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THE POTENTIAL ROLE OF HERBALS AS NEPHROPROTECTIVE – A NOVEL APPROACH

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ABSTRACT

Nephrotoxic injury is damage to either of the kidneys that results from exposure to toxic materials or usually through ingestion of that toxic substance. The kidneys are the primary organs of the urinary system that purifies the blood by removing wastes from it and excreting them in the form of urine. Every day, the kidneys filter about 45 gal (180 l) of blood, about four times as much as the amount that passes through other organ. Because of this high volume, the kidneys are more often exposed to toxic chemicals in the blood and are very vulnerable to injury from those substances. Exploration of traditional medicine is a mysteriously interesting now days because of its scientific significant and economic importance, which is a important task for the ethnobotanists. The people of India were well acquainted with a large number of indigenous medicinal plants than the natives of any other countries. Herbs are the principle form of medicine in India and they are becoming popular throughout the world. This includes so many species of ethnomedicinally important nephroprotective plants in and around the india. This review article provides comprehensive account on nephroprotective indigenous plants (with their botanical name, Family, parts used and the active principles, present in that plant).

Keywords: Nephrotoxicity, Nephroprotective plants, Herbals.

INTRODUCTION

Nephrotoxic injury is commonly caused by drugs such as antibiotics, analgesics, and contrast agents. In some cases, such as the aminoglycosides and amphotericin B, the drug itself will damage the kidneys [1]. When the kidneys are exposed to such toxic agent and the duration of exposure, either accidentally or intentionally damage can occur in a number of ways, depending upon the agent. People are using herbal medicines from centuries onwards for safety, efficacy, cultural acceptability and for lesser side effects. Plant and plant products have been utilized with varying success to cure and prevent diseases throughout the world [2]. Therapeutically important drugs can be developed from plant sources which are used in traditional systems of medicines. Indian traditional system of medicine is based on the empirical knowledge of observations and the experience and more than 5000 plants are used by different ethnic communities in India [3].

Nephroprotectives are the substances which possess protective activity against nephrotoxicity. Medicinal plants have curative properties due to the presence of various active principles in them [4]. Ancient literature has illustrated various herbs for the cure of kidney disease [5]. Administration of various medicinal plants possessing nephroprotective activity along with different nephrotoxic agents may attenuate its toxicity [6]. Ancient literature has prescribed various herbs for the cure of kidney disease. The term "Pashanabeda" has been cited in literature to identify a group of plants, which have been extensively used in indigenous system of medicine to dissolve urinary calculi & stones. Eg: *Aerva lanata*, *Crataeva nurvala*, *Pongamia prinnata* etc. Some other plants mentioned in literature include *T. terrestris*, *O. sanctum*, *Zea mays* etc [7]. In the present review an attempt is made to list out the plants that showed nephroprotective activity.

Plants showing potential against Nephrotoxicity

Protective effect of glycyrrhizin on Gentamycin induced acute renal failure in rats

The effects of glycyrrhizin (200 mg/kg/p.o) on renal function in association with the regulation of aquaporin 2 water channel in rats with Gentamycin (100 mg/kg/i.p) induced acute renal failure was investigated. Polyuria in rats with Gentamycin-induced acute renal failure was associated with down-regulation of renal aquaporin 2 in the inner and outer renal medulla, and cortex [8]. 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. The results suggest that glycyrrhizin treatment could ameliorate renal defects in rats with acute renal failure induced by Gentamycin method.

Effect of *Aerva lanata* on Gentamycin & Cisplatin models of acute renal failure in rats

The ethanol extract of entire plant of *Aerva lanata* was studied for its nephroprotective activity in Cisplatin & Gentamycin 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 levels & normalized the histopathological changes induced by Cisplatin model [9]. In the Gentamycin model, the rats in the preventive regimen showed good response to the ethanolic extract at 300 mg/kg. The findings suggest that the ethanol extract of *Aerva lanata* possesses nephroprotective activity with minimum toxicity and offer a promising role in the treatment of acute renal failure caused by nephrotoxins like Cisplatin & Gentamycin.

