Key-findings: Drug and chemical-induced nephrotoxicity commonly manifests as chronic or acute kidney disease, nephritis, nephrotic syndrome, and nephrosis. Renal replacement therapy requirements and mortalities from end-stage renal disease are set to rapidly increase in the next decade for which 43 different cytoprotective compounds which have the capability to suppress experimental nephrotoxicity are described.

Significance: The renal system performs essential homeostatic functions that play a significant role in eliminating toxicants, and its accumulation and recurrence in nephric tissues results in tubular degeneration and subsequent renal impairment. Global statistics of the latest chronic kidney disease prevalence is 13.4 % while the end-stage kidney disease requiring renal replacement therapy is 4–7 million per annum. The remedial compounds discussed herein had proven efficacy against nephrotoxicity manifested consequent to impaired antioxidant mechanisms in preclinical models produced by renal oxidative stress activators.

1. Introduction

1.1. Kidney functions

Renal physiology plays an important role in maintaining homeostasis by regulating; the water and acid-base balance, electrolyte composition, blood pressure, erythropoiesis, and production of some enzymes and hormones [1]. Its main function is the excretion of potentially harmful substances including drugs, infectious agents, and toxicants from the body [2]. Moreover, the kidneys possess the ability to coordinate inter-organ signalling as part of maintaining overall homeostasis that is regulated by the central nervous system (CNS) [1]. The proximal convoluted tubule (PCT) contains the highest load of mitochondria and as such is highly prone to oxidative stress that develops into mitochondrial dysfunction [3]. The epithelial cells in the PCT have been linked with gut microbial dysbiosis, through remote sensing of gut microbial metabolites and signalling between the gut-kidney axis [4]. Membrane transporters on the epithelial barriers allow the infiltration of potential toxic microbial products that reach the PCT *via* intestinal absorption and are excreted in urine [4]. High accumulation of toxic microbial secretory metabolites causes the induction of renal pathology. Thus, a nexus of renal mitochondria and the gut microbiome has been established that induces acute and/or chronic kidney disease [3] [4]. Another aspect of renal-interorgan dysfunction is the cardiorenal syndrome [5]. The pathophysiological changes that are associated with muscle loss in chronic kidney disease are caused by disrupted muscle proteostasis and cellular bioenergetics that degrade the kidney-skeletal muscle crosstalk [6]. As such, renal functionality involves alleviating toxicity caused by external agents, particularly chemotherapeutics, that offers clinical benefits (Fig. 1) [7]. Drug toxicity accounts up to 60 % of renal

* Corresponding author.
E-mail address: Hewausaramba.ranasinghe@live.vu.edu.au (R. Ranasinghe).

https://doi.org/10.1016/j.lfs.2023.121466
Received 31 October 2022; Received in revised form 27 January 2023; Accepted 27 January 2023
Available online 10 February 2023

dysfunction and induces renal pathophysiology that includes glomerulopathies [from immunotherapies, bisphosphonates, and vascular endothelial growth factor (VEGF) inhibitors], tubulopathies (from tenofovir, polymyxin and amphotericin B toxicity) and end-stage acute renal failure, to mention a few of the drug therapies that are utilized [8]. Thus, nephrotoxicity largely consists of renal injuries caused either directly or indirectly from medications that clinically present with glomerulopathies and tubulopathies [8]. This review aims at describing the most common sources of oxidative stress-manifested renal pathogenesis that could be mitigated by a choice of prospective pharmaco-modulatory therapies. These promising sources of anti-nephrotoxic treatment could provide valid therapeutic benefits in alleviating nephrotoxicity in the future.

1.2. Epidemiology of kidney disease

Once nephrotoxicity is established within the renal system, it will eventually develop into progressive kidney disease [9]. Toxicant exposure in the kidneys could rapidly develop acute kidney injury (AKI) and/or manifest as chronic kidney disease (CKD) that may extend over a long duration of time [10]. The average global estimated prevalence of kidney disease that was reported a decade ago was 13 % [11] with a projected estimate of patients requiring renal replacement therapy will be approximately 5.4 million in the year 2030 with the highest growth in Asia [12]. A marked difference also was reported in kidney disease statistics between developing and developed countries as well as between low socioeconomic regions and affluent populations leading an exuberant lifestyle [13]. Since chemotherapy is a major factor of nephrotoxicity and those treated for both renal and other cancers, develop terminal kidney disease from chemotherapy as a secondary complication in cancer patients [14]. New global renal carcinoma incidence was reported as 431,288 cases with an overall mortality of 179,368 in the year 2020 (Fig. 2) [15]. The 5-year prevalence in renal carcinoma was the highest in Asia and the lowest in Oceania, with the total standing at 1,207,547 cases that were reported [15]. The male population appears to be more at risk from renal carcinoma than the females around the globe, while the individuals diagnosed with hypertension, diabetes and smoking are more prone to developing renal cancer [15]. In the United States of America, an estimated 1 in 7 people or 37 million new cases of chronic kidney disease (CKD) are reported annually, with CKD being more common in non-Hispanic black females aged over 65 years [16]. CKD was reported as the 12th leading cause of global mortality in the year 2017.

In a meta-analysis involving 100 studies and approximately 6 million participants, Hill et al. in 2016 had reported the estimated global prevalence of the stages 1–5 (Fig. 3) from low chronic kidney disease to the highest as 3.5 %, 3.9 %, 7,6 %, 0.4 %, and 0.1 % respectively [17]. From the year 2010, a remarkable increase in the numbers of patients requiring renal replacement therapy (RRT) in different continents can be predicted up to 2030 (Fig. 4). RRT requirements will be highest in Asia, followed by Latin America and the Caribbean islands and least of all in Africa.

According to the published statistics by the Australian Institute of Health and Welfare (AIHW), there is a clear upward trend in the mortalities in both sexes from CKD in the Australian population between the years 2000 to 2020. The male population is more prone to CKD deaths than the female counterparts (Fig. 6). The stratification of CKD mortality statistics into age groups have shown that the age bracket of 85+ years is the most prone to CKD deaths while the risk increases from the age 65 onwards (Fig. 7). An approximately 10 % of the entire Australian population or 1.7 million persons were diagnosed and hospitalised with kidney disease during the years 2011 and 2012 [20]. In 2017–2018, those with biomedical symptoms of it had risen to 1.8 million which was up to 16 % of the national hospitalisations [21]. It is an alarming increase of 60 % in its diagnosis between a period of 6 years within the context that CKD encompassed all types of kidney disease in the Australian population that lasted for over 3 months and also had comorbidities with cardiovascular disease, hypertension, smoking, diabetes, obesity and being overweight [22]. The criteria for inclusion were those having a low estimated glomerular filtration rate (eGFR) below a threshold of 60 mL/min/1.73 m^2, proteinuria and albuminuria [23], because kidney disease remains largely undiagnosed for a long time [24] and symptoms are not felt by the patients before 90 % of the kidney function is lost. Another major factor in kidney disease is the age that

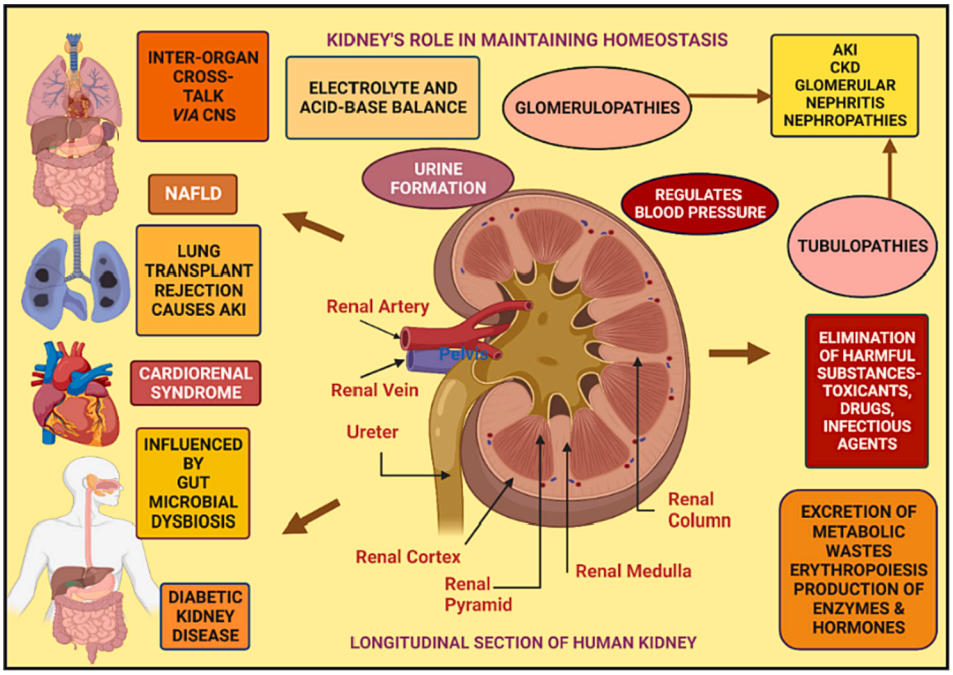


Fig. 1. Prime renal parameters that maintain homeostasis. The kidneys perform many salient physiological functions, those of which when impaired leads to multisystem pathophysiology that requires either renal replacement therapy or a kidney transplant. Legend: NAFLD-non-alcoholic fatty liver disease, AKI-acute kidney injury, CKD-chronic kidney disease, CNS-central nervous system.

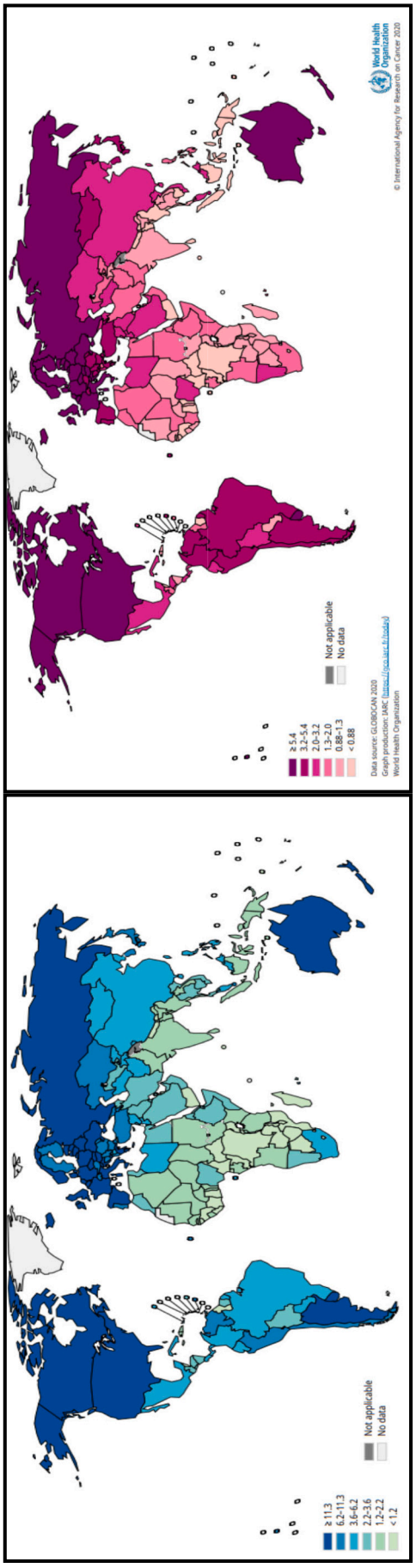


Fig. 2. A and B: Global prevalence of renal carcinoma in (A) males and (B) females in all age groups in 2020. The highest prevalence of renal cancer was reported for both genders are in North America, Europe, Russia, and Australia while the lowest incidence is seen in some parts of Africa, India, Japan, and the Pacific islands [15].

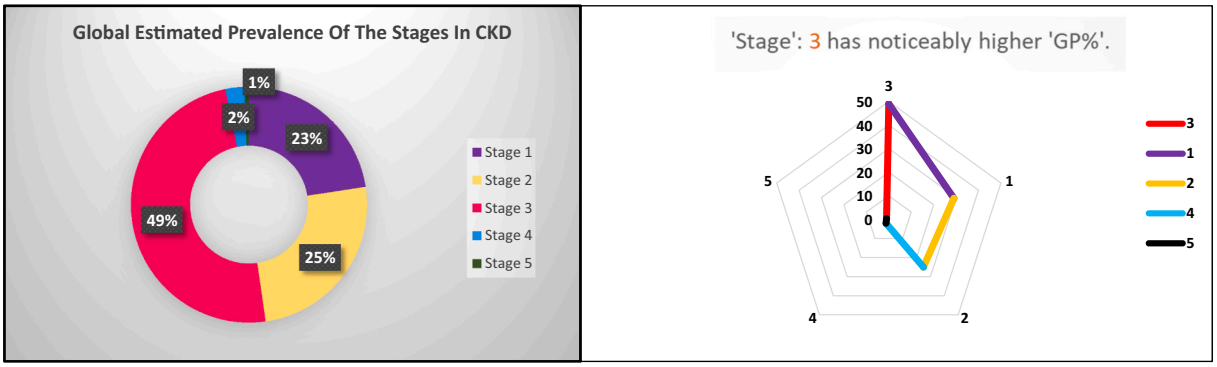
showed a 3 times over increase in the patients aged 65–74 years compared to those in the 55–64 age bracket [25]. Importantly, the number of Australians who had moderate to a severe loss of kidney function had doubled between the years 2000 and 2012 with a marked increase in the number of patients diagnosed within the CKD stages 3 and 5 as reported in the year 2018 [17], Further, the indigenous Australians diagnosed with kidney disease are 11 times more than their non-indigenous counterparts and are 3 times more prone to die of it [26]. However, CKD is also largely preventable if diagnosed early, before, the clinical picture is not deteriorated that is evident from Fig. 5 which displays the outcome of a survey on end-stage renal disease (ESRD) projected to the future [27]. The comorbidity that arose from Covid 19 and kidney disease were reportedly high and caused more mortalities. It may have been due to the pro-inflammatory cytokine-related oxidative stress, which then initiated a subsequent inflammatory immune response that made the patients further susceptible to viral infections [28].

2. Nephrotoxicity

Nephrotoxicity is the major dose-limiting side effect of many chemotherapeutics including cisplatin and doxorubicin therapy [29]. They are frontline antineoplastic drugs that cause nephrotoxicity which manifests due to oxidative stress [30]. Cisplatin-induced nephrotoxicity (CIN) appears as a comorbidity with cancer that induces pathological changes in the kidneys up to 28 to 36 % of cancer patients [31], particularly in those bearing solid tumours in lungs, ovary, and the nasopharynx [32]. High cisplatin toxicity-induced inflammation renders kidney tubules dysfunctional caused by the elevation of oxidative stress biomarkers [33], malondialdehyde (MDA) [34], tumour necrosis factor-alpha (TNF-a) [35], and decreased glutathione (GSH) [36], catalase (CAT) [37], and superoxide dismutase (SOD) [38], that result from high lipid peroxidation of the cellular membranes [39]. The inflammation in renal tissue occurs from denatured membrane-associated proteins [40], increased cellular apoptosis [41] and necrosis that suppresses antioxidant mechanisms in the kidneys. Mostly, nephrotoxicity is caused by superoxide anions, hydroxyl groups and hydrogen peroxide and other free radicals that are produced by the increased activity of the enzymes, NADPH oxidase (NOX), xanthine oxidase and adenosine deaminase.

The gold standard in practice to confirm clinical nephrotoxicity includes elevated serum creatinine, uric acid, sodium, potassium, calcium, ATPase levels and blood urea nitrogen while the same parameters are decreased in urine samples. The elevation of prominent biomarkers in serum and not in urine could be due to tubular obstruction and back-leakage of substances in the renal tubules leading to deficient protein synthesis, membrane lipid peroxidation [42] and excessive generation of free radicals in tubular cells [43]. Thus, the rapid decline of creatinine clearance (below 30 mL/min) [44] and the glomerular filtration rate below 60 mL/min/1.72 m^2 signifies renal dysfunction [45]. Impaired glomerular filtration is associated with mesangial cell contraction which causes loss of surface area for ultrafiltration [46] and modified ultrafiltration coefficient factors [47]. Progressive renal dysfunction occurs because of proximal and distal tubular damage primarily caused by chemotherapeutics and/or toxic agents mostly utilized for cancer treatment [48]. Renal oxidative stress is repressed by initiating its free radical scavenging mechanisms in healthy individuals but when impaired, pathological deficiencies are induced in the kidneys. Several of such deficiencies are mitochondrial and ATPase dysfunction [49], altered solute transport and cellular cation content [50], increased vascular resistance [51] and malabsorption of sodium in the proximal tubules [52] and sodium and water in the distal tubules [53].

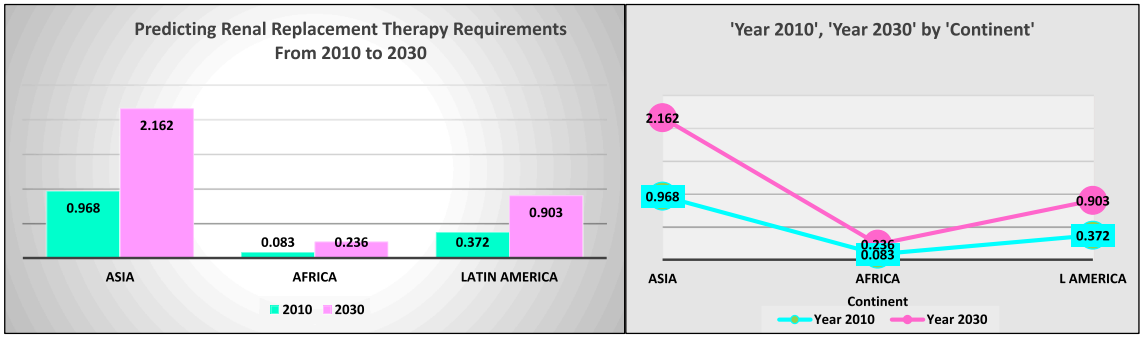
The aetiology of nephrotoxicity stems from therapeutics which usually account for up to 25 % or more all-cause occurrences of acute renal injury. The chief mechanisms of nephrotoxicity include the glomerular filtration rate (GFR) alterations, tubular cytotoxicity, interstitial nephritis, and crystal nephropathy [54]. The GFR is mostly caused



A B

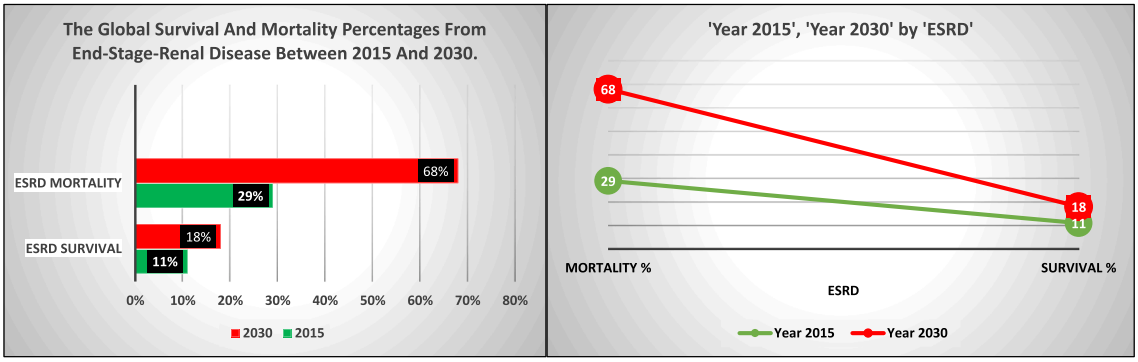
Fig. 3. A, B and C: (A) The global estimated prevalence (GP%) of the 5 stages in CKD. (B) A radar plot which highlights stage 3 having a noticeably higher GP%. (C) An interactive data plot of A. The CKD stages are mainly based on the estimated glomerular filtration rate (eGFR) as given below. eGFR is computed by a person's age, gender and the serum creatinine levels in blood.

- Stage 1 – with normal or high eGFR >90 mL/min.
- Stage 2 – Mild CKD (eGFR = 60–89 mL/min).
- Stage 3 – A moderate CKD (eGFR = 45–59 mL/min).
- Stage 4 – Severe CKD (eGFR = 15–29 mL/min).
- Stage 5 – End stage CKD (eGFR < 15 mL/min).



A B

Fig. 4. A, B and C: (A) Predicting renal replacement therapy (RRT) increase in the future [18]. (B) Analysis of the data which highlights the trend of change in RRT requirements between the years 2010 and 2030. (C) An interactive data plot of A in the Year 2030. An alarming increase in RRT is projected for the Year 2030 in Asia, which is a 123 % increase from its baseline (Year 2010). The differences in genetics, lifestyle, and diversified cultures between the continents could be attributed to the marked differences in the projected RRT requirement estimates shown above.



A B

Fig. 5. A, B and C: (A) The estimated global survival from end-stage-renal disease (ESRD) projected into the future. (B) Analysis of the data which highlights the change in ESRD mortality % and survivability % between the years 2015 to 2030. (C) An interactive data plot of A for the Year 2030. The mortality percentages from ESRD are expected to increase 3 times over between 2015 and 2030 while survival from ESRD shows a moderate increase [19].

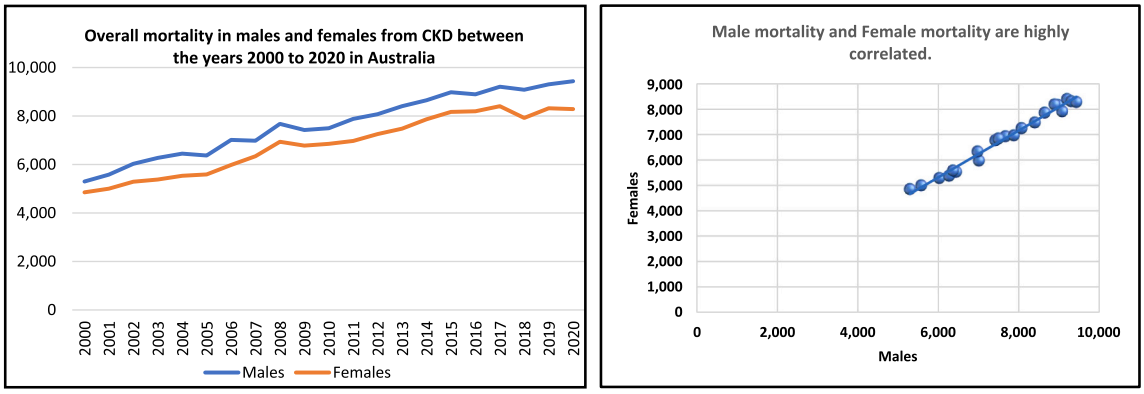


Fig. 6. A, B and (C-1 and 2): (A) Overall mortality in males and females from CKD between the years 2000 to 2020 in Australia. This graph shows an upward trend of increase in CKD mortality where there are considerably more male deaths than the females. (B) An analysis of the male and female values of overall mortality from CKD appears highly correlated between the genders. (C-1 and 2) Interactive data plots of the data in 6A for the males and females respectively.
(Data from https://www.aihw.gov.au/.)

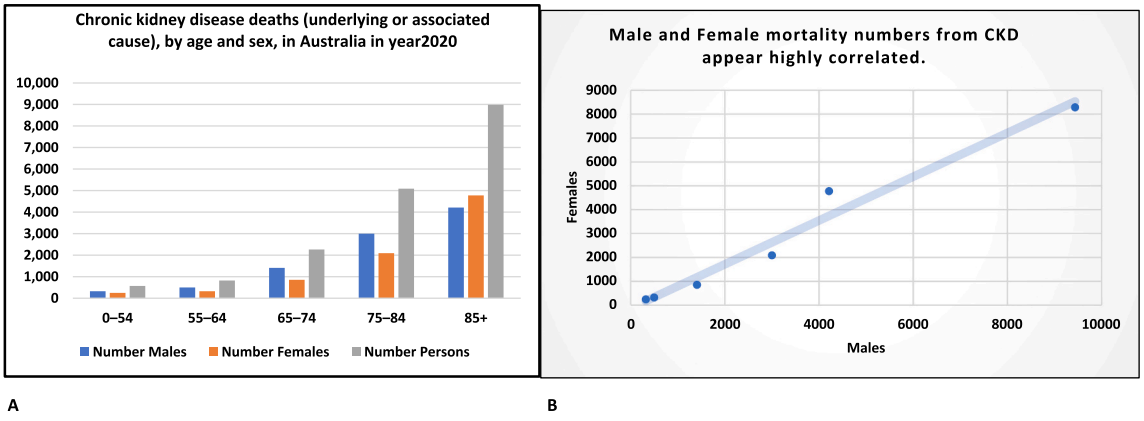


Fig. 7. A, B and C-1 and 2: (A) CKD deaths by age and gender in the Year 2020. (B) An analysis of the overall mortality from CKD shown as highly correlated between the genders. (C-1 and 2) Interactive data plots of the data in 7A for the males and females respectively. These data clearly specifies more deaths in both genders above the age group of +85 years. The increase in deaths becomes more prominent from the age of +65 years. The male mortality is markedly higher than the female deaths from CKD.
(Data from https://www.aihw.gov.au/.)

by changes in the intraglomerular haemodynamics while tubular cell toxicity arises commonly in the proximal tubules from free radical formation, mitochondrial damage and damage to the transport systems [50] that are primarily associated with drugs such as amphotericin B, cisplatin, adefovir, foscarnet, and aminoglycosides [55]. Acute interstitial nephritis is developed from non-steroidal anti-inflammatory drugs (NSAIDS) and rifamycin [56] but chronic inflammation in the kidneys is produced by analgesics, calcineurin inhibitors, lithium, and anti-cancer drugs [57]. Crystal nephropathy is formation of insoluble crystals within renal tissue that could happen due to antiviral drugs (acyclovir) and antibiotics (ampicillin). The primary sites of nephrotic damage are the glomerulus, proximal and distal tubules [58].

