World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

Screening models of nephrotoxicity and their molecular mechanism

Harveen Kour, Akashdeep Singh, Preeti Jaiswal, Anusha and Ramica Sharma *

Department of Pharmacology, University school of pharmaceutical sciences, Rayat-Bahra University, -SAS Nagar, Mohali, India.

World Journal of Biology Pharmacy and Health Sciences, 2023, 13(03), 234–251

Publication history: Received on 17 February 2023; revised on 26 March 2023; accepted on 29 March 2023

Article DOI: https://doi.org/10.30574/wjbphs.2023.13.3.0142

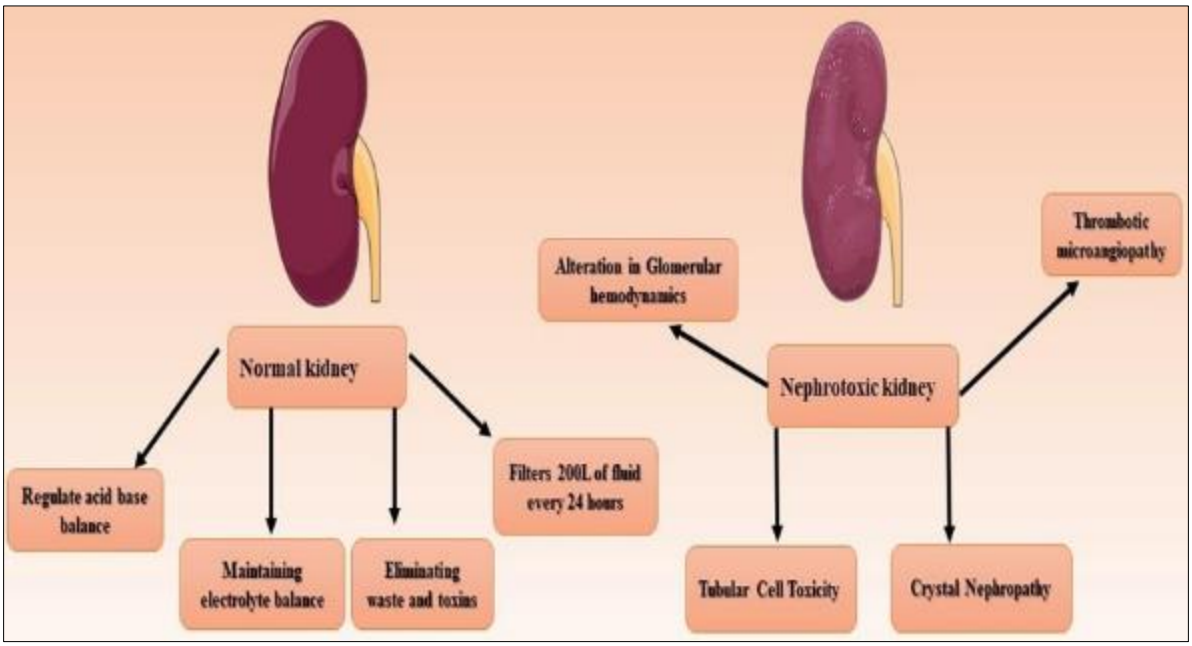
Abstract

Kidney is among the most vital organs in the anatomy of human body which filters 200 litres of fluid every 24 hours and has many more function which include regulating acid-base balance, maintaining electrolytes balance, eliminating waste and toxins products from the human body. Nephrotoxicity refers as the deterioration in the kidney function due to toxic effect of drugs and chemical and is characterized by alterations in glomerular hemodyanmics, renal tubular failure and thrombotic microangiopathy. Drug-induced nephrotoxicity is becoming more well identified as a principal reasons of kidney illness, such as acute kidney injury (AKI) and chronic kidney disease (CKD) (CKD). Nephrotoxicity covers a broad range, displaying damage to various nephron segments as a result of distinct pharmacological actions. There are various agents which exerts nephrotoxic effects through pathogenic mechanisms like non-steroidal agents (Indomerhacin, Paracetamol, Mefenamic acid), anticancer agents (Carmustine, Cisplatin, Methotrexate), antibiotics (Gentamicin, Tobramycin, Amikacin), antiviral (Acyclovir, Tenofovir, Cidofovir), antifungal (Amphotericin B, Vancomycin, Nystatin)and immunosuppresant drugs(Cyclosporine, Tacrolimus). Alteration in glomerular hemodynamics, tubular cell toxicity, inflammation, crystal nephropathy, rhabdomyolysis, and thrombotic microangiopathy are all possibilities for drug-induced nephrotoxicity. In this review, we have explained different experimental models for nephrotoxicity that might assist in developing novel drugs to cure nephrotoxicity.

Keywords: Nephrotoxicity; Renal tubular failure; Inflammation; CKD

* Corresponding author: Ramica Sharma

Graphical Abstract



Nephrotoxic effect of various drugs on kidney

1. Introduction

The kidney is a significant organ in the body that regulates the balance between acidity and alkalinity, electrolyte balance, blood filtration, as well as waste product excretion. Acute kidney damage is frequently caused by drugs and chronic kidney injury. When kidney function is destroyed by exogenous and endogenous toxicants, nephrotoxicity occurs. Nephrotoxicity occurs when kidney-specific detoxification and excretion do not work effectively. It is noted that hemodynamic changes in the glomerulus followed by irritation, nephritis caused by crystals, and thrombotic thrombocytic purpura results from nephrotoxicity [1]. Medication-induced nephrotoxicity has a variety of mechanisms that vary by pharmacological and drug class, however, they are generally classified based on the histological component of the kidney that is harmed. [2]. Renal impairment caused by nephrotoxic medicines is known as drug-induced nephrotoxicity. In several clinical circumstances, such as underlying renal dysfunction, cardiovascular disease, diabetes, and sepsis, it is a common concern. It was observed that chemicals like Amphotericin B, Carbon tetrachloride, Paracetamol, Acyclovir, Tacrolimus, Mefenamic acid, Aspirin, Gentamicin, Colistin, Tenofovir, Cyclosporin, Deltamethrin, and metals like Lithium, Chromium, Cisplatin, Mercury cause mild to moderate nephrotoxicity. To avoid drug-induced nephrotoxicity and progression to end-stage renal disease, early detection of deteriorating drug effects, as well as the patient's clinical history, basic renal function, drug-related risk factors, and nephrotoxic drug combinations, is critical. [3]. Analgesics like Paracetamol, Aspirin, mefenamic acid induce nephrotoxicity by causing Chronic Interstitial Nephritis, altered Intraglomerular Hemodynamics. Antimicrobials like Amphotericin B, Acyclovir, Gentamicin, Colistin promote Crystal Nephropathy, Acute Interstitial Nephritis, Tubular cell toxicity which ultimately results in Nephrotoxicity. Tacrolimus and Deltamethrin are immunosuppressive which induces nephrotoxicity by provoking interstitial nephritis, glomerulonephritis. Calcineurin Inhibitors like Tacrolimus and Cyclosporin induce nephrotoxicity by causing Thrombotic microangiopathy, altered intraglomerular hemodynamics, chronic interstitial nephritis [4].In order to find a viable pharmaceutical target for nephrotoxicity, many experimental models are used to produce nephrotoxicity. However, there is currently insufficient literature for a nephrotoxicity animal model.This review focuses on the chemicals and metals-induced nephrotoxicity-based animal model which will be further helpful in understanding the basic pathophysiology behind the drug-induced kidney damage or renal failure [5]

2. Experimental models for nephrotoxicity

In practically all biomedical research, animal models are a key tool for studying mechanisms. They involve the entire animal's complexity, making in vivo system monitoring extremely difficult. As the compounds are exposed in a sequential manner through absorption from the initial exposed location, metabolism, distribution, and elimination, an in vivo system accurately replicates the exposure profile and cellular function. However, the mechanism should be

essentially the same as in human reactions, and the unfavorable effect must be clinically significant. Small animals such as rats, mice, rabbits, and guinea pigs, as well as large animals such as pigs, cattle, sheep, and primates, can be used to research nephrotoxic effects, distribution, and clearance. They may be utilized to deduce the basic mechanism of xenobiotic actions, which will help researchers better understand how they affect human health. The experimental model, on the other hand, provides a road map for the identification of new molecular, noble signalling pathways for the benefit of humanity.[5]

