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Critical review of current animal models of nephrotoxicity

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Abstract

Nephrotoxicity occurs when the renal blood is exposed to a nephrotoxic drug or toxin that causes damage to the kidneys. This may lead to acute kidney failure. In this condition the kidney function deteriorates and may lead to chronic kidney failure. If unchecked, the kidney failure may lead to the death. When kidney damage occurs, the kidney fails to remove excess urine and waste leading to retention of nitrogenous waste products of metabolism in the blood. The biochemical parameters commonly used to evaluate kidney function are serum urea, creatinine, uric acid, potassium, sodium and chloride. The animal models play a very important role for understanding the mechanism of nephrotoxicity and development of effective therapy for its optimal management. Since there are many pathways for induction of renal failure, therefore, a large number of animal models have been developed to produce the clinical conditions of renal failure. The present review will help to find an appropriate model to evaluate the new drug or molecule that can protect from nephrotoxicity.

Keywords: Animal, Model, Nephrotoxicity

Introduction

Nephrotoxicity can be defined as a renal disease or dysfunction produced by medication of drugs and other environmental factors and it is directly related to the (ARF) Acute renal failure (Lakshmi and Kiran, 2012) and (AKI) Acute renal injury is a reversible loss of function of renal cells in kidney that result in rapid fall in glomerular filtration rate (GFR) as well as retention of minerals and water (C. Late, 1996).

It has been found that drugs are responsible for 20% of all cases for (ARF) acute renal failure. Drug like antibiotics, anticancer, anti-inflammatory, NSAIDS, aminoglycoside exhibit and adverse effect on renal function and couse lose of immune system responses in the body. So in recent time, interest in drug-induced nephrotoxicity has been increased with increasing number of drugs to affect the renal cells (Ganguli and Prakash, 2003; Ogunnowo, 2015).

Most of the drugs are found to be harmful nephrons produce one or more pathogenic mechanism in the kidney. Pathological conditions include: hemodynamic, changes tubular cells toxicity, nephritis syndrome, urinary tract infection, chronic intestinal nephritis, and (Singh et al., 2014).

The present comprehensively required the methodology information regarding various animal models of nephrotoxicity.

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Animal models of Nephrotoxicity

Cisplatin-induced nephrotoxicity

Cisplatin is an antineoplastic chemotherapeutic agent that is widely used for the treatment of solid malignant tumor such as head, neck, lungs, kidney, testis and ovarian cancer. Several cases of renal damage have been reported due to high dose of cisplatin (Yao et al., 2007). The mechanisms contributing for cisplatin-induced nephrotoxicity include direct tubular toxicity in the form of reactive oxygen species(ROS), mediated through inflammation, calcium overload, reduced glutathione, ATP depletion and phospholipase activation (Singh et al., 2012)

Nasri et al., 2013, evaluated nephrotoxicity in Wistar rats weighing 170-220g, at the dose of 7mg/kg/day intraperitonially (i.p), for consecutive 7 days and estimated the blood parameters in rats such as serum creatinine, protein estimation, blood urea nitrogen(BUN) level and urea level in urine to evaluate nephrotoxicity(Nasri, 2013). In an another study conducted by Singh et al consecutive Cisplatin was administered at 7.5mg/kg/day (in 0.1% of saline solution) dose by i.p route for 10 consecutive days to produce nephrotoxicity in rats. Blood sample was collected from rats after 10 days of the treatment. Serum was produced by centrifugation of the blood sample and stored at -20°C. Superoxide dismutase (SOD) and glutathione activity (GSH) was measured in the renal tissue to determine the oxidative stress. Another report documented the development of nephrotoxicity in 48 hrs with single i.p dose (12 mg/kg/day) of cisplatin (Joy and Nair, 2008).

Cyclosporine (CSA)-induced nephrotoxicity

Cyclosporine (CSA) is mainly used for organ transplantation. CSA have also used in bone marrow transplant as immunosuppressant and treatment which of autoimmune diseases (Andoh et al., 1996). Generally, CSA produced acute nephrotoxicity is the reversible abnormality related to the renal imbalance of vasoconstriction and vasodilators. The major role of CSA in nephrotoxicity is to produce vasoconstriction that results in decrease renal blood flow and glomerular filtration rate (Herbst et al., 1971; Couture et al., 1983).

