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REVIEW

A review: Systematic research approach on toxicity model of liver and kidney in laboratory animals

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Abstract

Therapeutic experiments are commonly performed on laboratory animals to investigate the possible mechanism(s) of action of toxic agents as well as drugs or substances under consideration. The use of toxins in laboratory animal models, including rats, is intended to cause toxicity. This study aimed to investigate different models of hepatotoxicity and nephrotoxicity in laboratory animals to help researchers advance their research goals. The current narrative review used databases such as 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.

KEYWORDS
animal, drug toxicity, drug-induced abnormality, liver dysfunction, renal injury

1 | 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.

2 | MATERIALS AND METHODS

This review used comprehensive data from main databases, including Scopus, Medline, Web of Science, and Embase. The searched

Fatemeh salami should be considered as co-first author.

terms were "kidney," "liver," "hepato," "renal," "toxicity," "mechanism," "rat," and other related keywords until June 2021. Inclusion criteria were articles published in English. The searched keywords were selected based on the MeSH alone and combined.

3 | RESULTS

3.1 | Cisplatin

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, periportal 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 H_2O_2 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 nephrotoxic 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 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]

3.2 | 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 $O_2\cdot^-$ 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 metabolization. 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 *p*-aminophenol, which by converting to a free radical binds to cellular proteins.[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 enzyme decreases CAT and SOD activities.[32] In rat liver, doxorubicin decreases CYP-450 and GSH levels in free radical formation, which results from a nonenzymatic mechanism. For instance, Fe^{3+} reacts with doxorubicin, and the iron atom obtains one electron and leads to Fe^{2+} doxorubicin free radical complex production. This complex can reduce oxygen to active oxygen species such as hydrogen peroxide.[33] As a result of oxidative metabolism, doxorubicin produces superoxide, H2O2, and hydroxyl in rats.[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.[35]

3.3.2 | Nephrotoxicity

Doxorubicin exerts harmful effects on renal tissue by increasing glomerular capillary penetrance and induces tubular degeneration.[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.[37,38]

Doxorubicin-induced nephrotoxicity is typically caused by optional damage of the proximal tubule cells.[39] Renal tubular deficiency through chemotherapy results in acute renal failure.[40] Doxorubicin induces renal injury by elevated generation of ROS, apoptosis, and a decrease in antioxidant enzymes.[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.[43] Aluminum induces mitochondrial permeability pores, which results in electron leakage and elevated radical oxygen species formation in the cytosol.[44] Because of facilitated specific transport system uptake, the liver is the target of aluminum toxicity.[45] In in vitro models, elevated cytosolic enzyme secretion by cultured hepatocytes subacutely exposed to aluminum has been reported.[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.[47–49]

3.4.2 | Nephrotoxicity

Aluminum has not been considered as an agent that reacts with GSH,[50] but the increase in LPO could result in an increase in oxidation reaction rates. According to studies, intraperitoneal usage of aluminum induces a temporal decrease in GSH in the liver, increases hem oxygenase activity, and then increases LPO level.[51] It has been shown that aluminum deposition in the liver was due to decreased GSH and GPx levels.[52] In renal proximal cells, aluminum could affect cellular metabolism by oxidative stress enhancement and therefore result in alterations.[53]

3.5 | CCl_4

Reactive oxygen metabolites are one of the assumed mechanisms in the nephrotoxicity of CCl_4.[54] In cultured hepatocyte cells, CCl_4 leads to increased trichloromethyl peroxyl radical production and hydrogen peroxide.[55] CCl_4 increases LPO and decreases renal reduced/oxidized GSH ratio and microsomal NADPH CYP-450 in the kidney cortex, microsomes, and mitochondria.[56] Antioxidants like SOD/CAT, melatonin, silibinin, ascorbate, propionyl, and carnitine improve renal toxicity resulting from CCl_4.[57]

3.6 | Acrylamide

Acrylamide can produce ROS. It is oxidized to glycinamide. 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.[58,59] Acrylamide can create oxidative stress that leads to apoptosis.[60] Exposure to acrylamide results in increased ROS production and GSH oxidation in isolated human monocyte.[61] After intestinal absorption, acrylamide often is conjugated with GSH and results in GSH store evacuation.[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.[63] The low levels of GSH lead to cellular oxidative stress and apoptosis, which is a potential mechanism for acrylamide toxicity.[64]