There are many biomarkers that are used to assess nephrotoxicity. These markers include urine proteins and enzymatic activity, proteinuria, kidney injury molecule (KIM-1), neutrophil gelatinase associated lipocalin (NGAL), type 4 collagen, osteopontin and clusterin [59]. Among the urinary enzymes that can be monitored are amino peptidases, alkaline phosphatase, alpha-glutathione-S-transferase, gamma-glutamyl-transferase, and *N*-acetyl-D-glycosaminidase [60]. High protein molecule accumulation in urine is another diagnostic tool [61]. Normally high and low weight protein molecules are reabsorbed in the glomerulus before entering the proximal convoluted tubule of the nephron [62]. Immunoglobulin G (IgG), albumin and transferrin are high molecular weight proteins that cause renal tissue damage and those which comprise of low molecular weight proteins are a1 and B2-macroglobulin, cystatin-C, and retinol binding protein [63]. KIM-1 is a recently introduced urinary biomarker and a type-1 glycoprotein that has greater sensitivity to renal damage [64] and surpasses the traditional ones such as serum creatinine (SCr), blood urea nitrogen (BUN) and proteinuria by signalling renal tissue injury in the PCT [65]. NGAL allows early detection of acute kidney damage and is produced as a by-product of tissue inflammation and during granulocyte maturation [66]. Type 4 collagen is a critical biomarker that indicates glomerular basement membrane damage [67]. Osteopontin produced in the bone, evaluates renal tissue injury caused by nephrotoxic drugs such as cisplatin, gentamicin, puromycin and angiotensin-2-receptor blockers [68]. Clusterin is another urinary glycoprotein biomarker that measures tubular injury in both PCT and DCT [69]. Nephrotoxicity could manifest in several different types of renal pathology. These disease states include glomerular nephritis, crystal nephropathy, rhabdomyolysis, acute or chronic interstitial nephritis, proximal renal tubular acidosis, acute and chronic tubular necrosis, and nephrotic syndrome [70]. When nephrotoxic drugs are being used, the toxicity could be reduced by isotonic repletion to dilute the drug concentration in serum [68].

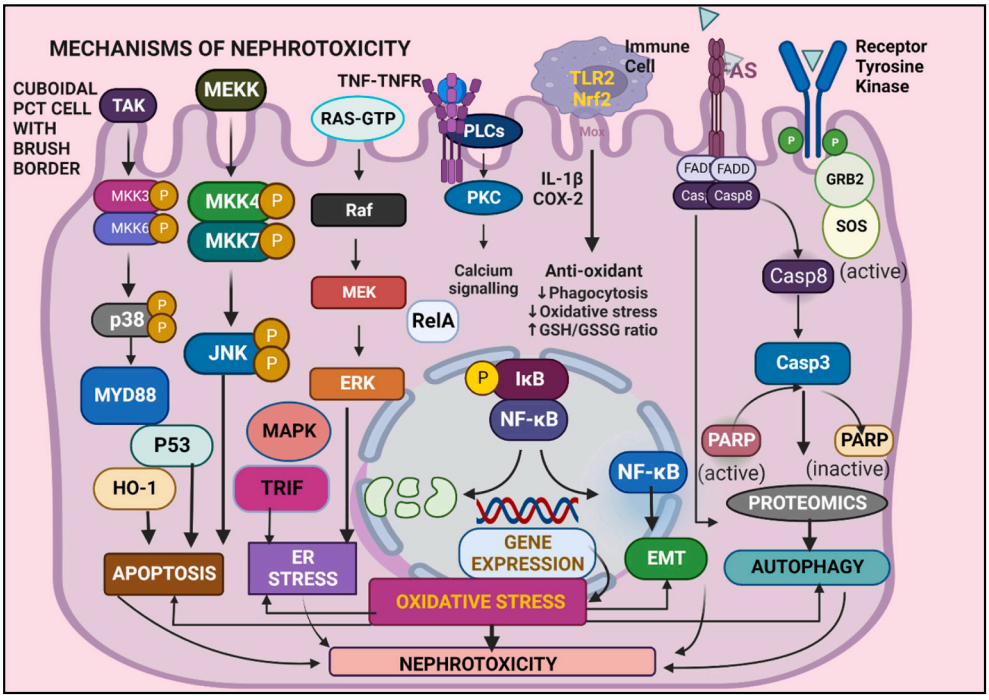


Fig. 8. Mechanisms of nephrotoxicity. Nephrotoxicity is caused by renal oxidative stress arising from various defective metabolic pathways. Such disruption will result in impaired gene expression, apoptosis, EMT, autophagy and ER stress being the major mechanisms that produce renal toxicity that will subsequently progress into renal failure. Legend: Casp3 – caspase 3, Casp8 - caspase 8, COX-2 – cyclooxygenase-2, EMT – epithelial mesenchyme transition, ER - endoplasmic reticulum, ERK - extracellular signal-regulated kinase, FAD - flavine adenine dinucleotide, FADD - Fas-associated death domain protein, Fas - a member of the TNFR family, GSH - glutathione, GSSG - glutathione disulfide, GRB2 - growth factor receptor-bound protein 2, HO1 – haem oxygenase-1, IkB - IKappaB kinase, IL-1β - interleukin 1-beta, JNK – Jun-N-terminal kinase, MAPK – mitogen-activated protein kinase, MKK - mitogen-activated protein kinase kinase, MKK3 - mitogen-activated protein kinase kinase kinase 3, MKK4 – mitogen-activated protein kinase kinase kinase 4, MKK6 – mitogen-activated protein kinase kinase kinase 6, MKK7 – mitogen–activated kinase kinase kinase 7, MYD88 – myloid differentiation factor 88, NF-kB - nuclear factor kappa beta, Nrf-2 - nuclear factor erythroid 2–related factor 2, P-phosphorylated version. PARP - poly-ADP-Ribose polymerase, PKC - protein kinase-C, PLCs - phospholipase-C, p38 – protein 38, p53 – protein 53, Raf-Mek - mitogen-activated protein kinase kinase, RAS-GTP - rat sarcoma virus super family-guanosine tri phosphate, RelA - NF-kB subunit 65 or protein 65, SOS - son of sevenless, TAK - transforming growth factor β-activated kinase, TLR2 - Toll-like receptor 2, TNF-TNFR - tumour necrosis factor-tumour necrosis factor receptor-1, TRIF - TIR-domain-containing adapter-inducing interferon-β.

2.1. *Mechanisms of nephrotoxicity*

The pathogenesis of nephrotoxicity is mediated by a variety of signalling pathways [71] of which protein-38 (p38), extracellular signal-regulated kinase (ERK), c-Jun-N-kinase (JNK)-mitogen-activated protein kinase (MAPK), nuclear factor kappa beta (NF-kB), nuclear factor-erythroid-2 related factor-2 (Nrf2) and fibrogenic cytokines are linked with molecular and cellular mechanisms of renal oxidative stress (Figs. 8 and 9) [72]. Intrarenal immunogenicity is modified by various mechanisms that result from nephrotoxicant activity [73]. The salient cellular mechanisms that lead up to nephrotoxicity, are apoptosis, autophagy, endoplasmic reticulum (ER) stress and epithelial mesenchymal transition (EMT) [74].

Apoptosis in the renal tubular cells occurs as a direct consequence of cytotoxic drug treatment [75]. Apoptosis is primarily mediated by deoxy ribonucleic acid (DNA) synthesis-inhibition and through activating the Fas (a type II membrane protein that belongs to the TNF superfamily/TNFR)-antigen ligand system, resulting from the elevation of intracellular calcium concentration and the expression of glucose transporter – one (GLUT1), a glucose transporter protein involved in stress responses [71]. A common cytotoxic mechanism of most anticancer drugs is the activation of various apoptotic stimuli that upregulates caspase-3 pathway *via* the release of cytochrome *c* from the mitochondria [76]. Interstitial tissue fibrosis is a cardinal factor of progressive kidney disease and apoptosis is one of its salient pathological mechanisms that induces renal fibrosis [77]. Severe apoptosis also causes mesangial matrix dilation that is characteristic of kidney pathology which is improved with the inhibition of apoptosis [78]. Thus, most of the structural damage to the kidneys are caused by cellular apoptosis which can be identified by terminal deoxynucleotidyl transferase-dUTP nick end labelling (TUNEL) staining, and transmission electron microscopy (TEM) observations [79].

The expression of BCl-2-associated X protein (Bax) and B-cell lymphoma-2 (Bcl-2) regulatory proteins play a key role in the mitochondrial-mediated apoptosis pathway [80]. Bcl-2 is an anti-apoptotic protein that blocks the mitochondrial permeability transition pore which in turn inactivates cytochrome-c release to the cytoplasm [81]. Bax is a proapoptotic protein that is found attached to the mitochondrial outer membrane. When bound to Bcl-2, it enters the mitochondria and allows the influx of cytochrome-c that subsequently activates the caspase cascade [82]. The cleaving of caspase 3 to active caspase 3 which is a reliable biomarker of apoptosis, occurs with degradation of cellular proteins and DNA fragmentation that results in cellular apoptosis.

The induction of apoptosis as a consequence of nephrotoxicity has been established by both *in vitro* and *in vivo* models [83]. The apoptosis mechanisms are mainly upregulated by ER stress resulting in mitochondrial fission, that represses the renal antioxidant mechanisms [84]. Mitochondrial perturbation induces various other stresses that stimulate EMT and sensitize the kidneys more to nephrotoxic agents [85]. EMT directly acts on the tubular epithelium and contributes to developing renal fibrosis that is stimulated by the profibrotic cytokine, transforming growth factor-beta-one (TGF-β1), in addition to the connective tissue growth factor (CGTF) protein [86]. Neutralizing both these proteins served to abrogate EMT in a human renal cell line that induced nephrotoxicity by cyclosporin A [87]. In this model, the CGTF expression was upregulated which is also a downstream mediator of the fibrotic process [87]. The ER stress mechanisms of nephrotoxicants also induce autophagy in kidney tissues which in part can be viewed as a beneficial outcome, because it eliminates misfolded proteins that brings about ER stress [88]. It was evidenced by the upregulation of an autophagosome biomarker, microtubular-associated protein light chain-3II, which when

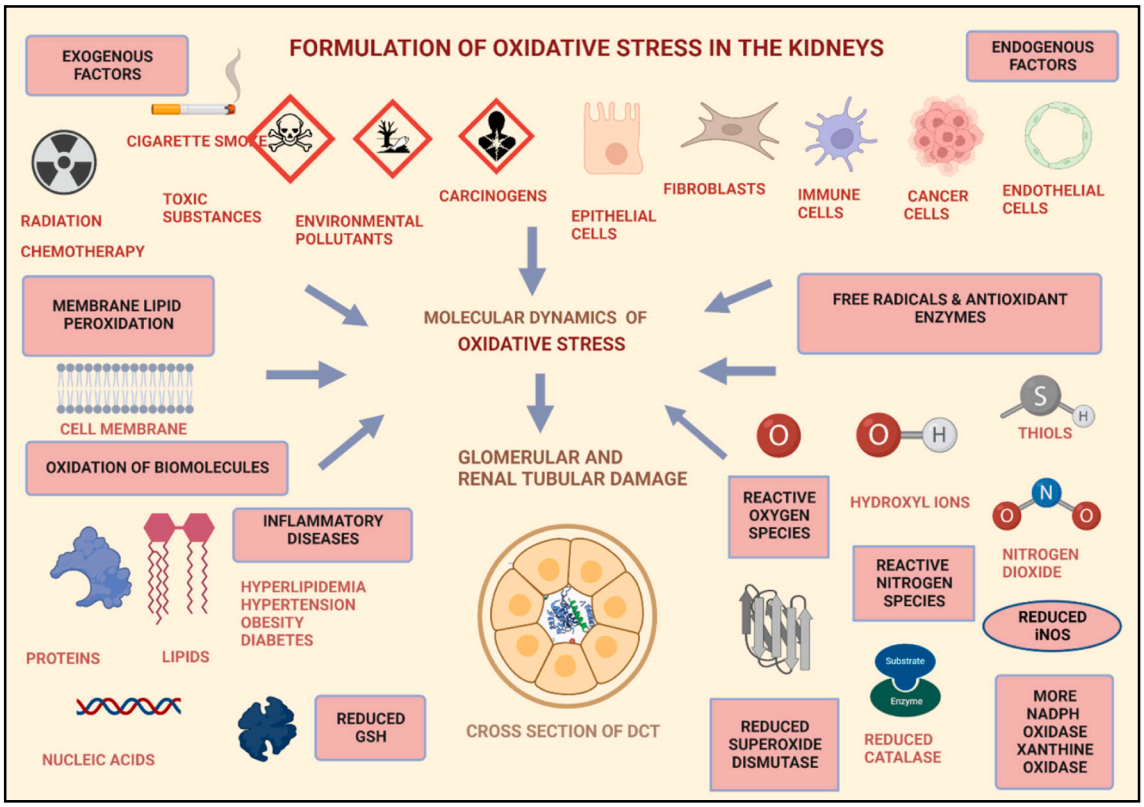


Fig. 9. Formulation of oxidative stress in the kidneys arising from various defunct metabolic pathways: exogenous and endogenous risk factors, membrane lipid peroxidation, free radical generation, reduced GSH and iNOS mechanisms, and oxidation of biomolecules. Legend: DCT - distal convoluted tubule, GSH - glutathione, iNOS - inducible nitric oxide synthase. NADPH - nicotinamide adenine di nucleotide phosphate.

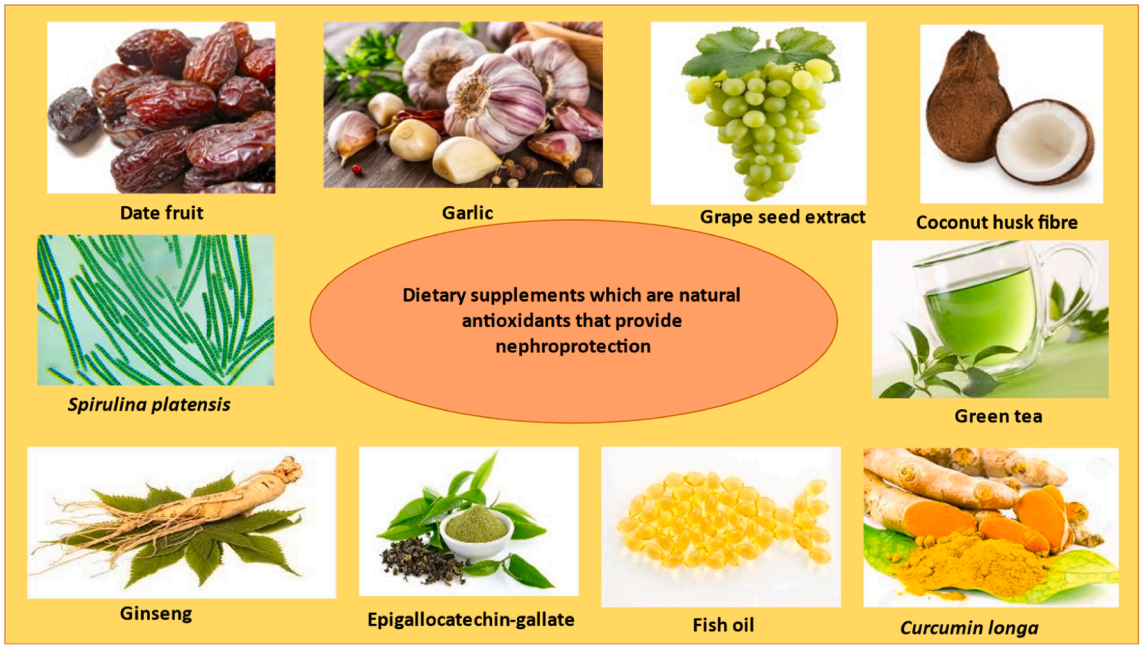


Fig. 10. Dietary supplements which possess natural antioxidant behaviour that are mentioned in this review. All these food supplements have attenuated nephrotoxicity induced by renal oxidative stress sources in preclinical research. (The links to source files are included as Supplementary material.)

blocked, alleviated autophagy in some nephrotoxicity models.

The generation of reactive oxygen species (ROS), by nephrotoxicants, particularly in the mitochondria is a potent source of ER stress, oxidative stress as well as nitrosative stress in the kidneys [89]. The inhibition of inducible nitric oxide synthase (iNOS) also leads to impaired renal vascular tone that adds to nitrosative stress [90]. Nephrotoxicity is typically characterized by a repertoire of vasoconstricting agents of which iNOS plays a significant role [91]. Normally

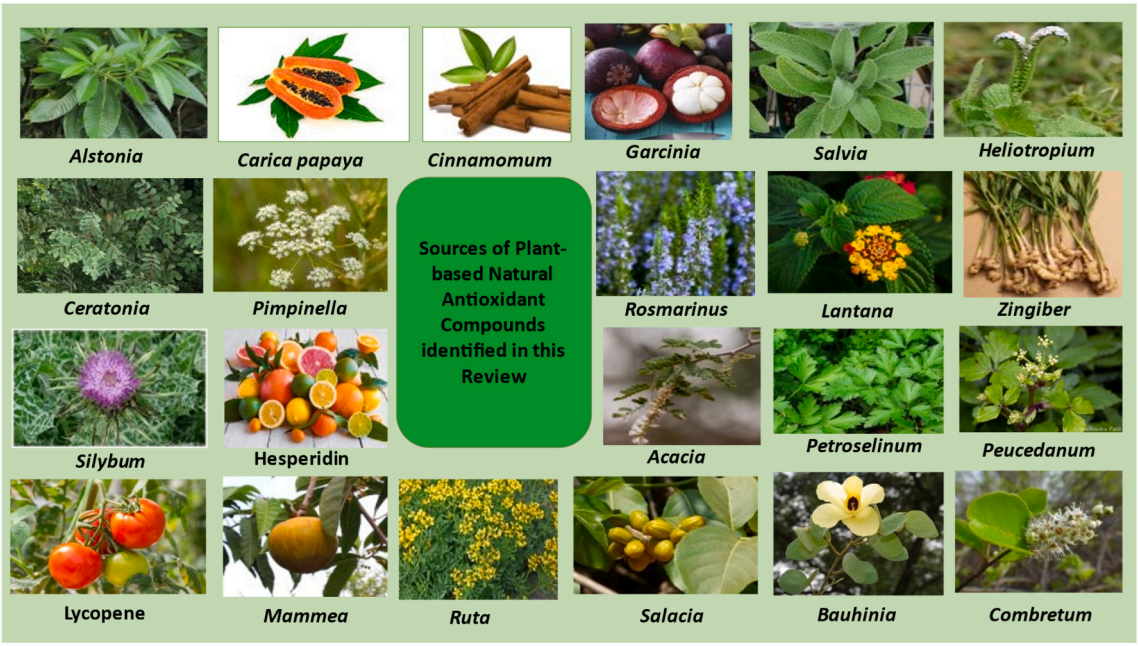


Fig. 11. Plant-based sources of natural antioxidant compounds identified in this review. The extracts from all these plants were found to be nephroprotective natural remedies capable of attenuating nephrotoxicity induced by oxidative stress in preclinical models. (The links to source files are given as Supplementary material.)

nitric oxide (NO) is synthesized from L-arginine using its isoforms; inducible, endothelial, and neural NO synthase [92]. The synthesis of iNOS is an important indicator of endothelial-dependent relaxation in the vasculature [93].

Depletion of NOs was shown to increase immune cell influx, impaired synthesis of extracellular matrix proteins, glomerular thrombosis, mesangial cell proliferation and ischemia in renal tissues [94]. The stimulation of iNOS production in kidney tissues also innervates the NF-kB pathway by IkB phosphorylation that is signified by widespread inflammation due to elevated ROS generation mechanisms [95].

The NF-kB is a transcription factor that is localized in the cytoplasm as homo and heterodimers of REL subfamily proteins and NF-kB subfamily proteins, that are activated *via* both canonical and non-canonical pathways [95]. Its activation has thus led to the pathogenesis of a variety of human diseases of which, oxidative stress plays a major role. Nephrotoxic drugs such as cisplatin can induce phosphorylation and subsequent translocation of NF-kB to the nucleus along with the degradation of the inhibitory protein IkBα [96]. NF-kB transcription activates the gene expression specific to a series of biological perturbations such as the release of inflammatory mediators, immune and inflammatory responses [97]. There are five distinct proteins which constitute as its target genes: protein (p); p65/REL A, REL B, c-REL, p50 and p52 and P50/P65 or REL A which are the most abundant forms [98]. The NF-kB pathway is closely linked to oxidative stress mechanisms which are activated when the ROS generation surpasses the cellular antioxidant capacity, mainly by reacting with cysteine residues and stimulating lipid peroxidation, DNA damage and strand breaks [99]. The typical NF-kB signalling is activated by the release of inflammatory cytokines TNF-alpha, interleukin one beta (IL-1β), inflammatory mediator, cyclooxygenase-two (COX-2) and lipopolysaccharides [100]. NF-kB target gene expression largely modulates inflammatory responses in situations of oxidative stress. However, there is evidence that ROS production could induce both pro and antioxidant reactions through the activation of those genes [101]. NF-kB pathway through the intracellular influx of calcium ions promote glycolysis as well, thereby letting the damaged renal tubules to partly recover from its nephrotoxic onslaught [102].

Nrf2 is a transcription factor which is linked to the redox balance in kidney cells is are directly related to the manifestation of acute and chronic kidney disease [103]. It maintains redox balance by activating antioxidant genes that sustainably suppress the generation of ROS and subsequent ROS-induced tissue damage [103]. Oxidative stress is an upstream activator of apoptosis that results from excess ROS as a consequence of nephrotoxicity. Nrf2 is ubiquitinated through Keap-1 but excess ROS degrades the Nrf2–Kelch-like ECH-associated protein-1 (Keap-1) complex and activates the tyrosine kinases which initiate the entry of Nrf2 into the nucleus and transcribes the expression of cytoprotective genes. Interestingly, Nrf2 mechanism is capable of attenuating both acute and chronic kidney disease [104,105].

A knowledge of the proteomics is required to better understand the toxicant-induced mechanisms of action, that is a prerequisite for the assessment of nephrotoxicity. Most of the nephrotoxicity-inducing molecular mechanisms involve the responsiveness of a diverse array of proteins [106]. These include protein kinases, [tyrosine receptor kinases including epithelial growth factor receptor (EGFR) serine/threonine protein kinases (protein kinase C), mitogen-activated protein kinases (MAPK) including c-Jun kinases, p38, ERK, glucose-regulated protein release by cysteine-S-conjugates, heat shock proteins], and so on [107]. The direct result of toxicant-induced stress responses is to evoke the release of a repertoire of different proteins. Oxidative stress can produce proteins which regulate protein damage, protein repair processes, stress-related gene transcription, mitogenesis, structural organization of cells, the release of antioxidant enzymes, cell survival or cell death [85,108–110]. Protein kinase activity is largely determined by the cellular localization, substrate availability and phosphorylation of proteins, where most of the substrates are transcription factors [111].

The mechanisms of protein metabolism are vital to delineate nephrotoxicity but the connection between gene expression and proteomics should also be investigated [112]. An early stress-responsive reaction in nephrotoxicity is the induction of pro-apoptotic gene expression in an attempt to remove the damaged cells, yet however, the toxic effect progressively debilitates the antioxidant mechanisms leading to acute kidney injury. Prolonged AKI over long periods of time will progress into chronic kidney disease in which fibrosis and necrosis is largely induced [113]. The breakdown of cellular homeostasis first begins with the biological dysfunction of upstream biochemical targets such as free calcium influx and non-protein-related thiol modification [114,115]. Further, the protein kinases are able to phosphorylate non-related

proteins that activate the expression of genes that are non-related to oxidative stress but modulate the cellular behaviour [116]. The family of protein kinases plays a vital role in determining the nephrotoxic effects by not only inducing biological perturbation in kidney tissue but also by activating the phosphorylation of other unrelated proteins in the vicinity. Ultimately the extent of toxicity and the biological outcome such as cell survival or cell death is determined by the balance between protein kinase activity and protein phosphatases [117].

Nephrotoxicity is also associated with the MAPK family of proteins which consists of multiple highly conservative serene/threonine activity pathways [118]. There are three main MAPK pathways that are innervated by extracellular signal transduction, and regulatory cellular processes such as proliferation, differentiation, migration, apoptosis, and survival, which are the JNK, p38, and ERK pathways [119]. The activation of proteins downstream of p38 leads to the degradation of IkB, that allows the activation of the NF-kB transcription leading to an increase of TNF-a. The TNF-a expression could also activate further degradation of IkBα in a positive feedback loop which continues to release more and more of inflammatory mediators [120]. The ERK pathway is stimulated by cell death and the growth factors of cell survivability [121]. The activation of JNK, stimulates proapoptotic signalling as a result of oxidative stress-related responses [122]. Ischemia and/or hypoxia in the kidneys provide the stimulus for activating JNK, p38 and the ERKs that are prevalent after cytotoxic acute kidney injury [123]. The activation of JNK is inhibited by *N*-acetyl-cysteine (NAC) [124] and a decrease in phosphorylated JNK induces the blocking of mono amino oxidase release by pargyline that prevents the formation of ROS [125]. Overall, the mechanisms of JNK activation lead to cell death signalling in the kidneys and when suppressed, prevents JNK-innervated renal cell apoptosis.

Another mechanism of nephrotoxicity is the activation of protein 53 (p53) signalling cascade by increased ROS generation that occurs due to DNA damage [75]. The cue to accelerate ROS production occurs when the genes responsible for innervating protein 54 (p54)-promoter binding activity are repressed [126]. The disruption of the DNA molecular structure activates the DNA damage sensing proteins (telangiectasia, ataxia, Rad-3) and checkpoint kinases [127] that lead to stimulating the downstream targets of renal tubular cell apoptosis, such as the caspases within the tubular mitochondria.

A large repertoire of pro-inflammatory cytokines and chemokines are released in response to nephrotoxicant assaults in the kidneys [128]. A strong link to nephrotoxic pathogenesis has been demonstrated with inflammatory responses stimulated by TNF-a, TGF-β, intercellular adhesion molecules (ICAM), monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein-2 (MIP-2), RANTES, IL-1β, interleukin-six (IL-6) and interleukin eighteen (IL-18) [129]. As the inflammatory responses take a firm hold, the expression of TNF-a is increased in kidney tubular cells which upregulates systemic inflammation and acute-phase responses. TNF-a reacts through two important receptors, tumour necrosis factor receptor type 1 and 2 (TNFR1 and TNFR2), in which the former triggers tubular cell death and renal tissue damage directly while the latter in conjunction with TNF-a indirectly induces nephrotoxicity in the kidneys [130,131].

Oxidative stress is also known to evoke cytoprotective mechanisms during kidney injury [132]. The best example comes from the haemoxygenase-1 (HO-1), a redox-sensitive microsomal enzyme that catalyses haem-oxygenase degradation to antioxidants biliverdin, carbon monoxide and iron metabolites [133]. In HO-1-deficient rat kidneys, renal tissues were more sensitized to nephrotoxicants [134], and its overexpression led to a marked reduction in cellular apoptosis *in vitro* [135]. Renal protection was also afforded by several other antioxidant compounds such as vitamins E and C, *N*-acetylcysteine, dimethyl thiourea, melatonin and selenium in several experimental models [136].