Andoh et al., 1996, has evaluated the nephrotoxicity in male Sprague-Dawley rats weighing 225-250 g. After one week on a low salt diet with italics font tap water, rats received 15 mg/kg/day CSA or vehicle for 14 days (Andoh et al., 1996). After 14 days, tail blood pressure (BP) was measured with plethysmograph (Natsune Seisakusyo, Tokyo, Japan) and rats were placed in metabolic cages for urine collection. After 24 hrs, the animal was anesthetized with i.p ketamine and the blood sample was collect and GFR and RBF (renal blood flow) measured (Waschulewski et al., 1993). C-insulin clearance and a blood flow levels were estimate ding one kidney was collected for histology after in italics perfusion (Andoh et al., 1996).

Nephrotoxicity was evaluated by Zahmatkesh et al., 2009, using male Wistar-rats weighing 200-250g. CSA was administered at a dose of 50 mg/kg/day per oral for 14 days to induce nephrotoxicity. After 14 days, CSA administered animals were kept in individual cages for 24 hrs for urine collection and blood was collected after 24 hrs by ocular puncture method. Finally, urinary sodium and potassium were determined using the flame photometer (Andoh et al., 1996). Creatinine clearance was calculated using serum and urinary creatinine estimated by alkali picrate method (Zahmatkesh et al., 2009). Ouyang et al., 2014, estimated the CSA induced nephrotoxicity at dose of 50 mg/kg/day by i.p route for 4 weeks. This method resulted in development of acute renal injury in rats (Ouyang et al., 2014)

Gentamicin-induced nephrotoxicity

Gentamicin is an aminoglycoside antibiotic, and is used to prevent infection against gram-negative bacteria (Chilwant and Muglikar, 2012). Nephrotoxicity is a major problem associated with gentamicin and accounting for 10-15 % of all cases in the world for acute renal failure. Gentamicin has a direct effect on proximal convoluted tubule in the kidney and it has an effect on the biological membrane (Ratnakar, 2000)

For induction of nephrotoxicity, adult male Sprague-Dawley rats (220-250 g) were used. They were maintained at 24 ± 1°C with the relative humanity of 40-45% and 12:12 hrs dark/light cycle and animals had given a standard diet and water. Rats were treated with gentamicin (120

mg/kg i.p.) daily for 7 days to produce nephrotoxicity include dissection of parameters evaluated(Anewesha Mukharjee et al., 2016). Ratnakar, 2000, induced nephrotoxicity in Wistar rats with gentamicin given at a dose of 80 mg/kg/day through i.p. route for 10 days. After 10 days animals were given mild anesthesia and the blood was collected by sinus puncture and serum was separated for the estimation of parameters such as blood urea nitrogen (BUN), serum creatinine and serum urea level. Rats were sacrificed and kidney was removed for the study of histology (Ratnakar, 2000). In another model, Okokon et al., 2011, evaluated the nephroprotective activity by gentamicin-induced nephrotoxicity with administering dose of gentamicin (100 mg/kg/day) i.p. for 8 days. After 8 days nephrotoxicity was evaluated by estimating decrease (Blood urea nitrogen) BUN level, serum creatinine and protein level in blood and histology changes of the kidney (Okokon et al., 2011)

NSAIDS- induced nephrotoxicity

Non-steroidal anti-inflammatory drug (NSAIDS) are usually considered safe but in reality even the use of NSAIDS at therapeutic doses may lead to nephrotoxicity (Dixit et al., 2010). Conditions that can lead to NSAIDS-induced renal damage include higher dose of the drug, volume depletion, nephritic syndrome, pre-existing renal disease, diuretic therapy, sodium and water retention (Ganguli and Prakash, 2003). Another mechanism for NSAIDS induced nephrotoxicity is inhibition of renal prostaglandins, disruption of renal cells and decrease renal blood flow in the kidney (Dixit et al., 2010). Paracetamol (Ilbey et al., 2009) and mefenamic acid (Somchit et al., 2014) are the two in present NSAIDS used for this puopose.

Paracetamol was used to induce nephrotoxicity in male Wistar rats (340-350 g) at a dose of 1000 mg/kg/day i.p for 24 days. At the end of the treatment, 24 hrs urine was collected for serum urea and creatinine level determination. Blood was collected for the estimation of urea, malondialdehyde (MDA) level, glutathione (GSH) and creatinine level. The kidney was removed for assessment of superoxide dismutase (SOD) (Lx, 2007) and catalysed (CAT) (Ilbey et al., 2009; Zheng et al., 2015).

