



CRITICAL ANALYSIS OF PROTECTIVE ROLE OF PLANTS AGAINST GENTAMICIN INDUCED NEPHROTOXICITY

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Abstract

Nephrotoxicity is one of the most common kidney problems caused by variety of toxic compounds. Gentamicin (GM) is a broad spectrum aminoglycoside commonly used for controlling life threatening infections caused by Gram (+ve) and Gram (-ve) bacilli. However, it causes nephrotoxicity in about 15-30% of treated subjects. Because of superiority of gentamicin in controlling life threatening infections, scientific community is exploring renoprotective role of plant species to minimize gentamicin induced nephrotoxicity. In the present review, we have critically evaluated studies made for exploring renoprotective role of 2 species of algae, 3 of fungi, 1 of gymnosperm and 145 of angiosperms in the experimental animals exposed to gentamicin (GM). Histopathological findings of kidney are not considered in this review since these are merely descriptive (qualitative) and therefore, comparison among plant species is difficult for identifying the most promising renoprotective plant species. Ameliorating role of plant species has been considered in view of protection/recovery in the serum biochemical parameters deciphering kidney functions (urea, creatinine, uric acid, blood urea nitrogen) and oxidative stress (MDA/LPO, GSH/GPX, CAT, SOD). Out of 151 species screened in the gentamicin treated animals, majority (108 species) were renoprotective (moderate – excellent) and reduce oxidative stress. It is likely that they differ in biomolecules. Plant species of excellent category may therefore, be explored for their ameliorative role to other nephrotoxicants both singly as well as in various combinations. The recommended dose of gentamicin for human is 20µg/kg body weight while several plant species were excellent in term of protection to experimental animals even at its higher doses (80-100mg/kg body weight), and therefore, there is a good scope for their clinical trials in the human beings treated with gentamicin. Presence of renoprotective properties among such a vast number of species highlights role of biodiversity in the welfare of mankind.

Key Words: Antioxidant, Creatinine, Gentamicin, Nephrotoxicant, Renoprotective plant species, Urea

Kidney is the only organ in the body that removes metabolic wastes such as urea, creatinine, uric acid etc. from the blood which are excreted through urine. Beside metabolic wastes; kidney also removes drugs and various toxic industrial and environmental agents in the blood. Because of increased blood flow (25% of the cardiac output) and presence of cellular transport systems within epithelial cells of the nephron, exposure to toxic substances is maximum in kidney. As a result, kidney related diseases are on rise particularly in the relatively more polluted areas.

Nephrotoxicity is one of the most common kidney problems with an estimated lifetime risk of 2-5% in Asia, 8-15% in

Europe, America and around 20% in the Middle East. It reduces glomerular filtration rate that raises level of blood urea nitrogen (azotemia) and creatinine in the serum leading to increased retention of fluids in the body (over hydration) and blood pressure (hypertension).

The ability of kidney to concentrate tubular fluid contents is a hallmark of renal function. The nephrotoxic compounds damage epithelial cells of tubules; thereby reduce urine concentrating capacity or tubular proteinuria, lysosomal enzymuria and mild glucosuria, decrease ammonium excretion and increase hydrogen ion concentration in the blood (acidosis). The outcome is concentration gradient which favors

influx of toxic compounds from the tubular fluid to the blood. This causes severe complications in the body such as edema, ascites, hepatomegaly etc. leading to acute renal failure.

The toxic compounds may be exogenous or endogenous. Radio contrast agents, aminoglycosides, antibiotics, chemotherapeutic agents, organic solvents, acetaminophen, illegal abortifacients, antineoplastic agents like cyclophosphamide, vincristin, cisplatin etc are important exogenous toxic agents. Their prolonged exposure may cause irreversible damage to renal system resulting in chronic renal failure (CRF), which led to permanent loss of excretory and endocrine functions of kidney.

Nephrotoxicants

Several toxicants may cause kidney failure. Following are some of the important nephrotoxic agents.

A) Metals & metalloid: Aluminum and its compound such as aluminum fluoride, Heavy metals such as mercury, cadmium, chromium, tin, lead, etc., and metalloid - arsenic

B) Antineoplastic agents

- **Alkylating agents:** Cisplatin, cyclophosphamide
- **Nitrosoureas:** Streptozotocin, carmustine, lomustine & semustine
- **Antimetabolites:** High doses of methotrexate, cytosine arabinose, 6-thioguanine, 5-fluorouracil
- **Antitumor antibiotics:** Mitomycin, mithramycin, doxorubicin
- **Biologic agents:** Recombinant leukocyte and interferon

C) Antimicrobial agents: Tetracycline, acyclovir, pentamidine, sulphadiazine, trimethoprim, rifampicin, amphotericin-B

D) Aminoglycosides: Gentamicin, amikacin, kanamycin, streptomycin

E) Anti-cancer drugs

- Cyclosporine
- Cisplatin
- Cyclophosphamide
- Methanoglobin forming agents

F) Miscellaneous

- **Radiocontrast agents:** Non-steroidal anti-inflammatory agents (NSAID's), ibuprofen, indomethacin, aspirin etc.

- **Liquor consumption**

G) Solvents and fuels

- Carbon tetrachloride
- Methanol
- Amyl alcohol
- Glycol

G) Environmental agents

- Fluoride
- Acid rains

I) Others

- Herbicides
- Pesticides
- Diseases stimulating overproduction of uric acid

Mechanism of Nephropathy

Nephrotoxic agents damage tubular epithelial cells either by reacting directly with cellular macromolecules and membrane components or indirectly through their metabolism. Heavy metals (Hg, Pb), organic cations (spermine, cationic amino acids, amino glycosides) and polyene antibiotics (amphotericin) interacting respectively with sulfhydryl groups, membrane phospholipids and cholesterol cause direct damage whereas indirect damage is caused by metabolites (fluoride and oxalates) formed in hepatic metabolism of methoxyflurane intermediates of cisplatin, cystine conjugates, cephaloridine and acetaminophen. These toxic metabolites also generate free radicals.

Nephrotoxicants accumulate mainly in the proximal tubular epithelial cells

Proximal straight (PT) and distal convoluted tubules (DT) of kidney are the major targets of toxicants since these accumulate in their epithelial cells. Because of brush border epithelial cells, PT absorbs and metabolizes toxicant more efficiently. This reduces exposure of DT cells to toxicant. Alterations in the DT cells are therefore, relatively less than that of proximal tubule cells (PT). The excessive injury in tubules lead to necrosis of tubular epithelial cells that significant increase urinary excretion of both brush border (alkaline phosphatase, g-glutamyl transferase) and intracellular enzymes (LDH, aspartate aminotransferase, alanine aminotransferase, and *N*-acetyl-b-D-glucosaminidase) (Agency for Toxic Substance and Disease Registry 1994, Gotelli et al. 1985, Guyton and Hall 2006,

Planas-Bohne 1977, Price 1982, World Health Organization 1991, Zalups and Diamond 1987, Zalups et al. 1988, Zalups 1998).

Nephrotoxicants also alter activity of many enzymes like acetyl cholinesterase, hexokinase, phosphor-oxidase and adenylyl cyclase, aspartate aminotransferase (AST), alanine amino transferase (ALT), acid and alkaline phosphatase and phosphorylase, lactate dehydrogenase (LDH), NADP (H) oxidase, lipases and phospholipases, creatinine phosphokinase etc.

Various studies have pointed out that nephrotoxicants increase oxidative stress either through excessive production of reactive oxygen species (ROS) such as superoxide radical (O_2^-), H_2O_2 and hydroxyl radical (OH^-) or disturb redox balance in the body by decreasing the activity of endogenous free radical scavengers such as superoxide dismutase, glutathione peroxidase and catalase. This leads to destruction of intracellular organelles, loss of microvilli, alterations in the number and size of the lysosomes and mitochondrial vacuolization followed by functional alterations such as DNA damage, inhibition of protein synthesis, glutathione depletion, lipid peroxidation and apoptosis. Because of excessive accumulation of free radicals, kidney loss copper and zinc that favor peroxidation of lipids and depletion of glutathione (Srinivasan et al. 2011, Ahmed and Sajida 2012, Ammar and Sabah 2013).

Na^+ - K^+ ATPase and Ca^{+2} - Mg^{+2} ATPase pumps regulate urinary Na^+ and Ca^{+2} losses from serum. Nephrotoxicant decreases activity of Na^+ - K^+ ATPase and Ca^{+2} - Mg^{+2} ATPase pumps (Cittanova 2002, Anner and Moosmayer 1982, Anner et al. 1983, Imesch et al. 1992) and also alter membrane permeability. This may allow increased fluid uptake and its accumulation in cell vacuoles. Nephrotoxicant also reduces reabsorption of number of plasma solutes such as glucose, amino acids, albumin, and other plasma proteins (Price 1982, Zalups and Diamond 1987, Zalups et al. 1998). The binding of different nephrotoxicants with aquaporins blockade their function. Nephrotoxicants render the collecting duct unresponsive to vasopressin or decrease vasopressin induced CAMP generation that leads to polyuria, polydipsia and weight loss (Turner et al. 1989, Yadav et al. 2016). Nephrotoxicant inhibits protein synthesis in the renal cells that induces necrosis of cells in the proximal tubule which can lead to acute renal failure (Sundin et al. 2001).

