INTRODUCTION

Toxicologists perform various experiments to determine the effects of toxins on humans and other living organisms. Cellular, molecular, and biochemical research experiments are performed to investigate the mechanism of action of toxic substances and their effects on the nervous system, immune system, and so on. Experiments in this area are mostly performed on laboratory organisms. Therefore, specialists inject a certain amount of a toxic substance into the living organism through food, inhalation, or skin and then examine the harmful effects caused by it on the body. They try to generalize the effects of these substances on humans. Of course, this is one of the methods used for obtaining toxicological information. The use of toxins in laboratory animal models is also sometimes intended to cause systemic or local toxicity. In these studies, after the development of toxicity in the animal in question, the authors prescribe a substance or drug that they intend to study for the first time and possibly this substance has beneficial effects in improving the toxicity process, and its effects on the desired parameters of the serum, urine, or tissue are evaluated.

Therefore, this study aimed to investigate different and common models of hepatotoxicity and nephrotoxicity in laboratory animals to help researchers advance their research goals.

MATERIALS AND METHODS

This review used comprehensive data from main databases, including Scopus, Medline, Web of Science, Scopus, and Embase and appropriate keywords until June 2021. Nephrotoxicity and hepatotoxicity models derived from some toxic agents such as cisplatin, acetaminophen, doxorubicin, some anticancer drugs, and other materials through various signaling pathways are investigated. To understand the models of renal or hepatotoxicity in laboratory animals, we have provided a list of toxic agents and their toxicity procedures in this review.
and endonuclease G were released from mitochondria; and caspase of caspase/direct inhibitor of apoptosis-binding protein with low Pi, another mechanism that participates in cisplatin-induced injury is apoptosis-inducing factor, second mitochondria-derived activator of cytochrome C, Omi/HtrA2, and caspase 2 was activated; cytochrome C, 20 which is involved in tubular epithelial apoptosis. Another mechanism that participates in cisplatin-induced injury is autophagy, a degradation process in which the organelles were damaged and then the digestive enzymes from lysosomes burst causing cell death. Renal epithelial cell treatment by cisplatin causes the fast expression of autophagy proteins.21–23

3.1.1 | Hepatotoxicity

Tumor cells treated with cisplatin lead to membrane peroxidation, mitochondria dysfunction, protein synthesis inhibition, and DNA damage.1,2 Cisplatin causes abnormalities in the liver, including inflammatory infiltration, hyperplasia, perportal fibrosis, hepatic cord disruption, blood sinusoid dilation, and hepatocyte apoptosis.3,4 Studies show that heavy metals such as cisplatin exert their toxic effects by induction of reactive oxygen species (ROS) production.5,6 Superoxide dismutase (SOD) and catalase (CAT) convert superoxide radicals first to H2O2 and then to molecular oxygen and water, as a cellular defense against ROS. An increase in ROS generation or decrease in antioxidant enzymes results in oxidative stress.7 Cisplatin elevates lipid peroxidation (LPO), an index of tissue damage, and empties thiol contents. Liver tissue damage through ROS leads to LPO increase via antioxidant enzyme disturbance (CAT, SOD, and glutathione peroxidase [GPx]) and total thiol contents.8

3.1.2 | Nephrotoxicity

The cellular pathways of cisplatin nephrotoxicity are complex. It was investigated primarily in vitro using cultured cells and revealed that low-administered doses of cisplatin result in renal tubular epithelial cell death and higher doses in necrosis.9,10 Cisplatin in nephrotic doses increases both cell death and then necrosis in the renal tissue in vivo.11,12 Renal epithelial cell death after cisplatin administration resulted from the launch of the extrinsic pathway activated through tumor necrosis factor (TNF) receptors, intrinsic mitochondrial pathway, and endoplasmic reticulum (ER) stress pathway.13 Inflammatory response stimulation by TNF-α in vivo aggravates cisplatin nephrotoxicity.13–15 After the renal epithelial cells were exposed to cisplatin, BCL2-associated X (Bax) was translocated to mitochondria; caspase 2 was activated; cytochrome C, Omi/HtrA2, apoptosis-inducing factor, second mitochondria-derived activator of caspase/direct inhibitor of apoptosis-binding protein with low Pi, and endonuclease G were released from mitochondria; and caspase 9 was activated.10,16,17 Treatment of renal epithelial cells with cisplatin in vitro led to activation of caspases 3, 8, and 9 after 12 h.18 Expression and activation of caspases, mainly 6 and 7,19 through Bax/BCL2-antagonist/killer pathway mediated the release of cytochrome C,20 which is involved in tubular epithelial apoptosis. Another mechanism that participates in cisplatin-induced injury is 3.2 | Acetaminophen

3.2.1 | Hepatotoxicity

Up to 50% of acetaminophen is metabolized in the liver through glucuronidation or sulfation, which produces nontoxic metabolites. About 10% of acetaminophen is metabolized in the cytochrome P450 2E1 (CYP2E1) path, leading to N-acetyl-p-benzoquinone imine (NAPQI) production which is very toxic. Higher-than-therapeutic doses and elevation of NAPQI production caused mitochondrial dysfunction, oxidative stress, and adenosine triphosphate (ATP) resource discharge, finally resulting in hepatocellular necrosis and cell death. The toxic free radical formation, as well as peroxynitrite (ONOO−), from O2·− and NO− is another mechanism of liver toxicity.24,25 ROS, for example, ONOO−, are negated by glutathione (GSH), which reduces acetaminophen toxicity. Due to mitochondrial membrane permeability dysfunction, ROS result in mitochondrial membrane disruption, organelle swelling, and eventually cellular necrosis.24–26 Glucuronization or sulfation is the main method of acetaminophen metabolism. However, in hepatotoxic doses of acetaminophen, most of it is metabolized to NAPQI, resulting in the evacuation of GSH.24,26 In the CYP2E1 pathway, NAPQI converts into nonreactive metabolites via enzymes, namely myeloperoxidase and cyclooxygenase-1. In the immune system, liver toxicity is hampered by the natural killer and natural killer T cells and causes pro-inflammatory cytokine release and hepatocyte cytotoxicity.27,28