What was so far described included the biochemical mechanisms and adaptive immunity that are associated with nephrotoxicity. But innate immunity which mounts a non-specific immune reaction by way of evoking an inflammatory response also exerts a considerable impact to resolve renal toxicity [137]. One of its primary mechanisms involves the toll-like receptors (TLRs) which are transmembrane type 1 sentinel glycoproteins [138]. They play a significant role in host surveillance by recognizing both danger-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPS) that act as the ligands which activate immune reactions [139]. There are 10 known TLRs in humans and 12 in mice and the most common pathways are the myeloid differentiation factor 88 (MYD88) and the TRI-containing adapter-inducing interferon β (TRIF pathway) which involve the TLRs 1, 2, 4–10 in the former and TLRs 3–4 in the latter [140]. The major function of the TLRs is to produce an inflammatory response by upregulating inflammatory mediators, complement, interferons, prostaglandins, chemokines, cytokines, and adhesion molecules [141]. Although the TLR responses readily sense kidney injury, particularly in the renal parenchymal cells, neutrophil infiltration, dendritic cell activation by interleukin ten (IL-10) and endogenous inflammatory mediators do not suffice to reduce the toxic effects, rather they serve to exacerbate the tissue injury [142,143]. Therefore, the clinical value of mounting anti-inflammatory responses to enhance renoprotection remains questionable in nephrotoxic settings in the kidneys. To mention the TLRs that play significant roles in nephrotoxic kidneys, they are functionally involved in a multitude of biological processes and are localized in the glomerulus, renal tubules, collecting ducts, renal parenchymal cells, mesangial matrix, podocytes, and renal vasculature. The best characterized TLR in kidney injury is TLR4, the ligand activation of which involves it in diverse proinflammatory processes [144]. TLR4 mainly responds to endogenous molecules arising from nephrotoxicity including lipopolysaccharides (LPS) from gram negative bacteria. It orchestrates AKI with increased pathogenicity that worsens tissue injury which is validated by studies in TLR4-knockout mice. The prominent inflammatory mechanism that is produced by TLR4 happens to be the p38, JNK and MAPK inflammatory pathway [145].

3. Oxidative stress in kidneys

Oxidative stress is a major factor that causes significant renal tubular damage, through the production of ROS which leads to prolonged lipid peroxidation and poses the risk of renal carcinogenesis [146]. Oxidative stress-related inflammatory disease conditions such as obesity, diabetes, hypertension, and hyperlipidaemia induce large scale ROS generation that require changes in food habits in these clinical cohorts [147]. Oxidative stress (Fig. 9) is produced in the kidneys by exogenous factors; cigarette smoke, toxins, carcinogens, radiation and pollution [148], and endogenous factors; inflammatory cells, epithelial and endothelial cells, fibroblasts, the respiratory chain, and oxidative enzymes xanthine and NOX [149]. The oxidative enzymes donate electrons to molecular oxygen from which superoxide and hydroxyl radicals are produced, and superoxide radicals are converted to hydrogen peroxide by SOD [150]. Hydrogen peroxide generates hydroxyl groups through the Fenton reaction that also is a source of ROS. ROS and reactive nitrogen species (RNS) are the major free radicals that are associated with oxidative stress in kidney cells, where ROS is generated largely from the oxidation of macro-molecules, proteins, lipids, and nucleic acids and the inhibition of antioxidant enzymes [151].

3.1. Sources of oxidative stress in kidneys

3.1.1. Effects of therapeutic-induced oxidative stress

The role of cisplatin in the kidney cells consists of covalent bonding of platinum that leads to adduct formation and acting as a DNA alkylator [152]. Cisplatin also triggers the release of ROS which subsequently impairs DNA functionality by inducing the breakdown of DNA repair mechanisms, transcription inhibition, cell cycle arrest, mitochondrial damage, reduced adenosine tri phosphate-ase (ATPase) activity, disrupted intracellular substance transport and restricted DNA movement

within the nucleus [153]. The other impaired DNA mechanisms include DNA degradation by endonucleases in the kidney tubules with subsequent renal tubular epithelial cell death [154]. Cisplatin treatment characteristically induces the elevation of serum urea, creatinine, and uric acid levels in the body as well as lipid peroxidation biomarker MDA, nitrosative stress marker NO and many cytokines including TNF-alpha [155]. It upregulates NOX, a membrane-bound enzyme which generates oxygen free radicals that diminishes membrane stability and causes DNA and protein denaturation [156]. The ensuing enzyme inactivation initiates mitochondrial dysfunction and interferes with the respiratory chain [157]. Enzymes and transporters that are present in the proximal tubular epithelium stimulate each step of cisplatin bioactivation to a potent nephrotoxin [158]. Cisplatin is metabolized to a nephrotoxin as a GSH conjugate and the first enzyme in this pathway was proposed as gamma-glutamyl-transferase evidenced by both cell culture studies and *in vivo* animal models [158]. The metabolic activation of cisplatin begins in the kidneys and causes the antioxidant mechanisms to be annihilated with marked glutathione depletion and the accumulation of thiol nephrotoxins that produce oxidative stress and cellular apoptosis [159]. The endogenous antioxidant system is overwhelmed by cisplatin reacting with the cytochrome P450 system that produces microsomal free radicals; superoxide anions, hydroxyl radicals, hydrogen peroxide and other reactive oxygen species [160]. Renal tissue damage which follows suit is jointly produced as a result of oxidative stress and tissue inflammation caused by a large repertoire of cytokines [161]. There are reports on cisplatin effect on brush border enzymes in both renal cortical and medulla homogenates in which, alkaline phosphatase, gamma glutaryl transpeptidase, leucine aminopeptidase, were markedly diminished with the exception of acid phosphatase level that was increased in a rat model [162]. Cisplatin also induced changes in carbohydrate metabolic enzymes; lactase dehydrogenase, hexokinase, malate-dehydrogenase, which were decreased but glucose-6-phosphatase was increased [163]. Overall, cisplatin inhibits mitochondrial function, induces depletion of sulfhydryl (SH) groups, DNA damage, apoptosis, and inflammation, leading to nephrotoxicity [164]. The major site of renal injury by cisplatin is found in the s3 segment of the PCT towards the outer margin of the renal medulla [165]. The varied sources of oxidative stress inducing compounds, their chief constituent and its chemical structure and the common names have been tabulated in Table 1.

Doxorubicin (Doxo) is an anticancer drug like cisplatin that causes nephrotoxicity and cardiomyopathy as its adverse effects [166]. Like cisplatin, Doxo too induces oxidative stress and membrane lipid peroxidation, thereby decreasing the antioxidant capacity of the kidneys [167]. Doxo exerts its nephrotoxic action by producing drug-induced free radicals that intensify oxidative stress in organelles causing damage to the kidney tubules [167]. Being a quinone compound of the anthracycline group, Doxo's quinine group undergoes an electron reduction catalysed by NADPH oxidoreductase that produces semiquinone free radicals [168]. They are oxidised by molecular oxygen to regenerate quinone free radicals in a cyclic redox process. Concomitant to this quinone regeneration is superoxide anion radical release. Dismutation of superoxide radicals yields hydrogen peroxide, which is the main compound that induces Doxo toxicity because iron ions also can combine with hydrogen peroxide to form hydroxyl free radicals. Iron-semiquinone free radicals are the most potent of free radicals produced from the Doxo treatment of cancer. Hydroxyl radicals are the most reactive of the free radicals which could be produced by iron reduction that occurs due to internal electron shifts. Reduced iron could again donate these electrons to molecular oxygen that generates more superoxide anion radicals. This free radical generation leads to nephrotoxicity, also with the downregulation of renal antioxidant enzymes. Furthermore, the histopathological lesions that appear in the kidneys after anticancer therapy include total degeneration of renal tubules, reduction in size of glomerular capillary tufts, cellular chromatin condensation, detachment of proximal tubular epithelial lining, inflammation within the Bowman's capsule causing dilatation and accumulation of homogenous exudates, necrosis, and loss of apical microvilli in both proximal and distal convoluted tubules [169]. Renal pathophysiology that manifests as kidney disease from renal tissue damage during chemotherapy occurs as the combined effects of biochemical, histological and ultrastructure changes in the kidneys. The latter consisted of cytoplasmic and mitochondrial vacuolization, detachment of basal membrane, fusion of foot processes, dissociation of mitochondria from basal membrane, accumulation of lysosomes and pinocytotic vesicles within cells [169].

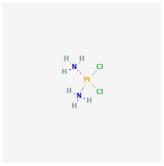
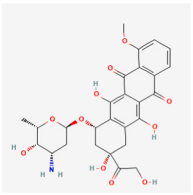
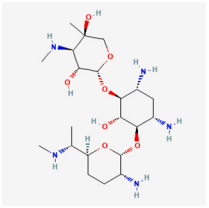
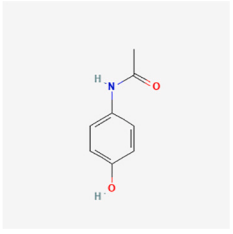
Gentamicin is also an aminoglycoside antibiotic used against aerobic gram-negative bacteria which plays a pivotal role in initiating oxidative stress in the kidneys [91]. Nephrotoxicity is the main side effect of gentamicin treatment caused primarily by ROS production [170]. It is a potent iron-chelator which catalyses free radical production leading to DNA and cellular damage [171]. It also halts protein synthesis causing tubular necrosis and induces protein denaturation and lipid peroxidation (measured by thiobarbituric reactive substances (TBARS) in the kidneys) [172]. About 10–20 % of gentamycin treated patients end up with acute renal failure [173]. Gentamicin administration significantly increased myeloperoxidase activity (which induces oxidation by hydrogen peroxide) in kidney tissues [174] and severe histological changes such as tubular vacuolization, tubular necrosis, and parietal cell hyperplasia [175].

The accumulation of gentamicin in the proximal renal tubule distorts the brush border network, paralyses the antioxidant mechanisms, increases; oxidative stress, glomerular congestion, endothelin-1 and TGF-β secretion, infiltration of monocyte/macrophages into renal cortex and medulla, and apoptosis [176]. Gentamicin further enhances the release of superoxide anions and hydrogen peroxide which interacts and forms an unstable hydroxyl radical that then interacts with ferrous ions [177]. Another effect of gentamicin nephrotoxicity is the loss of haemoglobin from the red blood cells, resulting in anaemia. Usually, the haematological parameters reflect the physiological status of both animals and humans. The level of the kidney hormone erythropoietin regulates the process of erythropoiesis in response to declining oxygen levels in tissues and is produced in the renal peritubular cells which directly influences the proximal tubular function [178]. The major determinant of gentamicin-induced anaemia is erythropoietin deficiency that is produced by kidney damage that ensues from nephrotoxicity [179]. Gentamicin significantly augments serum iron, ferritin, and the body's total iron-binding capacity, where gentamicin chelates mitochondrial iron thus forming an iron-gentamicin complex which is a source of free radicals that inhibits mitochondrial respiration [171]. Moreover, iron can directly initiate lipid peroxidation of the polyunsaturated fatty acids (PUFA), affecting the erythrocyte membrane integrity and the haemolysis of the erythrocytes serves to increase ferrous ions and ferritin in serum [180].

Gentamicin treatment leads to the elevation of serum urea, creatinine, excretion of total protein in urine and β2-microglobulin concentrations that signify nephrotoxicity which are also the common biochemical indicators of kidney function. High urinary proteinemia indicates kidney tubular damage and high serum urea and creatinine indicate glomerular damage [181]. A high urinary β2-microglobulin level appears when its renal re-absorptive threshold limit in plasma which is 5 mg/L is exceeded and also due to proximal tubular damage [182]. Gentamicin also disrupts the serum electrolyte balance with a marked decrease in sodium ions attributed to hyper dynamic circulation that also increases the serum potassium ion concentration [183]. A remarkable loss of sodium ions indicates the inability of the kidneys to conserve sodium and chloride ions at its normal levels. Similarly, the drop of sodium ion concentration may happen due to increased water intake or the production of endogenous water that causes haemodilution [184]. The increase in serum potassium ion concentration may occur due to reduced excretion and/or leakage of intracellular potassium ions caused by gentamicin-induced renal tubular epithelial damage [185].

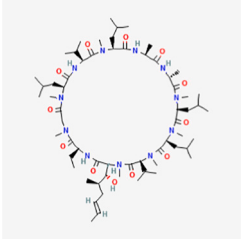
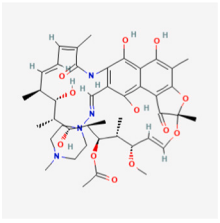
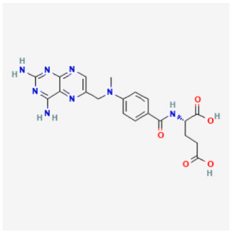
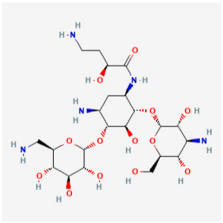
Amikacin is a broad-spectrum aminoglycoside antibiotic that is more

Table 1
Sources of renal oxidative stress. The compounds which cause renal oxidative stress: Nature of source, common and chemical names, chemical structures, impact on the kidneys and the references are included in this table.

Nature of source	Common name	Chemical compound	Chemical structure	Impact on the kidneys	Ref
Therapeutics	Cisplatin	Cis-diammine-dichloro-platinum (II)	Cisplatin  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 5460033, Cisplatin. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/5460033.	Generation of ROS, mitochondrial dysfunction, reduced ATPase, lipid peroxidation, DNA degradation, nitrosative stress, elevation of BUN, SCr, and uric acid in serum.	[153,154,234]
	Doxorubicin	Doxorubicin	Doxorubicin  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 31703, Doxorubicin. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Doxorubicin.	Generation of ROS, tubular damage and degeneration, membrane lipid peroxidation, decrease in antioxidant capacity of the kidneys, increased myeloperoxidase activity, elevation of BUN, and SCr in serum.	[167]
	Gentamicin	Gentamicin	Gentamicin  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 3467, Gentamicin. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Gentamicin.	Initiates oxidative stress, generates ROS and other free radicals, membrane lipid peroxidation, a potent ion-chelator which produces free radicals, kidney tubular vacuolization, tubular necrosis, parietal cell hyperplasia, elevation of BUN, SCr, excretion of total protein in urine, β-microglobulin, endothelin-1, TGF-β titres in serum.	[181,235]
	Paracetamol	Acetaminophen	Acetaminophen  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 1983, Acetaminophen. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Acetaminophen.	Up regulation of para-amino phenolic compounds, NO discharge and glutathione, tubular degeneration, tubular congestion, glomerular atrophy, cloudy swelling inside kidney tubules, leading to renal oxidative stress and free radical generation and immune cell infiltration.	[196,197]
	Ciclosporin	Ciclosporin	Ciclosporin	Oxidative stress induced by mitochondrial ROS and ER stress, lipid peroxidation. Chronic nephrotoxicity that characteristically progresses into tubular atrophy, renal fibrosis, inflammatory cell influx and inhibition of NO synthase activity that impairs endothelial-	[201,203]

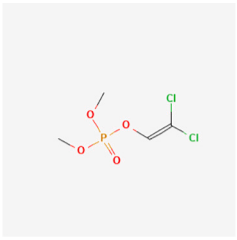
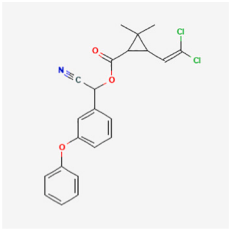
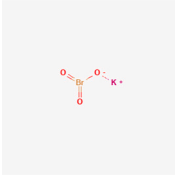
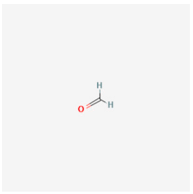
(*continued on next page*)

Table 1 (*continued*)

Nature of source	Common name	Chemical compound	Chemical structure	Impact on the kidneys	Ref
			dependent relaxation leading to arterial dysfunction.		
			 National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 5284373, Ciclosporin. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Ciclosporin.		
	Rifampicin	Rifampicin	Rifampicin  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 135398735, Rifampicin. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Rifampicin.	Diffused glomerular congestion, tubular and peritubular congestion, epithelial desquamation, blood vessel congestion and tubular casts, produces lipid peroxidation, glutathione depletion and a decrease in SOD and catalase.	[191,236]
	Methotrexate	Methotrexate	Methotrexate  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 126941, Methotrexate. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Methotrexate.	Oxidative stress inducer, generates free radicals, membrane lipid peroxidation and causes mitochondrial dysfunction. Increases chemosensitivity to ROS and apoptosis.	[187,189]
	Amikacin	Amikacin	Amikacin  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 37768, Amikacin. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Amikacin.	Causes nephrotoxicity and ototoxicity.	[237]
Metals	Chromium	Cr	Chromium (III) and chromium (VI) are the common oxidative states.	Oxidative stress inducer, generates ROS, membrane lipid peroxidation, glutathione depletion, tubular necrosis, detachment of epithelial lining of the PCT. Poor creatinine clearance, elevated SCr and BUN. Renal dysfunction.	[211,212]
	Cadmium	Cd	Cd+2	Occupational hazard, oxidative stress inducer, generates ROS, membrane lipid peroxidation, elevated serum biomarkers	[204,205]

(*continued on next page*)

Table 1 (*continued*)

Nature of source	Common name	Chemical compound	Chemical structure	Impact on the kidneys	Ref
				of oxidative stress, renal dysfunction arising from nephrotoxicity.	
	Lead	Pb	Pb (0) the metal, Pb (II) and Pb (IV)	Mitochondrial dysfunction, free radical generation leading to the oxidation of macromolecules, increase of TBARS, decrease in total glutathione, and altered SOD activity.	[210,221]
	Arsenic	As	Arsenic has a valence state of +5	Activates ROS production that stimulates the major stress-related protein families, decrease in cellular ATP.	[216,217]
Chemicals	DDVP	Dichlorvos 2,2-dichlorovinyl dimethyl phosphate	DDVP  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 3039, Dichlorvos. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Dichlorvos.	Causes disruption of the endogenous antioxidant system in the kidneys and accelerated cell death, degenerative changes in tubular and glomerular histology with congestion of blood vessels in the kidneys and increased serum and urinary biomarkers of renal dysfunction.	[224]
	Cypermethrin		Cypermethrin  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 2912, Cypermethrin. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Cypermethrin.	Proximal tubular dilatation, desquamation, and degeneration of tubules, narrowing of Bowman's capsules, dilated, and congested cortical blood vessels, atrophied, and fragmented glomeruli	[228]
	Potassium bromate	$KBrO_3$	Potassium bromate  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 23673461, Potassium bromate. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Potassium-bromate.	A partial carcinogen in humans, if ingested at a high dose causes renal toxicity. Renal mutagenesis is also reported at higher doses resulting in acute renal failure.	[225]
	Formalin	Formaldehyde	Formaldehyde  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 712, Formaldehyde. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Formaldehyde.	Vacuolization, loss of cellularity and desquamation of the epithelium lining the renal tubules, occlusion of tubular space, particularly the urine space in the tubules. Eosinophilic casts within tubules, vascular dilation and congestion, shrinkage or widening of glomerular space and inflammatory cell infiltration.	[232,233]

Legend: ATP - adenosine tri phosphate, ATPase - adenosine tri phosphatase, BUN - blood urea nitrogen, DNA - deoxyribo nucleic acid, ER - endoplasmic reticulum, NO - nitric oxide, PCT - proximal convoluted tubule, ROS - reactive oxygen species, SCr - serum creatinine, SOD - superoxide dismutase, TBARS - thiobarbituric acid reactive substances, TGF-β - transforming growth factor-beta.

effective than gentamicin at suppressing gram-negative bacterial infections for having low resistance [186], low cost, and synergism with beta-lactam antibiotics. However, nephrotoxicity and ototoxicity are produced as adverse effects of its use.

Methotrexate is a chemotherapeutic agent which is also an immune suppressant, which mainly concerns folate metabolism and inhibits dihydrofolate reductase action that limits the conversion of folic acid to tetrahydrofolate which is integral to DNA synthesis [187]. Also, it generates free radicals that affect membrane lipid peroxidation and develops into mitochondrial dysfunction. It is non-discriminatory towards healthy cells and develops oxidative stress by the accumulation of excess homocysteine that is not converted to methionine due to the inhibition of methylenetetrahydrofolate reductase (MTHFR) [188]. Methotrexate increases cell chemosensitivity to ROS and promotes subsequent apoptosis in high-proliferative haematopoietic cells in bone marrow and those in the gut mucosa, leading to severe renal and hepatic toxicity [189].

Rifampicin is an anti-bacterial drug that is widely used against tuberculosis and leprosy which necessitates long term use that also induces nephrotoxicity in both rats and humans. It induces hepatitis and nephritis in hypersensitive patients [190]. Rifampicin induces toxic effects in the kidneys, liver, gastrointestinal tract, and cardiovascular system [191]. In histology, diffused glomerular congestion, tubular and peritubular congestion, epithelial desquamation, blood vessel congestion and tubular casts were apparent in rats given 1 g/kg body weight every third day for two weeks [192,193]. It also produced lipid peroxidation measured by MDA and glutathione peroxidase (GPx), glutathione depletion and a decrease in SOD and catalase [194]. In serum, anti IgG antibody titres were elevated [194]. The urea, uric acid, creatinine and total protein levels in both serum and urine were markedly increased [192]. Prolonged rifampicin treatment produced acute tubular interstitial nephritis during which the circulating titres of anti-rifampicin antibodies and IgG were significantly raised with IgG deposits accumulating in the tubular basement membrane [195]. IgG light chains were found within the tubular lumen indicating inflammation and activation of adaptive immunity [195].

Paracetamol at 2 mg/kg administered 24 h prior to euthanasia in rats reportedly induced severe kidney damage [196]. Paracetamol caused the upregulation of para-amino phenolic compounds, glutathione conjugates and NO discharge, that increased oxidative stress in the kidneys [197]. The pathogenesis of paracetamol-induced nephrotoxicity exhibited glomerular atrophy, tubular congestion, immune cell accumulation, cloudy tubular swellings, tubular degeneration, basal membrane atrophy, focal cortical degeneration, necrosis, and varied sizes of kidney cells [198]. Known also as acetaminophen is an analgesic and antipyretic drug that causes renal toxicity at high doses and exhibit elevation of SCr and serum urea with a decrease in uric acid levels [199]. Renal tissue necrosis, tubular degeneration as well as metabolic disorders are characteristic of nephrotoxicity induced by acetaminophen overdose in which SCr and serum urea components are deranged [200].

Cyclosporin A (CsA) is an immunosuppressant agent used for the prevention of organ transplant rejection which induces nephrotoxicity as its prime side effect [201]. It exerts a considerable therapeutic effect on suppressing kidney, liver, and heart transplant rejection although its efficacy is greatly diminished by causing serious renal injury that delimits kidney function. CsA - nephrotoxicity manifests as an oxidative stress reaction that is induced by mitochondrial ROS and ER stress that produced lipid peroxidation [71] although CsA also stimulates autophagy that benefits renal damage by serving to reduce the extent of nephrotoxicity [202]. However, long term treatment of CsA develops into chronic nephrotoxicity that characteristically progresses into tubular atrophy, renal fibrosis, inflammatory cell influx and inhibition of NO synthase activity that impairs endothelial-dependent relaxation leading to arterial dysfunction [203].

3.1.2. *Effects of metal-induced oxidative stress*

Cadmium is an industrial pollutant and exposure to it is considered an occupational hazard that leads to nephrotoxicity [204]. The mechanism of action is thought to elevate oxidative stress in the kidneys, which is a critical target organ of cadmium toxicity [204]. It produces free radicals that cause oxidative damage and heightened lipid peroxidation in the kidneys [205]. A cadmium dose of 3 mg/kg body weight per day injected subcutaneously for 3 weeks in rats caused cadmium intoxication leading to renal damage and dysfunction [206]. Both serum and urinary biomarkers of renal damage were increased with cadmium toxicity in animal models [207]. Cadmium-induced nephropathies are characterized by marked upregulation of oxidative stress-related renal biochemical and molecular parameters. They consisted of; (i) diminished enzymic biomarkers (CAT, SOD, glutathione peroxidase, glutathione-s-transferase) [207], (ii) insufficient production of non-enzymic biomarkers (sulfhydryl groups, reduced vitamin C, E and glutathione) [208], (iii) increased lipid peroxidation biomarkers (lipid hydroperoxides, thiobarbituric acid reactive substances) [209] and (iv) glutathione metabolism-related markers (glucose-6-phosphate dehydrogenase and glutathione reductase) [210].

Chromium (VI) is an oxidative stress inducer that causes nephrotoxicity which progresses into renal dysfunction evidenced by poor creatinine clearance and increased serum creatinine and BUN in a preclinical model that received this compound [211]. Chromium is a multivalent metal element that exists in several different oxidative states, and the reduction of chromium (VI) (which is the most toxic form to both humans and animals) to chromium (III) results in the overproduction of ROS in kidney tissues [212]. Further, potassium dichromate induced proteinuria, protein carbonylation and lipid peroxidation, decreased glutathione peroxidase levels [213] and damaged kidney tissue architecture that showed necrosis and detachment of the epithelial lining from the proximal convoluted tubules [214].

Arsenic is a toxic metal that exists as trivalent or pentavalent compounds and the most toxic compounds that denature the enzymes involved in tissue respiration are the trivalent compounds [215]. Arsenic combines with the substrates linked with nicotinamide adenine dinucleotide (NAD) reduction after accumulation within mitochondria [216] and causes mitochondrial dysfunction by affecting adenosine tri phosphate (ATP) synthesis [210]. Decreased cellular ATP results in increased hydrogen peroxide levels that in turn induce oxidative stress and the release of ROS. Arsenic plays a detrimental role in oxidative phosphorylation by inhibiting succinic dehydrogenase activity and destabilizing the energy-linked functions of mitochondria by competing with phosphate [210]. It also activates ROS production that stimulates the major stress-related protein families [217]. Certain sulfhydryl-containing proteins and enzyme systems are altered by the exposure to arsenic compounds, but they can be reversed by the addition of excess glutathione [218]. The arsenic-induced ROS and subsequent oxidative stress may cause DNA damage and initiate carcinogenesis [219].

Acute lead (Pb) nephrotoxicity is limited to morphological and physiological changes in the PCT and is mostly followed by accumulation in the soft tissues of the kidney [210]. Lead toxicity commonly occurs by ingestion or occupational and/or accidental exposure [220]. It mainly manifests as defects in energy-driven transport functions including aminoaciduria, iron transport and glycosuria [210]. Renal pathogenesis occurs mostly by mitochondrial dysfunction, where in children affected by lead toxicity, there were conspicuous ultrastructural changes with swelling in their mitochondria [210]. However, exposure to moderate to high doses of lead induces free radical

generation leading to the oxidation of macromolecules [221]. Lead toxicity induces oxidative stress reactions with an increase of TBARS, decrease in total glutathione and altered SOD activity [221]. The renal toxicity that ensues is dependent upon the dose and length of exposure, age, and the target organ [221].