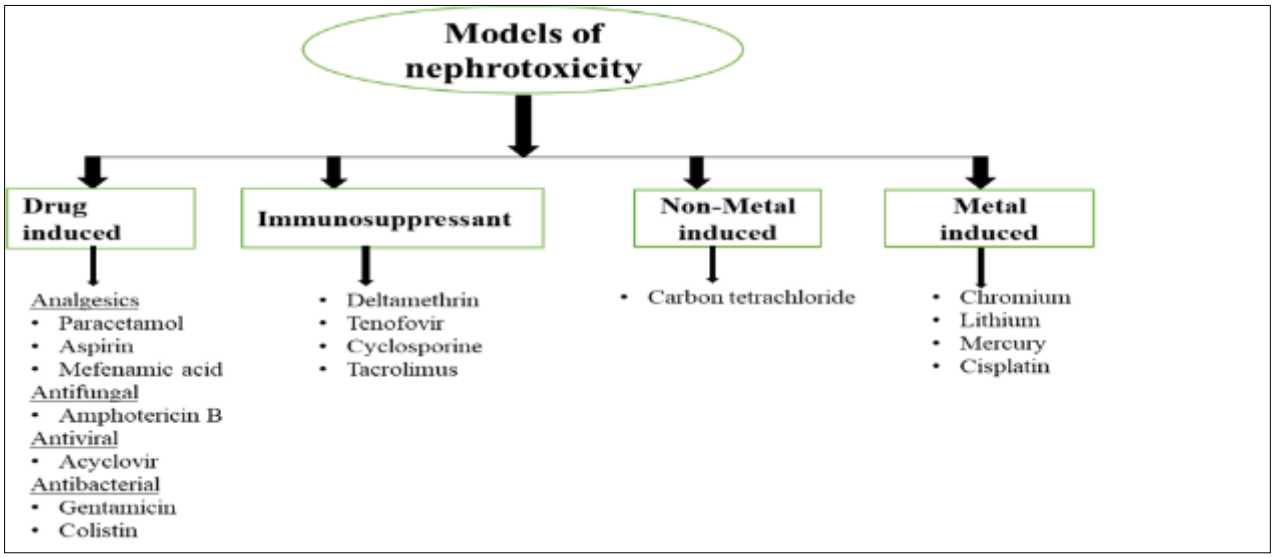


Figure 1 Various Models of Nephrotoxicity

3. Paracetamol induced nephrotoxicity

Paracetamol (PCM), the most extensively utilized as antipyretic and analgesic drug in the world and it is safe when used within the clinically recommended dose.[6]

3.1. Pathophysiology of PCM induced nephrotoxicity

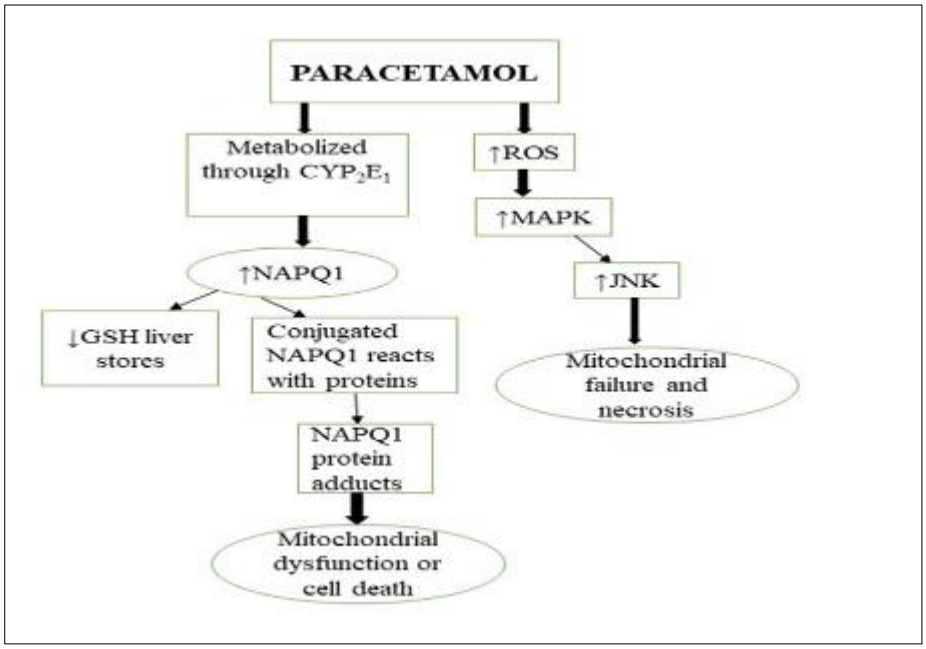


Figure 2 Paracetamol inducing nephrotoxicity by metabolizing through Cytochrome P450 family 2 subfamily E member1 (CYP_2E_1) which enhance the level of N-acetyl- p-benzoquinoneimine (NAPQ1), depletion in the level of glutathione (GSH). Conjugated NAPQ1 reacts with proteins to form protein adducts. Production of reactive oxygen

species (ROS) increases by enhancing Mitogen activated protein kinase(MAPK) and Jun N-terminal kinase(JNK). These all factors are responsible for mitochondrial damage and cell death.[7]

Table 1 Various Dosage of PCM induced Nephrotoxicity

Toxic dose of PCM	Route of Administration	Animal species	Reference
Single dose of 300 mg/kg	Orally	Albino Mice	8
500 mg/kg for six weeks	Orally	Albino Rat	9
Single dose of 640 mg/kg	Orally	Wistar Rat	10
Single dose of 2 g/kg	Orally	Albino Rat	11
750 mg/kg for seven days	Orally	Sprague-Dawley Rats	12

4. Aspirin induced nephrotoxicity

Aspirin is a class of medications used for analgesic and anti-inflammatory and is responsible for kidney damage in higher doses.[13]A major mechanism in the pathophysiology of Aspirin nephrotoxicity is oxidative damage. It has been reported that aspirin causes nephrotoxicity by lowering antioxidant production.[14]

Table 2 Various Dosage of Aspirin induced Nephrotoxicity

Toxic dose of Aspirin	Route of Administration	Species	References
50 mg/kg for four weeks	orally	Female Wistar Albino rats.	15
Single dose of 100 mg/kg	orally	Wistar rats of either sex.	16
Single dose of 600 mg/kg	orally	Female Wistar Albino rats.	17

5. Mefenamic acid introduced nephrotoxicity

Mefenamic acid non-steroidal anti-inflammatory medication (NSAID) act against inflammation, pain and pyrexia. Along with its potential medicinal applications, mefenamic acid is applied in clinical practice.[18]Mefenamic acid is utilized for inflammatory pain that includes post traumas and dental pain. Regardless of the wide usage, they cause are asserted with severe toxicity such as severe gastrointestinal tract disorders, hepatotoxicity and nephrotoxicity. Prostaglandin I2 and PGE2, which are released by both glomerular and medullary interstitial cells, are reported to be responsible in the mechanism. Vascular resistance will be alleviated, renal vascular beds will dilate, and organ perfusion will be restored. Blood flow will be redirected in juxtamedullary area starting from the renal cortex. NSAIDs impede prostaglandin production, causing acute ischemic renal insufficiency by reducing blood flow to the nephrons.[19]

Table 3 Various Dosage of Mefenamic acid induced Nephrotoxicity

Toxic dose of Mefenamic acid	Route of Administration	Reference	Animal Species
100 mg/kg for five days per week for four months	Orally	20	Sprague-Dawley Rats
100 mg/kg for fourteen weeks	I.P	21	Balb/c mice
200 mg/kg for fourteen weeks	I.P	21	Balb/c mice

6. Amphotericin b induced nephrotoxicity

Amphotericin B (AMB) is the gold standard for treatment if mycosis.[22]Despite its broad range of activity and widespread clinical use, drug-induced nephrotoxicity is prevalent. During treatment using amphotericin B, up to 80% of patients will see an episode of renal impairment.[23]Tubular damage followed by acute renal failure is a well-known problem associated with AMB.[24]Following AMB administration, there was an uptick in the lipid peroxidation products MDA,NO, and SOD activity, as well as a lower in the antioxidant enzyme catalase. It has been documented that increased

generation of reactive oxygen species play a vital role in pathogenesis of AMB induced nephrotoxicity. Additionally, AmB induces tubular dysfunction by forming pores in membranes.[25]

Table 4 Various Dosage of AMB induced Nephrotoxicity

Toxic dose of AMB	Route of Administration	Animal Species	Reference
Single dose 2 mg/kg for one week	I.V	Jcl:ICR mice	26
Single dose 4 mg/kg for one week	I.V	Jcl:ICR mice	26
10 mg/kg for four days	I.P	Sprague-Dawley Rats	27
15 mg/kg for five days	I.P	Wistar Rats	28
Single dose 50 mg/kg	I.P	Wistar-Albino rats	29

7. Acyclovir (acv) induced nephrotoxicity

Acyclovir is an important antiviral agent. Although the drug is well tolerated but severe nephrotoxicity has been observed with this drug.[30] Crystalluria has long been thought to be the aetiology of acyclovir-induced nephrotoxicity. Clinical evidence of nephrotoxicity in the absence of crystal formation, on the other hand, suggested that acyclovir could elicit direct injury to renal tubular cells.[31] ACV has been associated with a multitude of nephrotoxicity symptoms, including crystal nephropathy, acute interstitial nephritis, acute tubular necrosis, and obstructive nephropathy, according to studies. Direct assault on renal tubular cells and oxidative stress have been proposed as methods by which ACV induces nephrotoxicity. ACV also had a deleterious effect on kidney redox state, reducing antioxidants (SOD, CAT, GSH, and GPx) and elevating MDA levels. The activation of oxidative stress as a result of ROS production by ACV may have impaired kidney antioxidant concentrations. The released ROS may have depleted kidney antioxidants and promoted the oxidation of renal lipids (polyunsaturated fatty acids), resulting in an increase in MDA levels. It's possible that oxidative damage is a key indicator of ACV-induced renal impairment.[32]

Table 5 Various Dosage of Acyclovir induced Nephrotoxicity

Toxic dose of Acyclovir	Route of Administration	Animal Species	Reference
50 mg/kg for five days	I.P	Munich-Wistar rats.	33
150 mg/kg for seven days	I.P	Wistar Rats	34
150 mg/kg for nine days	I.P	Wistar Rats	35
600 mg/kg for nine days	I.P	ICR Mice	35
100 mg/kg Single dose	I.V	Sprague-Dawley Rats	36
300 mg/kg Single dose	I.V	Sprague-Dawley Rats	36
600 mg/kg Single dose	I.V	Sprague-Dawley Rats	36