3.2.2 | Nephrotoxicity

Elevated activity of the cytochrome P450 (CYP-450) system, chronic alcohol consumption, and intake of drugs that induce these enzymes, namely anticonvulsants, enhance acetaminophen toxicity.29 Although GSH has been known to be a key component in acetaminophen and in its metabolite detoxification, its conjugates play a role in the formation of nephrotoxic compounds. It is not clear yet whether renal damage is due to acetaminophen–GSH conjugate or one of its metabolites. Maybe the conjugate formation leads to GSH depletion, which prevents reactive metabolite detoxification.30 Prostaglandin endoperoxide synthetase (PGES), mainly in the medulla of the kidney, converts acetaminophen into toxic metabolites, whereas CYP-450 plays the main role in the cortex. As a result of these two pathways, poisonous metabolites are formed, followed by tissue necrosis and cell death, resulting in covalent binding to cellular proteins. PGES binds acetaminophen with high affinity, and reactive metabolite formation occurs. The enzyme N-deacetylase causes
acetaminophen-induced nephrotoxicity; it acts on NAPQI or acetaminophen and deacetylates its substrate to $\text{p}$-aminophenol, which by converting to a free radical binds to cellular proteins.\textsuperscript{31}

### 3.3 | Doxorubicin

#### 3.3.1 | Hepatotoxicity

Doxorubicin increases 53\% spontaneous formation of malonaldehyde in the liver. As malondialdehyde (MDA) increases, doxorubicin sustains one-electron reduction via nicotinamide adenine dinucleotide phosphate (NADPH) CYP-450 reductase, and antioxidant enzymes decreases CAT and SOD activities.\textsuperscript{32} In rat liver, doxorubicin decreases CYP-450 and GSH levels in free radical formation, which results from a nonenzymatic mechanism. For instance, $\text{Fe}^3+$ reacts with doxorubicin, and the iron atom obtains one electron and leads to $\text{Fe}^{2+}$ doxorubicin free radical complex production. This complex can reduce oxygen to active oxygen species such as hydrogen peroxide.\textsuperscript{33} As a result of oxidative metabolism, doxorubicin produces superoxide, H$_2$O$_2$, and hydroxyl in rats.\textsuperscript{34} In the doxorubicin-treated rats GSH-Px, SOD, and CAT levels increased significantly, indicating that doxorubicin generates free radicals and thereby attenuates cell damage. In addition to ROS production in tissue, doxorubicin decreases its detoxification property. Elevated SOD, CAT, and GSH-Px activities in liver tissues show that doxorubicin has hepatotoxic effects.\textsuperscript{35}

#### 3.3.2 | Nephrotoxicity

Doxorubicin exerts harmful effects on renal tissue by increasing glomerular capillary permeance and induces tubular degeneration.\textsuperscript{36} Doxorubicin’s detrimental effects on tissues such as the liver and heart presumably will change blood reserve to the kidney and alter the xenobiotic reclamation, resulting in nephropathy.\textsuperscript{37,38}

Doxorubicin-induced nephrotoxicity is typically caused by optional damage of the proximal tubule cells.\textsuperscript{39} Renal tubular deficiency through chemotherapy results in acute renal failure.\textsuperscript{40} Doxorubicin induces renal injury by elevated generation of ROS, apoptosis, and a decrease in antioxidant enzymes.\textsuperscript{41,42}

### 3.4 | Aluminum

#### 3.4.1 | Hepatotoxicity

Aluminum is a nonredox metal with pro-oxidant activity. It simplifies superoxide formation induced by some pro-oxidant agents.\textsuperscript{43} Aluminum induces mitochondrial permeability pores, which results in electron leakage and elevated radical oxygen species formation in the cytosol.\textsuperscript{44} Because of facilitated specific transport system uptake, the liver is the target of aluminum toxicity.\textsuperscript{45} In vitro models, elevated cytosolic enzyme secretion by cultured hepatocytes subacutely exposed to aluminum has been reported.\textsuperscript{46} Studies show that the balance between antioxidant and oxidant forces is interrupted in aluminum-treated rats, resulting in elevated free radical generation and antioxidant defense reduction, such as GSH content, CAT, GSH-Px, and glutathione-S-transferase (GST). Aluminum induces a disbalance when prescribed in various chemical forms and with different chronicity.\textsuperscript{47–49}

### 3.5 | CCl$_4$

Reactive oxygen metabolites are one of the assumed mechanisms in the nephrotoxicity of CCl$_4$.\textsuperscript{54} In cultured hepatocyte cells, CCl$_4$ leads to increased trichloromethyl peroxyl radical production and hydrogen peroxide.\textsuperscript{55} CCl$_4$ increases LPO and decreases renal reduced/oxidized GSH ratio and microsomal NADPH CYP-450 in the kidney cortex, microsomes, and mitochondria.\textsuperscript{56} Antioxidants like SOD/CAT, melatonin, silibinin, ascorbate, propionyl, and carnitine improve renal toxicity resulting from CCl$_4$.\textsuperscript{57}

### 3.6 | Acrylamide

Acrylamide can produce ROS. It is oxidized to glycaminamide. This substance interacts with the nucleophile group in cells such as SH, NH$_2$, or OH. The SOD and GST activities are enhanced, and the GSH count decreases with an increase in acrylamide concentration.\textsuperscript{58,59} Acrylamide can create oxidative stress that leads to apoptosis.\textsuperscript{60} Exposure to acrylamide results in increased ROS production and GSH oxidation in isolated human monocyte.\textsuperscript{61} After intestinal absorption, acrylamide often is conjugated with GSH and results in GSH store evacuation.\textsuperscript{62} Decrease in GSH levels may elevate ROS. ROS production results in the activation of the mitogen-activated protein kinase (MAPK)-JNKs, which exert an important effect in the regulation of cellular processes like apoptosis.\textsuperscript{63} The low levels of GSH lead to cellular oxidative stress and apoptosis, which is a potential mechanism for acrylamide toxicity.\textsuperscript{64}
3.7 | Manganese

Manganese exerts cellular toxicity via mechanisms, including direct or indirect ROS formation, biological molecule oxidation, and cellular calcium disruption. Elevated manganese results in complex blockade of the mitochondrial electron transport chain. A toxic outcome of these latter effects may be the intracellular labile iron pool increment.