Salviae radix extract prevents Cisplatin induced acute renal failure in rabbits

The study was carried out to determine that *Salviae radix* extract (SRE) exerts a beneficial effect against Cisplatin induced renal failure in rabbits [10]. Rabbits were pretreated with *Salviae radix* extract orally followed by Cisplatin injection (5 mg/kg ip). Cisplatin injection caused reduction in glomerular filtration rate, which was accompanied by an increase in serum creatinine levels. The fractional Na^+ 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 *Salviae radix* extract and its effect may be attributed to its antioxidant action.

Ginkgo biloba extract ameliorates Gentamycin induced nephrotoxicity in rats

The effect of *Ginkgo biloba* (EGb) extract has been studied in Gentamycin-induced nephrotoxicity in male wistar rats. *Ginkgo biloba* extract (300 mg/kg BW) was administered orally and concurrently with Gentamycin (80 mg/kg BW). Estimation of urine creatinine, glucose, blood urea, serum creatinine, plasma and kidney tissue was carried out after Gentamycin treatment [11]. Kidneys were examined using histological technique. Blood urea and serum creatinine were increased in Gentamycin treated groups and Creatinine clearance was significantly decreased. Changes in blood urea, serum creatinine and creatinine clearance induced by Gentamycin were significantly prevented by *Ginkgo biloba* extract. The rise in plasma and kidney tissue with Gentamycin, were significantly reduced to normal with *Ginkgo biloba* extract. Histomorphology showed necrosis and desquamation of tubular epithelial cells in renal cortex with Gentamycin, while it was normal with *Ginkgo biloba* extract [12]. These results suggest that supplementation of *Ginkgo biloba* extract may be helpful to reduce the nephrotoxicity induced by Gentamycin.

Effect of *cassia auriculata* root extract in Cisplatin & Gentamycin induced renal injury

The ethanol extract of the roots of *Cassia auriculata* was studied for its nephroprotective activity in Cisplatin- and Gentamycin-induced renal injury in male albino rats. In the Cisplatin model, the extract at doses of 300 and 600 mg/kg body weight reduced elevated blood urea and serum creatinine and normalized the histopathological changes in the curative regimen [13]. In the Gentamycin model, the ethanol extract at a dose of 600 mg/kg reduced blood urea and serum creatinine levels effectively in both the curative and the preventive regimen [14]. The extract was found to have significant nitric oxide free-radical-scavenging effect. These findings suggest that the probable mechanism of nephro-protection by *C.auriculata* against Cisplatin-and Gentamycin induced renal injury may be due to its antioxidant and free-radical-scavenging activity.

Flavonoid of *Drynaria fortunei* protects against acute renal failure

The flavonoid fraction (FF) from *Drynaria fortunei* was to investigate its biological activity expression in acute renal failure animal models i.e., Guinea pigs & mercuric chloride treated mice. Guinea pigs received 100 mg/kg of Gentamycin & 10 mg/kg of DF. DF treatment prevented the GM induced toxicity, i.e, the increase in creatinine levels [15].

Table No.1 Herbal formulations used in the treatment of kidney stones by native folklore [45]

