THE POTENTIAL ROLE OF HERBALS AS NEPHROPROTECTIVE – A NOVEL APPROACH

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INTRODUCTION

Nephrototoxic 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 sited 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 & 300mg/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 300mg/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 (5mg/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].
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.

| Plant Name           | Family          | Chemical constituents                                                                 |
|----------------------|-----------------|---------------------------------------------------------------------------------------|
| *Aerva lanata*       | Amaranthaceae   | Botulin, β-sitosterol, Amyrin, Hentriacantane.                                         |
| *Aerva javanica*     | Amaranthaceae   | Isoquercetin, 5 methylmellein, 2- hydroxy-3-O-β primeveroside naphthalene-1,4-dione [9] |
| *Bauhinia variegata linn* | salpiniacea  | Stigmasterol, flavone glycosides, lupeol, kaempferol-3-glucoside, β-sitosterol [51]   |
| *Cassia auriculata*  | fabaceae        | Tannins, Di-(2-ethyl) hexyl phthalate, Alkaloids, Resins,[39]                          |
| *Carica papaya*      | Caricaceae      | Flavonoids, Phenols, Alkaloids, Protein, Sterols, Terpenoids,[40]                     |
| *Ceratonia siliqua*  | Fabaceae        | Flavonoids [36]                                                                        |
| *Cucurbita pepo*     | Cucurbitaceae   | Flavonoids, Phenols, Alkaloids, Protein, Sterols, Terpenoids, [37]                    |
| *Dichrostachys cinera* | Morosaceae  | Flavonoids, Phenols, Alkaloids, Protein, Sterols, Terpenoids, [38]                    |
| *Ficus religiosa*    | Moraceae        | Amino acids and Tannins [28]                                                           |
| *Kigelia Africana*   | Bignoniaceae    | Iridoids, Naphthoquinones, Flavonoids, Terpenes, Tannins, Steroids, Saponins and Caffic acid [29] |
| *Pongamia pinnata*   | Papilionaceae   | Flowers Pongamol, Protien, Alkaloids, Tannins, Sugar, Resin and Fatty oil [10]        |
| *Vernonia cinerea*   | composita       | Triterpenoids like α-amyrin, β-amyrin and lupeol [31]                                  |
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 it’s antioxidant activity.
Evaluation of nephroprotective effect of Indian medicinal plants in experimental Gentamicin induced nephrotoxicity

The effect of administration of Indian medicinal plants, Withania somnifera, Emblica officinalis, Glycyrrhiza glabra on BUN, serum creatinine, bodyweight, renal histopathology were evaluated with administration of Gentamicin (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 Vero cells. 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 Gentamicin 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 possess 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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