3.8 | Opioids

Morphine causes oxidative stress by inducing ROS production and initiating oxidative damage. According to clinical studies, morphine addicts are at increased risk for chronic renal failure. Morphine induces tubular dilatation, glomerular expansion, peritubular and intraglomerular congestion, high kidney mass, and juxtaglomerular cells in mice (after 6 weeks of treatment). The liver biomarkers (AST, ALT, and GGT) increased in tramadol-treated rats, which might be due to high LPO. Tramadol also induces some histopathological changes, including hepatocyte degeneration, hemorrhage, hepatic congestion, and necrosis. The levels of blood urea nitrogen (BUN) and Cr significantly enhanced in the rats treated with tramadol. Furthermore, mononuclear cell infiltration, renal tubular vacuolization, and focal necrosis occurred after tramadol administration.

3.9 | Metals

One of the main metals that induce nephrotoxicity is copper. The related possible induction mechanisms can be oxidative stress, autophagy, and apoptosis, which resulted from various signaling pathways, including mammalian target of rapamycin, p53, and NF-κB, and the ER stress pathway. NO levels and oxidative stress play a major role in the mechanisms of toxicity for several nanoparticles, including copper oxide, which also results in the recruitment of inflammatory cells that mediate oxidative damage. Oxidative stress is a possible mechanism in hepatotoxicity induced by copper oxide. In the kidney, copper induces proteinuria, aminoaciduria, diminished glomerular filtration, and renal phosphaturia. In chicken kidney tissues, CuSO 4 induces mitochondrial dysfunction and cell apoptosis. Lead is another metal involved in toxicity. The acetate form of lead can accelerate proteasome activity, which is related to MAPK pathway and inflammatory response. Psm3 inhibition is a new anti-inflammatory strategy in lead acetate nephrotoxicity. Nano nickel oxide induces cytotoxicity through ROS formation and apoptosis in the HepG2 cell line. Another study has also indicated this issue. According to Magaye et al, nickel nanoparticles cause liver inflammation in rats. Nickel ferrite nanoparticles also induce cytotoxicity as well as oxidative stress in the hepatocellular carcinoma cells.

3.10 | Anticancer drugs

Cyclosporin A (CsA)–induced hepatotoxicity occurs mainly through some mechanisms, including hypermetabolic state in the liver and inhibition of ATP-dependent transport of bilirubin and bile salts through the hepatocyte canalicular membranes. Oxidative stress as one of the mechanisms of hepatotoxicity in experimental animals treated by CsA is presumable. CsA increases the activities of oxidants such as xanthine oxidase. Mitochondrial damage plays a critical role in CsA hepatotoxicity. Also, ER stress related to oxidative stress plays a role in CsA nephropathy. Renal-transplant patients treated with CsA showed upregulation of an ER stress marker in kidney biopsies. CsA-induced apoptosis in renal tubular cells relates to oxidative damage. Methotrexate toxicity effects occur through increasing ROS production. Imbalance between ROS production and antioxidants leads to oxidative stress and then pathological symptoms.

3.11 | Cadmium

Cadmium induces nephrotoxicity via ROS production, apoptosis, and inflammation in the renal tissue. Cadmium affects the S1 and S2 proximal segments that are the main action sites. Oxidant–antioxidant imbalance in the renal tissue is the main reason for kidney dysfunction in cadmium toxicity, which is parallel with increased NO and LPO levels. Higher doses of cadmium in animals resulted in membrane LPO and GSH reduction in the kidney and liver. Liver injury induced by cadmium is confirmed by increased levels of marker enzymes (AST and ALT).

3.12 | Valproic acid

Valproic acid (VPA) hepatotoxicity is due to dysfunction of hepatocyte mitochondria. Also, oxidative stress plays a role in VPA hepatotoxicity. Formation of ROS, LPO, and cellular antioxidant enzymes are various induction mechanisms of VPA hepatotoxicity. Inhibition of mitochondrial β-oxidation of fatty acids induced by VPA, defect in gluconeogenesis, and oxidative phosphorylation inhibition have been suggested in liver preparation.

Elevated levels of Cr, BUN, and renal tissue histopathological alterations are reported in VPA-treated animals. VPA inactivates antioxidant enzymes; according to several studies, oxidative stress occurred in the kidney after VPA administration. VPA decreased tissue antioxidant activity, increased LPO, and depleted GSH stores.
3.13 | Diclofenac

Nephrotoxic doses of diclofenac administrated to male mice resulted in severe renal damage, leading to apoptosis and/or necrosis. Diclofenac is a robust inducer of oxidative stress, which may be the cause of its apoptogenic effect.120

Diclofenac toxicity is related to mainly LPO and cellular macromolecule damage.121,122 Diclofenac causes enhanced levels of kidney MDA and H2O2. H2O2 level is enhanced during intracellular buildup of ROS concentration.123

3.14 | Thioacetamide

Thioacetamide induces the formation of free radicals derived from thioacetamide-S-oxide, which leads to apoptosis and necrosis.124 ROS production resulting from thioacetamide administration was followed by LPO, GSH depletion, and SH-thiol group reduction.125

3.15 | Carbofuran

Carbofuran increased MDA level in liver cells by generation of oxidative stress.126 Carbofuran also increased ALT, AST, and LDH and decreased these parameters in the liver tissue.127

3.16 | KBrO3

KBrO3 as a nephrotoxic agent is a trigger for ROS production, LPO, and 8-hydroxyguanosine modification in the DNA.128,129 Numerous works suggest that ROS production that causes LPO and reduction in antioxidant enzymes is a major mechanism of nephrotoxicity induced by KBrO3.130,131 Regarding KBrO3 effects on liver cells, vacuolization and sinusoidal dilatation studies have reported that these effects can be mainly related to the reduction of antioxidant enzymes and enhancement of xanthine oxidase and lipid peroxidase.132,133