Botanical name	Family	Method by which they used in the treatment of kidney stone
<i>Abrus precatorius L.</i>	Fabaceae	35-60ml of Leaf juice, taken early in the morning for 15 days[43]
<i>Abutilon indicum (L.)</i>	Malvaceae	3leaves taken orally early in the morning in empty stomach for 15 days [42]
<i>Aerva lanata (L.) Juss.</i>	Amaranthaceae	50-60 ml of extract with 5ml of extract of seeds of <i>Cuminum cyminum</i> and sugar taken orally once a day for 10 – 15 days [9]
<i>etBeta vulgaris L.</i>	Amaranthaceae	One glass of beet root juice taken early in the morning for 7 days [20]
<i>Celosia argentea L.</i>	Amaranthaceae	1gm of seeds powder taken once a day for 4-5 days.[21]
<i>Citrus medica L.</i>	Rutaceae	1fruit taken orally daily twice a day [22]
<i>Coccinia grandis (L.)</i>	Cucurbitaceae	20-40ml of extract of <i>Cuminum cyminum</i> seeds sugar and add 200 ml with <i>Phoenix sylvestris</i> , given orally once a day for 5 days [23]
<i>Colocasia esculenta (L.)</i>	Araceae	100ml of juice of rhizome was taken once a day for 15 days [24]
<i>Cornus canadensis</i>	Cornaceae	Drinking steeped plant [34]
<i>Cynodon dactylon (L.)</i>	Poaceae	10-20 ml of extract of roots, taken orally twice a day for 8 -10 days [25]
<i>Epigaea repens</i>	Ericaceae	Infusion of leaves [36]
<i>Gomphrena serrata L.</i>	Amaranthaceae	5ml of juice of leaves taken once a day for 5 days [26]
<i>Gossypium herbaceum</i>	Malvaceae	Unripe fruits roasted in burning ash and extract of fruit taken orally [27]
<i>Juniperus communis</i>	Cupressaceae	twig and berry tea [41]
<i>Kalanchoe pinnata Lam.</i>	Crassulaceae	Leaves Paste with <i>Eclipta prostrata</i> in equal proportion taken orally one or two pills twice a day for 20 days. [57]
<i>Lagenaria siceraria mol.</i>	Cucurbitaceae	5ml of seeds powder taken with sheep milk daily 1 time for 7days [44]
<i>Larix laricina</i>	Pinaceae	Chewing of gum [50]
<i>Ledum groenlandicum</i>	Ericaceae	Leaves infusion [56]
<i>Pedaliium murex L</i>	Pedaliaceae	Dried seed powder was taken with [52]
<i>Pinus strobus</i>	Pinaceae	Tea of plant parts [49]
<i>Sarracenia purpurea</i>	Sarraceniaceae	Drinking steeped root [48]
<i>Sesamum orientale L.</i>	Pedaliaceae	Whole plant with <i>Achyranthes aspera</i> whole plant burnt to ash, taken orally 15ml twice a day for 41 days [51]
<i>Solanum virginianum L.</i>	Solanaceae	Root powder mixed with curd and taken once a day for 7 days [54]
<i>Strychnos potatorum L.</i>	Loganiaceae	1 tea cup decoction of roots had taken orally twice a day for 20 days [53]
<i>Syzygium cumini (L.)</i>	Myrtaceae	Fruit powder was taken 1 spoon with water twice a day for 15 days [54]
<i>Tribulus terrestris L.</i>	Zygophyllaceae	5 gm of powdered fruits with 1 tea cup of milk taken orally twice a day for 2 weeks [57]
<i>Vigna unguiculata (L.)</i>	Fabaceae	100 ml of decoction of seeds taken p.o twice a day for 30 days [58]

Mice were treated once with 6 mg/kg of mercuric chloride, followed by 10 mg/kg of DF and creatinine levels were found to be significantly higher on the mercuric chloride treatment and is ameliorated by DF treatment. In conclusion, the present study suggests that DF prevents nephrotoxicity, improves kidney function and promotes kidney primary epithelial tubular cell regeneration [16].

Aged garlic extract attenuates Gentamycin induced renal damage and oxidative stress in rats

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

Nephrotoxicity was made evident by the following:

- 1) Increase in blood urea nitrogen and plasma creatinine
- 2) Decrease in plasma glutathione peroxidase (GPx) activity and the urinary increase in N-acetyl-beta-D-glucosaminidase activity and total protein
- 3) Necrosis of proximal tubular cells
- 4) 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 [17].

This alteration were prevented or ameliorated by AGE treatment. Furthermore Aged garlic extract prevented the nephrotoxicity. 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 the renal cortex [18]. This data suggest that the Aged garlic extract may be a useful agent for the treatment of nephrotoxicity.

The effects of *nigella sativa* oil in Gentamycin nephrotoxicity in rats

In this work, it was tested that whether the oral treatment of rats with *N. sativa* oil (0.5, 1.0 or 2.0 ml/kg/day) could reduce nephrotoxicity of Gentamycin (80 mg/kg/day IM) concomitantly with the oil.

Nephrotoxicity was evaluated by histopathologically and by measurement of concentration of urea, creatinine, Total Antioxidant Status (TAS) in plasma, reduced glutathione (GSH) and TAS in cortex of kidney. The results indicated that the treated groups caused moderate proximal tubular damage, significantly increased the concentration of creatinine and urea, and decreased that of TAS and GSH. Treated with *N. sativa* oil produced a dose-dependent amelioration of the biochemical and histological indices of Gentamycin nephrotoxicity that was significant at the two higher doses used, and it increased GSH and TAS concentrations in renal cortex and enhanced growth [19]. The result suggests that *N. sativa* may be useful in ameliorating the signs of Gentamycin nephrotoxicity in rats.

