

## Nephroprotective Plants: A Review

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*Abstract: Medicinal plants may serve as a vital source of potentially useful new compounds for the development of effective therapy to combat a variety of kidney problems. Many herbs have been proven to be effectual as nephroprotective agents while many more are claimed to be nephroprotective but there is lack of any such scientific evidence to support such claims. Developing a satisfactory herbal therapy to treat severe renal disorders requires systematic investigation of properties like acute renal failure, nephritic syndrome and chronic interstitial nephritis. Herbal medicines possess curative properties due to the presence of their chemical components. The present review is aimed to elucidate the list of nephroprotective medicinal plants, which are scientifically proved in treating renal disorders.*

**Keywords:** Medicinal plants, nephroprotective agents, renal disorders.

### 1. Introduction:

Man and his domesticated animals have since the time immemorial been largely dependent on plants for the essential for their existence by way of food, clothing, shelter and medicines etc, besides various other uses.<sup>1</sup> Since disease, decay and death always coexisted with life, the study of diseases and their treatment must have also been contemporaneous with the dawn of the human intellect. The primitive man must have used as therapeutical agents and remedial measures those things which he was able to procure most easily. There is no authentic record of medicines used by the primitive man. But the Rig-Veda which is the oldest book in the library of man supplies curious information on the subject.

In his work on plants and animal under domestication, Darwin says "From innumerable experiments made through dire necessity by savages of every land, with the result handed down by tradition, the nutritious, stimulating and medicinal properties of the most of unpromising plants were probably first discovered.

The doctrine of signatures would all account for the use of several plants as medicinal agents. The reason for the extensive use of vegetable drugs may be the fact that plants are everywhere at hand, their number is very great and their focus are distinct and peculiar and these are procured without trouble.

It is greatly to the credit of people of India, that they were acquainted with a far large no. of medicinal plants than the natives of any other country on the face of the earth.<sup>2</sup> Many Indian fruits, grains and vegetables employed as useful dietary articles forms a chief factor in the cure of diseases, as well as preservation of health and good nutrition.<sup>3</sup> Herbs have always been the principle form of medicine in India and they are becoming popular throughout the world, as people strive to stay healthy in the face of chronic stress and pollution and to treat illness with medicine that work in concert with the body's own defences. Thus medicinal plants play an important role in the lives of rural people.<sup>4</sup> A plant is said to be medicinal when "at least one part possesses therapeutic properties.

One may recognize four stages in the development of the implements in the treatment of disease. In the first stage, crude drug were employed, prepared in the roughest manner, such as powered cinchona or metallic antimony. In the next stage, these were converted to more active and more manageable forms, such as extractions or solutions, watery or alcoholic. In the third stage, the pure active principles, separated from the crude drugs were employed Eg: morphine and quinine. In the 4<sup>th</sup> stage, instead of

attempting to extract out medicine from the natural products in which they are contained, such substances are synthesized which possess particular desired actions.<sup>2</sup>

## 2. ANATOMY & PHYSIOLOGY OF KIDNEY [28]

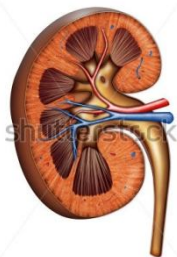


Figure: Section of Kidney

Paired kidneys are reddish bean shaped organs about 10-12cm long, 5-7cm wide, 3cm thick and has a mass of 135-150g.<sup>10</sup> The kidneys lie on the posterior abdominal wall, one on each side of vertebral column, behind the peritoneum and below diaphragm. They extend from the level of 12<sup>th</sup> thoracic vertebrae to 3<sup>rd</sup> lumbar vertebrae.<sup>9</sup> Near the centre of concave boarder is a deep vertical fissure called the renal hilum, through which the ureter emerges from the kidney along with blood vessels, lymphatic vessels & nerves.

The kidney consists of two distinct region, outer renal cortex & inner renal medulla. The urine collects to calyx and then to renal pelvis which empties into ureter. The functional unit of kidney is nephron and there are about 1million nephron in each kidney.<sup>10</sup>

**Nephron** [29]: The functional unit of the kidney is the nephron. Nephrons have several function related to haemostasis. They filter blood that is they permit some substance to pass into the kidney, as the filtered liquid (filtrate) moves through the nephron.