3.17 | Gentamicin

Gentamicin (80mg/kg) causes hepatotoxicity and nephrotoxicity by the increase in serum AST, ALT, TG, DB, TB, total protein, urea, sodium, potassium, and chloride levels. There was a significant increase in oxidative stress, indicating liver and kidney damage in gentamicin-treated rats.134 Oxidative stress plays a main role in gentamicin-induced nephrotoxicity.135 Gentamicin increases hydrogen peroxide, superoxide anion, and hydroxyl radical generation by mitochondria.136

3.18 | Ochratoxin A

Ochratoxin A (OTA) both in vitro and in vivo leads to overproduction of free radicals. Elevated ROS generation and oxidative injury are reported in this issue.137 Using Fe3+ as a cofactor, OTA triggers LPO. OTA-Fe3+ complex facilitates Fe3+ reduction, and the resultant OTA-Fe2+ complex generates free radicals leading to DNA damage and LPO.138,139

3.19 | Bisphenol A

Bisphenol A (BPA) causes apoptosis by the induction of adenylate kinase activation, TNF-α gene expression,140 and dysregulation of Ca2+ homeostasis.141 A high dose of bisphenol A elevates the formation of free radicals and reduces its ability to detoxify ROS. A high dose of BPA induces superoxide radical formation, and ONOO− causes tissue damage, leading to an increase in LPO levels. Therefore, activated caspases induce apoptotic signals, leading to apoptosis and hepatotoxicity in liver tissue.142

3.20 | Cyclophosphamide

Based on previous studies, oxidative stress is one of the principal causes of cyclophosphamide (CP)-induced hepatotoxicity. It seems that CP metabolites induce this mechanism. CP administration elevates MDA levels and also reduces GSH level and SOD, GST, CAT, and GPO activities.143 All these results reveal that CP-induced hepatotoxicity was related to GSH level, a main content in eliminating active metabolites and defending oxidative stress.144

A list of the toxic agents on liver has been provided in Table S1. Also, a list of toxic agents on kidney has been provided in Table S2.

4 | CONCLUSION

In recent years, the number of hospitalized patients with kidney and/or liver disorders due to normal or overuse of drugs has increased such that kidney poisoning due to drug use accounts for about 60% of acute kidney damage. Despite clinical supportive measures such as medication and electrolyte replacement, on average about 20% of patients undergoing treatment experience organ toxicity and related problems. Medicinal drugs and even substances derived from some medicinal plants can play a prominent therapeutic or preventive role in liver and/or kidney toxicity. Therefore, to initially evaluate the effect of any of the aforementioned substances, they should first be tested on laboratory animals that have hepato- and/or renal toxicity. To achieve this goal, it is important to understand the models of renal or hepatotoxicity induction in laboratory animals depending on the conditions. Substances or drugs can be used to create models of toxicity. In this review article, we tried to provide a list of toxic materials and drugs that cause hepato- and/or renal toxicity models in laboratory animals, along with relative protocols for creating those models for researchers so that they can make appropriate choices depending on the situation.
AUTHOR CONTRIBUTIONS
Reza Mohebbati designed the concept. Abbasali Abbasnezhad and Fatemeh Salami collected data and drafted manuscript. All authors reviewed and proofed final version.

ACKNOWLEDGMENTS
None.

CONFLICT OF INTEREST
None.