3.1.3. Effects of chemical-induced oxidative stress

Dichlorvos (2, 2-dichlorovinyl dimethyl phosphate – DDVP) is a broad-spectrum organophosphate pesticide that is widely used in agriculture and its use is directly linked with systemic toxicities including nephrotoxicity [222]. Its lipophilicity promotes inclusion in membrane lipids thereby altering the physicochemical properties in the membrane structure and organization leading to ROS production and subsequent oxidative stress [223]. Prolonged exposure to this pesticide results in the disruption of the endogenous antioxidant system in the kidneys and causes accelerated cell death [224]. DDVP also shows degenerative changes in tubular and glomerular histology with congestion of blood vessels in the kidneys and increased serum and urinary biomarkers of renal dysfunction.

Potassium bromate is a food additive used in dough conditioning in bakery products, also generated during water disinfection by ozonation, a partial carcinogen in humans and a total carcinogen in animals if ingested at a high dose [225]. It is poisonous at a dose of 46–92 mg/kg or above and causes organ toxicity, including the kidneys [226]. Renal mutagenesis is also reported at higher doses resulting in acute renal failure [227].

Cypermethrin is an insecticide which is a common source of kidney disease caused by renal antioxidant system dysfunction [228]. The cypermethrin-treated kidneys had severe histopathological lesions such as proximal tubular dilatation, desquamation, and degeneration of tubules, narrowing of Bowman's capsules, dilated, and congested cortical blood vessels, atrophied, and fragmented glomeruli [229,230]. Infiltration of immune cells within inter-tubular spaces, eroded Bowman's capsular wall and loss of normal appearance in kidney tubules have also been observed [231].

Formalin is a harmful chemical substance that is in an aqueous solution that consists of 40 % formaldehyde and displays acute renal toxicity [232]. The signs of nephrotoxicity consisted of vacuolization, loss of cellularity and desquamation of the epithelium lining the renal tubules, occlusion of tubular space, particularly the urine space in the tubules [233]. Also, there were eosinophilic casts within tubules, vascular dilation and congestion, shrinkage or widening of glomerular space, inflammatory cell infiltration and haemorrhage within interstitial spaces [233].

3.2. Mitigating oxidative stress in kidneys

3.2.1. Dietary supplements

A spectrum of dietary supplements (Fig. 10) and (Table 1) which possess antioxidant properties have been reported, particularly in attenuating experimental nephrotoxicity that culminates in acute and chronic kidney injury [238]. Fermented antioxidant functional foods rich in anthocyanin have been implicated in suppressing oxidative stress-related proximal tubular damage in a ferric nitrilotriacetate-induced animal model of renal injury and carcinogenesis [239,240]. As such, a preclinical model of iron chelated renal damage has shown significant restoration of function after dietary intake of fermented black soybeans [239]. Cyanidin-3-O-beta-glucoside, an intermediate product of anthocyanin catabolism, having formed the stable flavylium cation, donates electrons and transfer hydrogen atoms to hydroxyl groups thereby preventing free radical formation [241]. Furthermore, several dietary antioxidants (vitamin E, curcumin, coloured rice, garlic oil, probucol, lycopene) have also shown similar protective antioxidant effects in the same renal carcinogenic model [239].

Dates are a dietary supplement that is high in phenolic content consisting of natural procyanidins, ferulic, p-coumaric and sinapic acids, and flavonoids that possess antioxidant activity and hence, able to reduce the adverse effects of CIN. Other reported antioxidant substances that are equally potent in overcoming oxidative stress include lipoic acid, methionine, ascorbic acid, sodium thiosulfate, and sulfhydryl-containing drugs (captopril and *N*-acetylcysteine) [242]. Renal cellular apoptosis mainly occurs *via* both caspase-3-dependent and independent pathways because caspase 3 (a member of the family of protease enzymes) is an inflammatory and apoptosis biomarker [242]. Cisplatin-nephrotoxicity treated by a berne date extract had showed efficient anti-inflammatory, anti-apoptotic and antioxidant activity in an experimental rat model which could be a prospective treatment in clinical models as well [243].

Garlic exerts high therapeutic effects such as reno-protection, and contains organosulfur compounds (allicin and S-allyl cysteine) which are natural free radical scavengers [244] capable of increasing glutathione, CAT and SOD as part of the antioxidant defense system [245]. However, cisplatin therapy is accompanied by a significant progressive reduction in body weight that is attributed to renal tubular dysfunction caused by renal tissue damage [246]. Renal tubular damage that arises from cisplatin therapy causes a reduction in water reabsorption, excessive sodium excretion, polyuria, and dehydration which as a result produces marked weight loss [247]. The reno-somatic index better known as the kidney weight to body weight ratio showed an increase due to oedema in renal parenchyma tissue that arose from kidney tissue inflammation. These effects could be significantly attenuated by feeding garlic extract that proved its anti-inflammatory and reno-protective action in animal models.

Garlic extract prevented cisplatin-nephrotoxicity but also on several more reno-toxic compounds present in common foods such as cadmium and acrylamide (in vegetables, nuts, pulses, meats, and starchy foods) [248] and the chemotherapeutic doxorubicin that causes glomerular destruction and renal tubular injury [249]. Diallyl tetrasulfide (DTS), an antioxidant compound that is present in garlic, has demonstrated oxidative stress relieving properties in cadmium-induced renal toxicity in rats [250]. DTS effectively blocked cellular apoptosis and lipid peroxidation in rat kidneys with enhanced cytoprotective activities that preserved the normal kidney histology due to antioxidant and metal chelating properties [206].

The antioxidant properties of Diallyl sulfide, in garlic was also described as having nephroprotective effects by stimulating the Nrf2, responsible for activating the genes of antioxidant enzymes and regulate cellular redox responses [251]. Nrf2 transcriptome is normally repressed by the negative regulator, Keap 1, but when exposed to oxidative stress, it escapes Keap 1 repression and binds to the promoter region of those genes that produce antioxidant responses in cells [252]. The Nrf2 gene targets called the phase II enzymes were capable of restoring antioxidant status in glomerular and tubular cells by decreasing the production of iNOS, ROS and reactive nitrogen species (RNS), xenobiotics, nicotinamide adenine dinucleotide phosphate (NADPH), TNF-alpha, and nuclear factor kappa beta, that were the causative factors of gentamycin-induced renal oxidative stress in a rat model [252].

Grape seed extract exerts antioxidant properties due to its proanthocyanin content and have reported improvement of DNA oxidation caused by cisplatin therapy in an *in vivo* rat model of CIN [253]. The prime anticancer action of cisplatin consists of mediating DNA adduct formation which abrogates cell division and enhances both extrinsic and intrinsic pathways of apoptosis. These cell death mechanisms were mitigated by the pre-treatment with grape seed extract and omega-3 fish oil in two separate cohorts of rats, which produced significant improvement in the serum and urine biomarkers of CIN as well as the characteristic features that demonstrate DNA damage in the kidney cells [254]. The measurement of tail length, tail moment and tail intensity of the DNA molecules are genomic biomarkers which indicate DNA damage, which produced lesser degradation and significant restoration to normality in this study when these two treatments were administered before cisplatin was given [164]. Both procyanidin in the grape seed

extract and omega-3-fish oil were beneficial towards CIN because of their ability to scavenge free radicals, particularly to quench peroxyl and superoxide radicles [255]. Also it can augment antioxidant enzyme activity thereby preventing oxidative tissue damage, inhibiting DNA fragmentation and apoptosis in the kidney better than all the other antioxidant vitamins that have been evaluated [256].

Curcumin longa is a natural phenolic antioxidant compound used as a spice and food colouring that has attenuated CIN in a preclinical model [257]. This study demonstrated the efficacy of curcumin with alpha-tocopherol pre-treatment before cisplatin which produced amelioration of oxidative stress by downregulating all the characteristic biomarkers of renal oxidative stress injury [258]. The activity of these two compounds combined was more potent as antioxidants than when administered alone [259] [260]. Natural antioxidant activity was also reported from pre-treatment with alpha lipoic acid, caffeic acid phenethyl ester and wheat powder from the grains of *Triticum sativum* in CIN [261].

The extract derived from *Cocos nucifera* husk fibres using chloroform showed demonstrable efficacy in reducing kidney injury-related biomarkers; SCr and BUN when pre-treated with it before administering cisplatin [262]. This treatment augmented renal catalase, exhibited anticlastogenic effects and attenuated organ toxicity, high levels of serum aspartate aminotransferase, high MDA levels and a high frequency of (up to 92 %) micro-nucleated polychromatic erythrocytes, identified as adverse effects induced by cisplatin treatment in Wistar rats [262].

Green tea has shown remarkable antioxidant activity in the brain, liver, kidneys, and several cancers. Green tea has been protective against free radicals by being a scavenger of hydroxyl, peroxyl, superoxide and peroxynitrite radicals, through its antioxidant and iron-chelating action in mouse models. Doxo-induced nephrotoxicity was attenuated in mice by a green tea (*Camellia sinensis*) leaf extract which is rich in a mix of bioactive antioxidant polyphenols containing flavanols, catechin, theaflavins, epicatechin gallate, epigallocatechin gallate and thearubigins compounds [263]. This beverage was capable of elevating antioxidant enzymes (GSH, glutathione peroxidase and SOD) by reducing the oxidative damage caused by lipid peroxidation [264]. It reduces the oxidation of polyunsaturated fatty acids and proteins and prevents loss of membrane permeability, dysfunction of membrane and cellular proteins and the endogenous accumulation of hydroxyl radicals, as well [265].

Cypermethrin-induced nephrotoxicity was attenuated by treatment with an aqueous solution of epigallocatchecin-3-gallate (EGCG), in which biomarkers of kidney injury were reduced in both serum and kidney tissue homogenates [266]. All these severe pathologies and anatomical changes in the kidneys were significantly reduced by treatment with EGCG [266]. Interestingly, no alterations in the normal kidney tissue architecture were observed in the mouse kidneys in the group treated with only EGCG [266].

Spirulina platensis (SP), a blue green algal species in the family Oscillatoriaceae, is a dietary supplement that is composed of 60–70 % proteins, 4 % vitamins, minerals, amino and fatty acids [267] as well as antioxidant compounds such as sulfated polysaccharides and sulfolipids in addition to phycocyanin [268]. Sulfated polysaccharides mediate the repair of DNA damage, alleviating oxidative and nitrosative stress and reducing the production of proinflammatory cytokines [269,270]. Sulfolipids in SP suppress superoxide anion release, the demand for phosphorous and inhibit DNA polymerase activity [268]. SP combined with ascorbic acid, when administered to rabbits after inducing nephrotoxicity with Amikacin was effective in attenuating renal toxicity parameters and was superior to alleviating oxidative stress with either SP or ascorbic acid given alone [268].

Ginseng is a Chinese herbal medicine consisting of polyphenols, triterpenoid saponins and flavonoids which favour antioxidant action [271]. It has shown immunomodulatory effects and nephroprotective properties in a rat model pre-treated with ginseng before cisplatin administration [272], in which it vastly improved oxidative stress-related macroscopic renal tissue damage (vacuolization, necrosis, and degenerative changes) and initiated DNA repair processes, which altogether showed attenuation of nephrotoxicity [273].

Fish oil enriched with omega-3-fatty acids has displayed remarkable antioxidant effects as a dietary supplement that ameliorated cisplatin-induced nephrotoxicity in Wistar rats [254]. The brush border enzymes and enzymes involved in carbohydrate metabolism, together with antioxidant biomarkers were found restored to near normal levels in this study that were diminished by cisplatin administration.

3.2.2. Biochemical antioxidant compounds

N-acetyl cysteine (NAC) treatment with vitamin E was able to reduce severe nephrotoxicity that is induced by adverse drug reaction (ADR) in Wistar Swiss albino rats as an antioxidant which can attenuate renal pathologies through the replenishment of thiol compounds [274]. NAC is a precursor compound of glutathione, which has proven antioxidant properties [275]. Its treatment has reduced oxidative stress-induced renal metabolic diseases, radiographic contrast-induced nephropathies, *in vitro* and *in vivo* models of calcium oxalate urolithiases [276,277]. NAC with vitamin E [50 kg/body weight, intraperitoneal (IP) pre-treatment a day before] was sufficient to reduce the renal toxicity induced by ADR by maintaining near normal levels of urinary marker enzymes; alkaline phosphatase, gamma-glutamyl transferase and lactate dehydrogenase, reducing lipid peroxidation as well as necrosis in renal tissues [274].

Propolis is a resinous product of the beehives that contain a variety of bioactive compounds such as flavonoids and phenols; benzoic, cinnamic, ferulic and caffeic acids among its 19 different esters that are identified [278]. Most of these compounds are free radical scavengers and an ethanol extract of Egyptian propolis showed attenuation of renal damage that arose from gentamycin treatment [279]. Propolis is a broad-spectrum biological therapeutic agent [280] which is useful in immune system upregulation, oxygen radical scavenging, anti-lipid peroxidation and inhibition of DNA cleavage by hydrogen peroxide and ultra-violet (UV)-mediated photolysis [281]. Nephrotoxicity was confirmed by reduced eGFR, elevated SCr, BUN, necrotic renal cortex, and tubular damage [282]. Propolis effectively quenched singlet oxygen, superoxide anions, hydroxyl and peroxyl radicals, suppressed lipid peroxidation with elevated CAT, SOD and GSH-Px and their gene expression particularly, in the proximal tubular cells [283].

Hemin is a breakdown product of heme catabolism that induces heme oxygenase-1 activity (HO-1), which is normally initiated by free radical production as an adaptive response to curbing endogenous oxidative stress damage in the kidneys [284]. HO-1 stimulates free radical quenching in the body *via* the release of biliverdin, carbon monoxide (CO) and ferritin, each having different antioxidant capacity. HO-1 action converts biliverdin to bilirubin (catalysed by biliverdin reductase), a high free radical scavenger while CO activates Nrf-2-nuclear translocation that upregulates the gene expression of cytoprotective antioxidant enzymes by binding with the antioxidant responsive element, which is a regulatory enhancer sequence that is present in the promoter region of those genes [285].

Taurine (2-aminoethane sulfonic acid) is a non-essential sulfur-containing amino acid that is freely available in most mammalian cells [286]. The antioxidant effects of taurine were investigated in rats administered with methotrexate; a chemical compound is known to generate free radicals that develops into hepatorenal toxicity [287]. It impairs membrane integrity through lipid peroxidation and by ensuing oxidative stress reactions. Treatment with taurine caused marked antioxidant effects in biomarkers of oxidative stress (elevated serum creatinine, BUN, nitrate, MDA, caspase, depleted GSH, CAT and DNA fragmentation together with histological parameters).

L-Carnitine is biosynthesized in both kidneys and liver and is a natural antioxidant compound made primarily from the diet consisting of the amino acids, lysine, and methionine [288]. It is found as an intermediary in many metabolic processes, particularly in human

bioenergetic processes [180]. The kidneys play a major role in synthesis, excretion, and acylation of L-carnitine and were effective in containing oxidative stress induced by gentamicin in rats [180]. L-carnitine treatment significantly reduced the total oxidant status and increased the total antioxidant status in the rats by producing marked changes in the biomarkers of oxidative stress and haematologic parameters. A significant connection between the oxidative stress status and haemodynamic status was revealed from the above-mentioned study given L-carnitine treatment that could be promoted as a promising adjuvant therapy for alleviating renal nephrotoxicity. L-carnitine inhibited lipid peroxidation that arose from the interaction of superoxide radicals with hydrogen peroxide and delimited hydroxyl radical generation by iron through its iron chelating ability [289]. The kidney functions were remarkably improved by restoring the antioxidant enzymes SOD, CAT, and serum GSH to near normal levels as well as augmenting the endothelial functions by scavenging ROS and increasing nitric oxide availability [289]. The single strand breaks in DNA were repaired to prevent its oxidation through exposure to oxygen free radicals [290]. Further, the erythrocytes were protected from undergoing haemolysis by strengthening membrane stability, reducing deformability, increasing the total haemoglobin content and the erythrocyte count that was also evidenced by a study on haemodialysis patients treated with L-carnitine supplementation [291,292]. L-carnitine treatment was found to increase the erythrocyte life span by inhibiting apoptosis and delivering circulating free fatty acids to mitochondria for oxidation because the endogenous free fatty acids serve to inhibit the Na+/K+ pump activity, that was also reversed [293]. Additionally, it was found to augment erythropoietin activity in the kidneys and reduce serum ferrous ions and ferritin concentrations [294].

Melatonin secreted by the pineal gland has known cytoprotective effects against ROS-induced oxidative stress reactions and increased inflammatory protein release [295]. In addition to regulating other physiological functions, melatonin is a direct free radical scavenger, that suppressed reactive oxygen and nitrogen and species, singlet oxygen, peroxynitrite anions and the peroxynitrite metabolites such as peroxynitrous acid and hydrogen peroxide production. It also showed capability to stimulate the antioxidant enzyme augmentation, repress; lipid peroxidation, iNOS production, and the NF-kB inflammatory pathway, thereby ameliorating antibacterial drug-induced nephrotoxicity [296].

3.2.3. Chemical antioxidant compounds

Deferoxamine (DFO) is a metal ion chelator [of ferric (III)] that is commonly used to remove excess iron in persons suffering from iron overloading diseases [297]. It is also a very effective ROS quencher and displays nephroprotective properties in both preclinical and clinical models [298]. DFO has shown both *in vitro* and *in vivo* efficacy in both ADR and gentamycin-induced renal dysfunction [299]. Nephroprotection exerted by DFO is attributed to its high-affinity chromium-chelating ability [211]. However, DFO did not control the total chromium excretion in urine. Membrane permeability of DFO is low but accumulates in extracellular compartments and its nephroprotection mechanism of action is thought to arise extracellularly as in the plasma [300].

Ceftriaxone is a third-generation cephalosporin-A antibiotic found active against a range of diseases including nephrotoxicity that was induced by tobramycin, isepamicin, cyclosporin-A and cadmium treatment in rats [301]. The main benefit of ceftriaxone therapy is that it acts as a powerful ROS scavenger and its capacity to enhance antioxidant enzyme activity. In this study, ceftriaxone and vitamin E conjugated treatment was carried out 5 days before and after the cisplatin injection and showed marked antioxidant and anti-inflammatory effects compared to those when administered alone. This combined therapy exhibited amelioration of nephrotoxicity by restoring normal cellular redox status in the kidneys. Ceftriaxone was beneficial on other nephrotoxic studies such as xenobiotic-induced nephrotoxicity, diazinon [302] and deltamethrin-induced oxidative stress in animal models which might have been due to cephalosporins being multidentate chelating agents which contained thio-ether groups [303] that quenched free radicals and thereby prevented free radical-mediated oxidation.

Sodium selenite is an exogenous source of selenite required for the synthesis of selenoproteins which are potent endogenous free radical scavengers [304]. Nephrotoxicity reportedly occurs by the inhibition of selenium-compromised thioredoxin reductase (TR) pathway [305]. Therefore, selenium is vital for the TR activity in (i) antioxidant mechanisms, (ii) regulating the cellular redox status and (iii) regulating cellular processors that are controlled by the redox status [305]. Moreover, TR is readily inhibited by electrophiles formed by anticancer agents in clinical use including cisplatin [306]. Selenium attaches as a prosthetic group to important oxidative stress-related enzymes such as the seleno-cysteine containing enzymes [307]; glutathione peroxidase and TR which are critical for attenuating oxidative stress. However, excessive selenite causes toxicity by itself, but sodium selenite is also known to provide renoprotection against nephrotoxicity.

Cerium oxide is a metal oxide when trapped within nanoparticles named nanoceria have exhibited proven antioxidant and anti-inflammatory properties in alleviating nephrotoxicity [308]. Nanoceria showed similar physiochemical properties as bulk, unentrapped cerium oxide that are more potent due to having surface oxygen vacancies. Cerium can exist in two oxidative states due to possessing two valences: Ce +3 and Ce +4, that forms Ce_3O_2 and CeO_2 which determines its potential for switching over oxidation/reduction reactions [129]. It also has the ability to mimic SOD and catalase activity and importantly, it has proven efficacy in selectively sensitizing cancerous cells to radiation, thus protecting the healthy cells. In an *in vivo* model experimental nephrotoxicity, was found to have been caused by lipid peroxidation, DNA damage, mitochondrial dysfunction, caspase activation and pro-inflammatory cytokine release were repressed by nanoceria, thus making cerium oxide a versatile and a promising antioxidant agent that alleviates nephrotoxic renal tissue injury [309].

3.2.4. Plant-based natural antioxidant compounds

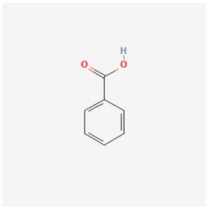
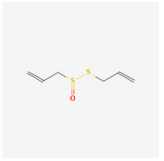
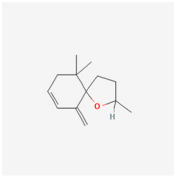
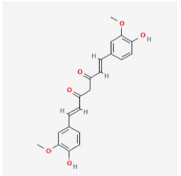
A repertoire of plant-based antioxidant compounds have been identified as having potential to ameliorate nephrotoxicity in preclinical research studies (Fig. 11 and Table 2).

Alstonia boonei (family Apocynaceae) stem and bark extract which is rich in phytochemicals; polyphenols, saponins, alkaloids, tannins, and flavonoids has been shown to possess antioxidant activity in DDVP-induced nephrotoxicity in male Wistar rats [224]. It has demonstrated protectivity against membrane lipid peroxidation in kidney tissue. Tubular degeneration, glomerular atrophy, leucocyte infiltration, was markedly reduced and kidney weight and serological biomarkers of oxidative stress and nephrotoxicity were brought to near normal levels, thus confirming its potency against renal oxidative stress damage [224].

Ceratonia siliqua L., Fabacae (Carob) leaf and pod extract is a popular beverage in the Middle Eastern countries which has proven antioxidant activity [310]. A methanol extract of Carob leaves and pods have displayed a remarkable reduction in cisplatin-induced nephrotoxicity by upregulating its free radical scavenging role and by augmenting the renal antioxidant enzymes and suppressing serological biomarkers [310].

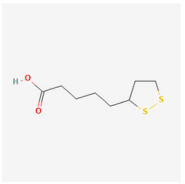
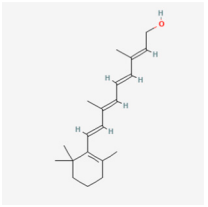
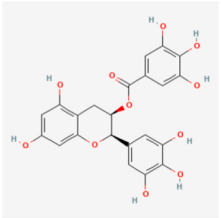
A methanol extract of *Carica papaya* (family Caricaceae) seeds have shown renoprotection activity against nephrotoxicity in a rat model [311]. It has been a folk medicine in Nigeria as an antidote for poison-related renal disorders. The concomitant administration of potassium bromate and *Carica papaya* seed extract was able to restore the brush border membrane-bound biomarker enzyme (gamma-glutamyl transferase, alkaline phosphatase, maltase, and leucine aminopeptidase) activity in a dose-dependent manner in both cortical and medullary kidney homogenates [312]. This seed extract has also demonstrated antioxidant behaviour by affecting the intraglomerular haemodynamics, reduction in renal blood flow, glomerular filtration rate, serum electrolytes and creatine clearance, by bringing those parameters to near normal levels

Table 2
The compounds which could mitigate renal oxidative stress: Nature of source, common and chemical names, chemical structures, impact on the kidneys and the references are included in this table.