The role of ginsenoside-rd in Cisplatin induced acute renal failure

Ginsenoside-Rd has been proved to decrease the severity of renal injury induced by Cisplatin, in which proximal urinaferous tubules represent the main site of injury. When ginsenoside-Rd was given orally at a dose of 1 or 5 mg/kg body weight/day prior to Cisplatin injection, the activities of the antioxidation enzymes superoxide dismutase and catalase were higher, while malondialdehyde levels in serum and renal tissue were lower in the treated rats than in the controls.

Table No.2 Plants containing protective activity against Cisplatin induced Nephrotoxicity

Plant Name	Family	Chemical constituents
<i>Aerva lanata</i>	<i>Amaranthaceae</i>	Botulin, β -sitosterol, Amyrin, Hentriacontane.
<i>Aerva javanica</i>	<i>Amaranthaceae</i>	Isoquercetin, 5 methylmellein, 2- hydroxy-3-O- β primeveroside naphthalene-1,4-dione [9]
<i>Bauhinia variegata</i> linn	<i>salpiniacea</i>	stigmasterol, flavone glycosides, lupeol, kaempferol-3-glucoside, β -setosterol [51]
<i>Cassia auriculata</i>	<i>fabaceae</i>	Tannins, Di-(2-ethyl) hexyl phthalate, Alkaloids, Resins,[39]
<i>Carica papaya</i>	<i>Caricaceae</i>	Flavonoids, Phenols, Alkaloids, Protein, Sterols, Terpenoids,[40]
<i>Ceratonia siliqua</i>	<i>Fabaceae</i>	Flavonoids [36]
<i>Cucurbita pepo</i>	<i>Cucurbitaceae</i>	Flavonoids, Phenols, Alkaloids, Protein, Sterols, Terpenoids, [37]
<i>Dichrostachys cinera</i>	<i>Mimosaceae</i>	Fixed oils, Steroids, Flavonoids,[38]
<i>Ficus religiosa</i>	<i>Moraceae</i>	Amino acids and Tannins [28]
<i>Kigelia Africana</i>	<i>Bignoniaceae</i>	Iridoids, Naphthoquinones, Flavonoids, Terpenes, Tannins, Steroids, Saponins and Caffeic acid [29]
<i>Pongamia pinnata</i>	<i>Papilionaceae</i>	Flowers Pongamol, Protien, Alkaloids, Tannins, Sugar, Resin and Fatty oil [10]
<i>Vernonia cinerea</i>	<i>compositae</i>	Triterpenoids like α -amyirin, β -amyirin and lupeol [31]

Table No.3 Plants containing protective activity against N-nitroso dimethyl amine induced Nephrotoxicity

Plant name	Family	Chemical constituents
<i>Euphorbia neriiifolia</i>	<i>Euphorbiaceae</i>	Saponins, Flavonoids, Tannins [32]

Table No.4 Plants containing protective activity against Alloxan induced Nephrotoxicity

Plant name	Family	Chemical constituents
<i>Tectona grandis</i>	<i>Verbanaceae</i>	Lapachol, Dehydro- α -lapachone, Methyl quinizarin & Squalene [33]

Table No.4 Plants containing protective activity against Alloxan induced Nephrotoxicity

Plant name	Family	Chemical constituents
<i>Ginkgo biloba</i>	<i>Ginkgoaceae</i>	Flavonoids, bilobalide, Ginkgolide A, GinkgolideB[13]

The levels of urea nitrogen and creatinine in serum were decreased in rats treated with ginsenoside-Rd. Decreased urinary levels of glucose, sodium and potassium reflected a protective action against the renal dysfunction caused by Cisplatin [20]. In addition, it was demonstrated that ginsenoside-Rd cultured proximal tubule cells exposed to Cisplatin.

Nephroprotective action of *Tribulus terrestris* and *Crataeva nurvala* in albino rats

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) were administered in injection route. Urine was examined for sugar, albumin, RBC & epithelial cells. Histopathological changes were also observed [21]. The extracts showed a dose dependant nephroprotective action against GM induced toxicity. The results indicate that the two plants extracts ameliorated the toxicity induced by Gentamycin.