### 2.1. STRUCTURE OF NEPHRON [28]

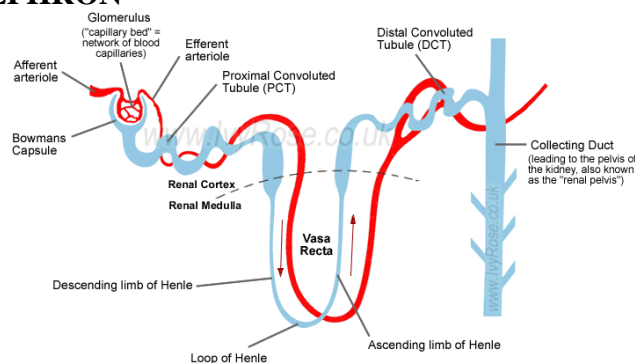


Figure: Nephron

It consists of a tubule closed at one end, and the other end opening into a collecting tubule. The closed end form Bowmann's capsule, which encloses the glomerulus. The remaining parts of nephron is about 3cm long & consist of

- Proximal convoluted tubule (PCT)
- Henley's loop
- Distal convoluted tubule

These nephrons are packed tightly to make up the kidney parenchyma.<sup>9</sup>

**2.2.. FUNCTIONS OF KIDNEY:** The main function of kidney can be categorized as-

- Formation of urine
- Water & electrolyte balance
- Production of hormones & enzymes

In the resting adult, kidney receives 1.2-1.3 litres of blood/min. In an adult, the GFR averages 120ml/min. The collecting duct of kidney is an area of fine control of ultrafiltrate composition & volume, where final adjustment in electrolyte composition is made by the action of mineralocorticoid & ADH. The hypertonicity of medullary interstitium plays an important role in concentrating the urine. The kidney not only excretes the metabolic substances, but also toxic agents from the body.<sup>6</sup> Hence kidney becomes one of the important targets for the toxicity of agents more than other organs in body. Factors that make kidney particularly prone to actions of nephrotoxicity include,

- High levels of toxins are delivered to the kidney's large blood supply.
- The large surface area of renal tubular epithelium provide site for toxin interaction & uptake.
- The availability of specific transport mechanisms that mediate cellular uptakes.
- The normal concentrating mechanism of kidney can increase concentration of toxins.

The presence of the metabolic processes in the renal tubular cell, can release toxic components & induce damage.

### **2.3. RENAL FAILURE**

The term renal failure primarily denotes failure of the excretory function of kidney, leading to the retention of nitrogenous waste products of metabolism in blood. In addition, there is failure of regulation of fluid & electrolyte balance along with endocrine dysfunction.<sup>7</sup> The renal failure is fundamentally categorized into acute renal failure & chronic renal failure.

### **2.4. ACUTE RENAL FAILURE**

There is a sudden and severe reduction in the glomerular filtration rate and kidney function that is often reversible over days or week if treated. There is oliguria or anuria accompanied by metabolic acidosis due to retention of H<sup>+</sup>, electrolyte imbalance, accumulation of other mainly nitrogenous waste products, and, if not associated with severe fluid loss, retention of water, i.e. substance normally excreted in urine are retained in the body.

Early recognition of ARF is critical, because it is often asymptomatic. It is detected by measuring serum creatinine level & is more specific than measurement of blood urea nitrogen (BUN). There are many causes of ARF which could be,

**2.5. Pre renal ARF:** It is due to under perfusion of kidney. It accounted for 21% of ARF cases. It can be thought of as "a good kidney looking at a bad world." It is quickly reversible with appropriate therapy.