8. Gentamicin induced nephrotoxicity

Gentamicin, aminoglycoside antibiotic, has widely been utilized as bactericidal agent that act against severe bacterial infection by gram negative bacterial infections. However long term us , it can also produce nephrotoxicity.[37] Gentamicin has been shown to cause kidney damage in 10-20% of patients after seven days of therapy, in addition to its therapeutically helpful effects. Despite the discovery of new antibiotics, gentamicin is still used because of its effectiveness against lactam-resistant bacteria, low levels of Enterobacteriaceae resistance, and inexpensive cost.[38] Some of the mechanisms of Gentamicin-induced nephrotoxicity include free radical generation, increased lipid peroxidation, and decreased endogenous antioxidant activity resulting in decreased glomerular filtration rate and renal dysfunction. Gentamicin exacerbated tubule damage by necrosing tubular epithelial cells, specifically in the proximal segment, and affecting the function of critical cellular components involved in water and solute transport.[39]

Table 6 Various Dosage of Gentamicin induced Nephrotoxicity

Toxic dose of Gentamicin	Route of Administration	Animal Species	Reference
50 mg/kg for seven weeks	I.V	Sprague-Dawley rats	40
100 mg/kg for seven days	I.V	Sprague-Dawley rats	40
100 mg/kg for seven days	I.P	Sprague-Dawley rats	41,42,43

9. Colistin induced nephrotoxicity

Colistin is an antibiotic generated by a strain of Bacillus polymixa known as colistinus. It is used to treat gram-negative bacterial infections. Colistin enhances the permeability of tubular epithelial cell membranes, leads to swelling and cell lysis, increase level of serum creatinine, caspase-1 and calpin-1 resulting nephrotoxicity.[44]

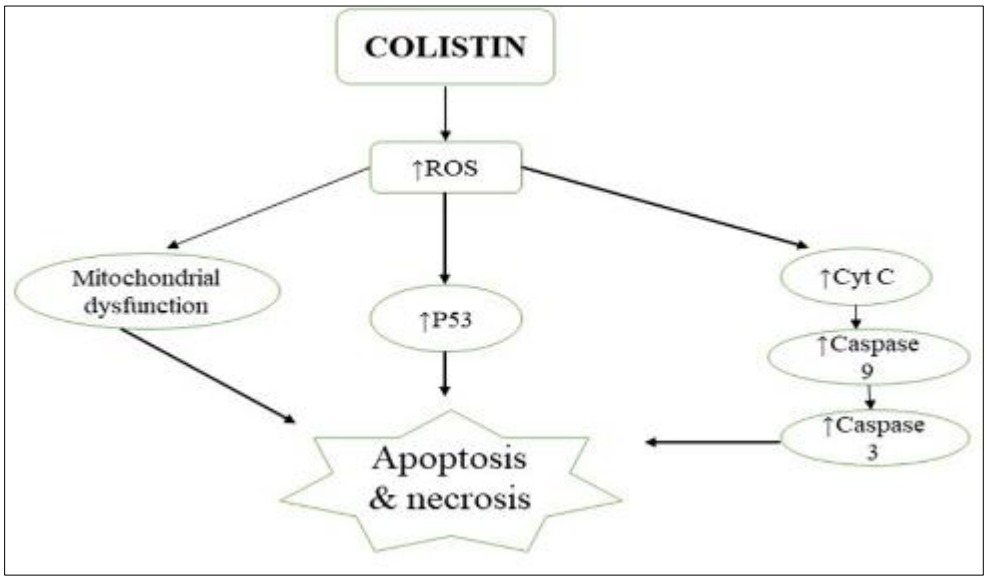


Figure 3 Colistin induces nephrotoxicity by upregulating cytochrome C (Cyt C) which increases the level of caspase 9 and caspase 3 leads to apoptosis and necrosis. Further, overproduction of ROS elevate P53 level results in mitochondrial dysfunctioning

Table 7 Various Dosage of Colistin induced Nephrotoxicity

Toxic dose of colistin	Route of administration	Species	References
20 or 50 mg/kg/day for 7 Days	I.P	Sprague-dawleyrats	45
600000 IU/Kg/day for 7 days	I.P	Male Wistar rats	46
750000 IU/kg/day for 7 days	I.P	Male Sprague-dawleyrats	47

10. Deltamethrin induced nephrotoxicity

DLM (deltamethrin) is a broad-spectrum pyrethroid insecticide. DLM accumulation can harm the kidneys by a variety of ways, including oxidative stress, apoptosis, and inflammation.[48].

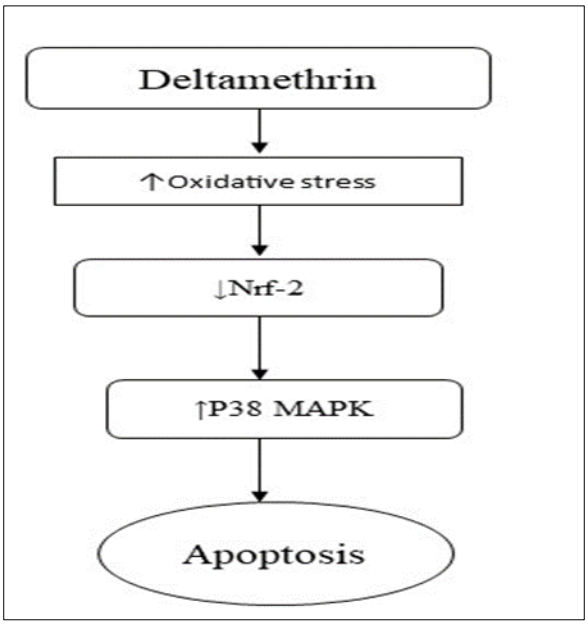


Figure 4 Exposure to DLM increases oxidative stress by suppressing the production of the Nrf-2 gene and by enhancing p38 MAPK which activates inflammatory and apoptotic pathways leads to nephrotoxicity.[49]

Table 8 Various Dosage of Delametharin induced Nephrotoxicity

Toxic dose of deltamethrin	Route of administration	Species	References
1.28 mg/kg for 30 days	oral	Male Sprague Dawley rats	49
6 mg/kg for 3 weeks	oral	Male Wistar albino rats	50
15 mg/kg for 30 days	oral	Male Swiss Albino mice	51

11. Tenofovir induced nephrotoxicity

The nucleoside reverse transcriptase inhibitor tenofovir is used to treat hepatitis B virus (HBV) and human immunodeficiency virus (HIV) infections. Approximately 15% of individuals when treated with tenofovir for a period of 2–9 years experienced tenofovir-induced nephrotoxicity. Fanconi syndrome, gradual deterioration in renal function, and nephrogenic diabetic insipidus (NDI) due to distal tubular dysfunction have been documented as the most common renal consequences of TDF.[52]

It causes proximal tubulopathy, which is thought to be caused in part by the obstruction of mitochondrial DNA polymerase, which reduces mitochondrial DNA (mtDNA) replication. Furthermore, mitochondrial damage may result in apoptosis.[53]

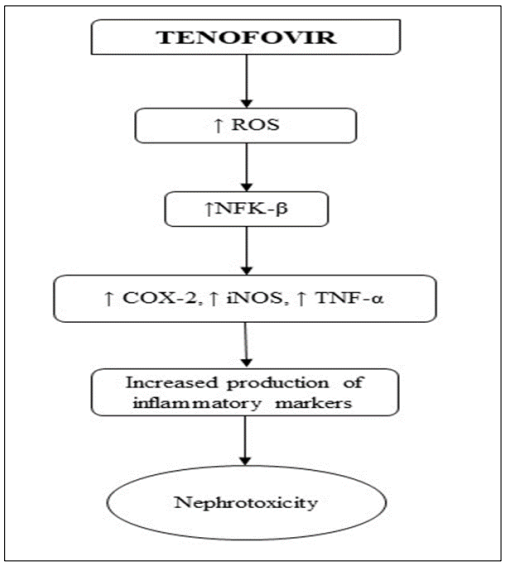


Figure 5 Oxidative stress including ROS are responsible for the activation of Nuclear Factor kappa B (NFkB) resulting in cellular damage. The targeted genes of NF-KB like cycloxygenase-2(COX-2), Tumor necrosis factor – α(TNF-α) and Inducible nitric oxide synthase (iNOS) promotes apoptosis, endothelial damage and renal failure

Table 9 Various Dosage of Mercury induced Nephrotoxicity

Toxic Dose of mercury	Route of administration	Species	References
100 mg/kg for eight weeks	orally	Wistar rats of either sex	54
Single dose of 150 mg/kg	orally	Adult male Wistar Rats	55
600 mg/kg for five weeks	orally	Adult male Wistar Rats	56