Nature of source	Common name	Scientific name	Chemical compounds	Chemical structure of principal constituent	Impact on the kidneys	Ref
Antioxidant dietary supplements	Date fruit	*Phoenix dactylifera* L	Natural procyanidins, ferulic, p-coumaric and sinapic acids, and flavonoids	Benzoic acid  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 243, Benzoic Acid. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Benzoic-Acid.	Anti-inflammatory, anti-apoptotic and antioxidant activity in an experimental rat model. Scavenges free radicals, particularly to quench peroxyl and superoxide radicles.	[243]
	Garlic	*Allium sativum* L	Organosulfur compounds (allicin and S-allyl cysteine)	Allicin  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 65036, Allicin. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Allicin.	Anti-inflammatory and reno-protective action in animal models.	[245]
	Grapes	*Vitis vinifera*	Procyanidins and phenolic compounds	Vitispirane  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 6450832, Vitispirane. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Vitispirane.	Augments antioxidant enzyme activity thereby preventing oxidative tissue damage, inhibiting DNA fragmentation and apoptosis in the kidney.	[256]
	Curcumin	*Curcumin longa*	Phenolic antioxidants	Curcumin  National Center for Biotechnology Information (2023).	Amelioration of oxidative stress by downregulating all the characteristic biomarkers of renal oxidative stress injury.	[258]

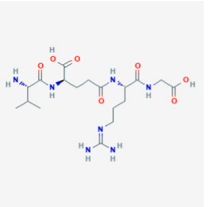
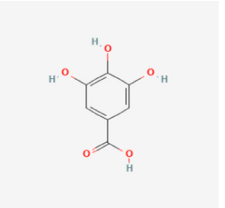
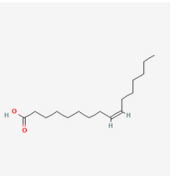
(*continued on next page*)

Table 2 (*continued*)

Nature of source	Common name	Scientific name	Chemical compounds	Chemical structure of principal constituent	Impact on the kidneys	Ref
				PubChem Compound Summary for CID 969516, Curcumin. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Curcumin.		
	Wheat	*Triticum sativum*	Alpha lipoic acid, caffeic acid phenethyl ester and wheat powder	Alpha lipoic acid  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 864, Thioctic acid. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Thioctic-acid.	Natural antioxidant activity.	[261]
	Fish oil	Omega-3-fatty acid	Retinal vitamin A palmitate	Retinol  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 445354, Retinol. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Retinol.	The brush border enzymes and enzymes involved in carbohydrate metabolism, together with antioxidant biomarkers were found restored to near normal levels that were diminished by cisplatin administration. https://pubchem.ncbi.nlm.nih.gov/compound/Retinal.	[350]
	Green tea	*Camellia sinensis*	Polyphenols containing flavanols, catechin, theaflavins, epicatechin gallate, epigallocatechin gallate and thearubigins	Epigallocatechin gallate  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 65064, (−)-Epigallocatechin gallate. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Epigallocatechin-gallate.	Protective against free radicals by being a scavenger of hydroxyl, peroxyl, superoxide and peroxynitrite radicals, through its antioxidant and iron-chelating action in mouse models. Reduces the oxidation of polyunsaturated fatty acids and proteins and prevents loss of membrane permeability, dysfunction of membrane and cellular proteins and the endogenous accumulation of hydroxyl radicals, as well.	[264,351,352]
	Ginseng	*Panax quinquefolius* L	Polyphenols, triterpenoid saponins, and flavonoids	Ginseng tetrapeptide	Possess antioxidant and nephroprotective effects, vastly improved oxidative stress-related macroscopic renal tissue damage (vacuolization, necrosis, and degenerative	[272,273]

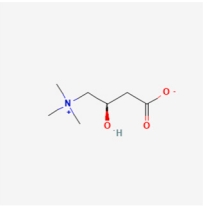
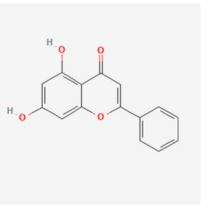
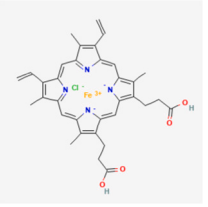
(*continued on next page*)

Table 2 (*continued*)

Nature of source	Common name	Scientific name	Chemical compounds	Chemical structure of principal constituent	Impact on the kidneys	Ref
				 National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 10253669, Ginseng Tetrapeptide. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Ginseng-Tetrapeptide.	changes) and initiated DNA repair processes, which showed attenuation of nephrotoxicity.	
	Coconut husk fibres	*Cocos nucifera* L	Complex carbohydrates, polyphenolic compounds (gallic acid, 4-hydroxybenzoic acid, ferulic acid, catechin, epicatechin) and condensed tannins	Gallic acid  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 370, Gallic Acid. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Gallic-Acid.	*Cocos nucifera* husk fibres using chloroform showed efficacy in reducing kidney injury-related biomarkers; SCr and BUN when pre-treated with it before administering cisplatin. Augments renal catalase exhibited anti-clastogenic effects and attenuated organ toxicity, high levels of serum aspartate aminotransferase, high MDA levels.	[262]
	Cyanobacteria/ blue-green alga	*Spirulina platensis*	Sulfated polysaccharides, sulfolipids, and phycocyanin	Palmitoleic acid  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 445638, Palmitoleic acid. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Palmitoleic-acid.	Mediate the repair of DNA damage, alleviating oxidative and nitrosative stress and reducing the production of proinflammatory cytokines.	[267,268]
Antioxidant biochemical compounds	Acetylcysteine	*N*-Acetyl cysteine	L-cysteine	Cysteine	Attenuates renal pathologies through the replenishment of thiol compounds. A precursor compound of glutathione. Has proven antioxidant properties. Reduces renal toxicity induced by adverse drug reactions by maintaining near normal levels of urinary marker enzymes; alkaline phosphatase,	[274,275]

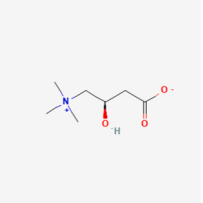
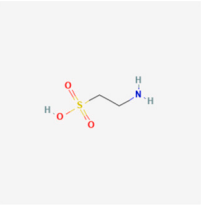
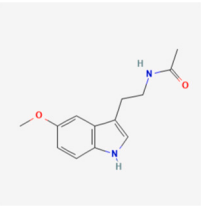
(*continued on next page*)

Table 2 (*continued*)

Nature of source	Common name	Scientific name	Chemical compounds	Chemical structure of principal constituent	Impact on the kidneys	Ref
				 National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 5862, Cysteine. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Cysteine.	gamma-glutamyl transferase and lactate dehydrogenase, reducing lipid peroxidation as well as necrosis in renal tissues.	
	Propolis	Bee glue	Resins, flavonoids (Chrysin, galangin, pinocembrin), phenols (benzoic, cinnamic, ferulic)	Chrysin  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 5281607, Chrysin. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Chrysin.	Effectively quench singlet oxygen, superoxide anions, hydroxyl and peroxyl radicals, suppress lipid peroxidation with elevated CAT, SOD and GSH-Px and their gene expression particularly, in the proximal tubular cells.	[278,283]
	Hemin	Hemin	Chlorohemin, heme chloride, Panhematin	Panhematin  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 455658, Panhematin. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Panhematin.	A breakdown product is HO-1 which is a free radical scavenger, attenuates oxidative stress and nephrotoxicity.	[284,353]
	L-Carnitine	Levocarnitine		Levocarnitine	L-Carnitine inhibited lipid peroxidation that arose from the interaction of superoxide radicals with hydrogen peroxide and delimited hydroxyl radical generation by iron through its iron chelating ability. Antioxidant, reno-protective and increases SOD, catalase and GSH.	[180]

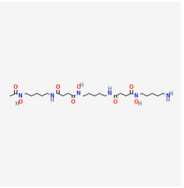
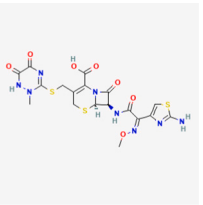
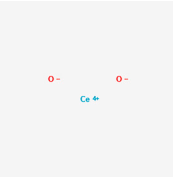
(*continued on next page*)

Table 2 (*continued*)

Nature of source	Common name	Scientific name	Chemical compounds	Chemical structure of principal constituent	Impact on the kidneys	Ref
				 National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 10917, Levocarnitine. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Levocarnitine.		
	Taurine	2-Aminoethane sulfonic acid		Taurine  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 211707, Taurin. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Taurin.	Marked antioxidant effects in biomarkers of oxidative stress.	[287,354]
	Melatonin	*N*-Acetyl-5-methoxytryptamine		Melatonin  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 896, Melatonin. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Melatonin.	Cytoprotective effects against ROS-induced oxidative stress reactions and increased inflammatory protein release. A direct free radical scavenger, that suppressed reactive oxygen and nitrogen and species, singlet oxygen, peroxynitrite anions and the peroxynitrite metabolites such as peroxynitrous acid and hydrogen peroxide production.	[296,355]
		Deferoxamine	Transferrin, ferritin, haemosiderin			[299,300,356]

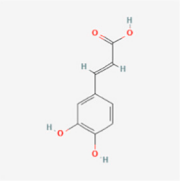
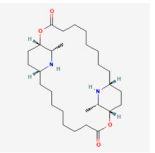
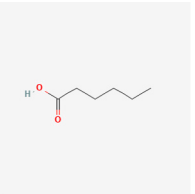
(*continued on next page*)

Table 2 (*continued*)

Nature of source	Common name	Scientific name	Chemical compounds	Chemical structure of principal constituent	Impact on the kidneys	Ref
Antioxidant chemical compounds	Desferal/ desferrioxamine			Deferoxamine  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 2973, Deferoxamine. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Deferoxamine.	A very effective ROS quencher and displays nephroprotective properties in both preclinical and clinical models.	
	Rocephin	Ceftriaxone	Ceftriaxone calcium salt	Ceftriaxone  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 5479530, Ceftriaxone. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Ceftriaxone.	A powerful ROS scavenger and its capacity to enhance antioxidant enzyme activity. Conjugated with Vitamin E, it ameliorates nephrotoxicity by restoring normal cellular redox status in the kidneys.	[302,303]
	Ceric oxide	Cerium oxide		Cerium oxide  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 10219615, cerium oxide (CeO2), hydrate (8CI,9CI). Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/10219615.	Antioxidant, anti-inflammatory and nephroprotective compound, mimics SOD and catalase activity.	[129,308]
	Sodium Selenite	Selenious acid		Sodium selenite 	Renoprotection against nephrotoxicity, free radical scavengers, antioxidant and regulates cellular redox status.	[304,305]

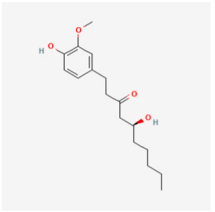
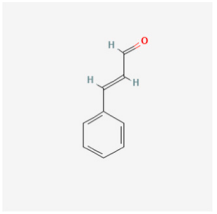
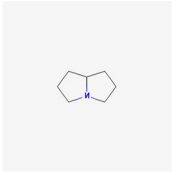
(*continued on next page*)

Table 2 (*continued*)

Nature of source	Common name	Scientific name	Chemical compounds	Chemical structure of principal constituent	Impact on the kidneys	Ref
				National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 24934, Sodium selenite. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Sodium-selenite.		
Antioxidant plant-based compounds	Cheese wood/ pattern wood/ stool wood	*Alstonia boonei*	Phenolic acids (caffeic, chlorogenic and ferulic acids, *etc.*), flavonoids (rutin and isoquercetin) and flavonolignans (Cinchonain isomers).	Caffeic acid  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 689043, Caffeic acid. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Caffeic-Acid.	Renoprotection against membrane lipid peroxidation in kidney tissue. Tubular degeneration, glomerular atrophy, leucocyte infiltration, was markedly reduced and kidney weight and serological biomarkers of oxidative stress and nephrotoxicity brought to near normal levels in a rat model.	
	Papaya	*Carica papaya*	Alkaloids, carpaine, pseudocarpaine saponins, tannins, papain, quimoipapain, benzyl isothiocyanate	Carpaine  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 442630, Carpaine. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Carpaine.	Restored the brush border membrane-bound biomarker enzyme (gamma-glutamyl transferase, alkaline phosphatase, maltase, and leucine aminopeptidase) activity. Has demonstrated antioxidant behaviour by affecting the intraglomerular haemodynamics, reduction in renal blood flow, glomerular filtration rate, serum electrolytes and creatine clearance, by bringing those parameters to near normal levels in a rat model.	[226,311,312]
	Carob	*Ceratonia siliqua*	Caproic acid (20 %) and pentanoic acid (15–25 %).	Caproic acid  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 8892, Hexanoic acid/Caproic acid. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Hexanoic-acid.	Upregulate free radical scavenging, augment the renal antioxidant enzymes and suppress serological biomarkers.	[310,357]

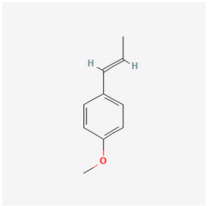
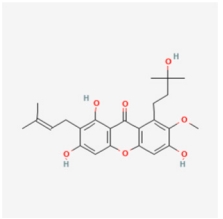
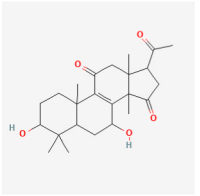
(*continued on next page*)

Table 2 (*continued*)

Nature of source	Common name	Scientific name	Chemical compounds	Chemical structure of principal constituent	Impact on the kidneys	Ref
	Ginger	*Zingiber officinalae*	Phenols (gingerols, shogaols, and paradols) and terpenes	Gingerol  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 442793, Gingerol. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Gingerol.	The proximal tubular pathology that resulted from gentamicin treatment including tubular oedema, necrosis, desquamation, diffused interstitial oedema, were markedly attenuated by gingerol as well as renal-ischemia re-perfusion injury in a dose-dependent manner. Gingerol compounds are antioxidants and free radical scavengers.	[316]
	Cinnamon	*Cinnamomum zeylanicum*	Resinous compounds (cinnamaldehyde, Cinnamomum, cinnamic acid) and volatile oils, phenolic compounds, tannins, pro-anthocyanidians, catechins and eugenol, flavonoids, saponin, alkaloids	Cinnamaldehyde  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 637511, Cinnamaldehyde. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Cinnamaldehyde.	Renal tissue damage such as damaged podocytes, infiltration into the Bowman capsular space and tubular dilatation in the PCT and DCT were markedly alleviated by the *Cinnamomum* extract treatment in a dose-dependent manner.	[347]
	Indian heliotrope	*Heliotropium indicum*	Pyrrolizidine alkaloids, volatile oils, triterpenes, amines, and sterols	Pyrrolizidine  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 12558, Pyrrolizidine. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Pyrrolizidine.	Antioxidant, nephroprotective, attenuates renal biomarkers of nephrotoxicity.	[358]
	Sage	*Salvia officinalis*	1,8 cineole, camphor, alpha-thujone, borneol, viridiflorol	1,8 cineole	Reduced the renal toxicity biomarkers; creatinine, urea, uric acid, and alkaline	[343,344]

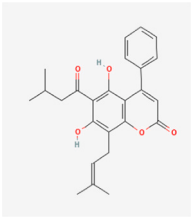
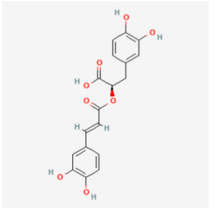
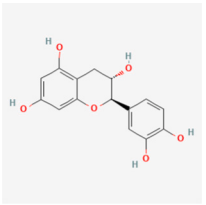
(*continued on next page*)

Table 2 (*continued*)

Nature of source	Common name	Scientific name	Chemical compounds	Chemical structure of principal constituent	Impact on the kidneys	Ref
				 National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 11218113, 2-Acetoxy-1,8-cineole, (+)-*endo*-. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/2-Acetoxy-1_8-cineole–endo.	phosphatase alongside replenishment of GSH. antioxidant and nephro-protective.	
	Alpha-mangosteen	*Garcinia mangostana* L	Xanthones, benzophenone Hydroxycitric acid	Garcinone-D  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 5495926, Garcinone D. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Garcinone-D.	The nephrotoxic biomarkers induced by cisplatin; increased serum and urinary creatinine, BUN, MDA, proteinuria, polyuria, urinary excretion of *N*-acetyl-β-glucosaminidase (NAG), hydrogen peroxide, and fractional excretion of sodium were significantly attenuated by alpha-mangosteen treatment.	[339,340]
	Gum Arabic	*Acacia senegal*		*Acacia senegal* extract  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 14109413, *Acacia senegal*, ext. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Acacia-senegal_-ext.	Synthesis of metalloenzymes which aid superoxide anion scavenging and lowering lipid peroxidation, reducing the serum urea concentration by stimulating nitrogen excretion in urine and by increasing the blood urea disposal.	[337,338]
		Pimpinella tirupatiensis		Trans-anethole	Antioxidant and against nephrotoxicity by suppressing SOD, CAT, MDA and GPx enzymes.	[336]

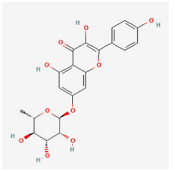
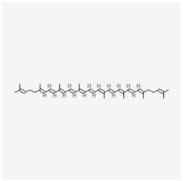
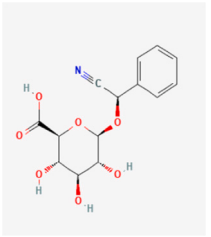
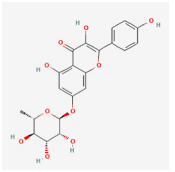
(*continued on next page*)

Table 2 (*continued*)

Nature of source	Common name	Scientific name	Chemical compounds	Chemical structure of principal constituent	Impact on the kidneys	Ref
				 National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 637563, Anethole. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Anethole		
		Rosmarinus officinalis	Rosmarinic acid, 1.8 cineol, camphor, alpha-pinene, limonene	Rosmarinic acid  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 5281792, Rosmarinic acid. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Rosmarinic-acid.	Possess oxidative stress relieving capabilities: reduced GSH content in a rat model by stimulating the enzyme glutamate cysteine ligase required for endogenous GSH biosynthesis, over the restoration of its potent oxidised form.	[334,359]
		Combretum micranthum	Cianidanol, epicatechin, gallic acid, isovitexin	Cianidanol  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 9064, Cianidanol. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Cianidanol.	Antioxidant and provides renoprotection by activating the arachidonic acid cascade.	[322,360]
	African mammee apple	*Mammea africana*	5-7-dihydroxy-8-(12-methyl-butryl)–4-N-pentyl coumarins, 4-phenyl and 4-alkylcoumarins and mesuxanthone B	Mammeisin	Possess renal cytoprotective activity by reducing SCr, serum urea levels and restoring distorted kidney tissue architecture in paracetamol-induced nephrotoxicity in rats. Shows potent free radical scavenging ability, reducing ROS and normalizing the kidney's antioxidant system.	[198,323]

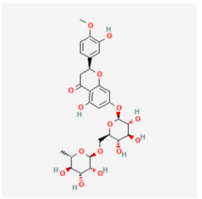
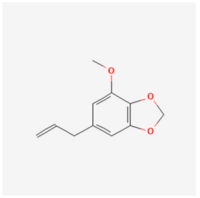
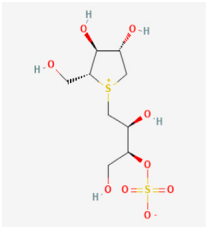
(*continued on next page*)

Table 2 (*continued*)

Nature of source	Common name	Scientific name	Chemical compounds	Chemical structure of principal constituent	Impact on the kidneys	Ref
				 National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 5281419, Mammeisin. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Mammeisin.		
	Tomato fruit	*Solanum lycopersicum*	Lycopene	Lycopene  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 446925, Lycopene. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Lycopene.	Enhances the activity of CAT, reduces nuclear damage such as karyomegaly in rat proximal tubular cells, reduces renal tissue necrosis and augments cellular GSH peroxidase activity.	[314]
	Vitamin B amygdalin (VB17)	Prunasin family (apple, prune, apricot, peach)	Amygdalin (VB17), (laetrile) Benzaldehyde, hydrocyanic acid	Amygdalin (VB17)  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 656516, D-Amygdalin. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/D-Amygdalin.	Inhibits interstitial fibrosis in kidney tissues and attenuates renal toxicity, injury, and DNA damage by altering cell proliferation and apoptosis.	[349]
	Yellow Bauhinia	*Bauhinia tomentosa*	Flavonoids, alkaloids, phenolic compounds, glycosides, lignin, saponins, tannins and phytosteroids	Kaempferol-7-rhamnoside  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 25079965,	*Bauhinia* restored many oxidative stress effects by augmenting GSH content and normalizing eGFR along with the shedding of the PCT epithelium. Tubular necrosis, lymphocyte infiltration into kidney tissue and serum biomarkers of kidney damage were all comparably alleviated by inhibiting p38 MAPK and caspase 3 activity.	[332]

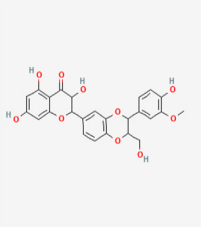
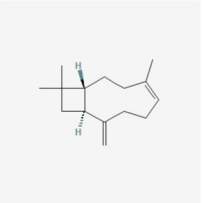
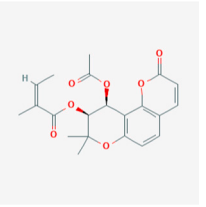
(*continued on next page*)

Table 2 (*continued*)

Nature of source	Common name	Scientific name	Chemical compounds	Chemical structure of principal constituent	Impact on the kidneys	Ref
				Kaempferol-7-rhamnoside. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Kaempferol-7-rhamnoside.		
	Citrus fruits	Hesperidin	Flavonoid	Hesperidin  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 10621, Hesperidin. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Hesperidin.	Adenoma, tubular oedema and vacuolation, atypical nuclear karyomegaly, protein casts in tubular lumen, atrophy of glomerular tufts and infiltration of immune cells, were all markedly alleviated with hesperidin treatment.	[318]
	Parsley	*Petroselinum sativum*	Flavonoids, coumarins, vitamin c-apigenin and its glycosides	Myristicin  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 4276, Myristicin. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Myristicin.	Attenuation of elevated SCr, BUN, and alkaline phosphatase levels, serum electrolytes (Na + and K+) with an increase in diuresis and urine volume. Normalized sodium and potassium ion excretion from the kidneys and augmented renal antioxidant enzymes.	[329]
	Oblong leaf salacia	*Salacia oblonga*	Salacinol, kotalanol, ponkoranol	Salacinol  National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 6451151, Salacinol. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Salacinol.	Histology showed preservation of glomeruli and Bowman's capsule structure and mild swelling of the renal tubules. Prevents GSH depletion, a free radical scavenger and has antioxidant activity.	[327,328]
	Rue/Sadab	*Ruta graveolens*	Flavonoids, alkaloids, volatile oils, coumarins	Rutin	Exerts its nephroprotection by potentiating the antioxidant defense system while inhibiting lipid peroxidation and preventing endogenous GSH decline.	[324,325]

(*continued on next page*)

Table 2 (*continued*)

Nature of source	Common name	Scientific name	Chemical compounds	Chemical structure of principal constituent	Impact on the kidneys	Ref
				 National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 5280805, Rutin. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Rutin.		
	Red sage	*Lantana camara*	Essential oils	β-Caryophyllene	Nephroprotective in a rat model.	[326]
				 National Center for Biotechnology Information (2023). PubChem Substance Record for SID 134971569, BHW853AU9H, Source: ChemIDplus. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/substance/134971569.		
	Hill carrot	*Peucedanum grande*	Phenolic compounds, flavonoids and coumarins	Praeruptorin A	Displays significant attenuation of nephrotoxicity by dose-dependent downregulation of lipid peroxidation, augmentation of the renal cellular GSH content, increased SOD activity, inhibition of BUN and SCr, and enhancing histological parameters with less; necrosis, desquamation, loss of brush border and cellular swelling in the PCT epithelial cells.	[319]
				 National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 38347607, (+)-Praeruptorin A. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/38347607.		
	Milk thistle	*Silybum marinum*	Flavonolignans, silymarin, silibinin, silychrystin, silidianin	Silymarin	Possesses powerful free radical scavenging properties that promotes mitochondrial ROS quenching and upregulating the renal endogenous antioxidant system.	[315]

(*continued on next page*)

Table 2 (*continued*)

Nature of source	Common name	Scientific name	Chemical compounds	Chemical structure of principal constituent	Impact on the kidneys	Ref
				National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 5213, Silymarin. Retrieved January 20, 2023 from https://pubchem.ncbi.nlm.nih.gov/compound/Silymarin		

Legend: ATP - adenosine tri phosphate, ATPase - adenosine tri phosphatase, BUN - blood urea nitrogen, CAT - catalase, DCT - distal convoluted tubule, DNA - deoxyribo nucleic acid, eGFR - estimated glomerular filtration rate, ER - endoplasmic reticulum, GSH-Px - glutathione peroxidase, GSH - glutathione, HO-1 - haemoxygenase-1, MAPK - mitogen-activated protein kinase, MDA - malondialdehyde, NO - nitric oxide, p38 – protein 38, PCT - proximal convoluted tubule, ROS - reactive oxygen species, SCr - serum creatinine, SOD - superoxide dismutase, TBARS - thiobarbituric acid reactive substances, TGF-β - transforming growth factor-beta.

on par with the control group [226].

Lycopene is a naturally occurring carotenoid that has antioxidant bioactivity and is present in tomato fruits [313]. Lycopene was highly efficient in suppressing singlet-oxygen and other free radicals released consequent to cisplatin administration at a dose of 4 mg/kg suspended in corn oil [313]. Oxidative stress is mainly caused by the disintegration of membranes due to lipid peroxidation, where lycopene was able to enhance the activity of CAT, reduce nuclear damage such as karyomegaly in rat proximal tubular cells, reduced renal tissue necrosis and augmented cellular GSH peroxidase activity [314].

The concurrent treatment of silymarin and oxytocin together against gentamicin-induced nephrotoxicity in albino rats was also reported [315]. Gentamycin nephrotoxicity manifests due to renal free radical generation and repressed renal antioxidant defense system, that particularly affects the proximal convoluted tubules with up to 20 % of the cases developing acute renal failure [315]. Silymarin is extracted from the seeds of *Silybum marianum* or milk thistle, that possesses powerful free radical scavenging properties that promotes mitochondrial ROS quenching and upregulating the renal endogenous antioxidant system [287]. This study also noted that gentamicin-nephrotoxicity is dependent on the dosage and the elapse of time between silymarin and oxytocin administration before the gentamicin treatment [315].

Ginger (*Zingiber officinale*) root extract mainly comprise of the polyphenols; [6]-gingerol, [8]-gingerol and [10]-gingerol and is nephroprotective in action against gentamicin-induced renal toxicity [316]. Gentamicin induces the deleterious free radicals; superoxide anions (O_2^-), peroxynitrite anions (ONOO-), hydroxyl radicals (OH) and hydrogen peroxide (H_2O_2) within the renal cortical mitochondrial membranes, and the main site of toxic injury is reportedly the PCT in which the re-absorptive function of filtered low-weight proteins is impaired [316]. The proximal tubular pathology that resulted from gentamicin treatment included tubular oedema, necrosis, desquamation, diffused interstitial oedema, all of which were markedly attenuated by gingerol as well as renal-ischemia re-perfusion injury in a dose-dependent manner [316]. Gentamicin treatment causes inflammatory responses, oxidative and nitrosative stress, vascular contraction, tissue necrosis and apoptosis, and was ameliorated by the gingerol fraction of the ginger root extract [316].

Hesperidin is a major flavonoid in a wide variety of citrus fruits which is also a non-nutritive polyphenolic compound that alleviates nephrotoxicity. Hesperidin possesses anti-inflammatory, hepatoprotective, anti-glycaemic and anti-cancer effects [317]. Diethylnitrosamine (DEN)-induced nephrotoxicity was ameliorated by treatment with hesperidin in rats [318]. DEN-induced histopathology that exhibited adenoma, tubular oedema and vacuolation, atypical nuclear karyomegaly, protein casts in tubular lumen, atrophy of glomerular tufts and infiltration of immune cells, were all markedly alleviated with hesperidin treatment [318].

Peucedanum grande is a traditional medicinal herb that grows mostly as a tropical shrub [319] which has a wide spectrum of bioactivities such as being a diuretic, kidney stone dissociative agent, a regulator of the menstrual cycle, reliever of irritation in mucous membranes such as mouth and an anti-inflammatory compound. Treatment with *P. grande* displayed significant attenuation of nephrotoxicity by dose-dependent downregulation of (i) lipid peroxidation, (ii) augmentation of the renal cellular GSH content, (iii) increased SOD activity, (iv) inhibition of BUN and SCr, and (v) enhancing histological parameters with less; necrosis, desquamation, loss of brush border and cellular swelling in the PCT epithelial cells [320].

Combretum micranthum is an ethnopharmacological medicinal plant [321] with proven antioxidant, anti-inflammatory and anti-diabetic properties that was effective at alleviating nephrotoxicity induced by cisplatin treatment [322]. The therapeutic action of it was confirmed by *in vitro* (human embryonic kidney cells-HEK-293 cells), *in vivo* (in rats) and in-silico (molecular docking) experiments that exhibited signs of nephrotoxicity alleviation [322]. The protective effect of *Combretum* was

attributed to cianidanol, epicatechin, gallic acid and isovitexin which were the main bioactive compounds which have shown efficacy in suppressing the NF-kB and soluble epoxide hydrolase (sEH) activity. Endogenous fatty acid epoxides in kidney tissue serve as an excellent substrate for sEH activity which is a component of the arachidonic acid cascade. It hydrolyses eicosanoid epoxides into dihydroxyeicosatrienoic acids known to provide renoprotection by repressing NO and proinflammatory mediators and inducing anti-hypertensive and vasodilator effects [322].

Mammea africana (Guttiferae) stem bark extract was shown to possess renal cytoprotective activity by reducing SCr, serum urea levels and restoring distorted kidney tissue architecture in paracetamol-induced nephrotoxicity in rats [198]. *M. africana* extract showed potent free radical scavenging ability, reducing ROS and normalizing the kidney's antioxidant system [323]. The prominent bioactive compounds in the stem bark extract was 5, -7-dihydroxy-8-(12-methylbutryl) –4-N-pentyl coumarins, 4-phenyl and 4-alkylcoumarins and mesuxanthone B, known to be effective against hypertension, diabetes, vasoconstriction, inflammation, mental disorders, microbial infections, and nephrotoxicity [198].