Somchit et al., 2014, used mefenamic acid-induce nephrotoxicity in mice for 14 days(100 & 200 mg/kg) 10% dimethyl sulfoxide/palm oil by Intraperitoneal injection of mefanic acid was given for 14 days in mice (30-40 g) to produce nephrotoxicity and evaluated the decrease of blood urea nitrogen level (BUN), serum creatinine, protein level in blood and TBARS level in the kidney. (Somchit et al., 2014)

Tacrolimus-induced nephrotoxicity

Tacrolimus is a calcineurin inhibitor. It is generally used as an immunosuppressant. Tacrolimus generates oxidative stress due to over production of reactive oxygen species (ROS) and cause disturbance in antioxidant defense system, there by producing therefore renal toxicity (Al-Harbi et al., 2014)

Butani et al., 2003, induced nephrotoxicity in adult male Lewis rats (250-300g) with Tacrolimus at a dose of 3 mg/kg/day by gastric gavage for 2 weeks. After 2 weeks, in there study was fall in glomerular filtration rate (GFR) which was due to the result of nephrotoxicity (Butani et al., 2003). Nephrotoxicity was induced in male Wistar albino rats (wt 150-200g) at a dose of tacrolimus 2 mg/kg/day by i.p route for 14 days. After 14 days, the assessment of oxidative stress, histology and structural changes in kidney was performed to ensure nephrotoxicity (Al-Harbi et al., 2014).

Folic acid-induced nephrotoxicity

Folic acid is a model compound used to study the physiology associated of acute renal failure (ARF). Folic acid generally produces renal damage through acute tubular necrosis, renal cortical scarring and tubular damage (Gupta et al., 2012). Another mechanism of folic acid induced nephrotoxicity is patchy atrophy and interstitial fibrosis in kidney (Long et al., 2001)

Gupta et al., 2012, have induced nephrotoxicity in male Bulb/c mice (20-30 g) with folic acid given at a dose of 100 mg/kg/day by i.p route for 7 days. After 7 days, nephrotoxicity was evaluated by the parameters such as creatinine, blood urea nitrogen (BUN) GSH, SOD, LPO, CAT. GSH-Px (Gupta et al., 2012). Long et al have produced nephrotoxicity in CDI mice administering folic acid at a dose of 240 mg/kg/day by i.p route for 14 days. After 14 days histopathology examination of

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the kidney confirmed the occurrence of nephrotoxicity (Long et al., 2001)

Thiazide-induced nephrotoxicity

Thiazide is mostly used for long term as treatment of hypertention.. The major concern with use of thiazide is that they cause hypokalemia, impair glucose tolerance and increase serum cholesterol(Hawkins and Houston, 2005; Risk, 2013). Rats received thiazide chronically showed evidence of subtle glomerular injury and wrinkling thickening of the glomerular membrane (Ellison and Loffing, 2009). Treatment with thiazide diuretics result in toxicity of the kidney and produce oxidative stress in renal cells. It may also produce potassium deficiency, glomerular ischemia and directly damage renal cells(Loffing et al., 1995, 1996).

Sathya et al., 2012, administered thiazide at a dose of 150µg/kg/day by oral route for 28 days. After 28 days was observed nephrotoxicity and histopathological changes in the kidney (Sathya and Kokilavani, 2012). Loghin et al., 2007, induced nephrotoxicity with daily administration of hydrocholorothiazide (HTCZ) (309 mg/kg) for 60 consecutive days. After 20 days of administration of HTCZ, there was intra and periglomerular blood stasis and after 40 days more structural changes were observed in the kidney. At the end of 60 day of the experiment, tubular dystrophic are the study by kidney and glomerular hypertrophy was found in rats (Loghin et al.,2007). Loffing et al., 2009, Nephrotoxicity was observed in rats at dose of HTCZ (40 mg/kg/day) for 3 days. It has been observed that HTCZ has produced massive apoptosis and peritubular inflammation in the kidney (Ellison and Loffing, 2009).