12. Cyclosporine induced nephrotoxicity

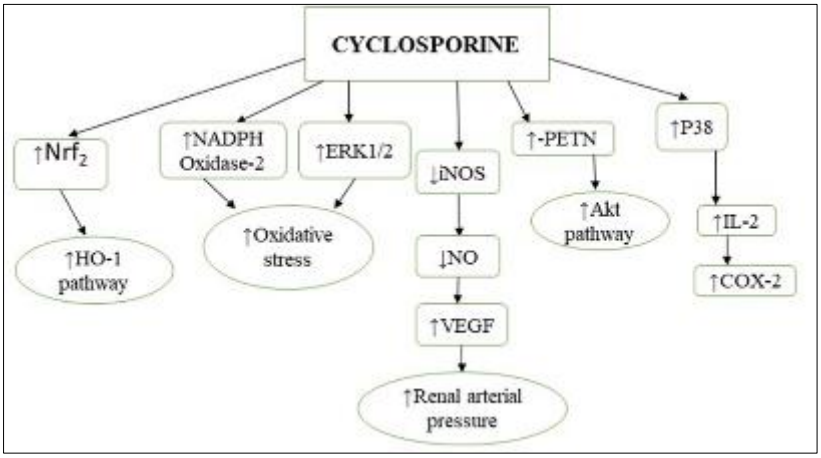


Figure 6 In CSA induced nephrotoxicity, extracellular signal regulated protein kinase ½ (ERK ½) and Nicotinamide adenine dinucleotide phosphate (NADPH) activates ROS causes renal failure. Reduced level of iNOS inhibits the production Nitric oxide (NO) and overexpression of Vascular endothelial growth factor (VEGF) leads to increased renal arterial pressure. CSA causes nephrotoxicity via PTEN/ Akt pathway (Phosphatase and tensin homolog deleted on chromosome 10). Activation of P38, interleukin-2(IL-2) and COX-2 involved in CSA nephrotoxicity. Rise in level of Nuclear factor erythroid 2-related factor 2(Nrf2) that promotes the expression of Heme oxygenase 1(HO-1) pathway thus resulting in renal toxicity

Cyclosporine (CSA) is an immunosuppressant drug. CSA increases the stress in endoplasmic reticulum and induces production of reactive oxygen species in mitochondria followed by nephrotoxicity.[57]

Table 10 Various Dosage of Cyclosporine induced Nephrotoxicity

Toxic dose of cyclosporine	Route of administration	Species	References
25 mg/kg for 14 days	Oral	Wistar rats	58
30 mg/kg/day for 16 weeks	S.C	Mice	59
30 mg/kg for 4 weeks	S.C	ICR Mice	60

13. Tacrolimus induced nephrotoxicity

Tacrolimus is a calcineurin inhibitor possessing immunosuppressive properties which can be used widely in renal transplantation. Long term use of tacrolimus induces nephrotoxicity.[61] Tacrolimus causes irreversible kidney damage, notably hyalinization and thickening of the arteriolar walls, vasoconstriction and ischemia, tubulointerstitial fibrosis, apoptosis, and atrophy.[62] The mechanisms underlying nephrotoxicity induced by tacrolimus are still ambiguous. Tacrolimus propensity to generate reactive oxygen species via activation of the nicotinamide adenine dinucleotide phosphate oxidase pathway has been linked to its nephrotoxicity in previous investigations. In nephrotoxic agent-induced nephrotoxicity, apoptosis is crucial. In apoptosis, the caspase family plays a vital function. Caspase-3, in particular, is a key effector enzyme in apoptosis-related kidney damage. Tacrolimus can create reactive oxygen species (ROS) and hinder antioxidant defences in the proximal tubules.[63]

Table 11 Various Dosage of Tacrolimus induced Nephrotoxicity

Toxic dose of Tacrolimus	Route of Administration	Reference	Animal Species
0.6mg/kg for thirty days	I.P	64	Albino-Wistar rats
1.5mg/kg for four weeks	S.C	65	Sprague-Dawley Rats
2mg/kg for two weeks	I.P	66	CD1 Mice
3mg/kg for two weeks	Orally	67	Lewis Rats

14. Carbon tetrachloride induced nephrotoxicity

Carbon tetrachloride (CCL_4) a widely known haloalkane, belong to the class of chemicals utilized as anthelmintics and grain fumigants. It is also used as intermediates which can result in nephrotoxicity by synthesis of chlorofluorocarbons.[68] Fatty liver disease, cirrhosis in the liver, centrilobular necrosis and acute tubular necrosis in the kidney ensue after CCl_4 exposure.[69] According to several studies, elevation of extracellular matrix triggers renal fibrosis. Further many studies have shown that CCL_4 when processed in proximal tubule cells of kidneys can produce oxidative radicals. It has been observed that CCL_4 therapy increases oxidative stress resulting fibrogenesis and renal inflammation. Exposure to CCL_4 both in vitro and invivo can result in kidney inflammation. By inhibiting the Nrf2 pathway, CCl_4 induces oxidative stress, inflammation, and fibrosis in the kidneys.[70]

Table 12 Various Dosage of CCL_4 induced Nephrotoxicity

Toxic dose of CCL_4	Route of Administration	Reference	Animal Species
0.5 ml/kg for seven days	Orally	71	Albino Wistar Rats
1.2 g/kg for seven days	I.P	72	ICR Mice
2 ml/kg for ten days	I.P	73	Wistar Albino Rats
2 ml/kg for two weeks	I.P	74	Albino Rats
5 mg/kg once a week for 4 months	I.P	75	Albino Rats

15. Chromium induced nephrotoxicity

In nature, chromium (Cr) exists in a variety of forms, the most stable of which are Cr (III) and Cr (VI).Chromium is a strong oxidizing agent, and serious or persistent chromium exposure (through inhalation, skin contact, or drinking water) causes toxicity in cells, cancer, mutagenesis, or genotoxicity in the body's important organs such as the lungs, liver, and kidneys.[76]Because heavy metals are excreted mostly through the kidneys, excess levels of hexavalent chromium [Cr (VI)] are accumulated there which causes nephrotoxicity.[77]Chromium has the ability to influence cellular functioning by blocking antioxidant enzymes and binding to antioxidant components such as Glutathione (GSH), contributing to oxidative stress. In, proximal convoluted tubules, chromium compounds are selectively deposited where they produce acute tubular necrosis in large dosages after parenteral administration.[78]

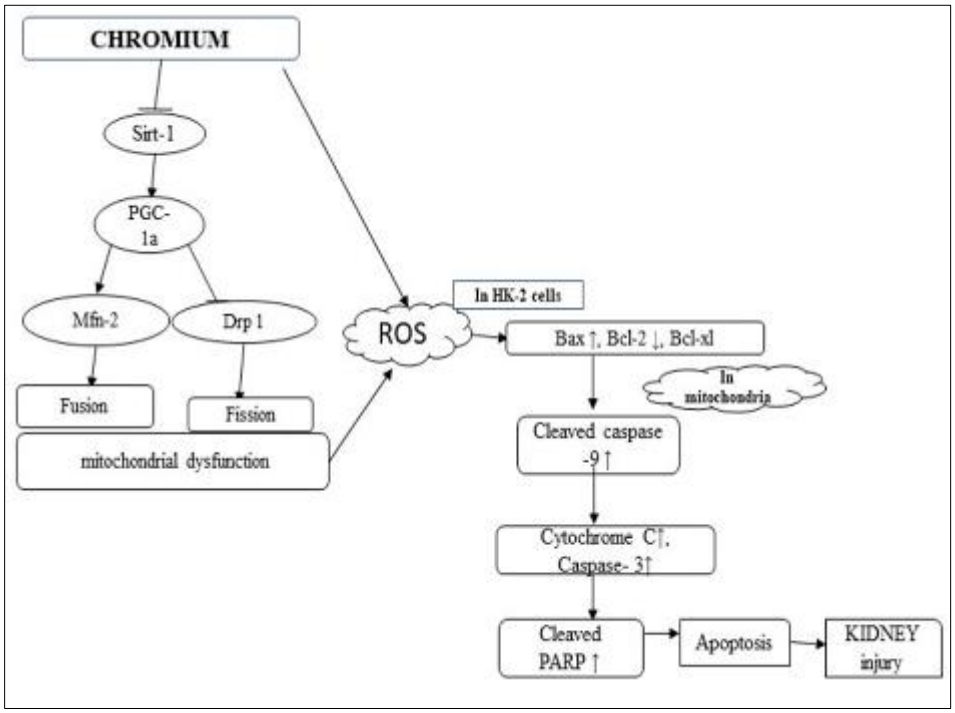


Figure 7 Motion-related protein 1 (DRP1) regulates mitochondrial fission, whereas mitofusin 1 (MFN1) and mitofusin 2 control mitochondrial fusion (MFN2). Peroxisome proliferation-activated receptor-g coactivator-1a (PGC-1a) controls DRP1 and MFN2 expression. PGC-1a is activated by the silent information regulator two ortholog 1 (Sirt1) through deacetylation. Defects in mitochondrial fusion and fission cause oxidative stress and apoptosis, among other things. The level of pro-apoptotic protein (Bax) increased in a dose-dependent manner, while the level of anti-apoptotic protein like B cells lymphoma 2 and B cells lymphoma 2-Extra large(Bcl-2 and Bcl-xl) decreased in a dose-dependent manner. Increased level of CYT-c and caspase-3 causes overproduction of cleaved Poly adenosine diphosphate ribose polymerase (PARP) which leads to apoptosis and kidney injury

Table 13 Various Dosage of Chromium induced Nephrotoxicity

Toxic dose of Chromium	Route of Administration	Species	Reference
6 mg/kg for four weeks	I.P.	Male wistar rats	79
10 mg/kg for seven days	I.P.	Male wistar Albino rats	80
15 mg/kg single dose	S.C., orally	Male Sprague–Dawley rats Male wistar rats	81,82