Ruta graveolens (commonly known as Sadab) is a plant of the family Rutaceae and contains many different phytochemical substances that possess medicinal properties [324]. Rutin is the active constituent in *R. graveolens* obtained as an ethanolic extract of plant leaves. *R. graveolens* is thought to exert its nephroprotection by potentiating the antioxidant defense system while inhibiting lipid peroxidation and preventing endogenous GSH decline [325].

A defatted methanolic extract obtained from the leaves of *Lantana camara* (Verbenaceae) and *Cucurbita pepo* (Cucurbitaceae) was nephroprotective in a rat model. *L. camara* nephroprotective effectivity was higher than that of *C. pepo* and was fractionated into an ethyl acetate extract and a butanoic extract of which the ethyl acetate derived fraction was more effective than the butanoic fraction [326].

Salacia oblonga (Celastaceae) is a woody climber in the tropical South Asia, that has curative properties for skin, sexual and bone diseases, diabetes, asthma, and obesity [327]. Reportedly the renal pathogenesis was evaluated by the levels of the endogenous antioxidant system (SOD, CAT, GPx, GSH and MDA) by preventing the depletion of GSH and its ROS and free radical scavenging ability. The active constituents in *Salacia* extract were predominantly flavonoids and alkaloids that are potent oxidative stress relieving phytochemicals [328]. Histology showed preservation of glomeruli and Bowman's capsule structure and mild swelling of the renal tubules [327].

Petroselinum sativum known as Parsley (Apiaceae) and *Eruca sativa* (Brassicaceae) are medicinal herbs that have displayed renoprotection in gentamicin – induced nephrotoxicity in rats [329]. Aquatic extracts of grounded seeds and rhizomes of these two herbal medicines showed attenuation of elevated SCr, BUN, and alkaline phosphatase levels, serum electrolytes (Na+ and K+) with an increase in diuresis and urine volume [329]. They also normalized sodium and potassium ion excretion from the kidneys and augmented renal antioxidant enzymes [329]. The mechanism of action in Parsley was suggested to be impairment of membrane-bound Na+/K+ pumps that caused depletion of those electrolytes, which in turn increased the osmotic water flow into the tubular lumen and thus, the urine volume [329].

Bauhinia tomentosa Linn. (Caesalpiniaceae) is a large shrub that is replenished with flavonoids, alkaloids, phenolic compounds, glycosides, lignin, saponins, tannins and phytosteroids as its major constituents that have bestowed a pharmacological role on a wide spectrum of disease conditions [330]. Due to containing these chemical constituents, *Bauhinia* root bark, young flowers, and dried seed extracts have been used for its medicinal properties consisting of anti-inflammatory, antifungal, antioxidant, stomachic, anthelminthic, and anti-bacterial effects [331]. *Bauhinia* restored many oxidative stress effects caused by cisplatin by augmenting GSH content and normalizing eGFR which is a major adverse effect of cisplatin treatment, along with the shedding of the PCT epithelium. Tubular necrosis, lymphocyte infiltration into kidney tissue and serum biomarkers of kidney damage were all comparably alleviated by inhibiting p38 MAPK and caspase 3 activity [332].

Rosmarinic acid is a caffeic acid ester and a phenolic compound that is naturally present in the family Lamiaceae and is the chief constituent of *Rosmarinus officianalis* Linn., commonly known as the Rosemary plant [333]. Rosmarinic acid possesses various medicinal properties including oxidative stress relieving capabilities and as such replenished the reduced GSH content in a rat model by stimulating the enzyme glutamate cysteine ligase required for endogenous GSH biosynthesis, over the restoration of its potent oxidised form [334]. Further, the ratio of serum GSH/oxidised glutathione (GSSG) was increased with rosmarinic acid that indicated regulation of redox homeostasis in the body [335].

Pimpinella tirupatiensis extract is a herbal medicine known for many systemic medicinal effects [336]. It was effective in its antioxidant behaviour against nephrotoxicity by suppressing SOD, CAT, MDA and GPx enzymes against acetaminophen-induced renal oxidative stress markers (BUN, SCr, MDA) in Wistar albino rats. The histological sections of kidney revealed preservation of glomerular and Bowman's capsule architecture with markedly reduced necrosis and augmented the waning GSH apparatus of the kidneys. Acetaminophen also caused marked changes in haematological parameters which were normalized by *P. tirupatiensis* treatment [336].

Gum Arabic (*Acacia senegal*; Leguminosae) is a gummy exudate that is obtained from the *Acacia* stem and branches, that contain calcium, magnesium, and potassium salts of the gum Arabic polysaccharides and are used in chronic renal haemodialysis patients [337]. It has demonstrable effects in superoxide anion scavenging and lowering lipid peroxidation as well as reducing the serum urea concentration by stimulating nitrogen excretion in urine and by increasing the blood urea disposal [338]. Gum Arabic powder treatment restored the oxidative stress parameters to normalcy and increased the trace element concentration in kidney tissues which may have occurred due to the *de novo* synthesis of metalloenzymes. The metalloenzymes play diverse roles in many metabolic reactions and increase the utilization of molecular oxygen that prevents superoxide radical formation [337].

Alpha-mangosteen is a xanthone compound extracted from the mangosteen (*Garcinia mangostana* Linn.) fruit pericarp, that possessed antioxidant and anti-inflammatory activity in male Wistar rats [339]. The nephrotoxic biomarkers that were induced by cisplatin; increased serum and urinary creatinine, BUN, MDA, proteinuria, polyuria, urinary excretion of *N*-acetyl-β-glucosaminidase (NAG), hydrogen peroxide, and fractional excretion of sodium (FeNa) were significantly attenuated by alpha-mangosteen treatment [339]. Further, the reduced circulating levels of GPx, GSH, osmolality and the protein carbonyl content which is an index of oxidised proteins were restored to near normal levels. In histology, the cisplatin-induced tubular degeneration, necrosis, and vacuolization was attenuated [339]. The lipoperoxidation marker, 4-hydroxynonenal (4-HNE) and nitrosative stress marker, 3-nitrotyrosine (3-NT) were also restored in the kidneys [340].

Heliotropium indicum Linn. is a native weed plant of Asia that has medicinal properties in healing wounds [341]. This plant also possesses antioxidant properties evidenced by decreasing oxidative stress parameters and the usual biomarkers of nephrotoxicity such as urea, creatinine and uric acid concentrations in both urine and serum. Pretreatment with *H. indicum* ethanolic extract ameliorated nephrotoxicity by restoring the antioxidant mechanisms [192].

Salvia officinalis (Lamiaceae) commonly known as Sage, is a medicinal plant that possesses therapeutic properties in alleviating many different diseases and given its flavonoid and phenolic acid content, it reduces experimental nephrotoxicity [342,343]. It served to augment the natural antioxidant defenses in the body and promoted anti-inflammatory cytokine secretion, particularly of interleukin-2 (IL-2), interleukin-4 (IL-4) and interleukin-10 (IL-10) [344]. Further, it reduced the renal toxicity biomarkers; creatinine, urea, uric acid, and alkaline phosphatase alongside replenishment of GSH. Marked histological

changes that were induced by formalin, vanadium, and cyclophosphamide-induced nephrotoxic injury was also reduced by treatment with *Salvia* aquatic extracts [344].

Cinnamomum zeylanicum (Family Lauraceae) or cinnamon is a popular spice and condiment which contains cinnamaldehyde as its chief constituent [345] and the cinnamon bark is predominantly composed of cinnamaldehyde, volatile oils, phenolic compounds, tannins, proanthocyanidians, catechins and eugenol [346]. Cinnamon bark extract has been medicinally effective as an antioxidant, anti-inflammatory, anti-viral, anti-fungal, antimicrobial, and anti-diabetic compound. The acetaminophen-induced renal tissue damage such as damaged podocytes, infiltration into the Bowman capsular space and tubular dilatation in the PCT and DCT were markedly alleviated by the *Cinnamomum* extract treatment in a dose-dependent manner [347]. Its therapeutic and reno-protective effect is attributed to the activity of the phytochemicals contained in cinnamon; the flavonoids, alkaloids, saponin and triterpenoid [347].

Vitamin B 17 (VB17) amygdalin is a drug derived from plant substances and a nitriloside consisting of natural cyanide compounds is obtainable from the seeds of the Prunasin family of apple, apricot, peaches, and almonds [348]. The two major constituents in VB17 are benzaldehyde and hydrocyanic acid which are combinedly analgesic and anti-cancer in action [349]. It has been effective against nephrotoxicity induced by Ehrlich ascites carcinoma (EAC) by inhibiting interstitial fibrosis in kidney tissues and being ameliorative of renal toxicity and injury and DNA damage by altering cell proliferation and apoptosis [349]. The compounds which have displayed antioxidant properties in preclinical research studies are tabulated in Table 2.

4. Conclusion

Nephrotoxicity is the major adverse side-effect of chemotherapy which still has no permanent cure. It mainly manifests from renal oxidative stress reactions that induce membrane lipid peroxidation, oxidation of macromolecules, free radical generation, depletion of endogenous glutathione, impaired antioxidant enzyme systems and immune destabilization. The outcome of oxidative stress reactions influences renal homeostasis, which leads to severe renal dysfunction that requires kidney transplantation or renal replacement therapy. This review has identified varied sources of renal oxidative stress followed by many mitigating compounds consisting of dietary supplements, biochemical and chemical antioxidant compounds and plant-based natural antioxidants that have been successful in *in vitro* and *in vivo* experiments. Thus, the possibilities of developing an effective cytoprotective therapeutic antioxidant formulation, that particularly enables the sustenance of chemotherapy while augmenting the renal antioxidant mechanisms remain numerous.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors of this review have consented for publication.

Funding

No funding has been received.

CRediT authorship contribution statement

RR created the concept, did the writing, organizing, and referencing of the manuscript. AZ, and MM offered constructive criticism, guidance and edited the manuscript.

Competing interest

No competing interests exist.

Acknowledgement

First author is a recipient of the Research Training Programme (RTP) Scholarship from the Australian Government for Ph.D. candidature.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lfs.2023.121466.

References

[1] V.G. Puelles, T.B. Huber, Kidneys control inter-organ homeostasis, Nat. Rev. Nephrol. 18 (4) (2022) 207–208.
[2] S. Gilbert, D.E. Weiner, National Kidney Foundation Primer on Kidney Diseases, E-Book, Elsevier Health Sciences, 2022.
[3] K.M. Ho, D.J. Morgan, The proximal tubule as the pathogenic and therapeutic target in acute kidney injury, Nephron (2022) 1–9.
[4] J. Jansen, Remote sensing and signaling in kidney proximal tubules stimulates gut microbiome-derived organic anion secretion, Proc. Natl. Acad. Sci. 116 (32) (2019) 16105–16110.
[5] J.A. D'Elia, G.P. Bayliss, L.A. Weinrauch, The diabetic cardiorenal nexus, Int. J. Mol. Sci. 23 (13) (2022) 7351.
[6] X.H. Wang, W.E. Mitch, S.R. Price, Pathophysiological mechanisms leading to muscle loss in chronic kidney disease, Nat. Rev. Nephrol. 18 (3) (2022) 138–152.
[7] J.V. Bonventre, et al., Next-generation biomarkers for detecting kidney toxicity, Nat. Biotechnol. 28 (5) (2010) 436–440.
[8] G.T.M. Sales, R.D. Foresto, Drug-induced nephrotoxicity, Rev. Assoc. Med. Bras. 66 (2020) s82–s90.
[9] E. Kwiatkowska, et al., The mechanism of drug nephrotoxicity and the methods for preventing kidney damage, Int. J. Mol. Sci. 22 (11) (2021) 6109.
[10] M.A. Perazella, M.H. Rosner, Drug-induced acute kidney injury, Clin. J. Am. Soc. Nephrol. 17 (8) (2022) 1220–1233, https://doi.org/10.2215/CJN.11290821.
[11] J.-C. Lv, L.-X. Zhang, Prevalence and disease burden of chronic kidney disease, in: Renal Fibrosis: Mechanisms and Therapies, 2019, pp. 3–15.
[12] J.S. Thurlow, et al., Global epidemiology of end-stage kidney disease and disparities in kidney replacement therapy, Am. J. Nephrol. 52 (2) (2021) 98–107.
[13] V. Jha, et al., Chronic kidney disease: global dimension and perspectives, Lancet 382 (9888) (2013) 260–272.
[14] J. Malyszko, et al., The link between kidney disease and cancer: complications and treatment, Lancet 396 (10246) (2020) 277–287.
[15] GLOBOCAN 2020, Global Cancer Observatory: Lyon Cedex, 2020.
[16] C.f.D.and Prevention Control, in: Chronic Kidney Disease in the United States, 2019, US Department of Health and Human Services, Centers for Disease Control and Prevention, Atlanta, GA, 2019, p. 3.
[17] N.R. Hill, et al., Global prevalence of chronic kidney disease–a systematic review and meta-analysis, PloS one 11 (7) (2016), e0158765.
[18] T. Liyanage, et al., Worldwide access to treatment for end-stage kidney disease: a systematic review, Lancet 385 (9981) (2015) 1975–1982.
[19] K.P. McCullough, et al., Projecting ESRD incidence and prevalence in the United States through 2030, J. Am. Soc. Nephrol. 30 (1) (2019) 127–135.
[20] D. Johnson, Diagnosis, classification and staging of chronic kidney disease, in: Sidney: Kidney Health Australia-caring for Australians With Renal Impairments (KHA-CARI), 2012, pp. 1–31.
[21] C. Liu, et al., Associations of a healthy lifestyle score from childhood to adulthood with subclinical kidney damage in midlife: a population-based cohort study, BMC Nephrol. 23 (1) (2022) 1–10.
[22] C. Weber, et al., Changing age-specific trends in incidence, comorbidities and mortality of hospitalised heart failure in Western Australia between 2001 and 2016, Int. J. Cardiol. 343 (2021) 56–62.
[23] W.G. Miller, et al., Optimal use of biomarkers for chronic kidney disease, Clin. Chem. 65 (8) (2019) 949–955.
[24] M. Jiwa, et al., The profile of patients with chronic kidney disease who regularly present at an australian general practice, Curr. Med. Res. Opin. 32 (1) (2016) 183–189.
[25] U. Mahmood, et al., Spectrum (characteristics) of patients with chronic kidney disease (CKD) with increasing age in a major metropolitan renal service, BMC Nephrol. 18 (1) (2017) 1–10.
[26] S.A. Stumpers, N.J. Thomson, Review of Kidney Disease Among Indigenous People, 2013.
[27] V.A. Luyckx, et al., Sustainable development goals relevant to kidney health: an update on progress, Nat. Rev. Nephrol. 17 (1) (2021) 15–32.
[28] R. Cai, et al., Mortality in chronic kidney disease patients with COVID-19: a systematic review and meta-analysis, Int. Urol. Nephrol. 53 (8) (2021) 1623–1629.

[29] R. Oun, Y.E. Moussa, N.J. Wheate, The side effects of platinum-based chemotherapy drugs: a review for chemists, Dalton Trans. 47 (19) (2018) 6645–6653.
[30] F. Hayati, et al., Prevention of cisplatin nephrotoxicity, J. Nephropharmacology 5 (1) (2016) 57.
[31] K. Tikoo, P. Kumar, J. Gupta, Rosiglitazone synergizes anticancer activity of cisplatin and reduces its nephrotoxicity in 7, 12-dimethyl benz a anthracene (DMBA) induced breast cancer rats, BMC Cancer 9 (1) (2009) 1–12.
[32] Y. Prasaja, N. Sutandyo, R. Andrajati, Incidence of cisplatin-induced nephrotoxicity and associated factors among cancer patients in Indonesia, Asian Pac. J. Cancer Prev. 16 (3) (2015) 1117–1122.
[33] X. Zhu, et al., S-allylmercaptocysteine attenuates cisplatin-induced nephrotoxicity through suppression of apoptosis, oxidative stress, and inflammation, Nutrients 9 (2) (2017) 166.
[34] S. Özen, et al., Role of caffeic acid phenethyl ester, an active component of propolis, against cisplatin-induced nephrotoxicity in rats, J. Appl. Toxicol. 24 (1) (2004) 27–35.
[35] Z.-Y. Teng, et al., Ancient chinese formula qiong-yu-gao protects against cisplatin-induced nephrotoxicity without reducing anti-tumor activity, Sci. Rep. 5 (1) (2015) 1–13.
[36] G.C. Kuriakose, M. Kurup, Effects of aulosira fertilisima against cisplatin-induced nephrotoxicity and oxidative stress in rats, Ren. Fail. 32 (2) (2010) 224–233.
[37] A. Borrego, et al., Protection by ozone preconditioning is mediated by the antioxidant system in cisplatin-induced nephrotoxicity in rats, Mediat. Inflamm. 13 (1) (2004) 13–19.
[38] K. Husain, et al., Protection by ebselen against cisplatin-induced nephrotoxicity: antioxidant system, Mol. Cell. Biochem. 178 (1) (1998) 127–133.
[39] P. Tripathi, S. Alshahrani, Mitigation of IL-1β, IL-6, TNF-α, and markers of apoptosis by ursolic acid against cisplatin-induced oxidative stress and nephrotoxicity in rats, Hum. Exp. Toxicol. 40 (12_suppl) (2021) S397–S405.
[40] N. Chebotareva, I. Bobkova, E. Shilov, Heat shock proteins and kidney disease: perspectives of HSP therapy, Cell Stress Chaperones 22 (3) (2017) 319–343.
[41] J.J. Xing, et al., Ginsenoside Rb3 provides protective effects against cisplatin-induced nephrotoxicity via regulation of AMPK-/mTOR-mediated autophagy and inhibition of apoptosis in vitro and in vivo, Cell Prolif. 52 (4) (2019), e12627.
[42] A.R. Morrison, D. Portilla, Lipid peroxidation and the kidney, in: Cellular Antioxidant Defense Mechanisms, CRC Press, 2019, pp. 173–184.
[43] P.M. Kidd, Glutathione: systemic protectant against oxidative and free radical damage, Altern. Med. Rev. 2 (3) (1997) 155–176.
[44] W. Lim, et al., Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal insufficiency, Ann. Intern. Med. 144 (9) (2006) 673–684.
[45] F. Zhou, et al., Association of serum uric acid levels with the incident of kidney disease and rapid eGFR decline in chinese individuals with eGFR> 60 mL/min/1.73 m2 and negative proteinuria, Clin. Exp. Nephrol. 23 (7) (2019) 871–879.
[46] M.N. Ghayur, J.C. Krepinsky, L.J. Janssen, Contractility of the renal glomerulus and mesangial cells: lingering doubts and strategies for the future, Med. Hypotheses Res. 4 (1) (2008) 1.
[47] B.M. Matata, et al., A single-center randomized trial of intraoperative zero-balanced ultrafiltration during cardiopulmonary bypass for patients with impaired kidney function undergoing cardiac surgery, J. Cardiothorac. Vasc. Anesth. 29 (5) (2015) 1236–1247.
[48] M.A. Perazella, Onco-nephrology: renal toxicities of chemotherapeutic agents, Clin. J. Am. Soc. Nephrol. 7 (10) (2012) 1713–1721.
[49] P. Manna, M. Sinha, P.C. Sil, Prophylactic role of arjunolic acid in response to streptozotocin mediated diabetic renal injury: activation of polyol pathway and oxidative stress responsive signaling cascades, Chem. Biol. Interact. 181 (3) (2009) 297–308.
[50] X. Yao, et al., Cisplatin nephrotoxicity: a review, Am J Med Sci 334 (2) (2007) 115–124.
[51] A.M. Tomsa, et al., Oxidative stress as a potential target in acute kidney injury, PeerJ 7 (2019), e8046.
[52] V. Vallon, S.C. Thomson, The tubular hypothesis of nephron filtration and diabetic kidney disease, Nat. Rev. Nephrol. 16 (6) (2020) 317–336.
[53] R. Mustaqeem, A. Arif, Renal tubular acidosis, in: StatPearls [Internet], StatPearls Publishing, 2022.
[54] M. Schetz, et al., Drug-induced acute kidney injury, Curr. Opin. Crit. Care 11 (6) (2005) 555–565.
[55] S.Y. Kim, A. Moon, Drug-induced nephrotoxicity and its biomarkers, Biomol. Ther. 20 (3) (2012) 268.
[56] R. Naqvi, et al., Acute tubulointerstitial nephritis/drug induced acute kidney injury; an experience from a single center in Pakistan, J. Renal Inj. Prev. 5 (1) (2016) 17.
[57] P. Paueksakon, A.B. Fogo, Drug-induced nephropathies, Histopathology 70 (1) (2017) 94–108.
[58] R.L. Chevalier, The proximal tubule is the primary target of injury and progression of kidney disease: role of the glomerulotubular junction, Am. J. Physiol. Ren. Physiol. 311 (1) (2016) F145–F161.
[59] M. Cabral, et al., Renal impairment assessment on adults living nearby a landfill: early kidney dysfunction biomarkers linked to the environmental exposure to heavy metals, Toxicol. Rep. 8 (2021) 386–394.
[60] B. Lisowska-Myjak, Serum and urinary biomarkers of acute kidney injury, Blood Purif. 29 (4) (2010) 357–365.
[61] S. Jain, et al., Proteomic analysis of urinary protein markers for accurate prediction of diabetic kidney disorder, JAPi 53 (513) (2005) 20.
[62] A. Tojo, S. Kinugasa, Mechanisms of glomerular albumin filtration and tubular reabsorption, Int. J. Nephrol. 2012 (2012).
[63] M. Artz, et al., Time course of proteinuria after living-donor kidney transplantation1, Transplantation 76 (2) (2003) 421–434.
[64] J. Fontanilla, W.K. Han, Kidney injury molecule-1 as an early detection tool for acute kidney injury and other kidney diseases, Expert Opin. Med. Diagn. 5 (2) (2011) 161–173.
[65] M.M. Hamdy, et al., Effects of furosemide and tadalafil in both conventional and nanoforms against adenine-induced chronic renal failure in rats, Eur. J. Med. Res. 27 (1) (2022) 1–17.
[66] A. Anadón, et al., Biomarkers of drug toxicity and safety evaluation, in: Biomarkers in Toxicology, Elsevier, 2019, pp. 655–691.
[67] J. Sand, F. Genovese, M. Karsdal, Type IV collagen, in: Biochemistry of Collagens, Laminins and Elastin, Elsevier, 2016, pp. 31–41.
[68] J.B. Patel, A. Sapra, Nephrotoxic Medications, 2020.
[69] N.S. Udawatte, et al., Predictive nephrotoxicity profiling of a novel antifungal small molecule in comparison to amphotericin B and voriconazole, Front. Pharmacol. 11 (2020) 511.
[70] A. Loh, A.H. Cohen, Drug-induced kidney disease-pathology and current concepts, Ann. Acad. Med. Singap. 38 (3) (2009) 240–250.
[71] Q. Wu, et al., Mechanism of cyclosporine a nephrotoxicity: oxidative stress, autophagy, and signalings, Food Chem. Toxicol. 118 (2018) 889–907.
[72] N. Santos, et al., Cisplatin-induced nephrotoxicity is associated with oxidative stress, redox state unbalance, impairment of energetic metabolism and apoptosis in rat kidney mitochondria, Arch. Toxicol. 81 (7) (2007) 495–504.
[73] Y.M. Yoo, E.B. Jeung, Melatonin suppresses cyclosporine A-induced autophagy in rat pituitary GH3 cells, J. Pineal Res. 48 (3) (2010) 204–211.
[74] Z. Mohammed-Ali, The Contribution of the Unfolded Protein Response (UPR) to Chronic Kidney Disease Development in a Mouse Model, 2017.
[75] M. Jiang, et al., Effects of hydroxyl radical scavenging on cisplatin-induced p53 activation, tubular cell apoptosis and nephrotoxicity, Biochem. Pharmacol. 73 (9) (2007) 1499–1510.
[76] J.-H. Woo, et al., Molecular mechanisms of curcumin-induced cytotoxicity: induction of apoptosis through generation of reactive oxygen species, down-regulation of bcl-X L and IAP, the release of cytochrome c and inhibition of akt, Carcinogenesis 24 (7) (2003) 1199–1208.
[77] X.-C. Zhao, Cell apoptosis and autophagy in renal fibrosis, in: Renal Fibrosis: Mechanisms and Therapies, 2019, pp. 557–584.
[78] X. Zhang, et al., The nephrotoxicity of T-2 toxin in mice caused by oxidative stress-mediated apoptosis is related to Nrf2 pathway, Food Chem. Toxicol. 149 (2021), 112027.
[79] G. Yuan, et al., Sub-chronic lead and cadmium co-induce apoptosis protein expression in liver and kidney of rats, Int. J. Clin. Exp. Pathol. 7 (6) (2014) 2905.
[80] C. Spampanato, et al., Simvastatin inhibits cancer cell growth by inducing apoptosis correlated to activation of bax and down-regulation of BCL-2 gene expression, Int. J. Oncol. 40 (4) (2012) 935–941.
[81] S.C. Borkan, The role of BCL-2 family members in acute kidney injury, in: Seminars in Nephrology, Elsevier, 2016.
[82] B. Yang, et al., A shift in the Bax/Bcl-2 balance may activate caspase-3 and modulate apoptosis in experimental glomerulonephritis, Kidney Int. 62 (4) (2002) 1301–1313.
[83] J.Y. Park, et al., Protective effects of processed ginseng and its active ginsenosides on cisplatin-induced nephrotoxicity: in vitro and in vivo studies, J. Agric. Food Chem. 63 (25) (2015) 5964–5969.
[84] Y. Zhong, et al., Inhibition of ER stress attenuates kidney injury and apoptosis induced by 3-MCPD via regulating mitochondrial fission/fusion and Ca2+ homeostasis, Cell Biol. Toxicol. 37 (5) (2021) 795–809.
[85] A.K. Aranda-Rivera, et al., Mitochondrial redox signaling and oxidative stress in kidney diseases, Biomolecules 11 (8) (2021) 1144.
[86] B.C. Baumann, Hypoxia-inducible Factors Regulate Type I Collagen Transcription in Renal Fibrosis, Northwestern University, 2016.
[87] T. McMorrow, et al., Cyclosporine a induced epithelial–mesenchymal transition in human renal proximal tubular epithelial cells, Nephrol. Dial. Transplant. 20 (10) (2005) 2215–2225.
[88] M. Kitamura, Endoplasmic reticulum stress and unfolded protein response in renal pathophysiology: janus faces, Am. J. Physiol. Ren. Physiol. 295 (2) (2008) F323–F334.
[89] T. Gómez-Sierra, et al., Isoliquiritigenin pretreatment induces endoplasmic reticulum stress-mediated hormesis and attenuates cisplatin-induced oxidative stress and damage in LLC-PK1 cells, Molecules 25 (19) (2020) 4442.
[90] H.-S. Huang, M.-C. Ma, J. Chen, Chronic L-arginine administration increases oxidative and nitrosative stress in rat hyperoxaluric kidneys and excessive crystal deposition, Am. J. Physiol. Ren. Physiol. 295 (2) (2008) F388–F396.
[91] B.H. Ali, et al., Experimental gentamicin nephrotoxicity and agents that modify it: a mini-review of recent research, Basic Clin. Pharmacol. Toxicol. 109 (4) (2011) 225–232.
[92] P. Mount, D.A. Power, Nitric oxide in the kidney: functions and regulation of synthesis, Acta Physiol. 187 (4) (2006) 433–446.
[93] C. Gunnett, et al., Mechanisms of inducible nitric oxide synthase–mediated vascular dysfunction, Arterioscler. Thromb. Vasc. Biol. 25 (8) (2005) 1617–1622.
[94] A.K. Lim, G.H. Tesch, Inflammation in diabetic nephropathy, Mediat. Inflamm. 2012 (2012).
[95] M.J. Paul-Clark, Nitric Oxide in Acute and Chronic Inflammation, Queen Mary University of London, 2002.
[96] C. Zoja, A. Benigni, G. Remuzzi, The Nrf2 pathway in the progression of renal disease, Nephrol. Dial. Transplant. 29 (suppl_1) (2014) i19–i24.