**2.6. Post renal ARF:** It is caused by obstruction of urinary tract. It accounted for 10% of cases.

**2.7. Intrinsic ARF:** It is due to disease in parenchyma. It accounted for 69% of cases. Among the renal causes of acute renal failure, acute tubular necrosis is more common accounting for 85% of incidence. ATN occurs due to either ischaemia or toxins. The toxins can be either exogenous or endogenous. The exogenous agents are radiocontrast agents, cyclosporins, antibiotics, chemotherapeutic agents, organic solvents, acetaminophen, & illegal abortifacients.<sup>7</sup>

## 2.8. CHRONIC RENAL FAILURE

It is a syndrome characterized by progressive & irreversible deterioration of renal due to slow destruction of renal parenchyma, eventually terminating in death when sufficient no. of nephrons have been damaged.<sup>8</sup> Various causes are glomerulonephritis, diabetes mellitus, chronic pyelonephritis, hypertension.<sup>9</sup> antineoplastic agents like cyclophosphamide, viniristne, cisplatin etc.<sup>7</sup>

**3. NEPHROTOXIC AGENTS:** Drugs, diagnostic agents & chemical are well known to be nephrotoxic. The following are some of the important nephrotoxic agents.<sup>11</sup>

### A) Heavy metal

Mercury, arsenic, lead, bismuth

### B) Antineoplastic agents

#### 1. Alkylating agent

Cisplatin, cyclophosphamide

Nitrosoureas: Streptozotocin, Carmustine, Lomustine & Semustine

#### 2. Antimetabolites

High dose Methotrexate, Cytosine Arabinose, high dose 6-thioguanine, 5-fluorouracil

#### 3. Antitumour antibiotics

Mitomycin, Mithramycin, Doxorubicin

Biologic agents

Recombinant leukocyte and interferon

### C) Antimicrobial agents

Tetracycline, Acyclovir, Pentamidine, Sulphadiazine, Trimethoprin, Rifampicin

### D) Aminoglycosides

Gentamicin, Amikacin, Kanamycin, Streptomycin

### E) Miscellaneous

1. Radiocontrast agents

2. Non-steroidal anti-inflammatory agents: Ibuprofen, Indomethacin, Aspirine

## 4. NEPHROPATHIES DUE TO TOXIC MECHANISM

Toxins may directly affect membrane permeability. Example: with amphotericin & polyene antibiotics. They can act by increasing the activity of membrane phospholipase & by inhibiting normal reconstruction of the membrane. Phospholipid degradation products, lysophospholipids & free fatty acids have membrane detergent properties. Even in the absence of major changes in membrane permeability, the failure of plasma membrane pumps will cause potential injury changes in the cation homeostasis of the cell eg: Na-K-ATPase & Ca ATPase pumps. The activity of each may be affected by limitation of ATP, compromise of function of enzyme protein or changes in the phospholipid

microenvironment surrounding the enzyme.<sup>12</sup> Toxin may also lead to remodelling of the surface of the renal tubular cell, thus changing the area available for transportation.

Numerous experiments have shown during cellular insult, an early and common change is the accumulation of intracellular Calcium. This increase is found at plasma membrane, in mitochondria and endoplasmic reticulum & in cytoplasm. An increase in intracellular Ca can modify the permeability of internal membrane of the mitochondria & thus change in the electrochemical gradient across it, which decreases the oxidative phosphorylative capacity of the mitochondria. Disordered permeability will then lead to loss of enzymes & nucleotides.<sup>12</sup>

In rats given gentamicin, the appearance of cellular necrosis & renal failure is well so related with an increase in Ca in renal cortex & mitochondria. The intracellular metabolism of drugs leads to the formation of reactive metabolites, which are toxic for cell, as are free radicals. The superoxide ion normally formed, during oxidation forms hydroxyl radicals, which lead to lipid peroxidation. This in turn causes oxidative deterioration of polyunsaturated lipids of membranes & causes the dramatic modification of structure & function. The toxic agent reduces the concentration of antioxidants, superoxide dismutase, glutathione, catalase, vit.E, ascorbic acid which are the protective tissues that reacts & remove reactive oxygen species.<sup>4</sup> Nephrotoxin induced changes in tubule cells integrity may be sublethal or lethal. Such prelethal changes include development of abnormally enlarged lysosomes & myeloid bodies, loss of brush border membrane & vacuolization & dilation of the endoplasmic reticulum. Enzymuria resulting from loss of some of these damaged membranes in the urine has been used to gauge the occurrence of renal tubule cell injury & to follow it serially.<sup>11</sup>