16. Mercury induced nephrotoxicity

Mercury (Hg) is a poisonous metal that can be found in its elemental (metallic), inorganic, and biological forms. Occupational and environmental contexts can expose humans to various types of mercury. The most common method of human exposure, however, is through the consumption of MeHg-contaminated food, particularly fish. MeHg is quickly absorbed by the gastrointestinal tract after consumption, after which mercuric ions enter the systemic circulation and are supplied to target organs.[83]. When animals or people are exposed to Hg°, the body quickly converts it to Hg+ and after oxidation it causes nephrotoxicity by promoting the development of reactive oxygen species (ROS). ROS causes alteration in mitochondria by blocking the permeable transition pore.[84]. Because mercuric ions can cause kidney injury, which may not be working at full capacity, may be more susceptible to the effects of Hg than healthy kidneys.[85]

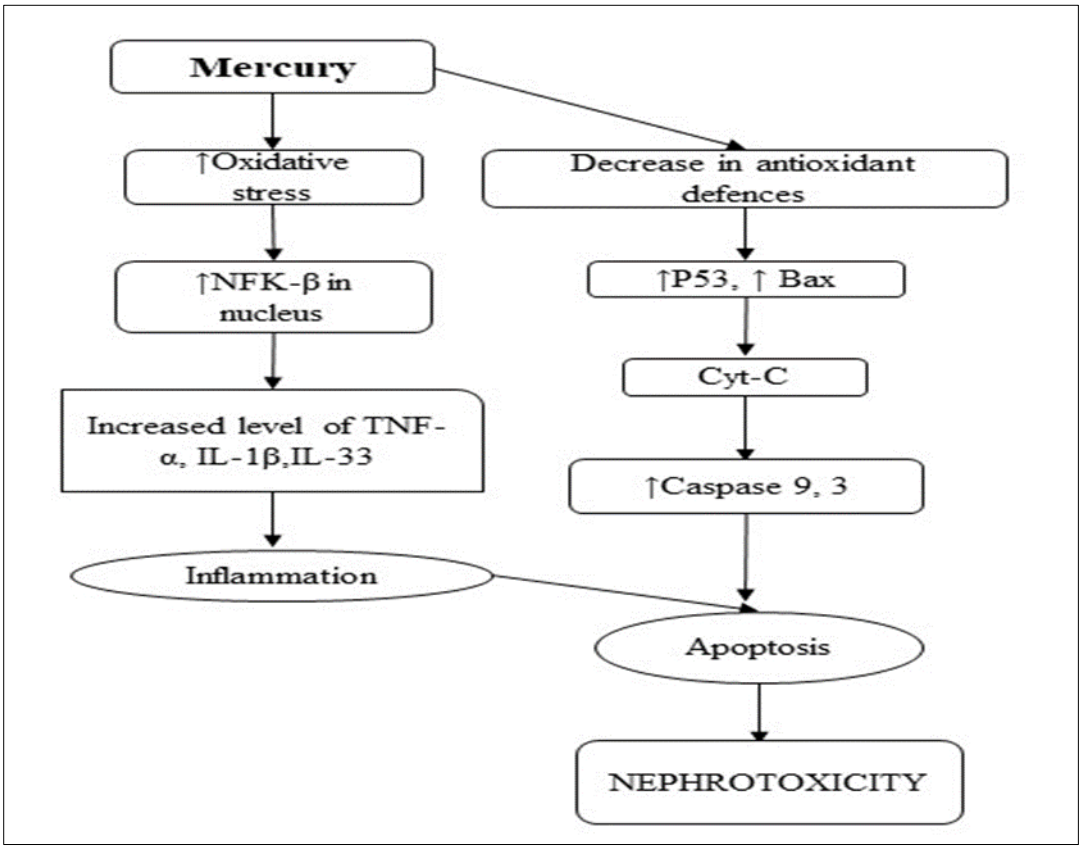


Figure 8 Activated NF-kB stimulates oxidative stress which further increases pro-inflammatory responses. Decreased antioxidants enhances the pro-apoptotic bodies and P53, increased cyt-c , caspase 9 and 3 results in apoptosis which further cause nephrotoxicity

Table 14 Various Dosage of Mercury induced Nephrotoxicity

Toxic Dose of mercury	Route of administration	Species	References
0.1, 1.0, 2.5, 5.0 mg/kg for 7 days	Orally	Swiss Albino Mice	86
Single-dose of 4 mg/kg	I.P.	Adult Male Wistar Rats	87
Single-dose of 250 mg/kg	I.P.	Male Sprague Dawley Rats	88

17. Lithium induced nephrotoxicity

Lithium is considered as the first therapeutic line for treatment of bipolar affective disorders and manic-depressive illness [89]. Lithium has been used in healthcare for almost 150 years. Garrod and Hammond advocated lithium salts as

a therapeutic for gout and uric acid nephrolithiasis in the eighteenth century. However, the medicine was taken off the market by the Food and Drug Administration (FDA) in the same year when several patients suffered a heart attack or hypertension as a result of lithium intoxication. However, it has the possibility to trigger renal damage, such as decreased urine concentrating ability and natriuresis, renal tubular acidosis, tubulointerstitial nephritis progressing to chronic kidney disease, and hypercalcemia.[90]

Renal toxicity can be categorized as the undesirable side effect of lithium therapy [91]Lithium detrimental effects are caused by processes that have yet to be elucidated. However, oxidative stress has been identified as one of the primary contributors of Li's harmful effects. ROS, such as superoxide and nitric oxide (NO), in particular, may play a role in the pathogenesis of Li-induced renal impairment. Lithium builds up in the collecting tubule, which is where its ability to change renal water excretion is most likely to be found. The ability of the cortical section of the collecting tubule in the kidneys to create cyclic adenosine monophosphate in response to antidiuretic hormone stimulation has been demonstrated decisively.[92]

Table 15 Various Dosage of Lithium induced Nephrotoxicity

Toxic dose of Lithium	Route of Administration	Animal Species	Reference
Single dose 2 mmol/kg for three weeks	I.P	Wistar Rats	93
25 mg/kg twice a day for 30 days	I.P	Wistar Albino Rats	94
25 mg/kg twice daily for 4 weeks	I.P	Wistar Albino Rats	95
50 mg/kg for twenty-eight days	I.P	Sprague-Dawley rats	96

18. Cisplatin induced nephrotoxicity

Cisplatin is a cancer chemotherapeutic drug that is extensively used and extremely effective. Nephrotoxicity is one of the most serious adverse effects of cisplatin. Increased activation of caspase3/7 and PARP(poly-ADA-ribose polymerase) cleavage was observed after comparing with NT3 cells in cisplatin treatment.[97]

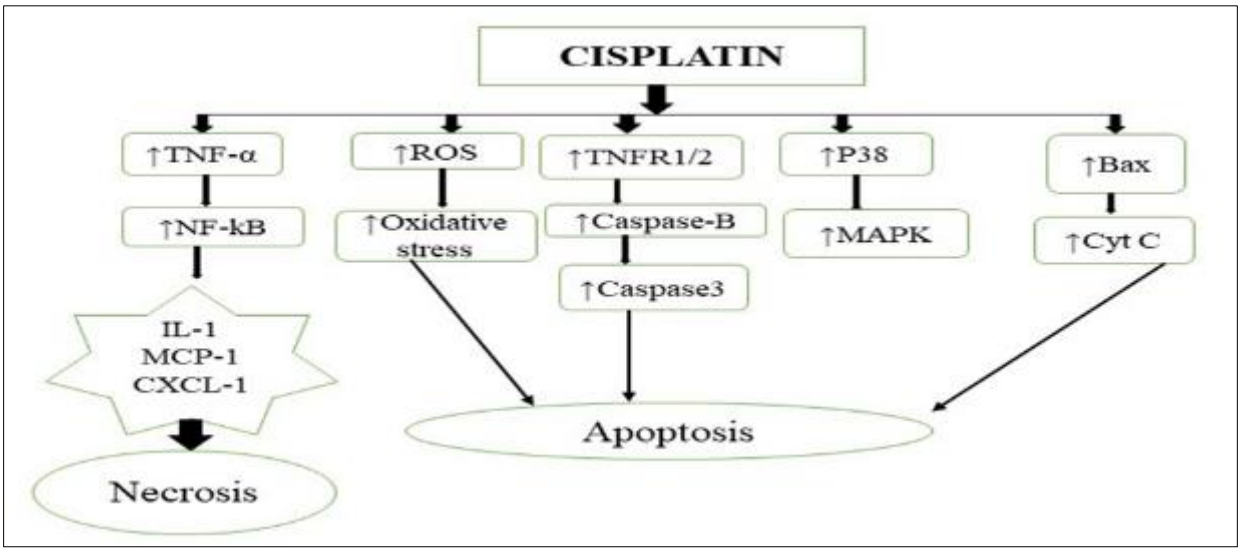


Figure 9 Cisplatin accumulation triggers increased production of TNF-α and NF-kB which further stimulates inflammation. Increased oxidative stress and Bax along with Cyt-c leads to apoptosis. Interleukin-1, Monocyte chemoattractant protein 1(MCP-1) and C-X-C Motif Chemokine Ligand 1(CXCL-1) cause renal tubular injury. Extrinsic apoptosis is caused by Tumor necrosis factor receptor ½(TNFR ½) signaling caspase-B and Caspase-3. Upregulation of MAPK due to increased P38 level resulting in apoptosis

Table 16 Various Dosage of Cisplatin induced Nephrotoxicity

Toxic dose of cisplatin	Route of administration	Species	References
6 mg/kg	I.P	F344 rats	98
1.6 to 4.8 mg kg−1for 4 weeks	I.P	Wistar rats	99
5 mg/kg for 10 days	I.P	Albino rats	100

19. Conclusion

This study reveals that overdose of drugs like PCM, Cisplatin, Chromium, Aspirin, Tacrolimus, Lithium, Gentamicin, Amphotericin B etc. induces nephrotoxicity. Nephrotoxicity is caused by drugs through processes including their intrinsic toxicity, as well as their transport and management by the kidneys. The incidence of nephrotoxicity is expected to be reduced by avoiding modifiable risk factors and overseeing therapeutic medication monitoring for high-risk groups. If the reversibility of renal damage has been proven, continuous dosage of the experimental medicine may be explored, but with more regular safety evaluations to see if renal function would stabilize or worsen. From the above study it can be concluded that early detection of high doses of various drugs reduces the risks by discontinuing the drug when worsening of renal function observed. Early detection of a medication-induced nephrotoxicity would be the most important factor in lowering the expenses of new drug safety testing. For the growth of pharmaceuticals, clinical trials should be executed, taking into deliberation of various drugs administration schemes as high or low doses used in preclinical studies. Above data shows that avoiding of that dose at which drug causes toxicity for better protection of kidney. Thus, the overview of this study will help in easy identification of suitable model of nephrotoxicity for further research and provides the road map for the future study on nephrotoxicity.