Gentamicin (GM) is a broad spectrum aminoglycoside commonly used for controlling life threatening infections caused by Gram (+ve) and Gram (-ve) bacilli. The epithelial cell linings of certain segments of the proximal renal tubules retain almost 5% of administered dose of gentamicin causing nephrotoxicity in about 15-30% of treated subjects evinced by increase in levels of creatinine, urea, uric acid/ blood urea nitrogen in the serum. Gentamicin also acts as an iron chelator and the iron-gentamicin complex is a potent catalyst of free radical generation resulting in oxidative stress. Because of superiority of gentamicin in controlling life threatening infections, scientific community is exploring ways to minimize gentamicin induced nephrotoxicity.

Medicinal Plants possessing nephroprotective activity

Therapeutic use of plants popular in underdeveloped and developing countries is now gaining acceptance worldwide because of its minimum/ almost nil side effects. Ayurveda is the medical science flourished in India in which ailments are cured with locally available medicinal plants. Because of diverse climate, India is a treasure of medicinal plants. Medicinal properties of plants are due to alkaloids, terpenoids, steroids, essential oils and antioxidants such as vitamins, flavanoids, phenols etc. As stated earlier, nephrotoxicants induces renal toxicity by increasing ROS generation and lipid peroxidation and therefore, medicinal plants rich in antioxidants may find application in minimizing nephrotoxicant toxicity. Phytochemicals may also reduce levels of creatinine, urea, uric acid/ blood urea nitrogen in the serum and thereby improve GFR.

Scientists have explored nephroprotective role of plant species used since ages either by the locals or reported in *Materia Medica* of the ancient system of medication, other than conventional allopathic system of medication. In the present review, we have critically evaluated studies made for exploring nephroprotective role of 2 species of algae, 3 of fungi, 1 of gymnosperm and 143 of angiosperms in the experimental animals exposed to gentamicin (GM).

Based on delivery of plant extract/powder (herbal preparation) to the experimental animals during the study, following 3 types of treatments were identified.

1. **Concomitant-** GM and herbal preparation were administered simultaneously. Herbal preparation given prior to GM exposure on the same day was also considered concomitant.

2. **Preventive-** Herbal preparation was administered to the experimental animals prior to entry into experimental protocol.
3. **Curative-** Herbal preparation was administered following GM exposure.

Histopathological findings of kidney are not considered in this review since these are merely descriptive (qualitative) and therefore, comparison among plant species is difficult for identifying the most promising renoprotective plant species. Ameliorating role of plant species has been considered in view of protection/recovery in the serum biochemical parameters deciphering kidney functions (urea, creatinine, uric acid, blood urea nitrogen) and oxidative stress (MDA/LPO, GSH/GPX, CAT, SOD). Further, protection level is classified in to following 6 grades.

A: Values of aforesaid parameters were almost similar to control { values of kidney markers and oxidative stress were higher (1-20%) than control values while of antioxidant levels were lower (1-20%) } than control.

B: Values of aforesaid parameters were more (21-30%) than control values for kidney markers and oxidative stress but lesser (21-30%) for antioxidant levels.

C: Values of aforesaid parameters were more (31-50%) than control values for kidney markers and oxidative stress but lesser (31-50%) for antioxidant levels.

D: Values of aforesaid parameters were more (51-70%) than control values for kidney markers and oxidative stress but lesser (51-70%) for antioxidant levels.

E: Values of aforesaid parameters were more (>70%) than control values for kidney markers and oxidative stress but lesser (>70%) for antioxidant levels.

Symbol **A^A** has been assigned to denote recovery in parameter/s even better than control; say for example when urea, creatinine and MDA/LPO levels were even lesser than control values and vice versa for antioxidants. The critical analysis of available data has been tabulated (Table 1-5). Based on quantum of serum biochemical data reported in various studies, data have been tabulated as follows.

1. Data on kidney functions + antioxidants levels at the termination of study
2. Data on kidney functions + antioxidants levels at different time intervals during the study period
3. Data on kidney functions at the termination of study

4. Data on kidney functions at different time intervals during the study period

Comparing values of serum biochemical parameters (denoting kidney functions, oxidative stress and antioxidant levels) in the gentamycin treated animals vis a vis control, following three categories were assigned to decipher ameliorating role of plant species.

1. **Excellent (E):** This includes plant species showing recovery of parameters in to 'A^A 'and 'A' grades.
2. **Good (G):** This includes plant species showing recovery of all parameters into 'A' grades.
3. **Moderate (M):** This includes plant species showing recovery of few parameters into either 'A^A 'or 'A' grade whereas of others in the lower grades. In case of only kidney parameters, one parameter may be of lower grade whereas for both kidney and oxidative stress parameters, two parameters may be of lower grade.
4. **Poor (P):** This includes plant species showing recovery of one parameter each of kidney function and oxidative stress into either 'A^A 'or 'A' grade whereas of others in the lower grades.

In majority of studies, optimum protection to the animals was accorded when gentamicin and herbal formulation were administered concomitantly. Normally renoprotection action of herbal formulation was dose dependent but an opposite trend was observed in few species.

- The protection/recovery of kidney functions and oxidative stress was moderate when algae and fungi were administered to the gentamicin treated animals (Table 1).
- The protection/recovery of kidney functions belonged to **excellent category** when plant parts of following plant species were administered to the gentamicin treated animals (Table 2-5).

Belowground organs

Root: *Croton zambesicus, Hemidesmus, Panax, Ipomea digitata*

Bulb: *Allium sativum*

Tuber: *Myrmecodia*

Aboveground organs

Leaf: *Casurina, Euclea, Psidium, Kalanchoe, Mentha and Moringa*

Shoot: *Eryngium*

Table 1. Ameliorative role of algae, fungi and gymnosperm on biochemical markers of kidney health and oxidative stress.

GM (mg/ Kg B. wt)	Plant	Prep- ration	Herbal		Prognosis						References	
			Dose mg/kg B. wt	Protocol	Kidney functions			Oxidative stress				
					U	C	BUN/ UA*	LPO/ MDA*	GSH/ GPX*	CAT		SOD
100 (1-7d)	<i>Spirulina platensis</i>	Whole plant	1000	Concomitant (1-7d)	D	A		D*	B/A*	A	Karadeniz et al. 2008a	
80 (3-10d)	<i>Spirulina fusiformis</i>	Whole plant	500 1000 1500	Preventive (1-2d) + Concomitant (3-10d)		E E A	E E C			D C A	C B A	Kuhad et al. 2006
50 (1-6d)	<i>Morchella esculenta</i>	Mycelia: Hydro- ethan. Ext.	250 500	Concomitant (1-6d)	E C	E E		A* C*	A/B* C/A*	B A	B A	Nitha and Janardhan an 2008
100 (1-8d)	<i>Pleurotus porrigens</i>	Meth. Ext. (dried fruiting body)	200 400	Concomitant (1-8d) + Curative (9-10d)	D C	D B	A A ^A					Moghadda m et al. 2010
100 (1-7d)	<i>Sacchar- omyces cerevisiae</i>	Whole plant	50% of diet	Curative (6-56d)	A ^A	C	A*		C	C	B	EL-Ghany et al. 2012
80 (1-7d)	<i>Volvariella volvacea</i>	Fruiting body: Aqua Ext.	500 1000	Concomitant (1-7d)	A A	D A	E* B*		A/C* A/A*	A A	B A	Kalava and Menon 2012
80 (3-10d)	<i>Ginkgo biloba</i>	Leaf Ext. (Ranbaxy lab.)	300	Preventive (1-2d) + Concomitant (3-10d)	A ^A	D		B*				Naidu et al. 2000
100 (1-8d)		Leaf : Etha. Ext.	200 400	Concomitant (1-8d)	E B	E B	D/C* C/A*					Mansoor et al. 2015

U = Urea, C = Creatinine, BUN = Blood urea nitrogen, UA = Uric acid, NA = Not available, Etha. = Ethanol, Ext.= Extract, d = day

Bark: *Spathodea* and *Cinnamomum zylenicum*

Gum: *Acacia senegal*

Fruit: *Solanum nigrum*, *Citrus aurantium*, *Mangifera*

Seed: *Benincosa*, *Carica*, *Foeniculum*, *Nigella*, *Trachyspermum*

Whole plant: *Hygrophila*, *Cuscuta*, *Kigelia*, *Morinda* and *Terminalia chebula*

Seeds of *Foeniculum* in combination with fruits of *Solanum nigrum* also protected kidney function under **excellent category**.