## 5. TOXIC ACTIVATION AND FREE RADICAL PRODUCTION

Numerous *in vivo* & *in vitro* studies have demonstrated the effect of free radicals like reactive oxygen metabolites viz. superoxide, hydroxyl ions & hydrogen peroxide which are important mediators of tissue injury. Free radicals can be defined as chemical species possessing unpaired electrons, which are formed by hemolytic cleavage of a covalent bond of a molecule, by loss of a single electron from a normal molecule or by the addition of a single electron to a normal molecule. Free radicals may be positively charged (cation radical), negatively charged (anion radical) or neutral. These free radicals have very short half-life, high reactivity & damaging activity towards macromolecules like proteins, DNA & lipids. These species may be either oxygen derived reactive oxygen species (ROS) or nitrogen derived reactive nitrogen species (RNS). ROS includes superoxide, hydroxyl, hydroperoxyl, peroxy, alkoxy as free radicals & hydrogen peroxide, hypochlorous acid, ozone & singlet oxygen as non-radicals. The RNS are mainly nitric oxide, peroxy nitrile, & nitrogen dioxide & dinitrogen trioxide. Free radical injury & oxidative stress have been implicated in many renal diseases like acute renal failure, IgA nephropathy, anaemia of chronic renal failure & ischaemic kidney.

Superoxide ion & hydroxyl radical are formed during natural oxidative reaction by the action of endoplasmic reticulum, mixed function oxidases, NADPH oxidases, xanthine oxidases etc. The hydroxyl radical is highly reactive species formed by process of Fenton's reaction. The hydroxyl radical can also be formed from oxidative metabolism of arachidonate by cyclooxygenase in the presence of hydroperoxides.<sup>4</sup>

Many studies have shown that infusion of ROS from a chemical or cellular origin produces glomerular dysfunction & injury to mesangial or endothelial cells with associated altered glomerular permselectivity

(proteinuria). H<sub>2</sub>O<sub>2</sub> perfusion via renal artery can produce mesangiolysis & endothelial cell detachment.<sup>13</sup>

### 5.1. FORMATION OF FREE RADICAL

Free radical can be formed in three ways:

- By hemolytic cleavage of covalent bond of a normal molecule, with each fragment retaining one of the paired electrons.
- By loss of single electron from normal molecule.
- By addition of a single electron to a normal molecule.<sup>14</sup> They are constantly generated in vivo.

### 5.2. PRODUCTION OF FREE RADICALS IN CELLS

Free radicals are produced by<sup>15</sup>

- Ionising radiation.
- Accidental or deliberate
- Some enzymes utilize free radicals at their active sites in the process of catalysis. Activated phagocytes also deliberately generate free radicals such as superoxide.
- These are produced by the leakage of electron transport chain such as those in mitochondria & Endoplasmic reticulum.
- Metabolites of certain compounds exert toxicity through free radical mechanism eg. Carbon tetrachloride is metabolized to toxic trichloromethyl free radicals by CYP 450 in liver.<sup>14</sup>