[97] L. Tesoriere, et al., Indicaxanthin inhibits NADPH oxidase (NOX)-1 activation and NF-κB-dependent release of inflammatory mediators and prevents the increase of epithelial permeability in IL-1β-exposed Caco-2 cells, Br. J. Nutr. 111 (3) (2014) 415–423.
[98] S. Giridharan, M. Srinivasan, Mechanisms of NF-κB p65 and strategies for therapeutic manipulation, J. Inflamm. Res. 11 (2018) 407.
[99] F. Pilo, E. Angelucci, A storm in the niche: iron, oxidative stress and haemopoiesis, Blood Rev. 32 (1) (2018) 29–35.
[100] F. Wu, et al., Inhibitory effects of honokiol on lipopolysaccharide-induced cellular responses and signaling events in human renal mesangial cells, Eur. J. Pharmacol. 654 (1) (2011) 117–121.
[101] M. Yu, Y.J. Kim, D.-H. Kang, Indoxyl sulfate–induced endothelial dysfunction in patients with chronic kidney disease via an induction of oxidative stress, Clin. J. Am. Soc. Nephrol. 6 (1) (2011) 30–39.
[102] M. Andreucci, T. Faga, A. Michael, Cytotoxic effects of contrast media on renal tubular cells. Pathogenesis of contrast-induced acute kidney injury and prevention, J. Biochem. Mol. Biol. Res. 1 (1) (2015).
[103] A. Duni, et al., Oxidative stress in the pathogenesis and evolution of chronic kidney disease: untangling Ariadne's thread, Int. J. Mol. Sci. 20 (15) (2019) 3711.
[104] L.M. Pedruzzi, et al., Nrf2–keap1 system versus NF-κB: the good and the evil in chronic kidney disease? Biochimie 94 (12) (2012) 2461–2466.
[105] Y. Gui, et al., Schisantherin a attenuates sepsis-induced acute kidney injury by suppressing inflammation via regulating the NRF2 pathway, Life Sci. 258 (2020), 118161.
[106] C. Xi, et al., Toxicity of triptolide and the molecular mechanisms involved, Biomed. Pharmacother. 90 (2017) 531–541.
[107] F. Liu, S. Zhuang, Role of receptor tyrosine kinase signaling in renal fibrosis, Int. J. Mol. Sci. 17 (6) (2016) 972.
[108] N.B. Flemming, L.A. Gallo, J.M. Forbes, Mitochondrial dysfunction and signaling in diabetic kidney disease: oxidative stress and beyond, in: Seminars in Nephrology, Elsevier, 2018.
[109] M. Sakashita, T. Tanaka, R. Inagi, Metabolic changes and oxidative stress in diabetic kidney disease, Antioxidants 10 (7) (2021) 1143.
[110] D.M. Small, et al., Oxidative stress, anti-oxidant therapies and chronic kidney disease, Nephrology 17 (4) (2012) 311–321.
[111] G. Firestone, J. Giampaolo, B. O'Keeffe, Stimulus-dependent regulation of serum and glucocorticoid inducible protein kinase (SGK) transcription, subcellular localization and enzymatic activity, Cell. Physiol. Biochem. 13 (1) (2003) 1–12.
[112] M.J. Dutt, K.H. Lee, Proteomic analysis, Curr. Opin. Biotechnol. 11 (2) (2000) 176–179.
[113] L.S. Chawla, et al., Acute kidney injury and chronic kidney disease as interconnected syndromes, N. Engl. J. Med. 371 (1) (2014) 58–66.
[114] A. Bhatnagar, Biochemical mechanism of irreversible cell injury caused by free radical-initiated reactions, Mol. Cell. Biochem. 137 (1) (1994) 9–16.
[115] S. Vasdev, et al., Dietary vitamin E and C supplementation prevents fructose induced hypertension in rats, Mol. Cell. Biochem. 241 (1) (2002) 107–114.
[116] S. Anwer, Regulation of Claudin-3 Expression in Kidney Tubular Epithelial Cells, University of Toronto, Canada, 2020.
[117] S.M. Keyse, Protein phosphatases and the regulation of mitogen-activated protein kinase signalling, Curr. Opin. Cell Biol. 12 (2) (2000) 186–192.
[118] H. Cassidy, et al., The role of MAPK in drug-induced kidney injury, J. Signal Transduction 2012 (2012).
[119] M. Cano, et al., Targeting pro-senescence mitogen activated protein kinase (Mapk) enzymes with bioactive natural compounds, Food Chem. Toxicol. 131 (2019), 110544.
[120] J. Nam, Biomechanical Thresholds Regulate Inflammation Through the NF-kB Pathway: Experiments and, 2009.
[121] Y. Mebratu, Y. Tesfaigzi, How ERK1/2 activation controls cell proliferation and cell death: is subcellular localization the answer? Cell Cycle 8 (8) (2009) 1168–1175.
[122] S. Wang, et al., Cadmium-induced apoptosis through reactive oxygen species-mediated mitochondrial oxidative stress and the JNK signaling pathway in TM3 cells, a model of mouse leydig cells, Toxicol. Appl. Pharmacol. 368 (2019) 37–48.
[123] B.J. Padanilam, Cell death induced by acute renal injury: a perspective on the contributions of apoptosis and necrosis, Am. J. Physiol. Ren. Physiol. 284 (4) (2003) F608–F627.
[124] J. DiMari, et al., N-acetyl cysteine ameliorates ischemic renal failure, Am. J. Physiol. Ren. Physiol. 272 (3) (1997) F292–F298.
[125] B. Van de Water, et al., Cellular stress responses and molecular mechanisms of nephrotoxicity, Toxicol. Lett. 162 (1) (2006) 83–93.
[126] K.R. McSweeney, et al., Mechanisms of cisplatin-induced acute kidney injury: pathological mechanisms, pharmacological interventions, and genetic mitigations, Cancers 13 (7) (2021) 1572.
[127] H. Niida, M. Nakanishi, DNA damage checkpoints in mammals, Mutagenesis 21 (1) (2006) 3–9.
[128] I.K. Domingo, A. Latif, A.P. Bhavsar, Pro-inflammatory signalling PRRopels cisplatin-induced toxicity, Int. J. Mol. Sci. 23 (13) (2022) 7227.
[129] M.A. Saifi, et al., Protective effect of nanoceria on cisplatin-induced nephrotoxicity by amelioration of oxidative stress and pro-inflammatory mechanisms, Biol. Trace Elem. Res. 189 (1) (2019) 145–156.
[130] Z. Dong, S. Atherton, Tumor necrosis factor-α in cisplatin nephrotoxicity: a homebred foe? Kidney Int. 72 (1) (2007) 5–7.
[131] V. Vielhauer, G. Stavrakis, T.N. Mayadas, Renal cell–expressed TNF receptor 2, not receptor 1, is essential for the development of glomerulonephritis, J. Clin. Invest. 115 (5) (2005) 1199–1209.
[132] I. Gusarov, E. Nudler, NO-mediated cytoprotection: instant adaptation to oxidative stress in bacteria, Proc. Natl. Acad. Sci. 102 (39) (2005) 13855–13860.
[133] D.-J. Slebos, S.W. Ryter, A.M. Choi, Heme oxygenase-1 and carbon monoxide in pulmonary medicine, Respir. Res. 4 (1) (2003) 1–13.
[134] B. Zhang, et al., Prion protein protects against renal ischemia/reperfusion injury, PloS one 10 (9) (2015), e0136923.
[135] F. Shiraishi, et al., Heme oxygenase-1 gene ablation or expression modulates cisplatin-induced renal tubular apoptosis, Am. J. Physiol. Ren. Physiol. 278 (5) (2000) F726–F736.
[136] N. Pabla, Z. Dong, Cisplatin nephrotoxicity: mechanisms and renoprotective strategies, Kidney Int. 73 (9) (2008) 994–1007.
[137] M.G. Netea, et al., Defining trained immunity and its role in health and disease, Nat. Rev. Immunol. 20 (6) (2020) 375–388.
[138] W.B. Reeves, Innate immunity in nephrotoxic acute kidney injury, Trans. Am. Clin. Climatol. Assoc. 130 (2019) 33.
[139] H.-J. Anders, D.O. Schlondorff, Innate immune receptors and autophagy: implications for autoimmune kidney injury, Kidney Int. 78 (1) (2010) 29–37.
[140] J.Q. Wang, et al., Toll-like receptors and cancer: MYD88 mutation and inflammation, Front. Immunol. 5 (2014) 367.
[141] A. Akcay, Q. Nguyen, C.L. Edelstein, Mediators of inflammation in acute kidney injury, Mediat. Inflamm. 2009 (2009).
[142] H.R. Jang, H. Rabb, Immune cells in experimental acute kidney injury, Nat. Rev. Nephrol. 11 (2) (2015) 88–101.
[143] R.K. Tadagavadi, W.B. Reeves, Renal dendritic cells ameliorate nephrotoxic acute kidney injury, J. Am. Soc. Nephrol. 21 (1) (2010) 53–63.
[144] P.G. Vallés, et al., Acute kidney injury: what part do toll-like receptors play? Int. J. Nephrol. Renov. Dis. 7 (2014) 241.
[145] B. Zhang, et al., TLR4 signaling mediates inflammation and tissue injury in nephrotoxicity, J. Am. Soc. Nephrol. 19 (5) (2008) 923–932.
[146] E. Ozbek, Induction of oxidative stress in kidney, Int. J. Nephrol. 2012 (2012).
[147] P. Manna, S.K. Jain, Obesity, oxidative stress, adipose tissue dysfunction, and the associated health risks: causes and therapeutic strategies, Metab. Syndr. Relat. Disord. 13 (10) (2015) 423–444.
[148] G. Aseervatham, et al., Environmental factors and unhealthy lifestyle influence oxidative stress in humans—an overview, Environ. Sci. Pollut. Res. 20 (7) (2013) 4356–4369.
[149] P. Kleniewska, et al., The NADPH oxidase family and its inhibitors, Arch. Immunol. Ther. Exp. 60 (4) (2012) 277–294.
[150] J. Lee, N. Koo, D.B. Min, Reactive oxygen species, aging, and antioxidative nutraceuticals, Compr. Rev. Food Sci. Food Saf. 3 (1) (2004) 21–33.
[151] M. Gyurászová, et al., Oxidative stress in the pathophysiology of kidney disease: implications for noninvasive monitoring and identification of biomarkers, Oxidative Med. Cell. Longev. 2020 (2020).
[152] S. Rottenberg, C. Disler, P. Perego, The rediscovery of platinum-based cancer therapy, Nat. Rev. Cancer 21 (1) (2021) 37–50.
[153] Y.-M. Choi, et al., Mechanism of cisplatin-induced cytotoxicity is correlated to impaired metabolism due to mitochondrial ROS generation, PloS one 10 (8) (2015), e0135083.
[154] L.A.B. Peres, A.D.D. Cunha Júnior, Acute nephrotoxicity of cisplatin: molecular mechanisms, Braz. J. Nephrol. 35 (2013) 332–340.
[155] E.O. Mahgoub, Effect of Genipin on Cisplatin-Induced Nephrotoxicity, 2016.
[156] X.-M. Meng, et al., NADPH oxidase 4 promotes cisplatin-induced acute kidney injury via ROS-mediated programmed cell death and inflammation, Lab. Investig. 98 (1) (2018) 63–78.
[157] R. Che, et al., Mitochondrial dysfunction in the pathophysiology of renal diseases, Am. J. Physiol. Ren. Physiol. 306 (4) (2014) F367–F378.
[158] M.H. Hanigan, P. Devarajan, Cisplatin nephrotoxicity: molecular mechanisms, Cancer Ther. 1 (2003) 47.
[159] M. Kitada, et al., Manganese superoxide dismutase dysfunction and the pathogenesis of kidney disease, Front. Physiol. 11 (2020) 755.
[160] H.E. Seifried, et al., A review of the interaction among dietary antioxidants and reactive oxygen species, J. Nutr. Biochem. 18 (9) (2007) 567–579.
[161] G. Anusiya, et al., A review of the therapeutic and biological effects of edible and wild mushrooms, Bioengineered 12 (2) (2021) 11239–11268.
[162] S.A. Khan S. Priyamvada S. Khan , Protective Effect of Green Tea Extract on Gentamicin Induced Gastro-and Hepatotoxicity in Rats.
[163] S.A. Khan, et al., Studies on the protective effect of green tea against cisplatin induced nephrotoxicity, Pharmacol. Res. 60 (5) (2009) 382–391.
[164] H.A. Hassan, et al., Amelioration of cisplatin-induced nephrotoxicity by grape seed extract and fish oil is mediated by lowering oxidative stress and DNA damage, Cytotechnology 66 (3) (2014) 419–429.
[165] W. Lieberthal, S.K. Nigam, Acute renal failure. I. Relative importance of proximal vs. distal tubular injury, Am. J. Physiol. Ren. Physiol. 275 (5) (1998) F623–F632.
[166] C. Calcabrini, et al., Sulforaphane potentiates anticancer effects of doxorubicin and cisplatin and mitigates their toxic effects, Front. Pharmacol. 11 (2020) 567.
[167] O.M. Ahmed, et al., Thyme oil and thymol abrogate doxorubicin-induced nephrotoxicity and cardiotoxicity in Wistar rats via repression of oxidative stress and enhancement of antioxidant defense mechanisms, Biocell 44 (1) (2020) 41.
[168] C. Guven, Y. Sevgiler, E. Taskin, Mitochondrial dysfunction associated with doxorubicin, Mitochondrial Dis. (2018) 323.
[169] A.Y. Nasr, H.A. Saleh, Aged garlic extract protects against oxidative stress and renal changes in cisplatin-treated adult male rats, Cancer Cell Int. 14 (1) (2014) 1–12.
[170] P. Randjelovic, et al., Gentamicin nephrotoxicity in animals: current knowledge and future perspectives, EXCLI J. 16 (2017) 388.

[171] R. Baliga, et al., Oxidant mechanisms in toxic acute renal failure, Drug Metab. Rev. 31 (4) (1999) 971–997.
[172] M. Ouédraogo, et al., Protective effect of Moringa oleifera leaves against gentamicin-induced nephrotoxicity in rabbits, Exp. Toxicol. Pathol. 65 (3) (2013) 335–339.
[173] A. Hasanvand, et al., Ameliorative effect of ferulic acid on gentamicininduced nephrotoxicity in a rat model; role of antioxidant effects, J. Renal Inj. Prev. 7 (2) (2018) 73–77.
[174] G. Sener, et al., Melatonin protects against gentamicin-induced nephrotoxicity in rats, J. Pineal Res. 32 (4) (2002) 231–236.
[175] C. Silan, et al., Gentamicin-induced nephrotoxicity in rats ameliorated and healing effects of resveratrol, Biol. Pharm. Bull. 30 (1) (2007) 79–83.
[176] H.Z. Mohamed, M.B. Shenouda, Amelioration of renal cortex histological alterations by aqueous garlic extract in gentamicin induced renal toxicity in albino rats: a histological and immunohistochemical study, Alex. J. Med. 57 (1) (2021) 28–37.
[177] K.A. Nath, et al., Reactive oxygen metabolites and iron in toxic acute renal failure, in: Mechanisms of Injury in Renal Disease and Toxicity, CRC Press, 2020, pp. 267–279.
[178] Z.A. Radi, Kidney pathophysiology, toxicology, and drug-induced injury in drug development, Int. J. Toxicol. 38 (3) (2019) 215–227.
[179] H. Scholz, et al., Kidney physiology and susceptibility to acute kidney injury: implications for renoprotection, Nat. Rev. Nephrol. 17 (5) (2021) 335–349.
[180] N.H. Meky, et al., The effect of L–carnitine on gentamicin-induced nephrotoxicity and associated anaemia in adult male albino rats, J. Sci. Res. Sci. 32 (part 2) (2015) 379–400.
[181] E. Hur, et al., The effects of vitamin D on gentamicin-induced acute kidney injury in experimental rat model, Int. J. Endocrinol. 2013 (2013).
[182] I.K. Al-Taee, et al., The clinical significance of β2-microglobulin in end-stage renal disease, Saudi J. Kidney Dis. Transpl. 14 (4) (2003) 492.
[183] H.D. Humes, Aminoglycoside nephrotoxicity, Kidney Int. 33 (4) (1988) 900–911.
[184] N.-A.P. Chukwuemeka , et al., Ameliorative Effect of Methanol Extract of Hymenocardia acida Leaves on Gentamicin-Induced Renal Toxicity in Rats.
[185] E.J. Sohn, D.G. Kang, H.S. Lee, Protective effects of glycyrrhizin on gentamicin-induced acute renal failure in rats, Pharmacol. Toxicol. 93 (3) (2003) 116–122.
[186] M.S. Ramirez, M.E. Tolmasky, Amikacin: uses, resistance, and prospects for inhibition, Molecules 22 (12) (2017) 2267.
[187] Y. Shulpekova, et al., The concept of folic acid in health and disease, Molecules 26 (12) (2021) 3731.
[188] S. Bhargava, S. Tyagi, Nutriepigenetic regulation by folate–homocysteine–methionine axis: a review, Mol. Cell. Biochem. 387 (1) (2014) 55–61.
[189] A.V. Gudkov, E.A. Komarova, Pathologies associated with the p53 response, Cold Spring Harb. Perspect. Biol. 2 (7) (2010), a001180.
[190] M. Rudraraju, V. Parvathagiri, M. Dugar, Rifampin induced acute tubulo-interstitial nephritis: rare event of commonly used drug, J. Case Rep. 7 (2) (2017) 133–135.
[191] U. Klotz, Pharmacokinetics and drug metabolism in the elderly, Drug Metab. Rev. 41 (2) (2009) 67–76.
[192] M.W. Abdullah, Renal Protective Activity of Heliotropium Indicum in Rifampicin Induced Nephrotoxicity Rats, 2016.
[193] K. Bhargavi, et al., Evaluation of nephro protectiveactivity of methanolic extract of seeds of vitis vinifera against rifampicin and carbontetra chloride induced nephro toxicity in wistar rats, Indian J. Res. Pharm. Biotechnol. 1 (5) (2013) 731.
[194] R. Jatwa, A. Kar, Protective Effect of L-ornithine-L-aspartate and Silymarin on Chemically Induced Kidney Toxicity and Thyroid Dysfunction in Mice, 2008.
[195] T.R. Nelson, Identification and Characterization of Tubulointerstitial Nephritis Antigen (TIN-ag), University of Minnesota, 1996.
[196] D. Canayakin, et al., Paracetamol-induced nephrotoxicity and oxidative stress in rats: the protective role of Nigella sativa, Pharm. Biol. 54 (10) (2016) 2082–2091.
[197] R.B. Pingili, A.K. Pawar, S.R. Challa, Effect of chrysin on the formation of N-acetyl-p-benzoquinoneimine, a toxic metabolite of paracetamol in rats and isolated rat hepatocytes, Chem. Biol. Interact. 302 (2019) 123–134.
[198] J.E. Okokon, B. Michael, Nephroprotective Activity of Mammea Africana Stem Bark Against Paracetamol Induced Kidney Injury, 2014.
[199] S.C. Shankaraiah Puligilla, S. Chukka, Prevention of Nephrotoxicity With Nutrient Morinda Citrifolia in Acetaminophen Induced Rats, 2021.
[200] B. Manoharan, Protective Effects of Hydroalcoholic Extract of Boerhaavia Diffusa Linn Against Cisplatin Induced Nephrotoxicity in Rats, KM College of Pharmacy, Madurai, 2014.
[201] C. Knoop, A. Haverich, S. Fischer, Immunosuppressive therapy after human lung transplantation, Eur. Respir. J. 23 (1) (2004) 159–171.
[202] H. Ateyya, Amelioration of cyclosporine induced nephrotoxicity by dipeptidyl peptidase inhibitor vildagliptin, Int. Immunopharmacol. 28 (1) (2015) 571–577.
[203] F.S. Shihab, et al., Effect of nitric oxide modulation on TGF-β1 and matrix proteins in chronic cyclosporine nephrotoxicity, Kidney Int. 58 (3) (2000) 1174–1185.
[204] V. Matović, et al., Insight into the oxidative stress induced by lead and/or cadmium in blood, liver and kidneys, Food Chem. Toxicol. 78 (2015) 130–140.
[205] H. Kara, F. Karataş, H. Canatan, Effect of single dose cadmium chloride administration on oxidative stress in male and female rats, Turk. J. Vet. Anim. Sci. 29 (1) (2005) 37–42.
[206] L. Pari, P. Murugavel, Role of diallyl tetrasulfide in ameliorating the cadmium induced biochemical changes in rats, Environ. Toxicol. Pharmacol. 20 (3) (2005) 493–500.
[207] S.M. Prabu, K. Shagirtha, J. Renugadevi, Quercetin in combination with vitamins (C and E) improves oxidative stress and renal injury in cadmium intoxicated rats, Eur. Rev. Med. Pharmacol. Sci. 14 (11) (2010) 903–914.
[208] T. Ramesh, et al., Sesbania grandiflora diminishes oxidative stress and ameliorates antioxidant capacity in liver and kidney of rats exposed to cigarette smoke, J. Physiol. Pharmacol. 61 (4) (2010) 467.
[209] D. Bagchi, et al., Cadmium-induced excretion of urinary lipid metabolites, DNA damage, glutathione depletion, and hepatic lipid peroxidation in Sprague-dawley rats, Biol. Trace Elem. Res. 52 (2) (1996) 143–154.
[210] R.A. Goyer, T.W. Clarkson, in: Toxic Effects of Metals. Casarett and Doull's Toxicology: The Basic Science of Poisons 5, 1996, pp. 691–736.
[211] E. Molina-Jijón, et al., Deferoxamine pretreatment prevents cr (VI)-induced nephrotoxicity and oxidant stress: role of cr (VI) chelation, Toxicology 291 (1–3) (2012) 93–101.
[212] E. Molina-Jijón, et al., Curcumin prevents cr (VI)-induced renal oxidant damage by a mitochondrial pathway, Free Radic. Biol. Med. 51 (8) (2011) 1543–1557.
[213] J. Pedraza-Chaverri, et al., Protective effects of garlic powder against potassium dichromate-induced oxidative stress and nephrotoxicity, Food Chem. Toxicol. 46 (2) (2008) 619–627.
[214] M.R. Khan, et al., Nephroprotective action of tocotrienol-rich fraction (TRF) from palm oil against potassium dichromate (K2Cr2O7)-induced acute renal injury in rats, Chem. Biol. Interact. 186 (2) (2010) 228–238.
[215] M. Yu, et al., Resveratrol protects against arsenic trioxide-induced nephrotoxicity by facilitating arsenic metabolism and decreasing oxidative stress, Arch. Toxicol. 87 (6) (2013) 1025–1035.
[216] E.F. Madden, B.A. Fowler, Mechanisms of nephrotoxicity from metal combinations: a review, Drug Chem. Toxicol. 23 (1) (2000) 1–12.
[217] A. Praveen, M. Gupta, Nitric oxide confronts arsenic stimulated oxidative stress and root architecture through distinct gene expression of auxin transporters, nutrient related genes and modulates biochemical responses in Oryza sativa L, Environ. Pollut. 240 (2018) 950–962.
[218] S. Im Chang, et al., Arsenic-induced toxicity and the protective role of ascorbic acid in mouse testis, Toxicol. Appl. Pharmacol. 218 (2) (2007) 196–203.
[219] C.-H. Lee, H.-S. Yu, Role of mitochondria, ROS, and DNA damage in arsenic induced carcinogenesis, Front. Biosci. (Schol. Ed.) 8 (2) (2016) 312–320.
[220] A. Ara, J.A. Usmani, Lead toxicity: a review, Interdiscip. Toxicol. 8 (2) (2015) 55.
[221] A.A. Berrahal, et al., Effect of age-dependent exposure to lead on hepatotoxicity and nephrotoxicity in male rats, Environ. Toxicol. 26 (1) (2011) 68–78.
[222] Y. Hou, et al., Effect of quercetin against dichlorvos induced nephrotoxicity in rats, Exp. Toxicol. Pathol. 66 (4) (2014) 211–218.
[223] B. BK, Nigrostriatal neuronal death following chronic dichlorvos exposure: crosstalk between mitochondrial impairments, α synuclein aggregation, oxidative damage and behavioral changes, Mol. Brain 3 (1) (2010) 1–20.
[224] A. Ojo, et al., Dichlorvos induced nephrotoxicity in rat kidney: protective effects of Alstonia boonei stem bark extract, Indian J. Pharmacol. 1 (2014) 429–437.
[225] V. Shanmugavel, et al., Potassium bromate: effects on bread components, health, environment and method of analysis: a review, Food Chem. 311 (2020), 125964.
[226] M. Kanadi, et al., Dose-dependent chemopreventive effect of methanol extract of Carica papaya seed on potassium bromate-induced nephrotoxicity in rats, Asian J. Biochem. Genet. Mol. Biol. 2 (1) (2019) 1–12.
[227] D. Delker, et al., Molecular biomarkers of oxidative stress associated with bromate carcinogenicity, Toxicology 221 (2–3) (2006) 158–165.
[228] P. Sankar, A.G. Telang, A. Manimaran, Protective effect of curcumin on cypermethrin-induced oxidative stress in wistar rats, Exp. Toxicol. Pathol. 64 (5) (2012) 487–493.
[229] R. Sharma, R. Jindal, C. Faggio, Impact of cypermethrin in nephrocytes of freshwater fish Catla catla, Environ. Toxicol. Pharmacol. 88 (2021), 103739.
[230] R. Majumder, A. Kaviraj, Histopathological alterations of gills, liver and kidney of freshwater fish, Oreochromis niloticus, exposed to cypermethrin, J. Aquat. Biol. Fish. 10 (1) (2022) 1–5.
[231] A.F. Khafaga, et al., Dietary Origanum vulgare essential oil attenuates cypermethrin-induced biochemical changes, oxidative stress, histopathological alterations, apoptosis, and reduces DNA damage in common carp (Cyprinus carpio), Aquat. Toxicol. 228 (2020), 105624.
[232] J.A. Kiernan, Formaldehyde, formalin, paraformaldehyde and glutaraldehyde: what they are and what they do, Microsc. Today 8 (1) (2000) 8–13.
[233] K.S. Frazier, et al., Proliferative and nonproliferative lesions of the rat and mouse urinary system, Toxicol. Pathol. 40 (4_suppl) (2012) 14S–86S.
[234] S. Dasari, et al., Pharmacological effects of cisplatin combination with natural products in cancer chemotherapy, Int. J. Mol. Sci. 23 (3) (2022) 1532.
[235] B.R. Griffin, S. Faubel, C.L. Edelstein, Biomarkers of drug-induced kidney toxicity, Ther. Drug Monit. 41 (2) (2019) 213.
[236] M. Asif, Study of clinically used and recently developed antimycobacterial agents, Orient Pharm Exp Med 12 (1) (2012) 15–34.
[237] D. Engler, et al., Use of amikacin in neonates and related ototoxicity: neonatology, Prof. Nurs. Today 17 (1) (2013) 24–27.
[238] S. Priyamvada, et al., Studies on the protective effect of dietary fish oil on gentamicin-induced nephrotoxicity and oxidative damage in rat kidney, Prostaglandins Leukot. Essent. Fat. Acids 78 (6) (2008) 369–381.
[239] Y. Okazaki, et al., A beverage containing fermented black soybean ameliorates ferric nitrilotriacetate-induced renal oxidative damage in rats, J. Clin. Biochem. Nutr. 47 (3) (2010) 198–207.
[240] Z. Cheng, et al., Ferroptosis resistance determines high susceptibility of murine A/J strain to iron-induced renal carcinogenesis, Cancer Sci. 113 (1) (2022) 65.
[241] M.G. Miguel, Anthocyanins: antioxidant and/or anti-inflammatory activities, J. Appl. Pharm. Sci. (Issue) (2011) 07–15.