ORCID
Reza Mohebbati @ https://orcid.org/0000-0002-1645-7094

REFERENCES
1. Cohen SM, Lippard SJ. Cisplatin: from DNA damage to cancer chemotherapy. Prog Nucleic Acid Res Mol Biol. 2001;67:93-130.
2. Sadowitz PD, Hubbard BA, Dabrowiak JC, et al. Kinetics of cisplatin binding to cellular DNA and modulations by thiol-blocking agents and thiol drugs. Drug Metab Dispos. 2002;30:183-190.
3. El-Sayyad HI, Ismail MF, Shalaby F, et al. Histopathological effects of cisplatin, doxorubicin and 5-fluorouracil (5-FU) on the liver of male albino rats. Int J Biol Sci. 2009;5:466.
4. Karadeniz A, Simsek N, Karakus E, et al. Royal jelly modulates oxidative stress and apoptosis in liver and kidneys of rats treated with cisplatin. Oxid Med Cell Longev. 2011;2011:981793.
5. Fatima S, Yusufi ANK, Mahmood R. Effect of cisplatin on renal brush border membrane enzymes and phosphate transport. Hum Exp Toxicol. 2004;23:547-554.
6. Baliga R, Zhang Z, Baliga M, et al. In vitro and in vivo evidence suggesting a role for iron in cisplatin-induced nephrotoxicity. Kidney Int. 1998;53:394-401.
7. Khan SA, Priyamvada S, Khan W, et al. Studies on the protective effect of green tea against cisplatin induced nephrotoxicity. Pharmacol Res. 2009;60:382-391.
8. Naqshbandi A, Khan W, Rizwan S, et al. Studies on the protective effect of flaxseed oil on cisplatin-induced hepatotoxicity. Hum Exp Toxicol. 2012;31:364-375.
9. Lieberthal W, Triaca V, Levine J. Mechanisms of death induced by cisplatin in proximal tubular epithelial cells: apoptosis vs. necrosis. Am J Physiol. 1996;270:F700-F708.
10. Lee RH, Song JM, Park MY, et al. Cisplatin-induced apoptosis by translocation of endogenous Bax in mouse collecting duct cells. Biochem Pharmacol. 2001;62:1013-1023.
11. Shiraiishi F, Curtis LM, Truong L, et al. Heme oxygenase-1 gene ablation or expression modulates cisplatin-induced renal tubular apoptosis. Am J Physiol Renal Physiol. 2000;278:F726-F736.
12. Megyesi J, Safirstein RL, Price PM. Induction of p21WAF1/CIP1/SDI1 in kidney tubule cells affects the course of cisplatin-induced acute renal failure. J Clin Invest. 1998;101:777-782.
13. Tsuruya K, Ninomiya T, Tokumoto M, et al. Direct involvement of the receptor-mediated apoptotic pathways in cisplatin-induced renal tubular cell death. Kidney Int. 2003;63:72-82.
14. Ramesh G, Reeves WB. TNF-α mediates chemokine and cytokine expression and renal injury in cisplatin nephrotoxicity. J Clin Invest. 2002;110:835-842.
15. Ramesh G, Reeves WB. TNFR2-mediated apoptosis and necrosis in cisplatin-induced acute renal failure. Am J Physiol Renal Physiol. 2003;285:F610-F618.
16. Cilenli L, Kyriazis GA, Soundarapandian MM, et al. Omi/HtrA2 protease mediates cisplatin-induced cell death in renal cells. Am J Physiol Renal Physiol. 2005;288:F371-F379.
17. Dursun B, He Z, Somerst H, et al. Caspases and calpain are independent mediators of cisplatin-induced endothelial cell necrosis. Am J Physiol Renal Physiol. 2006;291:F578-F587.
18. Kaushal GP, Kaushal V, Hong X, et al. Role and regulation of activation of caspases in cisplatin-induced injury to renal tubular epithelial cells. Kidney Int. 2001;60:1726-1736.
19. Yang C, Kaushal V, Haun R, et al. Transcriptional activation of caspase-6 and 7 genes by cisplatin-induced p53 and its functional significance in cisplatin nephrotoxicity. Cell Death Differ. 2008;15:530-544.
20. Jiang M, Wang CY, Huang S, et al. Cisplatin-induced apoptosis in p53-deficient renal cells via the intrinsic mitochondrial pathway. Am J Physiol Renal Physiol. 2009;296:F983-F993.
21. Kaushal GP, Kaushal V, Herzog C, et al. Autophagy delays apoptosis in renal tubular epithelial cells in cisplatin cytotoxicity. Autophagy. 2008;4:710-712.
22. Yang C, Kaushal V, Shah SV, et al. Autophagy is associated with cisplatin injury to renal tubular epithelial cells. Am J Physiol Renal Physiol. 2008;294:F777-F787.
23. Periyasamy-Thandavan S, Jiang M, Wei Q, et al. Autophagy is cytotoxic during cisplatin injury of renal proximal tubular cells. Kidney Int. 2008;74:631-640.
24. Jaeschke H, Mcgill MR, Ramachandran A. Oxidant stress, mitochondrial, and cell death mechanisms in drug-induced liver injury: lessons learned from acetylamino nephropathy. Drug Metab Rev. 2012;44:88-106.
25. Jaeschke H, Mcgill MR. Cytochrome P450-derived versus mitochondrial oxidant stress in acetylamino hepatotoxicity. Toxicol Lett. 2015;235:216-217.
26. Jaeschke H, Williams CD, Ramachandran A, et al. Acetylamino hepatotoxicity and repair: the role of sterile inflammation and innate immunity. Liver Int. 2012;32:8-20.
27. Yoon E, Babar A, Choudhary M, et al. Acetylamino-induced hepatoxicity: a comprehensive update. J Clin Transl Hepatol. 2016;4:131.
28. Yuan L, Kaplowitz N. Mechanisms of drug-induced liver injury. Clin Liver Dis. 2013;17:507-518.
29. Bray GP, Harrison PM, JG O’g, et al. Long-term anticonvulsant therapy worsens outcome in paracetamol-induced fulminant hepatic failure. Hum Exp Toxicol. 1992;11:265-270.
30. Stern ST, Bruno MK, Hennig GE, et al. Contribution of acetylamino-cysteine to acetylamino nephropathy in CD-1 mice: I. Enhancement of acetylamino nephropathy by acetylamino-cysteine. Toxicol Appl Pharmacol. 2005;202:151-159.
31. Mугford CA, Tarloff JB. The contribution of oxidation and deacetylation to acetylamino nephropathy in female Sprague-Dawley rats. Toxicol Lett. 1997;93:15-22.
32. Marchand DJ, Renton KW. Depression of cytochrome P-450-dependent drug biotransformation by adriamycin. Toxicol Appl Pharmacol. 1981;58:83-88.
33. Quiles JL, Huertas JR, Battino M, et al. Antioxidant nutrients and adriamycin toxicity. Toxicology. 2002;180:79-95.
34. Doroshow JH. Anthracycline antibiotic-stimulated superoxide, hydrogen peroxide, and hydroxyl radical production by NADH dehydrogenase. Cancer Res. 1983;43:4543-4551.
35. Kalender Y, Yel M, Kalender S. Doxorubicin hepatotoxicity and hepatic free radical metabolism in rats: the effects of vitamin E and catechin. Toxicology. 2005;209:39-45.
36. Lee VW, Harris DC. Adriamycin nephropathy: a model of focal segmental glomerulosclerosis. Nephrol Ther. 2011;16:30-38.
37. Granados-Principal S, Quiles JL, Ramirez-Tortosa CL, et al. New advances in molecular mechanisms and the prevention of adriamycin toxicity by antioxidant nutrients. Food Chem Toxicol. 2010;48:1425-1438.
38. Wapstra FH, Van Goor H, De Jong PE, et al. Dose of doxorubicin determines severity of renal damage and responsiveness to
ACE-inhibition in experimental nephrosis. J Pharmacol Toxicol Methods. 1999;41:69-73.

39. Grant MK, Seelig DM, Sharkey LC, et al. Sexual dimorphism of acute doxorubicin-induced nephrotoxicity in C57Bl/6 mice. PloS One. 2019;14:e0212486.

40. Ruggiero A, Ferrara P, Attinà G, et al. Renal toxicity and chemotherapy in children with cancer. Br J Clin Pharmacol. 2017:83:2605-2614.

41. Abdelmeguid NE, Chmaissi HN, Abou Zeinab NS. Protective effect of silymarin on cisplatin-induced nephrotoxicity in rats. Pak J Nutr. 2010;9:624-636.

42. Carvalho C, Santos RX, Cardoso S, et al. Doxorubicin: the good, the bad and the ugly effect. Curr Med Chem. 2009;16:3267-3285.