### PLANT SHOWING NEPHROPROTECTIVE ACTIVITY

Name of plants	Family	V. Name	Part used	Main Active Principle
1. <i>Abelmoschus esculentus L</i>	Malvaceae	Bhendi	fr, s, rt	Carotene, folic acid, thiamine riboflavin, tocopherol palmitic acid
2. <i>Abrus precatorius L</i>	Leguminosae	Gunja	rt, l	Glucoside, Alkaloid,
3. <i>Abutilon indicum L</i>	Malvaceae	Atibalaa	rt, b	Asparagines, Mucilage, Tannin, alkaloids
4. <i>Acacia arabica (Willd)</i>	Leguminosae	Babul	l	Tannin, Flavonoid
5. <i>Acacia catechu L</i>	Mimosaceae	Khair	b	Flavonoid, Tannin
6. <i>Acacia sinuate (Lour) Merrill</i>	Mimosaceae	Cikakai	p, b	Saponin, Flavonoid, Tannin
7. <i>Achilla millefolium L</i>	Compositae	Gandana	wp	Alkaloid, Essential oil
8. <i>Achyranthes aspera L</i>	Amaranthaceae	Aghada	r b	Alkaloids, saponin, Tannin Oil
9. <i>Adiantum Lunulatum Burm</i>	Polypodiaceae	Hansraj	l	Flavonoids, terpenoids, Tannin, Volatile oil
10. <i>Aerva lanata L Juss</i>	Amaranthaceae	Kupuri madhuri	wp	Amyrin, camphensterol, $\beta$ -sitosterols, flavonoides, glycoside
11. <i>Alangium salvifolium Wang</i>	Alanglanceae	Ankol	b	Alkaloids, Alkaline Lamarkine,
12. <i>Allium cepa L.</i>	Liliaceae	Onian	bu	Essential oil organic sulphide Flavonoid, phenolic acid
13. <i>Amaranthus spinosus L.</i>	Amaranthaceae	Kateli-chaulai	rt	Alkanes, Quinoline, sterols
14. <i>Anogeissus latifolia (Roxb)</i>	Combretaceae	Dhavara	b, rt	Tannins, calcium, gum, Quercetin
15. <i>Anona Squamosa L</i>	Annonaceae	Custard apple	l, s	Alkaloid Aminoacids, camphor, anonaie
16. <i>Apium graveolens L.</i>	Umbelliferae	Ajmoda	rt	Volatile oil, Flavonoids, Alkaloid
17. <i>Arachis hypogaea L</i>	Fabaceae	Mung-phali	s	Vit e, Flavonoid, Tannins
18. <i>Arctium lappa L.</i>	Compositae	Great Burdock	rt	Flavonoid Hexasaccharide, tannin volatile oil

19. <i>Asclepias syriaca L.</i>	Asclepiadaceae	Mohari	rt	Glucol, asclepiadin
20. <i>Asparagus racemosus Willd</i>	Liliaceae	Shatavari	rt	Oil, saponin
21. <i>Atropa belladonna L.</i>	Solanaceae	Belladonna	rt	Alkaloid, Tanin, starch,
22. <i>Azadirachta indica L</i>	Meliaceae	Nimb	l	Alkaloid, steroid, a. acid Azardin, Resin, tannine, fixed oils
23. <i>Bacopa monnieri L</i>	Scrophulariaceae	Brahmni	l	Essential oil, Alkaloid
24. <i>Balanites roxburghii L</i>	Balanitaceae	Hingol	rt, fr	Steroidal Saponin, Amino acid
25. <i>Baliospermum montanum Willd</i>	Euphorbiaceae	Danti	rt, l, s	Phorbol esters, Terpenoid, Flavonoids, hydrocarbon, sitosterol, D-glucoside
26. <i>Bambusa bamboo Von</i>	Arundinaceae	Bamboo	l	Cholin, betain, Nuclease, Urease,
27. <i>Bambusa nutans L</i>	Arundinaceae	Bamboo	l	Cholin, betain, Nuclease, Urease,