[242] E.-S.M. El-Sayed, A.M. Mansour, M.Y. Ghobara, Abrogation of cisplatin-induced nephrotoxicity in rats by Berne date extract through ameliorating oxidative stress, inflammation and apoptosis, Int. J. Pharm. Sci. Res. 6 (2015) 1226–1233.
[243] M.B. Mirza, et al., Ajwa dates: a highly nutritive fruit with the impending therapeutic application, in: Plant and Human Health, Volume 3, Springer, 2019, pp. 209–230.
[244] S. Mumtaz, et al., Therapeutic role of garlic and vitamins C and E against toxicity induced by lead on various organs, Environ. Sci. Pollut. Res. 27 (9) (2020) 8953–8964.
[245] B.R. Gudalwar, et al., Allium sativum, a potential phytopharmacological source of natural medicine for better health, GSC Adv. Res. Rev. 6 (3) (2021) 220–232.
[246] Y. Fu, et al., Chronic effects of repeated low-dose cisplatin treatment in mouse kidneys and renal tubular cells, Am. J. Physiol. Ren. Physiol. 317 (6) (2019) F1582–F1592.
[247] A. Karimi, et al., Sodium hydrogen sulfide (NaHS) ameliorates alterations caused by cisplatin in filtration slit diaphragm and podocyte cytoskeletal in rat kidney, J. Nephropathology 6 (3) (2017) 150.
[248] C.R.M. Armendáriz, et al., Unintentional contaminants in food, in: Food Safety and Protection, CRC Press, 2017, pp. 243–268.
[249] I.R. Sutejo, et al., Immunostimulant effect of garlic chives leaf ethanolic extract (Allium tuberosum) by increasing level of antioxidant at rats doxorubicin-induced rats, Indones. J. Cancer Chemoprevention 7 (3) (2016) 93–98.
[250] T. Lim, Allium sativum, in: Edible Medicinal and Non Medicinal Plants, Springer, 2015, pp. 210–360.
[251] S. Kalayarasan, et al., Diallyl sulfide enhances antioxidants and inhibits inflammation through the activation of Nrf2 against gentamicin-induced nephrotoxicity in wistar rats, Eur. J. Pharmacol. 606 (1–3) (2009) 162–171.
[252] F.E. Ali, et al., Targeting KEAP1/Nrf2, AKT, and PPAR-γ signals as a potential protective mechanism of diosmin against gentamicin-induced nephrotoxicity, Life Sci. 275 (2021), 119349.
[253] M. Gupta, et al., Grape seed extract: having a potential health benefits, J. Food Sci. Technol. 57 (4) (2020) 1205–1215.
[254] A. Naqshbandi, et al., Studies on the protective effect of dietary fish oil on cisplatin induced nephrotoxicity in rats, Food Chem. Toxicol. 50 (2) (2012) 265–273.
[255] M.A. Abd Eldaim, et al., Grape seeds proanthocyanidin extract ameliorates ehrlich solid tumor induced renal tissue and DNA damage in mice, Biomed. Pharmacother. 115 (2019), 108908.
[256] B.M. Ley, Phytonutrients: Medicinal Nutrients Found in Food, Bl Publications, 1998.
[257] A.E. Azab, M.O. Albasha, A.S.I. Elsayed, Prevention of nephropathy by some natural sources of antioxidants, Yangtze Med. 1 (04) (2017) 235.
[258] T. Gómez-Sierra, et al., Role of food-derived antioxidants against cisplatin induced-nephrotoxicity, Food Chem. Toxicol. 120 (2018) 230–242.
[259] R. Ulu, et al., Effects of curcumin on anion/cation transporters and multidrug response proteins in cisplatin induced nephrotoxicity, Int. J. Clin. Exp. Med. 9 (10) (2016) 19623–19633.
[260] S. Palipoch, et al., Amelioration of cisplatin-induced nephrotoxicity in rats by curcumin and α-tocopherol, Trop. J. Pharm. Res. 12 (6) (2013) 973–979.
[261] O.M. Atrooz, The antioxidant activity and polyphenolic contents of different plant seeds extracts, Pak. J. Biol. Sci. 12 (15) (2009) 1063–1068.
[262] O.A. Adaramoye, A.F. Azeez, O.E. Ola-Davies, Ameliorative effects of chloroform fraction of Cocos nucifera L. husk fiber against cisplatin-induced toxicity in rats, Pharmacogn. Res. 8 (2) (2016) 89.
[263] K.M. El Deib, M.M. Ahmed, Assessment of the protective role of green tea on doxorubicin induced hepatic and renal injuries in albino rats, J. Drug Res. Egypt 32 (1) (2011) 71–80.
[264] I.T. Abdel-Raheem, G.A. El-Sherbiny, A. Taye, Green tea ameliorates renal oxidative damage induced by gentamicin in rats, Pak. J. Pharm. Sci. 23 (1) (2010) 21–28.
[265] E. Yarnell, K. Abascal, Herbs and immunosuppressive drugs: calcineurin inhibitors, Altern. Complement. Ther. 19 (6) (2013) 315–322.
[266] K. Vinoth, et al., Attenuation of cypermethrin induced nephrotoxicity by (-) epigallocatechin gallate (EGCG) in male wistar rats, Sci. Hum. 1 (1) (2015) 665–684.
[267] V. Kameshwari, S. Selvaraj, S. Sundaramoorthy, Single cell protein spirulina-a nutrient treasure, Res. J. Pharmacol. Pharmacodyn. 12 (2) (2020) 49–54.
[268] M.M. Abdel-Daim, et al., Influence of Spirulina platensis and ascorbic acid on amikacin-induced nephrotoxicity in rabbits, Environ. Sci. Pollut. Res. 26 (8) (2019) 8080–8086.
[269] B. Bhat, Bio-Modulatory Properties of: (i) C-phycocyanin, A Biliprotein From Spirulina Platensis (ii) Novel Analogues of Uric Acid, Jawaharlal Nehru Centre for Advanced Scientific Research, 2001.
[270] T.K. Abouzed, et al., The protective impacts of Spirulina platensis against cisplatin-induced renal injury through the regulation of oxidative stress, pro-inflammatory cytokines and Bax/Bcl2, Toxicol. Res. 11 (1) (2022) 169–178.
[271] S.B. Chakraborty, P. Horn, C. Hancz, Application of phytochemicals as growth-promoters and endocrine modulators in fish culture, Rev. Aquac. 6 (1) (2014) 1–19.
[272] R. Sundararajan, A. Bharampuram, R. Koduru, A review on phytoconstituents for nephroprotective activity, Pharmacophore 5 (1) (2014) 160–182.
[273] M.I. Yousef, H.M. Hussien, Cisplatin-induced renal toxicity via tumor necrosis factor-α, interleukin 6, tumor suppressor P53, DNA damage, xanthine oxidase, histological changes, oxidative stress and nitric oxide in rats: protective effect of ginseng, Food Chem. Toxicol. 78 (2015) 17–25.
[274] P. Kalaiselvi, et al., Counteracting adriamycin-induced oxidative stress by administration of N-acetyl cysteine and vitamin E, Clin. Chem. Lab. Med. 43 (8) (2005) 834–840.
[275] G. Aldini, et al., N-acetylcysteine as an antioxidant and disulphide breaking agent: the reasons why, Free Radic. Res. 52 (7) (2018) 751–762.
[276] N.P. Singh, A. Ganguli, A.K. Gupta, Retarding chronic kidney disease progression: do we have a choice? J. Assoc. Physicians India 70 (5) (2022) 11–12.
[277] S.-L. Yu, et al., Oxalate impairs aminophospholipid translocase activity in renal epithelial cells via oxidative stress: implications for calcium oxalate urolithiasis, J. Urol. 186 (3) (2011) 1114–1120.
[278] A. Kurek-Górecka, et al., Structure and antioxidant activity of polyphenols derived from propolis, Molecules 19 (1) (2013) 78–101.
[279] B.A. Aldahmash, D.M. El-Nagar, K.E. Ibrahim, Reno-protective effects of propolis on gentamicin-induced acute renal toxicity in swiss albino mice, Nefrología (English Edition) 36 (6) (2016) 643–652.
[280] D.J. Bhuyan, et al., Broad-spectrum pharmacological activity of australian propolis and metabolomic-driven identification of marker metabolites of propolis samples from three continents, Food Funct. 12 (6) (2021) 2498–2519.
[281] M. Adnan, Radioprotective role of natural polyphenols: from sources to mechanisms, Anti Cancer Agents Med. Chem. 22 (1) (2022) 30–39.
[282] A.M. Mohamadin, Protective Effects of Caffeic Acid Phenylethyl Ester, A Main Component of Propolis Against Cyclosporine A-induced Nephrotoxicity in Rats, Faculty of Agriculture, Cairo University, Egypt, 2006.
[283] R. Shinohara, et al., Evaluation of antilipid peroxidative action of propolis ethanol extract, Phytother. Res. 16 (4) (2002) 340–347.
[284] A.A. Fouad, M.T. Yacoubi, M.H. El-Bidawy, Therapeutic potential of hemin in acetaminophen nephrotoxicity in rats, Environ. Toxicol. Pharmacol. 27 (2) (2009) 277–282.
[285] J.-S. Chen, et al., Nrf-2 mediated heme oxygenase-1 expression, an antioxidant-independent mechanism, contributes to anti-atherogenesis and vascular protective effects of Ginkgo biloba extract, Atherosclerosis 214 (2) (2011) 301–309.
[286] L.B.D. Moura, Taurine and Methionine Supplementation in Meagre (Argyrosomus regius) Fed High Plant Protein Diets, 2018.
[287] P.F. Surai, K. Earle-Payne, M.T. Kidd, Taurine as a natural antioxidant: from direct antioxidant effects to protective action in various toxicological models, Antioxidants 10 (12) (2021) 1876.
[288] G. Mingrone, Carnitine in type 2 diabetes, Ann. N. Y. Acad. Sci. 1033 (1) (2004) 99–107.
[289] P. Rajasekar, M.K. Ravichandran, C.V. Anuradha, Intraperitoneal L-carnitine regulates lipid metabolism and reduces oxidative stress in fructose-induced hyperlipidemic rats, Diabetol. Croat. 34 (3) (2005) 87–95.
[290] C.L. Garcia, et al., The protective effect of L-carnitine in peripheral blood human lymphocytes exposed to oxidative agents, Mutagenesis 21 (1) (2006) 21–27.
[291] J.-M. Hurot, et al., Effects of L-carnitine supplementation in maintenance hemodialysis patients: a systematic review, J. Am. Soc. Nephrol. 13 (3) (2002) 708–714.
[292] M.V. Kameneva, J.F. Antaki, Mechanical trauma to blood, in: Biomedical and Health Research-Commission of the European Communities Then IOS Press 69, 2007, p. 206.
[293] J. Kaur, D. Sharma, R. Singh, Acetyl-L-carnitine enhances Na+, K+-ATPase glutathione-S-transferase and multiple unit activity and reduces lipid peroxidation and lipofuscin concentration in aged rat brain regions, Neurosci. Lett. 301 (1) (2001) 1–4.
[294] M. Speich, A. Pineau, F. Ballereau, Minerals, trace elements and related biological variables in athletes and during physical activity, Clin. Chim. Acta 312 (1–2) (2001) 1–11.
[295] H.D. Lim, et al., Cytoprotective and anti-inflammatory effects of melatonin in hydrogen peroxide-stimulated CHON-001 human chondrocyte cell line and rabbit model of osteoarthritis via the SIRT1 pathway, J. Pineal Res. 53 (3) (2012) 225–237.
[296] S. Mehrzadi, et al., Melatonin synergistically enhances protective effect of atorvastatin against gentamicin-induced nephrotoxicity in rat kidney, Can. J. Physiol. Pharmacol. 94 (3) (2016) 265–271.
[297] S. Eslami, M.A. Ebrahimzadeh, P. Biparva, Green synthesis of safe zero valent iron nanoparticles by Myrtus communis leaf extract as an effective agent for reducing excessive iron in iron-overloaded mice, a thalassemia model, RSC Adv. 8 (46) (2018) 26144–26155.
[298] L. Zhou, et al., Polydatin attenuates cisplatin-induced acute kidney injury by inhibiting ferroptosis, Oxidative Med. Cell. Longev. 2022 (2022).
[299] T.H. Elmehallawi M.A. El-Demiaty , Protection From Gentamycin Ototoxicity By Deferoxamine As An Iron Chelator In Guinea Pig: Electrophysiological and Histopathological Study.
[300] J. Porter, et al., Recent insights into interactions of deferoxamine with cellular and plasma iron pools: implications for clinical use, Ann. N. Y. Acad. Sci. 1054 (1) (2005) 155–168.
[301] E. Hakimizadeh, et al., Ceftriaxone improves hepatorenal damages in mice subjected to D-galactose-induced aging, Life Sci. 258 (2020), 118119.
[302] M.M. Abdel-Daim, et al., Nephroprotective efficacy of ceftriaxone against cisplatin-induced subchronic renal fibrosis in rats, Naunyn Schmiedeberg's Arch. Pharmacol. 390 (3) (2017) 301–309.
[303] M.M. Abdel-Daim, et al., The ameliorative effects of ceftriaxone and vitamin E against cisplatin-induced nephrotoxicity, Environ. Sci. Pollut. Res. 26 (15) (2019) 15248–15254.
[304] S. Noori, T. Mahboob, Protective role of sodium selenite on cisplatin induced oxidative and renal stress, J Basic Appl Sci 4 (1) (2008) 5–12.

[305] Z. Madeja, et al., The role of thioredoxin reductase activity in selenium-induced cytotoxicity, Biochem. Pharmacol. 69 (12) (2005) 1765–1772.
[306] S. Eriksson, Thioredoxin Reductase as a Target Enzyme for Electrophilic Anticancer Drugs, Karolinska Institutet, Sweden, 2011.
[307] L. Flohé, et al., Selenium, the element of the moon, in life on earth, IUBMB Life 49 (5) (2000) 411–420.
[308] M.A. Saifi, S. Seal, C. Godugu, Nanoceria, the versatile nanoparticles: promising biomedical applications, J. Control. Release 338 (2021) 164–189.
[309] M.A. Ayza, et al., Potential protective effects of antioxidants against cyclophosphamide-induced nephrotoxicity, Int. J. Nephrol. 2022 (2022).
[310] F.Z. Ghanemi, M. Belarbi, Phytochemistry and pharmacology of Ceratonia siliqua L. leaves, J. Nat. Prod. Res. Appl. 1 (01) (2021) 69–82.
[311] A. Sharma, Carica papaya L. leaves: deciphering its antioxidant bioactives, biological activities, innovative products, and safety aspects, Oxidative Med. Cell. Longev. 2022 (2022).
[312] M. Rodrigues, et al., Herb-drug pharmacokinetic interaction between carica papaya extract and amiodarone in rats, J. Pharm. Pharm. Sci. 17 (3) (2014) 302–315.
[313] A. Atessahin, et al., Effects of lycopene against cisplatin-induced nephrotoxicity and oxidative stress in rats, Toxicology 212 (2–3) (2005) 116–123.
[314] S. Ojha, et al., Plant-derived agents for counteracting cisplatin-induced nephrotoxicity, Oxidative Med. Cell. Longev. 2016 (2016).
[315] M. Safwat, M. Radi, Evaluation of the antioxidant protective effect of oxytocin and silymarin against gentamicin-induced nephrotoxicity in rat, J. Vet. Med. Res. 21 (1) (2011) 1–7.
[316] F.A. Rodrigues, et al., Gingerol fraction from Zingiber officinale protects against gentamicin-induced nephrotoxicity, Antimicrob. Agents Chemother. 58 (4) (2014) 1872–1878.
[317] H. Parhiz, et al., Antioxidant and anti-inflammatory properties of the citrus flavonoids hesperidin and hesperetin: an updated review of their molecular mechanisms and experimental models, Phytother. Res. 29 (3) (2015) 323–331.
[318] R.R. Ahmed, et al., Hesperidin protects against diethylnitrosamine-induced nephrotoxicity through modulation of oxidative stress and inflammation, Natl. J. Physiol. Pharm. Pharmacol. 5 (5) (2015) 391–397.
[319] M. Aslam, et al., Peucedanum grande attenuates acute renal failure and oxidative stress induced by mercuric chloride in rodents, Am J PharmTech Res 2 (2012) 771–782.
[320] M. Aslam, et al., Nephroprotective action of Peucedanum grande against cadmium chloride induced renal toxicity in wistar rats, EXCLI J. 11 (2012) 444.
[321] S. Banfi, et al., Antibacterial activity of leaf extracts from Combretum micranthum and guiera senegalensis (Combretaceae), Res. J. Microbiol. 9 (2) (2014) 66.
[322] M. Kpemissi, et al., Antioxidant and nephroprotection activities of Combretum micranthum: a phytochemical, in-vitro and ex-vivo studies, Heliyon 5 (3) (2019), e01365.
[323] E.P. Nguelefack-Mbuyo, et al., In vitro antioxidant activity of extracts and coumarins from the stem bark of Mammea africana sabine, J. Complement. Integr. Med. 7 (1) (2010).
[324] S.A. Parray, et al., Ruta graveolens: from traditional system of medicine to modern pharmacology: an overview, Am J Pharm Tech Res 2 (2) (2012) 239–252.
[325] M.B. Ashour, et al., Assessment of the preventive effects of Salvia officinalis and Ruta graveolens ethanolic leaf extracts on chlorpyrifos-and methomyl-induced renal toxicity and oxidative stress in albino rats, Int. J. Prev. Treat. 6 (2) (2017) 34–44.
[326] M.M. El-Sayed, et al., Total phenolic and flavonoid contents and antioxidant activity of Lantana camara and Cucurbita pepo (Squash) extracts as well as GC-MS analysis of Lantana camara essential oils, World J Pharm Res 6 (1) (2017) 137–153.
[327] S. Palani, et al., Nephroprotective and antioxidant activities of Salacia oblonga on acetaminophen-induced toxicity in rats, Nat. Prod. Res. 25 (19) (2011) 1876–1880.
[328] A. Musini, J.P. Rao, A. Giri, Phytochemicals of Salacia oblonga responsible for free radical scavenging and antiproliferative activity against breast cancer cell lines (MDA-MB-231), Physiol. Mol. Biol. Plants 21 (4) (2015) 583–590.
[329] M.A. Shalaby, A.A.-E. Hammouda, Nephroprotective, diuretic and antioxidant effects of some medicinal herbs in gentamicin-nephrotoxic rats, J. Complement. Med. Res. 3 (1) (1970), 1-1.
[330] S. Kumar, et al., Kachnar (Bauhinia variegata), in: Antioxidants in Fruits: Properties and Health Benefits, Springer, 2020, pp. 365–377.
[331] R. Sharma, Protective effect of root extracts of bauhinia variegata Linn against cisplatin-induced nephrotoxicity in rats, SAJ Pharma Pharmacol. 5 (2019) 402.
[332] N. Kannan, K.M. Sakthivel, C. Guruvayoorappan, Nephroprotective effect of Bauhinia tomentosa Linn against cisplatin-induced renal damage, J. Environ. Pathol. Toxicol. Oncol. 35 (2) (2016).
[333] S.K. Amoah, et al., Rosmarinic acid–pharmaceutical and clinical aspects, Planta Med. 82 (05) (2016) 388–406.
[334] M. Nadeem, et al., Therapeutic potential of rosmarinic acid: a comprehensive review, Appl. Sci. 9 (15) (2019) 3139.
[335] M. Tavafi, H. Ahmadvand, Effect of rosmarinic acid on inhibition of gentamicin induced nephrotoxicity in rats, Tissue Cell 43 (6) (2011) 392–397.
[336] S. Palani, et al., Therapeutic efficacy of pimpinella tirupatiensis (Apiaceae) on acetaminophen induced nephrotoxicity and oxidative stress in male albino rats, Int J PharmTech Res 1 (3) (2009) 925–934.
[337] H.A. Mohamed, et al., The Reno protective effect of gum arabic in gamma-irradiated and cisplatin treated rats, Int. J. Sci. Res. Publ. 5 (6) (2015).
[338] B.H. Ali, et al., Effect of gum arabic on oxidative stress and inflammation in adenine–induced chronic renal failure in rats, PloS one 8 (2) (2013), e55242.
[339] J.M. Pérez-Rojas, et al., Renoprotection by α-mangostin is related to the attenuation in renal oxidative/nitrosative stress induced by cisplatin nephrotoxicity, Free Radic. Res. 43 (11) (2009) 1122–1132.
[340] M. Buelna-Chontal, et al., Protective effect of α-mangostin on cardiac reperfusion damage by attenuation of oxidative stress, J. Med. Food 14 (11) (2011) 1370–1374.
[341] G. Dash, M. Abdullah, A review on Heliotropium indicum L. (Boraginaceae), Int. J. Pharm. Sci. Res. 4 (4) (2013) 1253.
[342] G. Porras, et al., Ethnobotany and the role of plant natural products in antibiotic drug discovery, Chem. Rev. 121 (6) (2020) 3495–3560.
[343] A. Raal, A. Orav, E. Arak, Composition of the essential oil of Salvia officinalis L. From various european countries, Nat. Prod. Res. 21 (5) (2007) 406–411.
[344] A.A. Alzergy S.M. Elgharbawy E.H. Abdalwahed , Protective Role of Salvia officinalis Against Formalin Induce Nephrotoxicity in Swiss Albino Mice.
[345] F.A. Al-Bayati, M.J. Mohammed, Isolation, identification, and purification of cinnamaldehyde from Cinnamomum zeylanicum bark oil. An antibacterial study, Pharm. Biol. 47 (1) (2009) 61–66.
[346] M. Ervina, Y. Nawu, S. Esar, Comparison of in vitro antioxidant activity of infusion, extract and fractions of indonesian cinnamon (Cinnamomum burmannii) bark, Int. Food Res. J. 23 (3) (2016) 1346.
[347] M. Quyamuddin, et al., Nephroprotective activity of ethanolic extract of Cinnamomum zeylanicum bark against acetaminophen induced nephrotoxicity in albino rats, J. Drug Deliv. Ther. 10 (4-s) (2020) 80–86.
[348] J. Guo, et al., Amygdalin inhibits renal fibrosis in chronic kidney disease, Mol. Med. Rep. 7 (5) (2013) 1453–1457.
[349] T.F. Mutar, et al., Ameliorative effects of vitamin B17 on the kidney against ehrlich ascites carcinoma induced renal toxicity in mice, Environ. Toxicol. 35 (4) (2020) 528–537.
[350] J. Poirier, S. Kubow, in: The Relationship Between Alpha-Tocopherol, Selenium and Fish Oil in the Diet and Effects on the Heart and Liver. The Encyclopedia of Vitamin E, 2006, p. 273.
[351] N.T. Zaveri, Green tea and its polyphenolic catechins: medicinal uses in cancer and noncancer applications, Life Sci. 78 (18) (2006) 2073–2080.
[352] S.A. Wiseman, D.A. Balentine, B. Frei, Antioxidants in tea, Crit. Rev. Food Sci. Nutr. 37 (8) (1997) 705–718.
[353] S. Sassa, Why heme needs to be degraded to iron, biliverdin IXα, and carbon monoxide? Antioxid. Redox Signal. 6 (5) (2004) 819–824.
[354] M.A. Jwad B. Abbas U. Al-Kwaz , Journal Homepage:-www. journalijar. com.
[355] R.J. Reiter, et al., Biochemical reactivity of melatonin with reactive oxygen and nitrogen species, Cell Biochem. Biophys. 34 (2) (2001) 237–256.
[356] J. Velasquez, A.A. Wray, Deferoxamine, in: StatPearls [Internet], StatPearls Publishing, 2022.
[357] M.A. Farag, D.M. El-Kersh, Volatiles profiling in Ceratonia siliqua (Carob bean) from Egypt and in response to roasting as analyzed via solid-phase microextraction coupled to chemometrics, J. Adv. Res. 8 (4) (2017) 379–385.
[358] C. Sarkar, et al., Heliotropium indicum L.: from farm to a source of bioactive compounds with therapeutic activity, Evid. Based Complement. Alternat. Med. 2021 (2021).
[359] J.M. Andrade, et al., Rosmarinus officinalis L.: an update review of its phytochemistry and biological activity, Future Sci. OA 4 (4) (2018), FSO283.
[360] M. Kpemissi, Combretum micranthum G. Don protects hypertension induced by L-NAME by cardiovascular and renal remodelling through reversing inflammation and oxidative stress, J. Funct. Foods 94 (2022), 105132.