Compliance with ethical standards

Acknowledgments

The authors would like to thank S. Gurvinder Singh Bahra, Hon'ble Chancellor and Chairman, Rayat Bahra University, Mohali, who gave us a platform for pursuing this work. We are greatly indebted to Prof. (Dr.) Gurfateh Singh(Ex Head USPS Rayat Bahra University Mohali) and Mr. Suraj Sharma (Assistant Professor Pharmacology USPS Rayat Bahra University Mohali) for their kind assistance in preparing this manuscript.

Disclosure of conflict of interest

The authors have no conflict of interest.

References

[1] Kim SY, Moon A. Drug-induced nephrotoxicity and its biomarkers. Biomolecules &amp, therapeutics. 2012 May, 20(3):268.

[2] Nolin TD, Himmelfarb J. Mechanisms of drug-induced nephrotoxicity. Adverse drug reactions. 2010:111-30.

[3] Sari A. Nephrotoxic Effects of Drugs. Poisoning Mod. World New Tricks Old Dog. 2019 Jan 24.

[4] YNTHIA A. NAUGHTON, PharmD, BCPS, North Dakota State University College of Pharmacy, Nursing, and Allied Sciences, Fargo, North Dakota. Am Fam Physician. 2008 Sep 15, 78(6):743-750.

[5] Singh G, Dhadwal N, Harikumar SL. Experimental models for hepatotoxicity. Asian journal of pharmaceutical and clinical research. 2015 Mar 1:70-4.

[6] Samah A, Fatma A, Osama A. Effects of rosemary oil against hemato-biochemical alterations and renal oxidative damage induced by Paracetamol in rats.

[7] Chinnappan SM, George A, Thaggikuppe P, Choudhary Y, Choudhary VK, Ramani Y, Dewangan R. Nephroprotective effect of herbal extract Eurycoma longifolia on paracetamol-induced nephrotoxicity in rats. Evidence-Based Complementary and Alternative Medicine. 2019 May 13, 2019.

[8] Ahmad S, Zeb A. Nephroprotective property of Trifolium repens leaf extract against paracetamol-induced kidney damage in mice. 3 Biotech. 2020 Dec, 10(12):1-9.

[9] Samah A, Fatma A, Osama A. Effects of rosemary oil against hemato-biochemical alterations and renal oxidative damage induced by Paracetamol in rats.

[10] El-Maddawy ZK, El-Sayed YS. Comparative analysis of the protective effects of curcumin and N-acetyl cysteine against paracetamol-induced hepatic, renal, and testicular toxicity in Wistar rats. Environmental science and pollution research. 2018 Feb, 25(4):3468-79.

[11] Ramadan BK, Schaalan MF. The renoprotective effect of clover flowers honey on paracetamol-induced nephrotoxicity in adult male albino rats. Life Science Journal. 2011, 8(3):589-96.

[12] Hamid ZA, Budin SB, Jie NW, Hamid A, Husain K, Mohamed J. Nephroprotective effects of Zingiber zerumbet Smith ethyl acetate extract against paracetamol-induced nephrotoxicity and oxidative stress in rats. Journal of Zhejiang University Science B. 2012 Mar, 13(3):176-85.

[13] Luciano RL, Moeckel GW. Update on the native kidney biopsy: core curriculum 2019.American Journal of Kidney Diseases. 2019 Mar 1, 73(3):404-15

[14] Sarangi MS, S. K. H, Girish D, Mulkipatil B. EVALUATION OF NEPHROPROTECTIVE ACTIVITY OF KATAKABEEJA YOGA AGAINST ASPIRIN-INDUCED NEPHROTOXICITY IN WISTAR RATS. Int Ayurvedic Med J. 2021 Nov 26, p6(1):3208–18.

[15] Bozkurt Y, Bozkurt M, Turkçu G, Sancaktutar AA, Soylemez H, Penbegul N, et al., Caffeic acid phenethyl ester protects kidneys against acetylsalicylic acid toxicity in rats Ren Fail. 2019, 34(9):1150-5.

[16] Axelsen RA. Analgesic-induced renal papillary necrosis in the Gunn rat: the comparative nephrotoxicity of aspirin and phenacetin. J Pathol. 2016 Nov, 120(3):14550.

[17] Bouzenna H, Dhibi S, Samout N, Rjeibi I, Talarmin H, Elfeki A, et al.,The protective effect of Citrus limon essential oil on hepatotoxicity and nephrotoxicity induced by aspirin in rats. Biomed Pharmacother. 2016 Oct, 83:1327-1334.

[18] Jarrar QB, Hakim MN, Zakaria ZA, Cheema MS, Moshawih S. Renal ultrastructural alterations induced by various preparations of mefenamic acid. Ultrastructural pathology. 2020 Jan 2, 44(1):130-40.

[19] Somchit MN, Sanat F, Hui GE, Wahab SI, Ahmad Z. Mefenamic acid induced nephrotoxicity: An animal model. Advanced pharmaceutical bulletin. 2014 Dec, 4(4):401.

[20] Crespigny PC, Hewitson T, Birchall I, Kincaid-Smith P. Caffeine potentiates the nephrotoxicity of mefenamic acid on the rat renal papilla. American journal of nephrology. 1990, 10(4):311-5.

[21] Somchit MN, Sanat F, Hui GE, Wahab SI, Ahmad Z. Mefenamic acid induced nephrotoxicity: An animal model. Advanced pharmaceutical bulletin. 2014 Dec, 4(4):401.

[22] Fanos V, Cataldi L. Amphotericin B-induced nephrotoxicity: a review. Journal of chemotherapy. 2000 Jan 1, 12(6):463-70.

[23] Luber AD, Maa L, Lam M, Guglielmo BJ. Risk factors for amphotericin B-induced nephrotoxicity. Journal of Antimicrobial Chemotherapy. 1999 Feb 1, 43(2):267-71

[24] Fanos V, Cataldi L. Amphotericin B-induced nephrotoxicity: a review. Journal of chemotherapy. 2000 Jan 1, 12(6):463-70.

[25] Altuntaş A, Yılmaz HR, Altuntaş A, Uz E, Demir M, Gökçimen A, Aksu O, Bayram DŞ, Sezer MT. Caffeic acid phenethyl ester protects against amphotericin B induced nephrotoxicity in rat model. BioMed research international. 2014 Jan 1, 2014

[26] Tonomura Y, Yamamoto E, Kondo C, Itoh A, Tsuchiya N, Uehara T, Baba T. Amphotericin B-induced nephrotoxicity: characterization of blood and urinary biochemistry and renal morphology in mice. Human & experimental toxicology. 2009 May, 28(5):293-300.

[27] Cheng JT, Witty RT, Robinson RR, Yarger WE, Kennedy BM. Amphotericin B nephrotoxicity: increased renal resistance and tubule permeability. Kidney international. 1982 Dec 1, 22(6):626-33.

[28] Schlottfeldt FD, Fernandes SM, Martins DM, Cordeiro P, Fonseca CD, Watanabe M, Vattimo MD. Prevention of amphotericin B nephrotoxicity through use of phytotherapeutic medication. Revista da Escola de Enfermagem da USP. 2015, 49:74-9.

[29] Altuntaş A, Yılmaz HR, Altuntaş A, Uz E, Demir M, Gökçimen A, Aksu O, Bayram DŞ, Sezer MT. Caffeic acid phenethyl ester protects against amphotericin B induced nephrotoxicity in rat model. BioMed research international. 2014 Jan 1, 2014.

[30] Yildiz C, Ozsurekci Y, Gucer S, Cengiz AB, Topaloglu R. Acute kidney injury due to acyclovir. CEN case reports. 2013 May 1, 2(1):38-40.

[31] Gunness P, Aleksa K, Bend J, Koren G. Acyclovir-induced nephrotoxicity: the role of the acyclovir aldehyde metabolite. Translational Research. 2011 Nov 1, 158(5):290-301.

[32] Adikwu E, Kemelayefa J. Acyclovir-Induced Nephrotoxicity: The Protective Benefit of Curcumin. European Journal of Biology. 2021 Jun 1, 80(1):22-8.