43. Exley C. The pro-oxidant activity of aluminum. Free Radical Biol Med. 2004;36:380-387.

44. Toninello A, Clari G, Mancon M, et al. Aluminum as an inducer of the mitochondrial permeability transition. J Biol Inorg Chem. 2000;5:612-623.

45. Wihielm M, Jaeger DE, Schüll-Cablitz H, et al. Antioxidants prevent acute doxorubicin-induced alloxan-induced antioxidative stress in rats. Exp Neurol. 1999;7:49-57.

46. Brouillet E, Shinobu L, Mçgarvey U, et al. Manganese injection into the rat striatum produces excitotoxic lesions by impairing energy metabolism. Exp Neurol. 1993;120:89-94.

47. Archibald FS, Tyree C. Manganese poisoning and the attack of trivalent manganese upon catecholamines. Arch Biochem Biophys. 1987;256:638-650.

48. Abreo K, Alvarez-Hernandez X, Jain S. Antioxidants prevent liver injury in MPA bearing mice. J Biochem Mol Toxicol. 2001;15:207-214.

49. Diniz A, Santos C, Watanabe L, et al. Manganese exposure decreases mitochondrial cytochrome oxidase activity in PC12 cells. Environ Toxicol Pharmacol. 2018;13:e0202110.

50. Girardi G, Elias MM. Effectiveness of N-acetylcysteine in protecting against end-stage tetrachloride toxicity. Ann Clin Lab Sci. 2018;19:238-241.

51. Britto R, Sanchis J, Pires J, et al. Manganese exposure decreases mitochondrial cytochrome oxidase activity in PC12 cells. J Neurosci. 2001;21:310-317.

52. Miller NJ, Rice-Evans CA. The relative contributions of ascorbic acid and phenolic antioxidants to the total antioxidant activity of orange and apple fruit juices and blackcurrant drink. Food Chem. 1997;60:331-337.

53. Yousef M, El-Demerdash F. Acrylamide-induced oxidative stress and biochemical perturbations in rats. Toxicology. 2006;219:133-141.

54. Chen W, Shen Y, Su H, et al. Hispidin derived from Phellinus linteus affords protection against acrylamide-induced oxidative stress in Caco-2 cells. Chem Biol Interact. 2014;219:83-89.

55. Nakagawa-Yagi Y, Choi D-K, Ogane N, et al. Discovery of a novel compound: insight into mechanisms for acrylamide-induced axonopathy and colchicine-induced apoptotic neuronal cell death. Brain Res. 2001;909:8-19.

56. Rungby J, Ernst E. Experimentally induced lipid peroxidation after one hour of ischemia. J Trace Elem Med Biol. 2004;18:113-121.

57. Miller NJ, Rice-Evans CA. The relative contributions of ascorbic acid and phenolic antioxidants to the total antioxidant activity of orange and apple fruit juices and blackcurrant drink. Food Chem. 1997;60:331-337.

58. Youssef M, El-Demerdash F. Acrylamide-induced oxidative stress and biochemical perturbations in rats. Toxicology. 2006;219:133-141.

59. Chen W, Shen Y, Su H, et al. Hispidin derived from Phellinus linteus affords protection against acrylamide-induced oxidative stress in Caco-2 cells. Chem Biol Interact. 2014;219:83-89.

60. Liu Z, Song G, Zou C, et al. Acrylamide induces mitochondrial dysfunction and apoptosis in BV-2 microglial cells. Free Radic Biol Med. 2015;84:42-53.

61. Naruszewicz M, Zapoliska-Downar D, Kosièr M, et al. Chronic intake of potato chips in humans increases the production of reactive oxygen radicals by leukocytes and increases plasma C-reactive protein: a pilot study. Am J Clin Nutr. 2009;89:773-777.

62. Nakagawa-Yagi Y, Choi D-K, Ogane N, et al. Discovery of a novel compound: insight into mechanisms for acrylamide-induced axonopathy and colchicine-induced apoptotic neuronal cell death. Brain Res. 2001;909:8-19.

63. Valko M, Leibfritz D, Moncol J, et al. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol. 2007;39:44-84.

64. Circu ML, Rodríguez C, Maloney R, et al. Contribution of mitochondrial GSH transport to matrix GSH status and colonic epithelial cell apoptosis. Free Radical Biol Med. 2008;44:768-778.

65. Ali SF, Duhart HM, Newport GD, et al. Manganese-induced reactive oxygen species: comparison between Mn+2 and Mn+3. Neurodegeneration. 1995;4:329-334.

66. Brouillet E, Shinobu L, Mçgarvey U, et al. Manganese injection into the rat striatum produces excitotoxic lesions by impairing energy metabolism. Exp Neurol. 1993;120:89-94.

67. Archibald FS, Tyree C. Manganese poisoning and the attack of trivalent manganese upon catecholamines. Arch Biochem Biophys. 1987;256:638-650.

68. Gavin CE, Gunter KK, Gunter TE. Manganese and calcium efflux kinetics in brain mitochondria. Relevance to manganese toxicity. Biochem J. 1990;266:329-334.

69. Brown S, Taylor NL. Could mitochondrial dysfunction play a role in manganese toxicity? Environ Toxicol Pharmacol. 1999;7:49-57.

70. Galvani P, Fumagalli P, Santagostino A. Vulnerability of mitochondrial complex I in PC12 cells exposed to manganese. Eur J Pharmacol. 1995;293:377-383.

71. Turrens JF. Superoxide production by the mitochondrial respiratory chain. Biosci Rep. 1997;17:3-8.

72. Kwik-Uribe CL, Reaney S, Zhu Z, et al. Alterations in cellular IRP-dependent iron regulation by in vitro manganese exposure in undifferentiated PC12 cells. Brain Res. 2003;973:1-15.

73. Zheng W, Zhao Q. Iron overload following manganese exposure in cultured neuronal, but not neuroglial cells. Brain Res. 2001;897:175-179.

74. Eslami H, Sharifi AM. Effect of carnosine on the prevention of high-dose morphine-induced apoptosis of PC12 cells. J Med Bioeng. 2014;3(3):175-178.