Protective effect of *Pongamia pinnata* flowers against Cisplatin & Gentamycin induced nephrotoxicity in rats

When ethanolic extract of flowers of *Pongamia pinnata* (300 & 600mg/kg) was administered orally in rats followed by Cisplatin (5mg/kg ip) the toxicity of Cisplatin as measured by loss of body weight, elevated blood urea & serum creatinine were declined significantly. Similarly in Gentamycin (40mg/kg,sc) induced renal injury, the extract 600mg/kg normalized the increased blood levels of urea & serum creatinine

levels. Reversal of Cisplatin & Gentamycin renal cell damage was confirmed on histopathological examination. The results suggest that protective effect might be due to antioxidant property of two flavonoids such as kaempferol and 3,5,6,7,8-penta methoxy flavone [22].

Effect of *ocimum sanctum* aqueous leaf extract on gm induced nephrotoxicity in rats

Nephrotoxicity was induced in rats by GM (180mg/kg/day ip) *O.sanctum* aqueous leaf extract(OS) was given orally at a dose of 100 mg/kg/day along with GM. Concurrent administration of OS significantly prevented rise in levels of serum creatinine, blood urea & plasma MDA which are elevated by GM. It also significantly prevented the histological damage caused by GM. The results suggested that OS probably by virtue of its antioxidant property prevented GM induced nephrotoxicity in rats [23].

Renoprotective effect of grape seed extract in ethylene Glycol induced nephrotoxicity in mice

Nephroprotective activity was studied in ethylene glycol (EG) induced nephrotoxicity of Grape seed extract in mice. Mice received grape seed extract 100mg/kg bw, after EG (2ml/kg po) administration. Grape seed extract in mice produced significant reduction of urinary LDH, blood urea, creatinine levels & dilated tubules lined by normal intact epithelium indicating recovery [24]. The results suggest that the renoprotective effect of *Vitis vinifera* seed extract is due to its antioxidant activity.

Evaluation of nephroprotective effect of indian medicinal plants in experimental Gentamycin induced nephrotoxicity

The effect of administration of indian medicinal plants, *Withania somnifera*, *Embllica officinalis*, *Glycyrrhiza glabra* on BUN, serum creatinine, bodyweight, renal histopathology were evaluated with administration of Gentamycin (150mg/kg/day) in female rats. Concurrent administration of IMPs & alpha lipoic acid prevented the rise in BUN, serum creatinine, kidney to varying degrees [24]. Thus indian medicinal plants showed as protective agents against experimental nephrotoxicity.

Cytoprotective role of *Solanum nigrum* against gm induced kidney cell (vero cell) damage in-vitro

The ethanol extract of the whole plant of *Solanum nigrum* was tested in-vitro for its cytoprotection against Gentamycin-induced toxicity on Verocells. Cytotoxicity was significantly inhibited by the Trypan blue exclusion assay and mitochondrial dehydrogenase activity assay. The test extracts exhibited significant hydroxyl radical scavenging potential, thus suggesting its probable mechanism of cytoprotection.

The effect of treatment with the medicinal plant *Rhazya stricta* on Gentamycin induced nephrotoxicity

Crude aqueous extract of *Rhazya stricta* leaves (0.25, 0.5 and 1g/Kg) was given orally to rats and thereafter, concomitantly with Gentamycin (80mg/Kg/day). Nephrotoxicity were evaluated histopathologically and biochemically by measuring the levels of urea and creatinine, reduced glutathione (GSH), lipid peroxidation and superoxide dismutase (SOD) activity in kidney cortex. The results suggested that a dose-related amelioration in the indices of toxicity was noted when the two higher doses of the plant extract were given. The two higher doses, significantly and dose-dependently increased SOD activity and GSH concentration, and decreased that of lipid peroxides in the cortex of kidney. These results suggest that *R.stricta* aqueous extract may contain compounds that could potentially ameliorate Gentamycin nephrotoxicity in rats.

CONCLUSION

The present review concludes the potential role of different medicinal herbs possesses the protective effect against nephrotoxicity and some of them can be proved by animal models induced by different screening models in this review article.

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