Other than the above models, there are many other models which can be used to induce nephrotoxicity. These models include Tacrolimus is fall in GFR in kidney, Thiazide is produce tubular inflammation calcium tetra chloride is produce renal cell damages, Lead sulfate produce kidney disorders, Glycerol produced rhabdomylasis in kidney, Folic acid produce acute tubular necrosis and quinine produce decrease renal serum creatinine level and decrease renal blood flow. The details of all those models has been tabulated in table no. 1

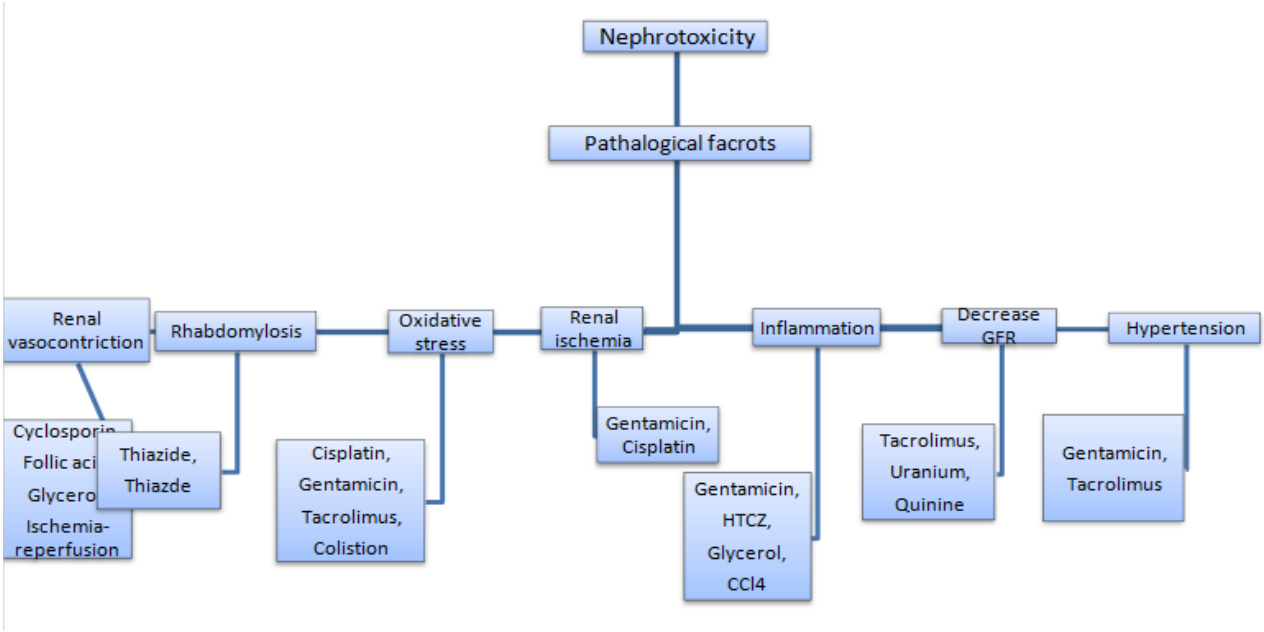

Table No. 1: Nephrotoxicity-induced animal models

S.No.	Drug/ obliged method	Animal model	Dose	Treatment schedule	Route	Parameters of evaluation	Action observed	References
1)	Ciaplatin	Wistar rats	7 mg/kg	7 consecutive days	i.p.	BUN, Creatinine relationship	Tubular atropy, cast, debris, tubular	(Nasri, 2013)
		Spregue-Dawley rats	7.5 mg/kg	10 consecutive days	i.p.	SOD, GSH, BUN, urea level	damage Acute tubuler necrosis and atropy.	(Singh et al., 2014)
		Swiss Albino rats	12 mg/kg	Single dose	i.p.	Serum creatinine, urea level	Hypomagnesemia, Tubular toxicity	(Joy and Nair, 2008)
2)	Cyclosporine	Sprague-Dawley rats	15 mg/kg	14 consecutive days	s.c.	Serum creatinine GFR, RBF,	Tubular collapse,	(Andoh et al., 1996)
		Wistar rats	50 mg/kg	14 consecutive days	p.o.	Serum and urinary creatinine, blood urea	Nephrocalcinosis, Hypomegnesemia	(Zahmatkesh et al., 2009)
3)	Gentamicin	Sprague-Dawley rats	80 mg/kg	28 days	i.p.	Serum creatinine, BUN, urine analysis	calcification, renal vasoconstriction, endothelial dysfunction	(Ouyang et al., 2014)
		Wister rats	120 mg/kg	8 consecutive days	i.p.	Blood urea, eerum creatinine	vasoconstriction, renal necrosis	(Ratnakar, 2000)
		Sprague-Dawley rats	80mg/kg	7 consecutive days	i.p.	Serum creatinine, BUN, NO	Renal ischemia, glomerularsclerosis	(Mukherjee et al., 2016)
4)	**NSAIDS** (Paracetomol)		1000 mg/kg	10 consecutive days	i.p.	Serum creatinine, BUN, proteins, GSH, TBARS	Renal mitochondrial dysfunction, renal inflammation	(Chilwant and Muglikar, 2012)
	(Mefanic acid)	Albin-Wistar rats	100-200 mg/kg	24 days	i.p		Acute tubular toxicity, increase renal oxidative	(Ilbey et al., 2009)
5)	Sulfonamide	Male Balb/c mice	96 mg/kg					
6)	**Drug of Abuse**							