- The plant parts of following plant species protected/recovered kidney functions to **good category** (Table 2-5).

Belowground organs

Root: *Cassia auriculata*, *Cyperus*, *Glycirrhiza*, *Garcinia kola*

Rhizome: *Zinziber*

Aboveground organs

Leaf: *Aloe*, *Aegle mermelos*, *Apium*, *Callestimon*, *Cynara*, *Urtica*, *Bryophyllum*, *Ficus carica*, *Sesbania grandiflora*

Shoot: *Phyllanthus flaternus*

Bark: *Ficus racemosa*

Flower: *Calotropis*, *Cocos nucifera*, *Crocus sativus*, *Punica*

Table 2. Ameliorative role of plant species on biochemical markers of kidney health.

GM (mg/ kg B. wt)	Plant	Prep.	Herbal		Prognosis : Kidney functions			References
			Dose mg/kg B. wt	Protocol	U	C	BUN/ UA*	
100 (1-7d)	<i>Abutilon indicum</i>	Root: Eth. Ext.	150 300	Concomitant (1-7d)		E D	A A	Jesurun and Lavakumar 2016
100 (1-8d)	<i>Acacia senegal</i>	Gum arabic: Aqua. Ext.	670	Concomitant (1-8)	A^A	A		Tahir et al. 2016
80 (5-10d)			200	Preventive (1-4d) + Concomitant (5-10d)	E	E		Ali et al. 2003
80 (1-8d)	<i>Adhatoda zeylanica</i>	Leaf: Eth. Ext.	500	Curative (9 d -18d)	E	A^A		Kumar et al. 2013
40 (1-13d)	<i>Aerva lanata</i>	Whole plant: Eth. Ext.	75 150	Curative (14-23d)	E C	E E		Shirwaikar et al. 2004
			300 300	Concomitant (1-13d)	A D	E E		
100 (3- 9d)	<i>Althaea officinalis</i>	Flower: Eth. Ext.	50	Preventive (1-2d) +	E E	E E		Talebi et al. 2014
			250	Concomitant (3-9 th d)	E	E		
			500					
100 (1-14d)	<i>Allium cepa</i>	Leaf: Eth. Ext.	200	Concomitant (1-14d)		E		Chinnala et al. 2017
			400				E	
120 (1-14d)	<i>Allium sativum</i>	Cloves: Aqua Ext.	4% of diet	Concomitant (1-14d)	A^A	A		Seckiner et al. 2014
10 (1-10d)			20	Concomitant (1-10d) Curative (11-20d)		A C	A D	
80 (1-7d)	<i>Aloe barbadensis</i>	Leaf: Aqua Ext.	100	Concomitant (1-7d)	E C	E E	A[*] A^{A*}	Chatterjee et al. 2012
			200					
80 (1-8d)	<i>Andrographis paniculata</i>	Root: Aqua Ext.	200	Concomitant (1-8d) + Curative (9-10d)	A	A	C	Singh et al. 2009
100 (1-8d)	<i>Bauhinia purpurea</i>	Leaf: Eth. Ext.	300	Concomitant (1-8d)	D	E	D/B[*]	Laxmi et al. 2009
		Unripe Pod: Eth. Ext.			B	B	A/A[*]	

100 (1-8d)	<i>Bauhinia variegata</i>	Fruit: Aqua Ext.	200	Concomitant (1-8d)	E	E	E	Sharma et al. 2011
		Fruit: Etha.			C	E	E	
		Fruit: Aqua	400		E	E	E	
		Fruit:Etha.			A	C	C	
		Leaf : Meth. Ext	400	Concomitant (1-8d)	A	B	A/A*	Prusty et al. 2012
80 (1-6d)	<i>Benincosa hispida</i>	Seed : Etha. Ext.	250 500	Concomitant (1-6d)	A^A A^A	E A		Qadrie et al. 2013
80 (1-10d)	<i>Boerhavia diffusa</i>	Himalaya capsule Plant Ext.	400 800	Curative (11-74d)	E C	E C	E* C*	Padmini and Kumar 2013
80 (1-8d)		Root	4g/kg	Concomitant (1-8d) + Curative (9-21d) Curative (9-21d)	A A	E A		Kulkarni et al. 2012
100 (1-8d)	<i>Boswellia serrata</i>	Gum: Aqua extract Metha. solub. (MS) Insolu. (MINS)	1000 650 (MS) 350 (MINS)	Concomitant (1-8d)		D C C	E E E	Alam et al. 2011
80 (1-16d)	<i>Bryophyllum pinnatum</i>	Leaf:Etha. Ext.	150 300	Concomitant (1-16d)	A A	A A		Sule and Arhoghro 2016a
40 (1-14d)	<i>Carica papaya</i>	Seed:Aqua Ext.	200	Concomitant (1-14d)		A^A	A/A*	Nale et al. 2012
40 (1-13d)	<i>Cassia auriculata</i>	Root: Etha. Ext.	600	Concomitant (1-13d)	A	A		Annie et al. 2005
			600	Curative (14-23d)	A	A		
100 (1-8d)	<i>Camellia sinensis</i>	Leaf:Etha. Ext.	300	Preventive (1-7d) + Concomitant (8-15d)	C	E		Veljković et al. 2015
80 (1-7d)	<i>Caesalpinia bonduc</i>	Leaf:Metha Ext.	250 500	Concomitant (1-7d)	E D			Noorani et al. 2011
100 (1-8d)	<i>Callestimon viminalis</i>	Leaf: Hydro- metha. Ext.	250 500	Concomitant (1-8d)	A	A	A/A*	Sallem et al. 2016

80 (1-21d)	<i>Cinnamomum tamala</i>	Leaf: Etha. Ext.	200	Concomitant (1-21d)		D	A/A *	Ullah et al. 2013a
100 (1-28d)	<i>Cinnamomum zeylanicum</i>	Peel powder: Etha. Ext.	50 100 200	Concomitant (1-28d)		B A ^A A ^A	E/D * E/A * A/A *	Tanomand and Najafian 2013
80 (1-21d)	<i>Citrullus colocynthis</i>	Whole plant: Etha. Ext.	25	Concomitant (1-21d)		E	E/D *	Ullah et al. 2013b
80 (1-7)	<i>Cola nitida</i>	Fruit: Aqua Ext. Fruit: Etha. Ext.	200 500 200 500	Concomitant (1-7d)	E E	E D		Abou et al. 2016
90 (1-7d)	<i>Costus afer</i>	Leaf: Aqua Extra.	375 750 1125	Concomitant (1-7d)	A ^A E A ^A	E E E		Ezejiolor et al. 2014
100 (1-10d) 75 + 75 at 12h interval	<i>Curcuma longa</i> (CL)	Rhizome : Curcu- min pigment	200 400	Concomitant (1-10d) Preventive (1-5d)+ Concomitant (6-12d)	C	A E	D * E	Azab et al. 2014 Negrette-Guzmán et al. 2015 In vitro study
80 (1-6d)	<i>Crocus sativus</i>	Safranal: Aqua extract	0.5mL/ kg B. wt.	Concomitant (1-6d)	A	A		Boroushak and Sadeghnia 2009
80 (1-14d)		Petal: Hydro Etha. Ext.	40 80 80	Concomitant (1-14d)		C E	C/A * E/A *	Omidi and Torabi 2016
80 (7-14d)				Preventive (1-6d)		D	D/A *	
100 (1-10D)		Saffron: Aqua extract	5	Concomitant (1-10d)		E	E	Derakhshanfar et al. 2015
40 (1-10d)		Stigma: Etha. Ext.	50	Concomitant (1-10d)		A	A	Dhar et al. 2013
100 (1-8d)	<i>Croton zambesicus</i>	Root: Etha. Ext.	27 54 81	Concomitant (1-8d)	A ^A A ^A A ^A	A ^A A ^A A ^A	A * A * A *	Okokon et al. 2011
100 (1-8d)	<i>Cuscuta reflexa</i>	Whole plant : Hydro metha. Ext.	200 400 600	Concomitant (1-8d)	A A A	A A ^A A ^A	C/C * B/C * A/A *	Alamgeer et al. 2017
100 (1-12d)	<i>Dalbergia sissoo</i>	Leaf : Etha. Ext.	100 200	Concomitant (1-12d)	C B	C A	E * C *	Saxena et al. 2016