28. <i>Barleria prionitis Linn.</i>	Aceanthaceae	Kate-Koranti	fl, l	Essential oil, Flavonoid Glycoside, $\beta$ -sitosterol
29. <i>Basella alba L</i>	Basellaceae	Indian spinach	l	Iodine, fluorine, carotenoids Flavonoid
30. <i>Benincasa</i>	Cucurbitaceae	White gourd	fr, s	Glucose, mannitol $\beta$ -sitosterol, protene
<b>Talele et al. Int J Pharm Pharm Sci, Vol 4, Issue 1, 8-16 11 hispida (Thunb) Cogn</b>				
31. <i>Boerhavia diffusa L.</i>	Nyctaginaceae	Punarnava	wp	Flavonoid, Alkaloids, triacontanol, hentriacontane, $\beta$ -sitosterol
32. <i>Boswellia serrata roxb</i>	Burseraceae	Dhupali, Salai	g	Tanins, pentosans, lignin, holocellulose, $\beta$ -sitosterol
33. <i>Brassica oleracea L</i>	Brassicaceae	Cabbage	l	Essential, amino acid
34. <i>Butea monosperma Lam</i>	Fabaceae	Palash	l	Glucoside Butine, proteolytic lipolytic enzyme, Flavonoid
35. <i>Cajanus cajan L millsp</i>	Fabaceae	Tuvar	l, s	Amino acid, galactosid
36. <i>Carica papaya L.</i>	Caricaceae	Papaya	fr	Alkaloid, papain enzymes.
37. <i>Cardiospermum halicacabum L.</i>	Sapindaceae	Kanphuti	rt, l	Alkaloid, $\beta$ -sitosterol
38. <i>Cassia absus L.</i>	Caesalpiniaceae	Ran Kulith	s, l	Alkaloid, Sitosterol, Glucoside.
39. <i>Cassia fistula L.</i>	Caesalpiniaceae	Bahava	l, po	glycoside, Tannin, Flavonoid.
40. <i>Chelidonium majus L.</i>	Papaveraceae	Celandine	fl	Alkaloids, Flavonoids
41. <i>Cocos nucifera L</i>	Arecaceae	Coconut	fr, s, l	Saccharose sorbitol alcohol, ketones
42. <i>Commiphora mukul Engl</i>	Burseraceae	Guggal	g	Guggulsterone, Flavonoid.
43. <i>Cordia dichotoma Forst</i>	Boraginaceae	Bhoker	fr	Alkaloid, Tannin
44. <i>Curculigo orchioides Gaertn</i>	Amaryllidaceae	Kalimusli	rt	Saponine, curculigo, phenolic glycoside
45. <i>Cynodon dactylon Pers</i>	Gramineae	Durva	rt	$\beta$ -ionone, 2-propionic 4-hydroxybenzoic
46. <i>Cyperus rotundus L</i>	Cyperaceae	Nagermot ha	rh	Essential oil, cyperene, cyperol, starch $\beta$ -sitosterol
47. <i>Datura metel L</i>	Solanaceae	Datura	l, fl	Alkaloid, scopolamine, hyposcyamine, atropin, vit C
48. <i>Daucus carota L</i>	Umbelliferae	Carrot	rt, l	Oil, carotol essential oil, Flavones
49. <i>Demostachya bipinnata L</i>	Compositae	Kush	rt	Alkaloid, Terpenoid
50. <i>Desmodium gangeticum L</i>	Fabaceae	Salpan	rt	Alkaloids
51. <i>Digitalis Purpurea L</i>	Scrophulariaceae	Hrutpatri	l	Glycosides, flavonoids, saponin
52. <i>Dolichos biflorus L</i>	Leguminosae	Kulith	s	Urease, lectin carbohydrate
53. <i>Elettaria cardamomum Maton.</i>	Zingiberaceae	Chhoti Elaichi	s	Palmitic acid
54. <i>Ficus religiosa L</i>	Moraceae	Piple	b, l	Arabinose, mannose, glucose $\beta$ -sitosterol D-glucoside
55. <i>Foeniculum vulgare Mill</i>	Apiaceae	Saunf	s, fl	Oil, Methyl Chavicol, Limonene Essential oil