7).	(Morphine Sulphate) Morphine-HCL Thiazide Hydrocholorthiazide (HTCZ)	Long Evans male rats Sprague-Dawley rats Male Albino rats Adult male Wistar rats Male Wistar rats	8 mg/kg 10-160 mg/kg 150 µg/ml 309 mg/kg	14 consecutive days 60 consecutive days 15 consecutive days 21 consecutive days 28 consecutive days 60 consecutive days	i.p. p.o. s.c. i.p. p.o. per oral	GSH, Urea, SOD, MDA, CAT ,creatinine BUN, creatinine Renal blood flow Morphology of kidney GSH, SOD, CAT, GSHx, LPo Decrease ß-D-glucuronidase in and n-acetyl-d-glucosaminidase in kidney. Serum creatinine analysis, necropsy, histology	stress. glomerular damage Glomerular necrosis Tubular atrophy, glomerular necrosis Acute interstitial, tubular toxicity Proteinuria, Decrease urinary excretion Focal glomerularsclerosic, oxidative stress. nucleation, crystal growth, crystal aggregation & retention Tubular dystrophy, glomerular hypertrophy	(Somchit et al., 2014) (Islam et al., 2012) (Ebb, 1958) (Garnaut et al., 2002) (Sathya and Kokilavani, 2012) (Loghin et al., 1999)

	HTCZ	Male Wistar rats	40 mg/kg	3 consecutive days	p.o.	Urinary output, blood analysis analysis Level of Na+ and K+	Tubular inflammation, massive apoptosis cell death	(Loffing et al., 1996)
8)	**Calcinerium inhibitor**							
	Tacrolimus	Male Lawis rats	3 mg/kg	2 weeks	p.o.	Insulin clearance, urinary prostaglandins analysis	Fall in GFR, reduce animal weight	(Butani et al., 2003)
	Tacrolimus	Male Wistar rats	2 mg/kg	28 consecutive days	i.p.	GSH, CAT, histology of kidney	Nephritic syndrome, increase oxidative stress	(Al-Harbi et al., 2014)
9)	Ccl4 induced	Male Albino rats	0.5 ml/kg in olive oil	7 consecutive days	i.p.	LPO, GSH, SOD, Total protein, histology	Lose kidney weight, chronic renal injury	(El-Mohsen Ali and Abdelhafiz Abdelaziz, 2014)
		Albino rats	0,5 ml/kg in olive oil	42 consecutive days	i.p.	Serum, protein level, inflammation mediators, antioxidants parameters	Oxidative stress, Inflammation, acute and chronic renal tissue injury	(Mohamed et al., 2014)
		Sprague-Dawley rats	0.7 mg/.kg in olive oil	11 consecutive days	i.p.	SOD, CAT, GSH, renal cortex	Renal cells damage, acute tubular necrosis	(Ozturk et al., 2003)
10)	Folic acid	Male balb/c mice	100 mg/kg	7 consecutive days	i.p.	GSH, SOD, LPO, CAT. (GSH-Px)	Acute tubular necrosis, renal cortical scarring.	(Gupta et al., 2012)
		CDI mice	240 mg/kg	14 consecutive days	i.p.	Cortical tubule, flattened carticak epithelia, dilated tubule lumina were note	tubular damage, patchy atrophy, interstitial fibrosis	(Long et al., 2001)
11)	Glycerol-induced	Inbred rats	10 ml/kg	15 consecutive days	i.m.	Scr, CCcr, fractional excretion of sodium	ARF, tubular regeneration	(Backenroth et al., 1998)
		Female Wister rats	10ml/kg					