100 (1-8d)	<i>Daucus carota</i>	Root: Eth. Ext.	200 400	Concomitant (1-8d)	C A	E C	C/C* B/B*	Sodimbaku et al. 2016
80 (1-5d)	<i>Echinodorus macrophyllus</i>	Leaf : Eth. Ext.	30	Concomitant (1-5d)		C		Portella et al. 2012
80 (1-7d)	<i>Elephantopus scaber</i>	Leaf: Eth. Ext.	200 400 600	Concomitant (1-7d)	E D A	E E E		Sahoo et al. 2012
80 (1-8d)	<i>Elettaria cardmomum</i>	Seed: Aqua Ext.	100 200	Curative (9-21d)	C A	D C		Elkomy et al. 2015
80 (1-7d)	<i>Entandrophra gmaangolense</i>	Bark : Aqua Ext.	200 500	Concomitant (1-7d)	E E	E D		Abou et al. 2016
		Bark: Eth. Ext.	200 500		E E	E D		
100 (1-10d)	<i>Eryngium caucasicum</i>	Shoot: Hydro- metha. Ext.	200 400	Concomitant (1-10d)	B A^A	B A	C A^A	Eslami et al. 2011
200 (1-8d)	<i>Ficus carica</i>	Leaf: Eth. Ext.	400	Concomitant (1-8d)	A	A		Ghafoor et al. 2015
80 (1-14)	<i>Garcina kola</i>	Root: Metha. Dichlo. methane fraction	250	Concomitant (1-14d)	A A	A^A A^A	B* B*	Komolafe et al. 2016
80 (1-7d)	<i>Gomphrena celosioides</i>	Aqua. Ext. (Leaf + Stem + Flower)	200 500	Concomitant (1-7d)	E E	E D		Abou et al. 2016
		Etha. Ext. (Leaf + Stem + Flower)	200 500	Concomitant (1-7d)	E E	E D		
90 (1-6d)	<i>Hemidesmus indicus</i>	Root Powder	5000	Curative Male (7-12d) Female		A A	A A^A	Kotnis et al. 2004
80 (7-14d)	<i>Ipomoea aquatica</i>	Leaf: Eth. Ext.	500	Preventive (1- 6d)	D	A		Sharmin et al. 2016
40 (1-14d)	<i>Jasminum grandiflorum</i>	Leaf: Meth. Ext.	100 200	Concomitant (1-14d)	E D	E D	E/E* C/C*	Venkataiah et al. 2013

100 (4-8d)	<i>Khaya senegalensis</i>	Stem bark: Aqua. Ext.	250 500	Preventive (1- 3d) + Concomitant (4-8d)	E E	A^A C		El Badvi et al. 2012
80 (1-7d)	<i>Kigelia africana</i>	Whole plant: Metha. Ext.	100 200	Concomitant (1-7d)	A^A C	A E		Hoque et al. 2016
100 (1-8d)	<i>Kalanchoe pinnata</i>	Leaf : aqua Ext.	125	Concomitant (1-8d)	A	A^A	A/A*	Harlalka et al. 2007
80 (1-8d)	<i>Lagenaria siceraria</i>	Seed: Metha. Ext.	250	Concomitant (1-8d)		A	B/A*	Mahurkar et al. 2012
		Seed: Aqua. Ext.	250			A	A/A*	
100 (1-7d)	<i>Lantana camara</i>	Root: Etha. Ext.	200	Concomitant (1-7d)	E	E	C	Vyas and Argal 2012
40 (1-14d)	<i>Momordica charantia</i>	Leaf : Hydro- Etha. Ext.	100 200	Concomitant (1-14d)	E E	E D		Chawari et al. 2011
100 (1-10d)	<i>Morinda citrifolia</i>	Ext.	500	Concomitant (1-10d)	A^A	A^A		Anitha and Dass 2014
100 (1-12d)	<i>Nelumbo nucifera</i>	Root: Etha. Ext.	100	Concomitant (1-12d)	A	A	B*	Dubey et al. 2014
		Flower: Etha. Ext.	100		B	B	E*	
		Leaf : Etha. Ext.	100		B	C	D*	
180	<i>Ocimum sanctum</i>	Leaf: Aqua. Ext.	100			A		Kumar et al. 2014
100 (1-10d)	<i>Panax ginseng</i>	Root	100 200	Concomitant (1-10d)	D A^A	E A	A A	Kalkan et al. 2012
80 (1- 15d)			100	Concomitant (1- 15d)	C	B		Qadir et al. 2011
80 (22-28d)		Red ginseng (root)	100	Preventive (1-21) + + Concomitant (22-28d)		A	A^A	Lee et al. 2013
40 (1- 12d)	<i>Physalis alkekengi</i>	Fruit: Etha. Ext.	450	Concomitant (1- 12d)	B	E		Ahmad et al. 2010
40 (1- 5d)				Curative (6- 12d)	C	E		

80 (21 st d)	<i>Phyllanthus amarus</i>	Leaf: Etha. Ext.	200 300	Preventive (1- 20d)	A B		Sule and Arhoghro 2016b	
40 (1- 14d)		Whole plant: Aqua Ext.	100 200 400	Concomitant (1- 14d)	E E D	E D A	Adeneye and Benebo 2008	
80 (4-11d)		Seed: Meth. Ext.	250	Preventive (1- 3d) + Concomitant (4- 11d)	A E	A B	Bakhtiary et al. 2012	
100 (1- 10d)	<i>Phyllanthus acidus</i>	Leaf : Meth. Ext.	50 100 200	Concomitant (1- 10d)	E E E	A A A	Vidya et al. 2013	
80 (1-9d)	<i>Phyllanthus niruri</i>	Whole plant : Meth. Ext	200 400	Curative (10-19d)	C B	A A	A A	Gaddam et al. 2015
80 (1-8d)	<i>Phyllanthus fraternus</i>	Shoot : Meth. Ext.	100 200	Curative (9-16d)		E A	D A	Kalyani et al. 2012
80 (1-8d)			200	Concomitant (1- 8d)		B	B	
100 (1- 8d)	<i>Pimpinella anisum</i>	Shoot : Eth. Ext.	300	Concomitant (1- 8d)		E	E	Ashtiyani et al. 2017
80 (8-14d)	<i>Piper cubeba</i>	Berry (Dry) Powder	810 1220	Preventive (1-7d) + Concomitant (8-14d)	C C	E C		Zaid et al. 2012
80 (1-7d)			810 1220	Curative (8-14d)	C E	C C		
40 (1-13d)	<i>Pongamia pinnata</i>	Flower: Eth. Ext.	600	Concomitant (1-13d) Curative (14-23d)	C B	A A		Shirwaikar et al. 2003
100 (1-8d)	<i>Punica granatum</i>	Fruit: Aqua ext.	100	Concomitant (1-8d) Concomitant (8 th d)	B E	D E	B [*] A [*]	Ali and Saeed 2012
100 (4-8d)	<i>Rheum emodi</i>	Revand Hindi (drug): Metha. Ext.	350 - Water solu. 350 - Water insolu.	Preventive (1-3d) + Concomitant (4-8d)	D A	D D		Alam et al. 2005

100 (1-8d)	<i>Rubus ellipticus</i>	Fruit: Pet. Ether Ext.	200	Concomitant (1-8d)	C	A	E	Sharma and Kumar 2011
		Fruit: Etha. Ext.			A	A	A	
		Fruit: Aqua Ext.			A	A	C	
100 (1-10d)	<i>Rosmarinus officinalis</i>	Leaf : Aqua Ext.	220	Concomitant (1-10d)	A	A^A	C*	Azab et al. 2014
80 (1-21d)	<i>Rosa damascene + Cichorium intybus</i>	Flower (Rosa) + Root (Cichori um): Aqua Ext.	250 (RD) 500 (RD) 250 (CI) 500 (CI) 250 (RD) +250 (CI) 500 (RD) + 500 (CI)	Concomitant (1-21d)	E E E E E E E E C	E E E E E E E E D	E E E E E E E E E	Khaliq et al. 2014
80 (1-10d)	<i>Sesbania grandiflora</i>	Leaf : Aqua Ext. Leaf: Etha. Ext. Leaf : Acetone Ext.	300	Concomitant (1-10d)	A A A	A A A	A* A* A*	Padmalochana and Dhana rajan 2015
100 (1-10d)	<i>Strychnos potatorum</i>	Seed: Etha. Ext.	100 200 300	Concomitant (1-10d)	C A A	E B B		Varghese et al. 2011
80 (1-21d)	<i>Tamarindus indica</i>	Fruit: Hydro- Etha. Ext.	200	Concomitant (1-21d)		C	A/A*	Ullah et al. 2014b
80 (1-7d)	<i>Tecoma stans</i>	Flower: Etha. Ext.	500	Concomitant (1-7d)	E	C	A^A*	Mohan et al. 2016
80 (1-8d)		Flower: Ethyl acetate Ext.	100 200 300	Concomitant (1-8d)	C B A	E E E	D/A* C/A* A/A*	Raju et al. 2011

80 (1-7d)	<i>Terminalia chebula</i>	Aqua Ext.	125 250	Concomitant (1-7d)	A A	A A	Sivachandran and Hariharan 2012
80 (1-7d)	<i>Trema guineensis</i>	Leaf: Hydro hydro Etha. Ext.	100 200	Concomitant (1-7d)	B B	C C	Cyril et al. 2016
		Leaf : Aqua extract	100 200		A A	C C	
100 (1-14d)	<i>Trianthema portulacastrum</i>	Leaf : Etha. Ext.	200	Concomitant (1-14d)	A	A^A B	Balamurugan et al. 2009
80 (1-8d)	<i>Tribulus terrestris</i>	Fruit: Aqua ext. (Kwath)	4000	Concomitant (1-8d) + Curative (9-21d)	D	E	Kulkarni et al. 2012
				Curative (9-21d)	A	E	
100 (61-68d)	<i>Vitis vinifera</i>	Seed: n- Hexane & Meth. Ext.	40	Preventive (1-60d) + Concomitant (61-68d)		E E	Safa et al. 2010
100 (15-22d)	<i>Withania somnifera</i>	Root : Meth. Ext.	500	Preventive (1-14d) + Concomitant (15-22d)	B	B	Choudhury et al. 2014
100 (1-8d)	<i>Zea mays</i>	Shoot: Meth. Ext.	200 300 400 500	Concomitant (1-8d)	E E E E	C D E E	Sepehri et al. 2009

Table 3. Effects of herbal extracts on the recovery of biochemical markers of kidney health at different time intervals.