[33] Dos Santos Mde F, Dos Santos OF, Boim MA, Razvickas CV, de Moura LA, Ajzen H, Nephrotoxicity of acyclovir and ganciclovir in rats: evaluation of glomerular hemodynamics. J Am SocNephrol. 1997 Mar, 8(3):361-7.

[34] Adikwu E, Kemelayefa J. Acyclovir-Induced Nephrotoxicity: The Protective Benefit of Curcumin. European Journal of Biology. 2021, 80(1):22-8.

[35] Lu H, Han YJ, Xu JD, Xing WM, Chen J. Proteomic characterization of acyclovir-induced nephrotoxicity in a mouse model. PLoS One. 2014 Jul 23, 9(7)

[36] Xing W, Gu L, Zhang X, Xu J, Lu H. A metabolic profiling analysis of the nephrotoxicity of acyclovir in rats using ultra performance liquid chromatography/mass spectrometry. Environ ToxicolPharmacol. 2016 Sep, 46:234-240

[37] Promsan S, Jaikumkao K, Pongchaidecha A, Chattipakorn N, Chatsudthipong V, Arjinajarn P, Pompimon W, Lungkaphin A. Pinocembrin attenuates gentamicin-induced nephrotoxicity in rats. Canadian journal of physiology and pharmacology. 2016, 94(08):808-18.

[38] Emami E, Dehkordi AH, Maghsoudi A, Nasri H, Vahedi A. A histopathological study on the effects of atorvastatin against gentamicin-induced renal injury.

[39] Atsamo AD, LontsieSongmene A, MetchiDonfack MF, Ngouateu OB, Nguelefack TB, Dimo T. Aqueous Extract from Cinnamomum zeylanicum (Lauraceae) Stem Bark Ameliorates Gentamicin-Induced Nephrotoxicity in Rats by Modulating Oxidative Stress and Inflammatory Markers. Evidence-Based Complementary and Alternative Medicine. 2021 Jul 20, 2021

[40] Luo QH, Chen ML, Chen ZL, Huang C, Cheng AC, Fang J, Tang L, Geng Y. Evaluation of KIM-1 and NGAL as early indicators for assessment of gentamycin-induced nephrotoxicity in vivo and in vitro. Kidney and Blood Pressure Research. 2016, 41(6):911-8.

[41] Khaksari M, Esmaili S, Abedloo R, Khastar H. Palmatine ameliorates nephrotoxicity and hepatotoxicity induced by gentamicin in rats. Archives of physiology and biochemistry. 2019 Jun 26:1-6.

[42] Jafarey M, ChangiziAshtiyani S, Najafi H. Calcium dobesilate for prevention of gentamicin-induced nephrotoxicity in rats. Iran J Kidney Dis. 2014 Jan, 8(1):46-52.

[43] Ince S, Kucukkurt I, Demirel HH, Arslan-Acaroz D, Varol N. Boron, a trace mineral, alleviates gentamicin-induced nephrotoxicity in rats. Biological trace element research. 2020 Jun, 195(2):515-24.

[44] Ordooei Javan, A., Shokouhi, S. &Sahraei, Z. A review on colistin nephrotoxicity. Eur J Clin Pharmacol 71, 801–810 (2015).

[45] Lee EH, Kim S, Choi MS, Yang H, Park SM, Oh HA, Moon KS, Han JS, Kim YB, Yoon S, Oh JH. Gene networking in colistin-induced nephrotoxicity reveals an adverse outcome pathway triggered by proteotoxic stress. Int J Mol Med. 2019 Mar, 43(3):1343-1355.

[46] Eronmosele JE, Olurishe TO, Olorukooba AB. Investigation of treatment-time differences in colistin-induced nephrotoxicity in Wistar rats. Chronobiol Int. 2021 Feb, 38(2):224-233.

[47] Burak Dumludaga , Mehmet KursatDericib , Osman Sutcuoglua , BetulOgutc , OzgeTugcePasaoglud , IpekIsıkGonulc and Ulver Dericia Role of silymarin (Silybum marianum) in the prevention of colistin-induced acute nephrotoxicity in rats DRUG AND CHEMICAL TOXICOLOGY.

[48] Deng, N., Jiang, H., Wu, P., Yang, Q., Li, S., Li, J., Wang, X., Han, B., Han, B., Lv, Z., & Zhang, Z. (2021). Inhibition of the Nrf2/p38MAPK pathway involved in deltamethrin-induced apoptosis and fibrosis in quail kidney. Food and Chemical Toxicology, 155, 112382.

[49] Küçükler S, Kandemir FM, Özdemir S, Çomaklı S, Caglayan C. Protective effects of rutin against deltamethrin-induced hepatotoxicity and nephrotoxicity in rats via regulation of oxidative stress, inflammation, and apoptosis. Environ Sci Pollut Res Int. 2021 Jul 3

[50] Ahmed WMS, Abdel-Azeem NM, Ibrahim MA, Helmy NA, Radi AM (2021). The impact of cinnamon oil on hepatorenal toxicity and antioxidant related gene expression induced by deltamethrin in rat. Adv. Anim. Vet. Sci. 9(7): 1071-1077.

[51] Abdel-Daim, M., El-Bialy, B. E., Rahman, H. G. A., Radi, A. M., Hefny, H. A., & Hassan, A. M. (2016). Antagonistic effects of Spirulina platensis against sub-acute deltamethrin toxicity in mice: Biochemical and histopathological studies. Biomedicine & Pharmacotherapy, 77, 79–85.

[52] Jafari, A., Khalili, H., &Dashti-Khavidaki, S. (2014). Tenofovir-induced nephrotoxicity: incidence, mechanism, risk factors, prognosis and proposed agents for prevention. European Journal of Clinical Pharmacology, 70(9), 1029–1040.

[53] Fernandez-Fernandez B, Montoya-Ferrer A, Sanz AB, et al. Tenofovir nephrotoxicity: 2011 update. AIDS Res Treat. 2011, 2011:354908.

[54] Ramamoorthy H, Abraham P, Isaac B. Mitochondrial dysfunction and electron transport chain complex defect in a rat model of tenofovirdisoproxil fumarate nephrotoxicity. J BiochemMolToxicol. 2015 Jun, 28(6):246-55.

[55] Ramamoorthy H, Abraham P, Isaac B. Preclinical efficacy of melatonin in the amelioration of tenofovir nephrotoxicity by the attenuation of oxidative stress, nitrosative stress and inflammation in rats. Journal of basic and clinical physiology and pharmacology. 2014 Nov 1, 25(4):387-99.

[56] Abraham P, Ramamoorthy H, Isaac B. Depletion of the cellular antioxidant system contributes to tenofovirdisoproxil fumarate - induced mitochondrial damage and increased oxido-nitrosative stress in the kidney. J Biomed Sci. 2016 Aug 19, 20(1):61

[57] Wu Q, Wang X, Nepovimova E, Wang Y, Yang H, Kuca K. Mechanism of cyclosporine A nephrotoxicity: Oxidative stress, autophagy, and signalings. Food ChemToxicol. 2018 Aug, 118:889-907

[58] Tan YC, Abdulttar M, Ahmeda AF, Abdul Karim Khan N, Murugaiyah V, Ahmad A, Hassan Z, Kaur G, Abdulla MH, Johns EJ. Apocynin and catalase prevent hypertension and kidney injury in Cyclosporine A-induced nephrotoxicity in rats. PLoS One. 2020 Apr 16, 15(4):e0231472.

[59] Nguyen, L.T., Saad, S., Shi, Y. et al. Lysyl oxidase inhibitors attenuate cyclosporin A-induced nephropathy in mouse. Sci Rep 11, 12437 (2021).

[60] Min, H.S., Lee, J.E., Ghee, J.Y., Kang, Y.S., Cha, J.J., Han, J.Y., Han, S.Y., Cha, D.R. A Novel Dipeptidyl Peptidase-4 Inhibitor DA-1229 Ameliorates Tubulointerstitial Fibrosis in Cyclosporine Nephrotoxicity in Mice. Life 2021, 11, 251.

[61] Vandenbussche C, Van der Hauwaert C, Dewaeles E, Franczak J, Hennino MF, Gnemmi V, Savary G, Tavernier Q, Nottet N, Paquet A, Perrais M. Tacrolimus-induced nephrotoxicity in mice is associated with microRNA deregulation. Archives of toxicology. 2018 Apr, 92(4):1539-50

[62] Luo K, Lim SW, Jin J, Jin L, Gil HW, Hwang HS, Yang CW. Cilastatin protects against tacrolimus-induced nephrotoxicity via anti-oxidative and anti-apoptotic properties. BMC nephrology. 2019 Dec, 20(1):1-1.

[63] Park CS, Jang HJ, Lee JH, Oh MY, Kim HJ. Tetrahydrocurcumin ameliorates tacrolimus-induced nephrotoxicity via inhibiting apoptosis. InTransplantation Proceedings 2018 Nov 1 (Vol. 50, No. 9, pp. 2854-2859). Elsevier

[64] Ali AS, Almalki AS, Alharthy BT. Effect of Kaempferol on Tacrolimus-Induced Nephrotoxicity and Calcineurin B1 Expression Level in Animal Model. J ExpPharmacol. 2020, Dec:397-407

[65] Luo K, Lim SW, Jin J, Jin L, Gil HW, Hwang HS, Yang CW. Cilastatin protects against tacrolimus-induced nephrotoxicity via anti-oxidative and anti-apoptotic properties. BMC nephrology. 2019 Dec, 20(1):1-1.