		Male Sprague-Dawley		3 consecutive days	i.m.			
12)	Ischemia-reperfusion	rats	10 ml/kg					
						Urea, creatinine, MPO, MDA, oxidative stress	Oxidative stress, rhabdomylasis, myoglobinuric renal failure	(Al Asmari et al., 2017)
		Male Wistar rats		8 consecutive days	-			
13)	**Mercuric** Hgcl2	Sprague-Dawley rats	Right kidney artery to clamping 30 min.					
							Renal dysfunction & damage, rhabdomylasis	(Korrapati et al., 2012)
	Hgcl2		Left renal clamp for 45 min.	30 min.	-	Blood, urine, renal function, inflammation, histology		
		Male Swiss Albino rats	5mg/kg					
	Hgcl2			45 min.	i.p.		Chronic kidney disease, AKI	(Wei and Dong, 2012)
		Male Long Evans hooded rats	2.5 µml/kg		i.v.	BUN, Scr		
				7 consecutive days		BUN, creatinine	AKI, vasoconstriction or necrosis	(Tanaka et al., 2013)
14).	Osmotic-nephrosis	Male Wistar Albino rats	5 mg/kg		I.p			
				12 consecutive days			ARF	
						SCr, BUN, TBARS, NO, histology		(Gado and Aldahmash, 2013)
			250 µl				Cellular and tubular necrosis	
15)	Uranium (Uranyl acetate dehydrate) UAD	Necrotromized mice	RCM (Radiocontrat media	3 consecutive days	i.v.	Urine analysis quantification of mercury in tissue, histology		(Zalups and Diamond, 1987)
		Rabbit			p.o.		Renal toxicity, proximal tubule dysfunction	
	Uranium		20% Sucrose					
				20 min. single dose		Urea, creatinine, MDA, total thiol graphs, histology		
		Male Sprague-Dawley rats			s.c.			
	Uranium		5 mg/kg					(Boroushaki et al., 2016)
							Renal tubular necrosis	
16)				7 consecutive days	i.m.			
	Doxorubicin	Albino Wistar rats	0.2 mg/kg					
					i.p.	Serum, urea, creatinine	Swelling renal tubular cells, vacuolization	(Linkermann et al., 2013)
		Male Sprague-Dawley rats	5 mg/kg	14 consecutive days				
17)	Quinine				i.p.	Histology, pathological characters	Proximal renal tubular damage, histological changes	(Dickenmann et al., 2008)
		Male Wistar rats	20mg/kg	28 consecuti	i.p.	SOD,		

		Adult Albino rats	15 mg.kg	ve days		TBARS, GSSG, GSH	Decrease GFR rate	(Bellés et al., 2007)
				2 consecuti	p.o.			
18)		Male	40 mg/kg	ve days		Crs, BUN, albumin	Vacuolization of tubular cells, tubular necrosis	(Vicente-Vicente et al., 2010)
	Acyclovir	Wistar rats			i.p.			
				10				
		Male	10mg/kg	consecuti		SOD, CAT,		
		Wistar rats		ve days		GPx, MDA, or total	Tubular	
				Single	i.v.	protein	atrophy,	(Zheng et al., 2015)
19)			5 mg/kg	dose			oxidative stress	
	Adrigamycin	Male				CAT, GSH,		
		Wistar rats				GPx, NO	Renal cellular	
20).				5			damage,	(Oktem et al., 2011)
	Cadmium (CdCHl2)			consecuti			oxidative	
				ve days		Serum, urea,	stress	
					i.p.	LPO,		
			2.5, g/kg			creatinine,	Decrease renal	(Mansour et al., 1999)
21)		Male				total protein	serum, urea	
	Carbolatin	Swiss-Albino rats		Single			and electrolyte	
				dose		Urea,	level	
					p.o.	creatinine,		
			5 mg/kg			sodium,	Reduction	(Olurishe et al., 2014)
						potassium,	renal	
22)		Male				chloride	clearance,	
	Diclofenac	Wistar rats		5	i.p.		decrease	
	sodium		256 mg-300	consecuti		Creatinine,	urinary quinine	
				ve days		urine	clearance	
23)		Male	mg/kg			volume,		(Onyeji et al., 1992)
	Colistin	Wistar rats				AUC	Glomerular	
							hemodynamic,	
					i.p.		renal damage	
24)							and failure,	
	Tacrolimus		10, 50,			GFR, Body	nephropathy,	(Dos Santos et al., 1997)
		Male	100	2		Wt., TRVR,	crystalluria	
		Wistar rats	mg/kg	weeks	i.v.	SNGFR,		
						proximal		
						tubule		
		Male	5.25 mg&			pressure	Proteinuria,	
		Sprague-	12.5		i.p.		albuminuria,	
25)		Dawley	mg/kg	21			hypoalbumine	
	Ranitidine	rats		consecuti			mia,	
				ve days			hyperlipidemia	(Elbaky et al., 2006)
		Male	2 mg/kg					
		Wistar rats				GSH, GST,	Proteinuria,	
26)				5		DT, LPO	calciuria,	
	Nickel-induced			consecuti			glycosuria,	
				ve days	i.p.		tubular	
							necrosis	
								(Adefegha et al., 2015)
27)						Total protein,	Renal	
	Lead-induced	Male	100			urea,	dysfunction,	