GM (mg/ kg B. wt)	Plant	Prep.	Herbal		Day/ Week	Prognosis: Kidney functions			References	
			Dose mg/kg B. wt	Protocol		U	C	BUN/UA		
80 (6-10d)	<i>Aloe barba- densis</i>	Leaf: Ethan. Extr.	20mL + 20mL = 40mL	Preventive (1-5d) + Concomitant (6-10d)	10d		D	D	Virani et al. 2016	
80 (16-20d)				Preventive (1-15d) + Concomitant (16-20d)	20d		A	B		
80 (26-30d)					Preventive (1-25d) + Concomitant (26-30d)	30d		A		A
80 (1-21d)	<i>Citrus aurantium</i>	Fruit: Etha. Ext.	200	Concomitant (1-21d)	1d 11d 21d		A^A A B	A^A/A[*] A^A/A[*] A^A/A[*]	Ullah et al. 2014a	
100 (11-18d)		<i>Mangifera indica</i>	Fruit: Vimang (Comm- ercial Ext.)	50 100	Preventive (1-10d) + Concomitant (11-18d)	11d 18d 11d 18d	C E C E	A D A D		Rad et al. 2011
100 (11-18d)			Fruit: Hydro- alcoholic Ext.	200 400		11d 18d 11d 18d	A^A A A C	A A^A C A^A		
100 (11-18d)	Fruit: Vimang		100	Concomitant (11-18d)	11d 18d 11d 18d	A^A E A^A D	A E A A^A			
80 (1-21d)	<i>Mentha piperita</i>	Leaf : Etha. Ext.	200	Concomitant (1-21d)	0d 11d 21d		A^A A^A B	A^A/A[*] A^A/A[*] A^A/A[*]	Ullah et al. 2013c	
80 (1-10d)		<i>Moringa oleifera</i>	Leaf : Hydro- Etha. Ext.	150 300	Concomitant (1-10d)	0d 4d 7d 10d 0d 4d 7d 10d	A^A A C E A^A A B C	A A B B A^A A^A C A		Ouédraogo et al. 2013
80 (1-21d)			Fruit : Etha. Ext.	200	Concomitant (1-21d)	0d 11 d 21 d		A B D		
100 (1-7d)	<i>Myrme- codia tuberosa</i>		Tuber : Aqua Ext.	1000 2000 4000	Concomitant (1-7d)	0 d 7 d 0 d 7 d 0 d 7 d		A E A B A B	A E A C A C	

80 (1-26d)	<i>Nigella sativa</i>	Seed oil	2mL/kg	Concomitant (1-26d)	1d 10 d 14 d 18 d 22 d 26 d	A ^A A A ^A A ^A A ^A A ^A	B A B A ^A A A	Rehman et al. 2012
80 (1-10d)				Curative (11-26d)	1d 10 d 14 d 18 d 22 d 26 d	A ^A E E D C C	E E C C D A	
80 (1-26d)		Seed oil	2mL/kg	Concomitant (1-26d)	0d 4d 8d 12d 16d 20d	A ^A C A ^A A ^A A ^A A ^A	C A A A ^A A A	Saleem et al. 2012
10 mM (31-40d)	<i>Panax ginseng</i>	Root: Aqua Ext.	100	Preventive (1-30d) + Concomitant (31-40d)	3d 10d	A E	A E	Shin et al. 2014
80 (1- 6d)	<i>Phoenix dactylifera</i>	Fruit flesh : Aqua Ext.	50% of diet	Concomitant (1- 6d)	6d	A	A	Al-Qarawi et al. 2008
				Preventive (1- 22d) + Concomitant (23- 28d)	28d	A	A	
		Pits: Aqua Ext.	Drin- king water (2:1)	Concomitant (1- 6d)	6d	A	A	
				Preventive (1- 22d) + Concomitant (23- 28d)	28d	A	A	

Table 4. Ameliorative role of plant species on biochemical markers of kidney health and oxidative stress.

Dose mg/kg B. wt	Plant	Prep.	Herbal		Prognosis						References	
			Dose mg/kg B. wt	Protocol	Kidney functions			Oxidative stress				
					U	C	BUN /UA*	LPO/ MDA*	GSH/ GPX*	CAT		SOD
100 (9-16d)	<i>Aegle marmelos</i>	Leaf:	250	Preventive	E	E	E	E*	D	D	Kore et al. 2011a	
		Aqua Ext.	500	(1-8d) + Concomitant	D	C	D	C*	C	D		
			750	(9-16d)	A	A	A	A*	B	B		
40 (1-13d)	<i>Alangium salvifolium</i>	Bark:	250	Concomitant		E	D	B*	D	B	Geetha and Ramarao 2014	
		Ethan. Ext.	500	(1-13d) + Curative		B	E	A*	D	A		
			750	(14-21d)		E	A	A*	A	A		
		750	(14-21d)		E	A	C*	D	A			
80 (1-14d)	<i>Allium sativum</i>	Clove: Aqua Homo.	500	Concomitant (1-14d)				D*	B*		Fadil et al. 2016	
80 (NA)	<i>Amorpho- phallus paeoniifolius</i>	Corm:	250	Not available	E	D		C	B		Madhurima 2010	
		Metha. Ext.	500		C	A		A	A			
100 (1-7d)	<i>Apium graveolens Var. rapaceum</i>	Dry powder of Celery	5% of diet	Curative (8-56d)	A	A	A*		C*	C	El-Ghany et al. 2012	
40 (1-14D)	<i>Aristolochia indica</i>	Leaf: Ethan.Ext.	500	Concomitant (1-14d)	A^A	C		A*	C/A*	A	A	Arivazhagan and Vimala- stalin 2014
40 (1-30d)	<i>Asarum europaeum</i>	Leaf:	200	Concomitant	C	E		E*		D	C	Mamilla- pallai and Akkiraju 2015
		Ethan. Ext.	400	(1-30d)	B	E		C*		C	B	
80 (1-15d)	<i>Bacopa monniera</i>	Shoot:	100	Concomitant	A	A	C*		B/A*	B	B	Kannan et al. 2011
		Ethan. Ext.	200	(1-15d)	A^A	A	C*		A/A*	A	A	
80 (1-7d)	<i>Barringtonia acutangula</i>	Leaf : Metha. Ext.	200	Concomitant (1-7d)	E	E		E	B*	B	D	Mishra et al. 2014
80 (1-8d)	<i>Bauhinia purpurea</i>	Bark:	400	Concomitant (1-8d)	E	E		E*	C		C	Rana et al. 2014
		Eth. Ext.			E	E		E*	C		C	
85 (21-28d)	<i>Beta vulgaris</i>	Root :	250	Preventive (1-20d) +	E	E	E*	E*		A		EL Gamal et al. 2014
		Eth. Ext.	500	Concomitant (21-28d)	E	E	E*	E*		A		
80 (1-14d)	<i>Calotropis procera</i>	Flower:	150	Concomitant	B	A				A		Javed et al. 2015
		Aqua Ext.	300	(1-14d)	A	A				A		
80 (1-6d)	<i>Casuarina equisetifolia</i>	Leaf: Metha.	300	Curative (7-35d)	C	A	A^{A*}	A*	A		A	El-Tantawy et al. 2013
80 (29-34d)		Ext.	300	Preventive (1-28d)	A	A	A^{A*}	A*	A		A	