75. Samarghandian S, Afshari R, Farkhondeh T. Effect of long-term manganese injection and ascorbic acid administration on the hematological and biochemical parameters in rats exposed to aluminium. J Trace Elem Med Biol. 2004;18:113-121.

76. Esparza J, Gomez M, Roveu M, et al. Aluminum-induced pro-oxidant effects in rats: protective role of exogenous melatonin. J Pineal Res. 2003;35:32-39.

77. Abubakar M, Taylor A, Ferns G. Aluminium administration is associated with enhanced hepatic oxidant stress that may be offset by dietary vitamin E in the rat. Int J Exp Pathol. 2003;84:49-54.

78. Girardi G, Elias MM. Effectiveness of N-acetylcysteine in protecting against merciric chloride-induced nephrotoxicity. Toxicology. 1991;67:155-164.

79. Jeffery EH, Abreo K, Burgess E, et al. Systemic aluminum toxicity: effects on bone, hematopoietic tissue, and kidney. J Toxicol Environ Health A. 1996;48:649-666.

80. El-Maraghy SA, Gad MZ, Fahim AT, et al. Effect of cadmium and aluminium intake on the antioxidant status and lipid peroxidation in rat tissues. J Biochem Mol Toxicol. 2001;15:207-214.

81. Mahieu ST, Gionotti M, Millen N, et al. Effect of chronic accumulation of aluminum on renal function, cortical renal oxidative stress and cortical renal organic anion transport in rats. Arch Toxicol. 2003;77:605-612.

82. Recknagel RO, Glende EA Jr, Dolak JA, et al. Mechanisms of carbon tetrachloride toxicity. Pharmacol Ther. 1989;43:159-154.

83. Knight J, Cheung A, Pieper R, et al. Increased urinary lipoperoxide levels in renal transplant patients. Ann Clin Lab Sci. 1989;19:238-241.

84. Runghy J, Ernst E. Experimentally induced lipid peroxidation after exposure to chromium, mercury or silver: interactions with carbon tetrachloride. Pharmacol Toxicol. 1992;70:205-207.

85. Miller NJ, Rice-Evans CA. The relative contributions of ascorbic acid and phenolic antioxidants to the total antioxidant activity of orange and apple fruit juices and blackcurrant drink. Food Chem. 1997;60:331-337.
82. Alharbi B, Fadda L, Ali HM. Evaluation of the renoprotective effect of nanotoric acid against toxic dose of copper sulfate: role of vascular cell adhesion molecule-1, kidney injury molecule-1, and signal transducer and activator of transcription 3 protein expressions. *J Biochem Mol Toxicol*. 2019;33:e22243.

83. Zhao H, Wang Y, Fei D, et al. Destruction of redox and mitochondrial dynamics co-contributes to programmed cell death in chicken kidney under arsenite or/copper (II) exposure. *Ecotoxicol Environ Saf*. 2019;179:167-174.

84. Ashkenazi A. Targeting death and decoy receptors of the tumour-necrosis factor superfamily. *Nat Rev Cancer*. 2002;2:420-430.

85. Josephine A, Amudha G, Veena CK, et al. Oxidative and nitrosative stress mediated renal cellular damage induced by cyclosporine A: role of sulphated polysaccharides. *Bioll Pharm Bull*. 2007;30:1254-1259.

86. Malik Z. Proteasomal degradation regulates expression of porphobilinogen deaminase (PBGD) mutants of acute intermittent p. *Biochim Biophys Acta*. 2006;1762:819-827.

87. Böhme M, Jedlitschky G, Leier I, et al. ATP-dependent export pumps and their inhibition by cyclosporins. *Adv Enzyme Regul*. 1994;34:371-380.

88. Zhong Z, Li X, Yamashina S, et al. Cyclosporin a causes a hypermetabolic state and hypoxia in the liver: prevention by dietary glycine. *J Pharmacol Exp Ther*. 2001;299:858-865.

89. Magaye RR, Yue X, Zou B, et al. Acute toxicity of nickel nanoparticles in rats after intravenous injection. *Int J Nanomedicine*. 2014;9:1393-1402.

90. Ahmad M, Akhtar MJ, Alhadlaq HA, et al. Comparative cytotoxic response of nickel ferrite nanoparticles in human liver HepG2 and breast MFC-7 cancer cells. *Chemosphere*. 2015;135:278-288.

91. Zhong Z, Li X, Yamashina S, et al. Cyclosporin a causes a hypermetabolic state and hypoxia in the liver: prevention by dietary glycine. *J Pharmacol Exp Ther*. 2001;299:858-865.

92. Kadmon M, Klínenmann C, Böhme M, et al. Inhibition by cyclosporin a of adenosine triphosphate-dependent transport from the hepatocyte into bile. *Gastroenterology*. 1993;104:1507-1514.

93. Böhme M, Jedlitschky G, Leier I, et al. ATP-dependent export pumps and their inhibition by cyclosporins. *Adv Enzyme Regul*. 1994;34:371-380.

94. Kwas M, Esrefoglu M, Sogutlu G, et al. Melatonin prevents cyclosporine-induced hepatotoxicity in rats. *Med Princ Pract*. 2009;18:407-410.

95. Akbulut S, Elbe H, Eris C, et al. Effects of antioxidant agents against cyclosporine-induced hepatitis. *J Surg Res*. 2015;193:658-666.

96. Josephine A, Amudha G, Veena CK, et al. Oxidative and nitrosative stress mediated renal cellular damage induced by cyclosporine A: role of sulphated polysaccharides. *Bioll Pharm Bull*. 2007;30:1254-1259.

97. Böhme M, Jedlitschky G, Leier I, et al. ATP-dependent export pumps and their inhibition by cyclosporins. *Adv Enzyme Regul*. 1994;34:371-380.

98. Chong WC, Shastri MD, Eri R. Endoplasmic reticulum stress and oxidative stress: a vicious nexus implicated in bowel disease pathophysiology. *Int J Mol Sci*. 2017;18:771.

99. Pallet N, Rabant M, Xu- Dubois Y-C, et al. Response of human renal tubular cells to cyclosporine and sirolimus: a toxicogenomic study. *Toxicol Appl Pharmacol*. 2008;229:184-196.