[66] Oyouni AA, Saggu S, Tousson E, Rehman H. Immunosuppressant drug tacrolimus induced mitochondrial nephrotoxicity, modified PCNA and Bcl-2 expression attenuated by Ocimumbasilicum L. in CD1 mice. Toxicology reports. 2018 Jan 1, 5:687-94.

[67] Butani L, Afshinnik A, Johnson J, Javaheri D, Peck S, German JB, Perez RV. Amelioration of tacrolimus-induced nephrotoxicity in rats using juniper oil. Transplantation. 2003 Jul 27, 76(2):306-11

[68] Yoshioka H, Usuda H, Fukuishi N, Nonogaki T, Onosaka S. Carbon tetrachloride-induced nephrotoxicity in mice is prevented by pretreatment with zinc sulfate. Biological and pharmaceutical Bulletin. 2016 Jun 1, 39(6):1042-6.

[69] Ozturk F, Ucar M, Ozturk IC, Vardi N, Batcioglu K. Carbon tetrachloride-induced nephrotoxicity and protective effect of betaine in Sprague-Dawley rats. Urology. 2003 Aug 1, 62(2):353-6.

[70] Ma JQ, Zhang YJ, Tian ZK, Liu CM. Bixin attenuates carbon tetrachloride induced oxidative stress, inflammation and fibrosis in kidney by regulating the Nrf2/TLR4/MyD88 and PPAR-γ/TGF-β1/Smad3 pathway. International Immunopharmacology. 2021 Jan 1, 90:107117.

[71] Rahmouni F, Badraoui R, Amri N, Elleuch A, El-Feki A, Rebai T, Saoudi M. Hepatotoxicity and nephrotoxicity in rats induced by carbon tetrachloride and the protective effects of Teucrium polium and vitamin C. Toxicology mechanisms and methods. 2019 Jun 13, 29(5):313-21.

[72] Kim S, Na JY, Song K, Kwon J. In vivo protective effect of phosphatidylcholine on carbon tetrachloride induced nephrotoxicity. Experimental and Toxicologic Pathology. 2016 Nov 1, 68(10):553-8.

[73] Moneim AE, El-Khadragy MF. The potential effects of pomegranate (Punica granatum) juice on carbon tetrachloride-induced nephrotoxicity in rats. Journal of physiology and biochemistry. 2013 Sep 1, 69(3):359-70.

[74] Izzularab BM, Megeed M, Yehia M. Propolis nanoparticles modulate the inflammatory and apoptotic pathways in carbon tetrachloride-induced liver fibrosis and nephropathy in rats. Environmental Toxicology. 2021 Jan, 36(1):55-66.

[75] Khan MR, Rizvi W, Khan GN, Khan RA, Shaheen S. Carbon tetrachloride-induced nephrotoxicity in rats: Protective role of Digera muricata. Journal of ethnopharmacology. 2009 Feb 25, 122(1):91-9.

[76] Sahu BD, Koneru M, Bijargi SR, Kota A, Sistla R. Chromium-induced nephrotoxicity and ameliorative effect of carvedilol in rats: Involvement of oxidative stress, apoptosis and inflammation. Chem Biol Interact. 2014 Nov 5, 223:69-79.

[77] Goodarzi Z, Karami E, Ahmadizadeh M. Simvastatin attenuates chromium-induced nephrotoxicity in rats. J Nephropathol. 2019 Jan, 6(1):5-9.

[78] Hassan, M. H., Zaghloul, D. A.-A. M., Mahmoud, M. A., Abdel-Moaty, Z. N., & Toghan, R. (2021). Protective Effect of Lactoferrin against Chromium Induced Adverse Renal Changes in Rats: Oxidative Stress Theory. American Journal of Biochemistry and Biotechnology, 17(2), 181–191.

[79] Han B, Li S, Lv Y, Yang D, Li J, Yang Q, et al. Dietary melatonin attenuates chromium-induced lung injuryviaactivating the Sirt1/Pgc-1α/Nrf2 pathway. Food & Function. Food & Function, 2019, 10(9):5555–65.

[80] Hfaiedh M, Brahmi D, Zourgui MN, Zourgui L. Phytochemical analysis and nephroprotective effect of cactus (Opuntiaficus-indica) cladodes on sodium dichromate-induced kidney injury in rats. ApplPhysiolNutrMetab. 2019 Mar, 44(3):239-247.

[81] Sahu BD, Koneru M, Bijargi SR, Kota A, Sistla R. Chromium-induced nephrotoxicity and ameliorative effect of carvedilol in rats: Involvement of oxidative stress, apoptosis and inflammation. ChemBiol Interact. 20145, 223:69-79.

[82] El-Guendouz S, Zizi S, Elamine Y, Lyoussi B. Preliminary screening of the possible protective effect of Moroccan propolis against chromium-induced nephrotoxicity in animal model. Veterinary World. 2020 Jul, 13(7):1327.

[83] Bridges, Christy C., Zalups, Rudolfs K. (2017). The aging kidney and the nephrotoxic effects of mercury. Journal of Toxicology and Environmental Health, Part B, 20(2), 55–80.

[84] Holditch SJ, Brown CN, Lombardi AM, Nguyen KN, Edelstein CL. Recent advances in models, mechanisms, biomarkers, and interventions in cisplatin-induced acute kidney injury. International journal of molecular sciences. 2019 Jan, 20(12):3011.

[85] Bridges CC, Zalups RK. The aging kidney and the nephrotoxic effects of mercury. J Toxicol Environ Health B Crit Rev. 2017, 20(2):55-80.

[86] Sharma MK, Sharma A, Kumar A, Kumar M. Evaluation of protective efficacy of Spirulina fusiformis against mercury induced nephrotoxicity in Swiss albino mice. Food ChemToxicol. Jun, 45(6):879-87.

[87] Hazelhoff MH, Torres AM. Effect of erythropoietin on mercury-induced nephrotoxicity: Role of membrane transporters. Hum ExpToxicol. 2021 Mar, 40(3):515-525.

[88] Shin YJ, Kim JJ, Kim YJ, Kim WH, Park EY, Kim IY, et al. Protective Effects of Quercetin 3. Against $HgCl_2$-Induced Nephrotoxicity in Sprague-Dawley Rats. J Med Food. 2015 May, 18(5):524-34.

[89] Aboulthana WM, Ibrahim NE. A renoprotective role of chitosan against lithium-induced renal toxicity in rats. Bulletin of the National Research Centre. 2018 Dec, 42(1):1-1.

[90] Shaterpour M, Shaki F, Ghasemi M, Jafari-Sabet M, Ziar A, Ataee R. The protective effect of curcumin against lithium-induced nephrotoxicity in rats. Pharmaceutical and Biomedical Research. 2017 Aug 10, 3(2):33-8.

[91] Aboulthana WM, Ibrahim NE. A renoprotective role of chitosan against lithium-induced renal toxicity in rats. Bulletin of the National Research Centre. 2018 Dec, 42(1):1-1.

[92] Oktem F, Ozguner F, Sulak O, Olgar Ş, Akturk O, Yilmaz HR, Altuntas I. Lithium-induced renal toxicity in rats: protection by a novel antioxidant caffeic acid phenethyl ester. Molecular and Cellular Biochemistry. 2005 Sep, 277(1):109-15.

[93] Shaterpour M, Shaki F, Ghasemi M, Jafari-Sabet M, Ziar A, Ataee R. The protective effect of curcumin against lithium-induced nephrotoxicity in rats. Pharmaceutical and Biomedical Research. 2017 Aug 10, 3(2):33-8.

[94] Aboulthana WM, Ibrahim NE. A renoprotective role of chitosan against lithium induced renal toxicity in rats. Bulletin of the National Research Centre. 2018 Dec, 42(1):1-11

[95] Oktem F, Ozguner F, Sulak O, Olgar Ş, Akturk O, Yilmaz HR, Altuntas I. Lithium-induced renal toxicity in rats: protection by a novel antioxidant caffeic acid phenethyl ester. Molecular and Cellular Biochemistry. 2005 Sep, 277(1):109-15.

[96] Ommati MM, Niknahad H, Farshad O, Azarpira N, Heidari R. In vitro and in vivo evidence on the role of mitochondrial impairment as a mechanism of lithium-induced nephrotoxicity. Biological Trace Element Research. 2021 May, 199(5):1908-18.

[97] Wang X, Bonventre JV, Parrish AR. The aging kidney: increased susceptibility to nephrotoxicity. Int J Mol Sci. 2014 Sep 1, 15(9):15358-76

[98] Nakagawa, M., Karim, M.R., Izawa, T., Kuwamura, M., Yamate, J. Immunophenotypical Characterization of M1/M2 Macrophages and Lymphocytes in Cisplatin-Induced Rat Progressive Renal Fibrosis. Cells 2021, 10, 257.

[99] Al Za'abi, M., Al Salam, S., Al Suleimani, Y. et al. Effects of repeated increasing doses of cisplatin as models of acute kidney injury and chronic kidney disease in rats. Naunyn-Schmiedeberg's Arch Pharmacol 394, 249––259 (2021).

[100] Mohd Naushad MohdUroojTasleemAhmadGulam Mohammed HusainMunawwar Husain Kazmi Mohammad Zakir Nephroprotective effect of Apium graveolens L. against Cisplatin-induced nephrotoxicity https://doi.org/10.1016/j.jaim.2021.06.005