100 (50 + 50 twice) (1-15d)	<i>Camellia sinensis</i>	Tablet of green tea Ext.	300	Concomitant (1-15d) + Curative (16-30d)		C	C		A	A		Salem et al. 2010
80 (1-7d)		Leaf: Metha. Ext.	300	Concomitant (1-7d)		E	B		A	A	A	Khan et al. 2009
80 (15-22d)	<i>Citrus medica</i>	Fruit : Etha. Ext.	250 500	Preventive (1-14d) + Concomitant (15-22d)	E E	D C	E* E*	E* E*				AL-Yahya et al. 2015
100 (1-24d)	<i>Cocos nucifera</i>	Milk	1mL/ day	Concomitant (1-24d)	A	A		A*		A	A	Ehimigbai and Ananobi 2015
80 (1-16d)		Inflo. sap powder	20	Concomitant (1-16d)	A	A	A*		B/A*	A	A	Jose et al. 2017
80 (10-19d)	<i>Cucumis sativus</i>	Seed: Hydro- ethanolic Ext.	200 400	Preventive (1-9d)		E C	D B	E E	D C	D B	C B	Pransanthi and Adikay 2016
80 (1-9d)			200 400	Curative (10-19d)		D A	C A	E D	D A	C A	C B	
100 (8-15d)	<i>Curcuma longa (CL)</i>	Rhizome: Curcu- min	200	Preventive (1-7d) + Concomitant (8-15d) + Curative (16-57d)		B	A		A/A*	A	A	El-Zawahry and Kheir 2007
80 (5-10d)			200	Preventive (1-4d) + Concomitant (5-10d)	C	B			A		A	Ali et al. 2005
100 (8-15d)			100	Preventive (1-7d) + Concomitant (8-15d)	A	B		A*		A		Bayomy et al. 2011
100 (15-21d)			200	Preventive (1-14d) + Concomitant (15-21d)	B	B		E*	A/A*	A	A	Farombi and Ekor 2006
100 (1-7d)	CL	Powder with diet	5%	Curative (8-56d)	A	B	E*		B*	C	B	El-Ghany et al. 2012
80 (36-42d)	CL	Rhizome powder: Aqua Ext.	150	Preventive (1-35d) + Concomitant (36-42d)	B	A	A*	A^{A*}	B/C*	B	A	Shalaby & Hammouda 2014
	<i>Eruca sativa (ES)</i>	Seed: Aqua Ext.	150		B	A	A*	A*	A/B*	A	A	
	<i>Petroselinum</i>	Seed:	150		B	A	A*	A^{A*}	C/C*	C	B	

	CL + PS + ES	As above	50+50 +50		A	A ^A	A [*]	A [*]	A/A [*]	A	A	
100 (6-12d)	<i>Crocus sativus</i>	Pigment crocin: Aqua extract	100	Preventive (1-5d) + Concomitant (6-12d)		E	E	A [*]				Yarijani et al. 2016
80 (6-10d)		Saffron: Aqua Ext.	40 80	Preventive (1-5d) + Concomitant (6-10d)		D C	E C	E [*] C [*]				Ajami et al. 2010
100 (1-10d)	<i>Cynara scolymus</i>	Leaf: Aqua Ext.	200 400 600	Concomitant (1-10d)		B A A	C/B [*] A/A [*] A ^A /A [*]	B A [*] A [*]				Khattab et al. 2016
100 (4-10d)	<i>Cyperus scariosus</i>	Root : Hydro alcoholic Ext.	150	Preventive (1-3d) + Concomitant (4-10d)	E	E		E [*]	A		E	Gajjar et al. 2016
100 (1-7d)				Curative (8-18d)	A	A		E [*]	E		D	
100 (4-10d)			250	Preventive (1-3d) + Concomitant (4-10d)	E	E		C [*]	C		D	
100(1-7d)				Curative (8-18d)	A	B		A [*]	E		D	
100 (3-10d)	<i>Euclea divinorum</i>	Leaf: Crude Ext. Metha. fraction Aqua fraction	100 150 200 100 100	Preventive (1-2d) + Concomitant (3-10d)		D E E B	A C D A	A [*] A [*] A [*] A [*]	A A A A	A A C A	A A A A	Feyissa et al. 2013
100 (1-6d)	<i>Elaeocarpus ganitrus</i>	Seed: Eth. Ext.	100 200 400	Concomitant (1-6d)		E E D	E/A [*] D/A [*] A/ A ^{A*}		C B A	A A A	A B C	Kakalij et al. 2014
80 (1-8d)	<i>Enicostemma littorale</i>	Whole plant Metha. Ext.	2500	Concomitant (1-8d)		E	D	D [*]	E/C [*]	A	A	Bhatt et al. 2011
120 (1-7d)	<i>Fenulago angulata</i>	Whole plant : Hydro-Etha. Ext.	200 400 800	Concomitant (1-7d)	E E C	E A ^A E	E [*] D [*] B [*]	E [*] E [*] A [*]		C C A	C E B	Valipour et al. 2016
80 (1-21d)	<i>Foeniculum vulgare</i> (FV) & <i>Solanum nigrum</i> (SN)	Seeds of FV & Fruits of SN	250 (FV) 250 (SN) 500 (FV) 500(SN) 250 (FV) + 250 SN) 500 (FV) + 500 (SN)	Concomitant (1-21d)	A A A ^A A ^A A A ^A A ^A	A A A A A A		E [*] E [*] C [*] D [*] D [*] A [*]		B B A A B A		Shaheen et al. 2014

200 (1-8d)	<i>Ficus carica</i>	Fruit:	250	Concomitant	E	E	E	E*	D	D		Kore et al. 2011b
		Hydro-Etha. Ext.	500	(1-8d)	D	C	D	C*	C	D		
			750		A	A	A	A*	B	B		
80 (1-11d)	<i>Ficus racemosa</i>	Bark:	200	Concomitant	A	A		A	A	C	C	Shivalinge and Vrushabendra 2012
		Aqua Ext.	400	(1-11d)	A	A		A	A	C	C	Ekor et al. 2006
80 (1-12d)	<i>Glycine max</i>	Seed:	500	Concomitant	A	A			A		B	Yousef and Alkreathy 2016
		Phenolic ext.	1000	(1-12d)	A	A			E		A	Srinivasan et al. 2015
100 (8-12d)	<i>Glycyrrhiza glabra</i>	Capsule	150	Preventive (1-7d)		A	A/A*	A*	C			Kang et al. 2013
40 (1-13d)	<i>Graptophyllum pictum</i>	Leaf:	75	Curative (14-23d)	A	E		A		A	E	Kalantar et al. 2016
		Phenolic Ext.	150		A	E		A		A	A	
			300		A	E		A		A	A	
100 (1-12d)	<i>Houttuynia cordata</i>	Leaf :	500	Concomitant		B	E	A*	A	A	B	Kalaiselvan et al. 2010
		Metha. Ext.	1000	(1-12d)		A	B	A^{A*}	A^A	A	A	
80 (1- 5d)	<i>Ipomoea digitata</i>	Root :	500	Concomitant (1- 5d)	A	A^A		B*	A			
80 (1-10d)	<i>Lavandula officinalis</i>	Leaf:	100	Concomitant		E	E	E*	C			
		Etha. Ext.	200	(1-10d) +		E	E	A^{A*}	B			
			400	Curative (11d)		E	B	C*	A			
100 (1-8d)	<i>Macrothelypteris oligophlebia</i>	Rhizome :	250	Concomitant		C	C	A*	D*	A	A	Wu et al. 2012
		Etha. Ext.	500	(1-8d)		A	B	A*	A*	A	A	
40 (1-13d)	<i>Mimosa pudica</i>	Root:	200	Concomitant		E	E	C*	A	B		Geetha et al. 2015
		Etha. Ext.	400	(1-13d) +		E	D	A*	B	A		
			600	Curative (14-21d)		E	B	A*	C	A		
			600	Curative (14-21d)		E	D	C*	A	A		
100 (1-6d)	<i>Mucuna pruriens</i>	Seed:	200	Concomitant	B	C		E	C	B	B	Modi et al. 2008
		Aqua Ext.	400	(1-6d)	A	A		E	A	A	A	
80 (35-42d)	<i>Momordica dioica</i>	Leaf :	200	Preventive (1-34d) +	E	E	C		C/A*	E	C	Manimala et al. 2015
		Etha. Ext.	400	Concomitant (35-42d)	D	E	A		C/A*	B	A	
40		Fruit	200		C	E		A*	C			Jain and Singhai 2010
			200		C	E		D*	A			
50 +50 (8-12d)	<i>Moringa oleifera</i>	Leaf: Powder	10,000	Preventive (1-7d) + Concomitant (8-12d)		B	A	A*	B/A*	A	A	Elazab and El-Habashi 2015