## 6. PHARMACOLOGICAL EVOLUTION OF SOME IMPORTANT PLANT-



*Aerva lanata*



*Pongamia pinnata*



*Salviae radix*



*Ginkgo biloba*



*Cassia auriculata*



*Nigella sativa*



*Drynaria fortunei*



### **6.1. EFFECT OF *Aerva lanata* ON GENTAMICIN & CISPLATIN MODELS OF ACUTE RENAL FAILURE<sup>17</sup>**

The ethanol extract of entire plant of *Aerva lanata* was studied for its nephroprotective activity in cisplatin & gentamicin induced acute renal injury in albino rats of either sex. In the curative regimen, the extract at dose levels of 75, 150 & 300 mg/kg showed dose dependant reduction in the elevated blood urea and serum creatinine & normalized the histopathological changes in the cisplatin model. In the gentamicin model, the rats in the preventive regimen also showed good response to the ethanol extract at 300 mg/kg. The findings suggest that the ethanol extract of *Aerva lanata* possesses marked nephroprotective activity with minimal toxicity and could offer a promising role in the treatment of acute renal failure caused by nephrotoxins like cisplatin & gentamicin.

### **6.2 PROTECTIVE EFFECT OF *Pongamia pinnata* FLOWERS AGAINST CISPLATIN & GENTAMICIN INDUCED NEPHROTOXICITY IN RATS<sup>18</sup>**

When ethanolic extract of flowers of *Pongamia pinnata* (300 & 600 mg/kg) was administered orally in rats followed by cisplatin (5 mg/kg ip), toxicity of cisplatin as measured by loss of body weight, elevated blood urea & serum creatinine declined significantly. Similarly in gentamicin (40 mg/kg sc) induced renal injury, the extract 600 mg/kg normalized the raised blood levels of urea & serum creatinine levels. Reversal of cisplatin & gentamicin renal cell damage was confirmed on histopathological examination. The results suggested that the protective effects is through antioxidant property of two flavonoids kaempferol and 3,5,6,7,8-penta methoxy flavone.

### **6.3. *Salviae radix* EXTRACT PREVENTS CISPLATIN INDUCED ACUTE RENAL FAILURE IN RABBITS<sup>19</sup>**

The present study was carried out to determine if *Salviae radix* extract (SRE) exerts a beneficial effect against cisplatin induced renal failure in rabbits. Rabbits were pretreated with SRE orally followed by cisplatin injection (5 mg/kg ip). Cisplatin injection caused a reduction in GFR, which was accompanied by an increase in serum creatinine levels. The fractional Na<sup>+</sup> excretion and lipid peroxidation were also increased. All these changes were prevented by SRE pretreatment. Cisplatin treatment invitro in renal cortical slices increased LDH release and lipid peroxidation, which were prevented by SRE and its effect may be attributed to its antioxidant action.

### **6.4. PROTECTIVE EFFECT OF *glycyrrhizin* ON GENTAMICIN INDUCED ACUTE RENAL FAILURE IN RATS<sup>20</sup>**

The effects of glycyrrhizin (200 mg/kg/day) on renal function in association with the regulation of aquaporin 2 water channel in rats with gentamicin (100 mg/kg/day)-induced acute renal failure was investigated. Polyuria in rats with gentamicin-induced acute renal failure was associated with down-regulation of renal aquaporin 2 in the inner and outer renal medulla, and cortex. Glycyrrhizin administration restored the expression of aquaporin 2 with paralleled changes in urine output. Changes in renal functional parameters, such as creatinine clearance, urinary osmolality, and solute-free reabsorption, accompanying acute renal failure were also partially restored after administration of glycyrrhizin. Histological changes in rats with gentamicin-induced acute renal failure were also

abrogated by glycyrrhizin treatment. The above results suggest that glycyrrhizin treatment could ameliorate renal defects in rats with acute renal failure induced by gentamicin.

### **6.5. *Ginkgo biloba* EXTRACT AMELIORATES GM INDUCED NEPHROTOXICITY IN RATS<sup>21</sup>**

The effect of *Ginkgo biloba* (EGb), a plant extract with an antioxidant effect, has been studied on gentamicin-induced nephrotoxicity in male wistar rats. *Ginkgo biloba* extract (300 mg/kg BW) was administered orally concurrently with gentamicin (80 mg/kg BW). Estimations of urine creatinine, glucose, blood urea, serum creatinine, plasma and kidney tissue MDA were carried out after gentamicin treatment. Kidneys were examined using histological techniques. Blood urea and serum creatinine were increased with gentamicin. Creatinine clearance was significantly decreased with gentamicin. Changes in blood urea, serum creatinine and creatinine clearance induced by gentamicin were significantly prevented by *Ginkgo biloba* extract. There was a rise in plasma and kidney tissue MDA with gentamicin, which was significantly reduced to normal with *Ginkgo biloba* extract. Histomorphology showed necrosis and desquamation of tubular epithelial cells in renal cortex with gentamicin, while it was normal with *Ginkgo biloba* extract. These data suggest that supplementation of *Ginkgo biloba* extract may be helpful to reduce gentamicin nephrotoxicity.

### **6.6. EFFECT OF *Cassia auriculata* ROOT EXTRACT ON CISPLATIN & GM INDUCED RENAL INJURY<sup>22</sup>**

The ethanol extract of the roots of *Cassia auriculata* was studied for its nephroprotective activity in cisplatin- and gentamicin-induced renal injury in male albino rats. In the cisplatin model, the extract at doses of 300 and 600 mg/kg body wt. reduced elevated blood urea and serum creatinine and normalized the histopathological changes in the curative regimen. In the gentamicin model, the ethanol extract at a dose of 600 mg/kg body wt. reduced blood urea and serum creatinine effectively in both the curative and the preventive regimen. The extract had a marked nitric oxide free-radical-scavenging effect. The findings suggest that the probable mechanism of nephroprotection by *C.auriculata* against cisplatin- and gentamicin-induced renal injury could be due to its antioxidant and free-radical-scavenging property.