100. Torun A, Caban K, Amarowicz M, et al. Oxidative stress and liver morphology in experimental cyclosporine A-induced hepatotoxicity. *Biomed Res Int*. 2016;2016:1-9.

101. Hickey E, Raje R, Reid V, et al. Diclofenac induced in vivo nephrotoxicity may involve oxidative stress mediated renal cellular damage induced by cyclosporine A: role of sulphated polysaccharides. *Bioll Pharm Bull*. 2007;30:1254-1259.

102. Ungprasert P, Cheungpasitporn W, Crowson CS, et al. Individual non-steroidal anti-inflammatory drugs and risk of acute kidney injury: a systematic review and meta-analysis of observational studies. *Eur J Intern Med*. 2015;26:285-291.
122. Lonappan L, Brar SK, Das RK, et al. Diclofenac and its transformation products: environmental occurrence and toxicity-a review. *Environ Int.* 2016;96:127-138.

123. Klaunig JE, Kamendulis LM, Hocevar BA. Oxidative stress and oxidative damage in carcinogenesis. *Toxicol Pathol.* 2010;38:96-109.

124. Hamilton JP, Potter JJ, Koganti L, et al. Effects of vitamin D3 stimulation of thioredoxin-interacting protein in hepatocellular carcinoma. *Hepatol Res.* 2014;44:1357-1366.

125. Tait SW, Green DR. Mitochondrial regulation of cell death. *Cold Spring Harb Perspect Biol.* 2013;5:a008706.

126. Jaiswal SK, Gupta VK, Siddiqi NJ, et al. Hepatoprotective effect of *Citrus Limon* fruit extract against carbofuran induced toxicity in Wistar rats. *Chin J Biol.* 2015;2015:686071.

127. Fetoui H, Garoui EM, Zeghal N. Lambda- cyhalothrin- induced biochemical and histopathological changes in the liver of rats: ameliorative effect of ascorbic acid. *Exp Toxicol Pathol.* 2009;61:189-196.

128. Spassova MA, Miller DJ, Nikolov AS. Kinetic modeling reveals the roles of reactive oxygen species scavenging and DNA repair processes in shaping the dose-response curve of KBrO3-induced DNA damage. *Oxid Med Cell Longev.* 2015;2015:1-12.

129. Kurokawa Y, Takamura N, Matsuoka C, et al. Comparative studies on lipid peroxidation in the kidney of rats, mice, and hamsters and on the effect of cysteine, glutathione, and diethyl maleate treatment on mortality and nephrotoxicity after administration of potassium bromate. *J Am Coll Toxicol.* 1987;6:489-501.

130. Nishioka H, Fujii H, Sun B, et al. Comparative efficacy of oligonol, catechin and (-)-epigallocatechin 3-O-gallate in modulating the potassium bromate-induced renal toxicity in rats. *Toxicology.* 2006;226:181-187.

131. Abd-Allah AR, Al-Majed AA, Mostafa AM, et al. Protective effect of arabic gum against cardiotoxicity induced by doxorubicin in mice: a possible mechanism of protection. *J Biochem Mol Toxicol.* 2002;16:254-259.

132. Rehab O, Abuelgasim AI, Elmahdi B. Effect of potassium bromate on liver and blood constituents of wistar albino rats. *Am J Food Technol.* 2008;3:310-314.

133. Khan N, Sharma S, Sultana S. *Nigella sativa* (black cumin) ameliorates potassium bromate-induced early events of carcinogenesis: diminution of oxidative stress. *Hum Exp Toxicol.* 2003;22:193-203.

134. Noorani AA, Gupta K, Bhadada K, et al. Protective effect of methanolic leaf extract of *Caesalpinia bonduc* (L.) on gentamicin-induced hepatotoxicity and nephrotoxicity in rats. *Iran J Pharmacol Ther.* 2011;10:21-20.

135. Wang Y, Iwatani H, Ito T, et al. Fetal cells in mother rats contribute to the remodeling of liver and kidney after injury. *Biochem Biophys Res Commun.* 2004;325:961-967.

136. Yang C-L, Du X-H, Han Y-X. Renal cortical mitochondria are the source of oxygen free radicals enhanced by gentamicin. *Ren Fail.* 1995;17:21-26.

137. Sorrenti V, Di Giacomo C, Acquaviva R, et al. Toxicity of ochratoxin a and its modulation by antioxidants: a review. *Toxins.* 2013;5:1742-1766.

138. Rahimtula A, Bérézat J-C, Bussacchini-Griot V, et al. Lipid peroxidation as a possible cause of ochratoxin a toxicity. *Biochem Pharmacol.* 1988;37:4469-4477.

139. Omar RF, Hasinoff BB, Meijilla F, et al. Mechanism of ochratoxin a stimulated lipid peroxidation. *Biochem Pharmacol.* 1990;40:1183-1191.

140. Kovacic P. *How safe is bisphenol A? Fundamentals of toxicity: metabolism, electron transfer and oxidative stress.* Elsevier; 2010.

141. Lee J-H, Li Y-C, Ip S-W, et al. The role of Ca2+ in baicaline-induced apoptosis in human breast MDA-MB-231 cancer cells through mitochondria-and caspase-3-dependent pathway. *Anticancer Res.* 2008;28:1701-1711.

142. Kourouma A, Quan C, Duan P, et al. Bisphenol a induces apoptosis in liver cells through induction of ROS. *Adv Toxicol.* 2015;2015:901983.

143. Zhu H, Long M-H, Wu J, et al. Ginseng alleviates cyclophosphamide-induced hepatotoxicity via reversing disordered homeostasis of glutathione and bile acid. *Sci Rep.* 2015;5:1-14.

144. Lu SC. Regulation of glutathione synthesis. *Mol Aspects Med.* 2009;30:42-59.

**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Abbasnezhad A, Salami F, Mohebbati R. A review: Systematic research approach on toxicity model of liver and kidney in laboratory animals. *Anim Models Exp Med.* 2022;5:436-444. doi: 10.1002/ame2.12230