100 (1-14d)	<i>Nelumbo nucifera</i>	Flower: Eth. Ext.	200 400	Concomitant (1-14d)	A A^A	E C	C[*] B[*]	A/B[*] A/A[*]	A A	A A	Saraswathi and Shoba 2015	
80 (1-6d)	<i>Nigella sativa</i>	Seed Oil	0.2mL /kg	Concomitant (1-6d)	B	C	A[*]	A[*]		A	Yaman and Balicki 2010	
			0.4 mL/kg		A	A	A[*]	A[*]		A		
100 (1-8d)		Seed : Hexane Ext.	5 mL /kg	Concomitant (9-15d)		E		B			Begum et al. 2006	
100 (1-7d)	<i>Ocimum gratissimum</i>	Leaf : Aqua. Ext.	100 200 400	Curative (8-14d)	A A A	E D D		A A A			Ogundipe et al. 2016	
70 (1-28d)	<i>Olea europaea</i>	Leaf : Eth. Ext.	20 40 80 160	Concomitant (1-28d)	E D E	E D C		C[*] B[*] A[*] B[*]	B[*] A[*] B[*] B[*]	D C C C	A A A A	Abd El- Rahman 2016
80 (1-7d)	<i>Oroxylum indicum</i>	Whole plant : Metha. + Dichloro methane Ext.	200	Concomitant (1-7d)	E		E	E[*] B[*]	B[*] B	A	Mishra et al. 2014	
80 (1-9d)	<i>Orthosiphon stamineus</i>	Metha. Ext.	100 200 200	Curative (10-19d) Preventive	C A A	E A A	C A A				Kannappan et al. 2010	
100 (1-10)	<i>Panax ginseng</i>	Root	200	Concomitant (1- 10d)	C		C	A[*] C/A[*]		B	Karadeniz et al. 2008b	
100 (1- 8d)	<i>Pedaliium murex</i>	Fruit : Eth. Ext. Fruit : Aqua. Ext.	600	Concomitant (1- 8d)			D A	B A A A A	B A A A A	A A A A A	Sreedevi et al. 2011	
100 (1-14d)	<i>Pistacia khinjuk</i>	Fruit : Eth. Ext	150 300 600	Concomitant (1-14d)			E E A	E D A	B[*] A[*] A[*]	A A A	Ghaedi et al. 2014	
80 (1-15d)	<i>Portulaca oleracea</i>	Whole plant: Aqua. Ext.	400	Concomitant (1-15d)	A		A	A[*] B[*]	A A	A A	Mouhamed and Elshafeey 2011	
80 (4-11d)	<i>Psidium guajava</i>	Leaf: Eth. Ext.	200 400	Preventive (1-3d) + Concomitant (4-11d)	C A^A	E A^A		A A^A	A A		Patel et al. 2012	
80 (1-8d)	<i>Punica granatum</i>	Fruit : Ext.	150	Concomitant (1-8d)				A^A*			Primarizky et al. 2016	

100 (1-6d)		Fruit : Aqua Ext.	100µL	Concomitant (1-6d)	C	E	A*	A				Cekmen et al. 2013
100 (3-9d)		Flower: Hydro Ethan. Ext.	25 50	Preventive (1-2d) + Conc- omitant (3-9d)		A D	A E	D* E*				Sadeghi et al. 2015
80 (5-10d)	<i>Rhazya stricta</i>	Leaf: Aqua ext.	250 500 1000	Preventive (1-4d) + Concomitant (5-10d)	E E D	E E A		C A A	C A A			Ali 2002
100 (1-15d)	<i>Rheum emodi</i>	Rhizome: Chloro. Ext. Pet Ether Ext. Chloro. Ext. fractions	100 100 50	Concomitant (1-15d)		E E	E E					Aslam et al. 2014
					SBF* SCF* SH* CHL* RE*	E D E C E	E E D E E	E E E E E	A A A A D	A A E A C	A C A B E	
100 (1-8d)	<i>Sida rhom- boidea</i>	Leaf: Aqua Ext.	200 400	Concomitant (1-8d)	C B	C A	N A	E C	B A	D B	E C	Thounaojam et al. 2010
100 (1-8d)	<i>Sida cordifolia</i>	Root: Aqua Ext.	200 400	Concomitant (1-8d)	E E	E E	E C		A A	B A		Makwana et al. 2012
100 (1-5d)	<i>Sesamum indicum</i>	Seed oil	0.5mL /kg	Concomitant (1-5d)		A	A	A				Hsu et al. 2011
80 (4-11d)	<i>Spathodea campanulate</i>	Bark: Eth. Ext.	250 500	Preventive (1-3d) Conc- omitant (4-11d)	A^A A^A	B A^A		A^A A^A	C B			Shanmukha et al. 2010
100 (1-8d)	<i>Solanum nigrum</i>	Aqua Ext.	100	Concomitant (1-8d)	B	C			A A	A A		Priya and Venkata- lakshmi 2011
100 (1-8d)	<i>Solanum xantho- carpum</i>	Fruit: Eth. Ext.	200 400	Concomitant (1-8d)	A D	A C	A B	A C	C A^A	C E	C A^A	Hussain et al. 2012
100 (1-10d)	<i>Sonchus asper</i>	Whole plant: Meth. Ext.	100 200	Concomitant (1-10d)	B B	E C			A A	C B	C A	Khan et al. 2011
40 (1-7d)	<i>Tephrosia purpurea</i>	Leaf : Eth. Ext.	200	Curative (7-16d) Concomitant (1-7d)	B C	E E		E* C*	A C		C A	Jain et al. 2013
80 (1-14d)	<i>Terminalia ivorensis</i>	Stem bark :Eth. Ext.	100 800 1000	Concomitant (1-14d)	C A A	E C D		B A A	C B A	B A A	B A A	Ansah et al. 2016
80 (1-15d)	<i>Terminalia bellerica</i>	Stem: Eth. Ext. Aqua Ext.	500	Concomitant (1-15d)	D B	A A	C* A*	C* A*	B A	B A	B A	Fatima and Sultana 2016
80 (1-8d)	<i>Sphaeranthus indicus</i>	Whole plant: Eth. Ext.	150 300	Curative (9-19d)		E A	E E		A/A* A/A*	A A	A A^A	Mathew et al. 2009

80 (1-14d)	<i>Trachyspermum ammi</i>	Seed: Aqua Ext.	300 600	Concomitant (1-14d)	A A ^A	A A	A A ^A		A A		Ishaq et al. 2015	
400	<i>Trianthema portulacastrum</i>	Whole plant powder	1000	NA	B	A	A [*]	C	C/A [*]	C	Vallabi and Elango 2015	
100 (1-8d)	<i>Trichosanthes dioica</i>	Leaf: Meth. Ext.	200 400	Concomitant (1-8d)	E C	E C	C B	E A ^A	C A	C B	Gupta et al. 2015	
100 (1-8d)	<i>Trigonella foenum graecum</i>	Seed: Aqua Ext.	200 400	Concomitant (1-8d)	E D	E E		E [*] E [*]	D C	D D	Kaur et al. 2016	
100 (1-10d)	<i>Urtica dioica</i>	Leaf: Eth. Ext.	100	Concomitant (1-10d)	A	A		D [*] A [*]	A E	A	Salih 2015	
80 (1-7d)	<i>Vitex negundo</i>	Root: Meth.a. + Dichloro methane Ext.	200	Concomitant (1-7d)	D	D		C [*]	B [*]	B	A	Mishra et al. 2014
80 (8-21d)	<i>Vitis vinifera</i>	Seed Ext.	150	Preventive (1-7d) + Concomitant (8-21d)	A	C		C [*]	B /A [*]			El- Ashmawy et al. 2006
100 (1-7d)	<i>Zingiber officinale</i>	Rhizome Powder	5% of diet	Curative (8-56d)	A	A	A [*]		D [*]	C	B	El-Ghany et al. 2012
100 (1-7d)		Rhizome: gingerol fraction	6.25 12.5 25	Concomitant (5-7d) Curative (8-9d)	C A A ^A	C B A	E E B	E [*] D [*] A [*]	D C A	C C B		Rodrigues et al. 2014

Fractions of chloroform Ext.: SBF = NaHCO₃ fraction, SCF = Na₂CO₃ fraction, SHF = Sodium hydrate fraction, CHL= solutes in left out chloroform layer, RE = ppt formed after adding NaHCO₃ in chloroform Ext.

Table 5. Ameliorative role of plant species on biochemical markers of kidney health and oxidative stress at different time intervals.