		Wistar rats	mg/kg	Single dose	i.p.	creatinine, uric acid, ALT, ASTC, ALP	decrease serum magnesium, excreted tubular filtration and secretion	(Husain et al., 2004)
		Swiss albino mice	3, 5, and 10 mg/kg	7 consecutive days	i.p.	Plasma creatinine, BUN, Blood urea, LPO, CAT, SOD,	Oxidative stress, blocking PGE synthesis	
		Female rats	100 µmol/ Pb/kg	14 consecutive days		GSH-Px, SOD, renal xanthine	Oxidative stress, histology changes in kidney.	(Bolat and Selcuk, 2013)
						Urea, creatinine, fibrinogen, anti thrombin,	Oxidative stress, reperfusion injury	(Yousef et al., 2011)
				Single dose		MDA, NO, SOD, ADA		
						Urinary NAG, SOD, plasma creatinine, histology		(Al-Harbi et al., 2014)
				8 consecutive days		BUN, creatinine, monodialdehyde, GSH,	Met hemoglobin	
				7 consecutive days		CAT, histology of kidney	Produce ROS, LPO, cell apoptosis	(Malfará et al., 2005)
						Renal blood flow, protein in blood	Produce kidney disorder	(Kadi and Dahdouh, 2016)
						Serum, urea, creatinine, uric acid, histology		(Adeniyi et al., 2012)
						Level of Pb, uric acid, creatinine, histology, ERY		

Elaborate here all the short terms used in the table: BUN- blood urea nitrogen, GFR- glomerular filtration rate, GSH- glutathione, TBARS- thiobarbituric acid reactive substance, SOD- superoxide dismutase, MDA- malondialdehyde, CAT- catalyse, LPo – lipid peroxidation, OS- Oxidative stress, GSH-px- glutathione reductase, Scr- serum creatinine, CCcr- creatinine clearance, MPO- myeloperoxidase, NO- nitric oxide, AUC- area under curve, TRVR- total renal vascular resistance, SNGFR- single nephrones glomerular filtration rate, DT- diphorase activities, AlT- alanine aminotransferase, AST- aspirate transaminase, ALP- alkaline phosphates, ADAC- amino deaminase, ERY- erythrocyte protoporphyrin.

Conclusion

Nephrotoxicity has multiple etiology and mechanisms. Different animal models of nephrotoxicity with different compounds have been analyzed in the past. These models generally depend on renal tubular injury which is directly related to induce nephrotoxicity Therefore different models have been produced with different mechanisms in kidney such as tubular necrosis and injury, renal ischemia perfusion, imbalance sodium potassium level, tubular atrophy and glomerular necrosis. The most commonly used models of nephrotoxicity are cisplatin, gentamicin and cyclosporine-induced nephrotoxicity. In this models has been most of drug-induced nephrotoxicity mechanisms, changes are reversible. Decrease renal functions evidenced by rise in serum creatinine, BUN, urea level, and decrease tubular secretion with kidney damage and urine abnormalities. Selection of appropriate animal model is critical and important in evaluating the nephroprotective effect of test drugs and it depends upon the proposed mechanism of nephroprotective drugs and pathological condition for which this drug is being developed.

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