### **6.7. *Aged garlic extract* ATTENUATES GM INDUCED RENAL DAMAGE AND OXIDATIVE STRESS IN RATS<sup>23</sup>**

Aged garlic extract (AGE), an antioxidant, has a protective role in this experimental model of male Wistar rats were studied. AGE was given at a dose of (1.2 mL/kg/12 hours) followed by GM (70 mg/kg/12 hours). Nephrotoxicity was made evident by:

- the increase in blood urea nitrogen and plasma creatinine
- the decrease in plasma glutathione peroxidase (GPx) activity and the urinary increase in N-acetyl-beta-D-glucosaminidase activity and total protein
- necrosis of proximal tubular cells
- Increase in the renal levels of oxidative stress markers: nitrotyrosine and protein carbonyl groups and the decrease in manganese superoxide dismutase (Mn-SOD), GPx, and glutathione reductase (GR) activities.

These alterations were prevented or ameliorated by AGE treatment. Furthermore, AGE prevented the GM-induced the protective effect of AGE was associated with the decrease in the oxidative stress and

the preservation of Mn-SOD, GPx, and GR activities in renal cortex. These data suggest that AGE may be a useful agent for the prevention of GM-nephrotoxicity.

#### 6.8. THE EFFECTS OF *Nigella sativa* OIL ON GM NEPHROTOXICITY IN RATS<sup>24</sup>

In this work, tested whether oral treatment of rats with *N. sativa* oil (0.5, 1.0 or 2.0 ml/kg/day) would ameliorate nephrotoxicity of GM (80 mg/kg/day im) concomitantly with the oil. Nephrotoxicity was evaluated histopathologically and by measurement of concentrations of urea, creatinine and total antioxidant status (TAS) in plasma and reduced glutathione (GSH) and TAS in kidney cortex. The results indicated that GM treatment caused moderate proximal tubular damage, significantly increased the concentrations of creatinine and urea, and decreased that of TAS and GSH. Treatment with *N. sativa* oil produced a dose-dependent amelioration of the biochemical and histological indices of GM nephrotoxicity that was significant at the two higher doses used, and it increased GSH and TAS concentrations in renal cortex and enhanced growth. The results suggest that *N. sativa* may be useful in ameliorating signs of GM nephrotoxicity in rats.

#### 6.9. FLAVONOID OF *Drynaria fortunei* PROTECTS AGAINST ARF<sup>25</sup>

The flavonoid fraction (FF) from *Drynaria fortunei* was investigated to determine its biological activity expression in three acute renal failure animal models Guinea pigs & mercuric chloride treated mice. Guinea pigs received 100 mg/kg of gentamicin & 10 mg/kg of FF. FF treatment prevented the GM toxicity, ie; the increase in BUN and creatinine levels. Mice were treated once with 6 mg/kg of mercuric chloride, followed by 10 mg/kg of FF. BUN and creatinine levels were found to be significantly higher on the mercuric chloride treatment and is ameliorated by FF treatment. In conclusion, the present study suggests that FF prevents nephrotoxicity, improves kidney function and promotes kidney primary epithelial tubular cell regeneration.

#### 6.10. NEPHROPROTECTIVE ACTION OF *Tribulus terrestris* AND *Crataeva nurvala* IN ALBINO RATS<sup>27</sup>



Nephrotoxic model was developed in male albino rats by administering GM. The aqueous extract of fruits of *T. terrestris* (65 or 130mg/kg) and *C. nurvala* (70 or 145mg/kg) after GM administration. Urine was examined for sugar, albumin, RBC & epithelial cells. Histopathological changes were also noted. The drug showed a dose dependant nephroprotective action against GM toxicity. The results indicate that the two indigenous plants would ameliorate renal effects in albino rats with acute renal failure induced by GM. Diuretic properties of the plant are due to the presence of a large amount of nitrates as well as the essential oil which occurs in seeds.

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