GM (mg/Kg B. wt)	Plant	Prep- eration	Herbal		Day	Prognosis						References	
			Dose mg/kg B. wt	Protocol		Kidney functions			Oxidative stress				
					U	C	BUN/ UA*	LPO/ MDA*	GSH/ GPX*	CAT	SOD		
150 (1-10d)	<i>Boerhavia diffusa</i>	Aqueous Ext. of whole plant	200 400	Concomitant (1-10d)	1d 11d	A ^A A	A		B [*]	A		Sawardekar and Patel 2015	
80 (1-8d)	<i>Hygrophila spinosa</i>	Ethan. Ext. of whole plant	50 250	Curative (9-30d)	1d 9d 15d 30d	A ^A E D	A ^A E E					Bibu et al. 2010	
					30d	A ^A	E		C	E	E	E	
					1d 9d 15d 30d	A ^A E A A ^A	A ^A E A ^A A ^A						
80 (1-8d)	<i>Eclipta alba</i>	Leaf: Meth. Ext.	300 600	Concomitant (1-8d)	0d 8d 0d 8d	A ^A A ^A A ^A A ^A	A ^A C A C	A ^A A A ^A		E A A	E A	E	Dungca 2016
80 (1-9d)	<i>Verbascum thapsus</i>	Leaf: Meth. Ext.	250	Concomitant (1-9d)	1d 3 d 5 d 9 d	A C A ^A D	A A A A	A C C					Pal et al. 2013
			500		1 d 3 d 5 d 9 d	A B B C	A A A A	A B B A	D D E	E C	C C	C A	

Seed: *Glycine max*, *Kalonchoe*, *Phyllanthus amarus*, *Sesamum*, *Mucuna*, *Cucumis sativus*

Fruit: *Rubus elliptus*, *Phoenix dactylifera*, *Petalium*, *Pistacia*, *Solanum xanthocarpum*

Milk: *Cocos nucifera*

Whole plant: *Boerhavia*, *Orthosiphon*, *Portulaca*

Curcuma rhizome in combination with seeds of *Petroselinium* and *Eruca* improved kidney function to **good category**.

- **Moderate** protection/recovery in kidney functions was observed when plant parts of following plant species were administered to the gentamicin treated animals (Table 2-5).

Belowground organs

Root: *Andrographis*, *Daucus*

Rhizome: *Curcuma longa*, *Macrothelypteris*, *Nelumbo*

Aboveground organs

Leaf: *Aristolochia*, *Bauhinia variegata*, *Dalbergia*, *Eclipta*, *Houttuynia*, *Rosamarinus*, *Sida rhomboidea*, *Trema*, *Verbascum* and *Trianthema*

Shoot: *Bacopa*, *Terminalia bellerica*, *Terminalia ivorensis*

Seed: *Elettaria*, *Eruca*, *Lagenaria*, *Petroselinium*, *Strychnos*, *Vitis vinifera*

Flower: *Nelumbo nucifera*, *Pongamia pinnata*

Fruit: *Bauhinia purpurea*, *Tamarindus indica*, *Morus alba*

Whole plant: *Trianthema*, *Phyllanthus niruri*

- The plant parts of following species belonged to **excellent category** for protection/recovery of oxidative stress and antioxidant levels (Table 4,5).

Leaf: *Houttuynia*, *Psidium*

Whole plant: *Sphaeranthus*

Fruit: *Punica*

- The plant parts of following plant species belonged to **good category** for protection/recovery of oxidative stress and antioxidant levels (Table 4, 5).

Belowground organs

Root: *Sida cordifolia*

Rhizome: *Curcuma longa*, *Macrothelypteris*

Corm: *Amorphillus*

Aboveground organs

Leaf: *Casuarina*, *Camellia sinensis*, *Cynara*, *Euclea*, *Graptophyllum*, *Ocimum gratissimum*, *Rhazya*

Shoot: *Bacopa*, *Terminalia bellerica*

Bark: *Alangium*, *Terminalia ivorensis*

Flower: *Calotropis*, *Cocos nucifera*

Fruit: *Petalium*, *Pistacia*

Milk: *Cocos nucifera*

Seed: *Punica*, *Sesamum*, *Nigella*, *Trachyspermum*

Whole plant: *Boerhavia*, *Orthosiphon*

Combination: *Curcuma* (rhizome) + *Petroselinium* (seed) + *Eruca* (seed)

Foeniculum (seed) + *Solanum nigrum* (fruit)

The plant parts of following plant species belonged to **moderate category** for protection/recovery of oxidative stress and antioxidant levels (Table 4, 5).

Belowground organs

Root: *Vitex*, *Glycyrrhiza*, *Ipomea digitata*, *Mimosa pudica*, *Panax*

Aboveground organs

Leaf: *Aegle*, *Aristolochia*, *Eclipta*, *Lavandula*, *Momordica dioica*, *Moringa*, *Olea*, *Sida rhomboidea*, *Tephrosia*, *Trichosanthes*

Bark: *Ficus racemosa*, *Spathodea*

Flower: *Cocos*, *Momordica dioica*, *Nelumbo*

Seed: *Eruca*, *Elaeocarpus*, *Foeniculum*, *Petroselinium*, *Glycine*, *Vitis*

Whole plant: *Portulaca*, *Ferulago*, *Sonchus*, *Trianthema*

Punarnava (*Boerhaavia diffusa*), *Gokshur* (*Tribulus terrestris*), *Haritaki* (*Terminalia chebula*), *Neem* (*Azadirachta indica*), *Daruharidra* (*Berberis aristata*) and *Patol* (*Trichosanthes dioica*) are some of the species used in treating kidney disorders in the Ayurvedic treatment. *Bilvadi agada* is an ayurvedic drug having nephroprotective role in gentamicin exposed Wistar rats (Kanna et al.2015). It is mixture of *Aegle marmelos*, *Ocimum sanctum*, *Pongamia pinnata*, *Valeriana wallichii*, *Cedrus deodara*, *Phyllanthus emblica*, *Terminalia chebula* and *Terminalia bellirica*, *Zinziber officinale*, *Piper nigrum*, *Piper longum*, *Curcuma longa*, *Berberis aristata* and *goat's urine*.

Interestingly, *Aegle marmelos* (Moderate), *Boerhaavia diffusa* (Excellent), *Curcuma longa* (Moderate), *Ocimum sanctum* (Good), *Pongamia pinnata* (Moderate), *Tribulus terrestris* (Moderate), *Terminalia chebula* (Excellent), *Terminalia bellirica* (Moderate),

Tricosanthes dioica (Moderate) and *Zinziber officinale* (Moderate) were also found renoprotective in the experimental studies (Table 2,4).

Out of 142 species (angiosperms) screened in the gentamicin treated animals, majority (105 species) were effective (moderate – excellent) for renoprotection and reducing oxidative stress. Many of them are used in preparing renoprotective drugs in the Ayurvedic system. Plant species of excellent category may be explored for ameliorative role to other nephrotoxicants singly as well as in various combinations. The recommended dose of gentamicin for human is 20µg/kg body weight while several plant species were excellent in term of protection to experimental animals even at its higher doses (80-100mg/kg body weight), and therefore, there is a good scope for their clinical trials in the human beings treated with gentamicin.

Presence of renoprotective properties among such a vast number of species highlights role of biodiversity in the welfare of mankind. *Cuscuta* considered as an obnoxious stem parasite is a very interesting example that nature blesses to the mankind because of its excellent renoprotective properties. Several of renoprotective species are cultivated for human consumption while others grow wild on wastelands, farmlands and forests. Interestingly many of them are used daily in the preparation of the Indian cuisines.

Interestingly few of the most promising renoprotective plant species grow luxuriantly on wastelands, farmlands and forests in the Rajasthan. Thirty two plant species growing wild or naturalised in the State of Rajasthan have been screened for their reno-protective role. These are; *Abutilon indicum*, *Acacia senegal*, *Adhatoda zeylanica*, *Aegle marmelos*, *Aloe barbadensis*, *Bacopa monniera*, *Bauhinia purpurea*, *Bauhinia variegata*, *Boerhavia diffusa*, *Boswellia serrata*, *Calotropis procera*, *Citrullus colocynthis*, *Cuscuta reflexa*, *Dalbergia sissoo*, *Eclipta alba*, *Gomphrena celosioides*, *Ipomoea aquatica*, *Nelumbo nucifera*, *Pedaliium murex*, *Phyllanthus niruri*, *Portulaca oleracea*, *Sida cordifolia*, *Solanum nigrum*, *Solanum xanthocarpum*, *Sonchus asper*, *Tamarindus indica*, *Terminalia bellerica*, *Terminalia chebula*, *Trianthema portulacastrum*, *Tribulus terrestris*, *Vitex negundo* and *Withania somnifera*. Out of these 32 species, 3 species were excellent (*Acacia senegal*, *Cuscuta reflexa*, *Eclipta alba*) while others were good to moderate for renoprotection. Natural calamities such as drought, diseases

(microbial and viral) and insect damages affect their growth little since these have evolved through natural selection. Their cultivation may be promoted on wastelands and farmlands in the rural areas to prosper sustainable development since these are less demanding in comparison to conventional crops. Various government organizations should come forward in developing technology for cultivation of elite renoprotective species, network for their collection and storage practice after harvest and linkage with Pharma industry. Such interventions will benefit farmers particularly those engaged in subsistence farming while country will be benefitted by their export because of increasing demand for herbal drugs globally.

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