3.7 | Manganese

Manganese exerts cellular toxicity via mechanisms, including direct or indirect ROS formation,[65,66] biological molecule oxidation,[67] and cellular calcium disruption.[68] Elevated manganese results in complex blockage of the mitochondrial electron transport chain.[69,70] Manganese-mediated direct oxidation of catecholamines like dopamine[67] and, therefore, oxidative stress increase may occur.[71] According to some studies, in vitro manganese exposure disturbs the regulation of cellular iron by altering the iron regulatory protein (IRP) binding activity and IRP-regulated iron homeostatic proteins.[72,73] A toxic outcome of these latter effects may be the intracellular labile iron pool increment.[72]

3.8 | Opioids

Morphine causes oxidative stress by inducing ROS production and initiating oxidative damage.[74] According to clinical studies, morphine addicts are at increased risk for chronic renal failure.[75,76] Morphine induces tubular dilatation, glomerular expansion, peritubular and intraglomerular congestion, high kidney mass, and juxtaglomerular cells in mice (after 6 weeks of treatment).[77] The liver biomarkers (AST, ALT, and $_{\gamma}$GT) increased in tramadol-treated rats,[78] which might be due to high LPO.[79] Tramadol also induces some histopathological changes, including hepatocyte degeneration, hemorrhage, hepatic congestion, and necrosis.[80] 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.[78]

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.[81–83] 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.[84,85] Oxidative stress is a possible mechanism in hepatotoxicity induced by copper oxide.[86] In the kidney, copper induces proteinuria, aminoaciduria, diminished glomerular filtration, and renal phosphaturia.[87] In chicken kidney tissues, $CuSO_4$ induces mitochondrial dysfunction and cell apoptosis.[83] 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.[88,89] Psma3 inhibition is a new anti-inflammatory strategy in lead acetate nephrotoxicity.[90] Nano nickel oxide induces cytotoxicity through ROS formation and apoptosis in the HepG2 cell line.[91] Another study has also indicated this issue.[92] According to Magaye et al,[93] nickel nanoparticles cause liver inflammation in rats. Nickel ferrite nanoparticles also induce cytotoxicity as well as oxidative stress in the hepatocellular carcinoma cells.[94]

3.10 | Anticancer drugs

Cyclosporin A (CsA)–induced hepatotoxicity occurs mainly through some mechanisms, including hypermetabolic state in the liver[95] and inhibition of ATP-dependent transport of bilirubin and bile salts through the hepatocyte canalicular membranes.[96,97] Oxidative stress as one of the mechanisms of hepatotoxicity in experimental animals treated by CsA is presumable.[98,99] CsA increases the activities of oxidants such as xanthine oxidase.[100] Mitochondrial damage plays a critical role in CsA hepatotoxicity.[101] Also, ER stress related to oxidative stress plays a role in CsA nephropathy.[102] Renal-transplant patients treated with CsA showed upregulation of an ER stress marker in kidney biopsies.[103] CsA-induced apoptosis in renal tubular cells relates to oxidative damage.[104] Methotrexate toxicity effects occur through increasing ROS production. Imbalance between ROS production and antioxidants leads to oxidative stress and then pathological symptoms.[105]

3.11 | Cadmium

Cadmium induces nephrotoxicity via ROS production, apoptosis, and inflammation in the renal tissue.[106,107] 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.[108] Higher doses of cadmium in animals resulted in membrane LPO and GSH reduction in the kidney and liver.[109] Liver injury induced by cadmium is confirmed by increased levels of marker enzymes (AST and ALT).[110]

3.12 | Valproic acid

Valproic acid (VPA) hepatotoxicity is due to dysfunction of hepatocyte mitochondria.[111] Also, oxidative stress plays a role in VPA hepatotoxicity.[112] Formation of ROS, LPO, and cellular antioxidant enzymes are various induction mechanisms of VPA hepatotoxicity.[112,113] Inhibition of mitochondrial β-oxidation of fatty acids induced by VPA, defect in gluconeogenesis, and oxidative phosphorylation inhibition have been suggested in liver preparation.[112,114]

Elevated levels of Cr, BUN, and renal tissue histopathological alterations are reported in VPA-treated animals.[115] VPA inactivates antioxidant enzymes[116]; according to several studies, oxidative stress occurred in the kidney after VPA administration.[117,118] VPA decreased tissue antioxidant activity, increased LPO, and depleted GSH stores.[119]

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 H_2O_2. H_2O_2 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 | $KBrO_3$

$KBrO_3$ 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 $KBrO_3$.[130,131] Regarding $KBrO_3$ 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 (80 mg/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 Fe^{3+} as a cofactor, OTA triggers LPO. OTA-Fe^{3+} complex facilitates Fe^{3+} reduction, and the resultant OTA-Fe^{2+} 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 Ca^{2+} 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.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

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

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