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(REVIEW ARTICLE)

A review of medicinal plants with nephroprotective effects

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Abstract

In this study, online databases including Web Science, PubMed, Scopus and Science Direct, were searched to investigate an alternative nephroprotective remedy against gentamicin, paracetamol, profenofos, D galactosamine (D-GalN), chronic-stress, sepsis and cytotoxic drugs induced kidney injury as well as streptozotocin induced diabetic nephropathy, in addition to chemically induced nephrolithiasis. The review showed that many medicinal plants can attenuate the biochemical, functional and structural renal toxicities of a wide range of drugs and toxins representing effective nephroprotective alternatives.

Keywords: Medicinal plants; Pharmacology; Nephroprotective; Toxicology

1. Introduction

Kidneys play an important part in the maintenance of our endocrine and acid-base balance, blood pressure, erythropoiesis etc. Nephrotoxicity is one of the most common kidney problems and occurs when body is exposed to a drug or toxin [1-2]. Many medicinal plants exhibited nephroprotective effect of renal tissues against kidney injuries induced by gentamicin, paracetamol, profenofos, D galactosamine (D-GalN), chronic-stress, sepsis and cytotoxic drugs induced kidney injury as well as streptozotocin induced diabetic nephropathy, in addition to chemically induced nephrolithiasis via modulating of the expression of inflammatory mediators, oxidative stress and apoptotic mediators [3-4]. The current review will highlight the medicinal plants with nephroprotective effects.

2. Plants with nephroprotective effects

2.1. Bauhinia variegate

The antioxidant and nephroprotective effect in gentamicin-induced nephrotoxicity of the ethanolic and aqueous extracts of root of *Bauhinia variegata* Linn (200 and 400 mg/kg bw, orally) was examined in rats. Both ethanolic and aqueous root extracts of *Bauhinia variegata* produced significant free radical scavenging activity. Both extracts produced significant nephroprotective activity in gentamicin induced nephrotoxicity model as evident by decrease in elevated serum creatinine, serum urea, urine creatinine and BUN levels, which was further confirmed by histopathological study. Nephroprotective activity of the ethanolic and aqueous extracts of root of *Bauhinia variegata* at a dose of 400 mg/kg bw was evaluated by gentamicin and cisplatin induced nephrotoxicity in rats. Both extracts showed nephroprotective activity in both gentamicin and cisplatin induced nephrotoxicity models as evident by decrease in serum creatinine, serum urea, urine creatinine and BUN levels in extract treated groups which was elevated by gentamicin and cisplatin in the respective models, which also confirmed by histopathological study [5-6].

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2.2. Benincasa hispida

The nephroprotective activity of hydro-alcoholic extract of *Benincasa hispida* whole fruit extract was investigated in paracetamol induced nephrotoxicity in rats. Treatment with hydro-alcoholic extract of *Benincasahispida*whole fruit extract at doses of 200 and 400 mg/kg bw prevented the paracetamol - induced nephrotoxicity and oxidative impairments of the kidney, as evidenced by a significantly reduced in kidney weight, blood urea, blood creatinine, urinary glucose, urinary potassium level and also increased body weight, urine volume, urinary creatinine and blood total protein level. Hydro-alcoholic extract of *Benincasa hispida* whole fruit extract significantly increased the tissue GSH levels and reduced lipid peroxidation levels. Furthermore, it was confirmed by the histopathological observation that the degenerative changes caused by paracetamol were also restored by treatment with hydro-alcoholic extract of *Benincasahispida*whole fruit extract [7-8]. It was also produced nephroprotective activity against mercury poisoning in rats [9-10].

2.3. Brassica nigra

The protective effect of the methanol extract of *Brassica nigra* leaves was investigated against Dgalactosamine (D-GalN)-induced hepatic and nephrotoxicity in Wistar rats. The D-GalN-induced toxicity was evident from a significant increase ($p < 0.001$) in the serum and tissue inflammatory markers in toxic rats, when compared with the control (saline alone treated animals). The *Brassica nigra*pretreated groups (200 and 400 mg/kg bw) showed significant ($p < 0.001$) reduction in the DGalN-induced toxicity as obvious from biochemical parameters. Histopathological observations confirm the protective effect of *Brassica nigra* leaf extract by reduction in hepatic and renal tissue damage. Accordingly, the crude methanol extract of *Brassica nigra* leaf lacks inherent toxicity and exhibits hepatic and nephroprotective [11-12].

2.4. Brassica rapa

The effect of the ethanol extract of the roots of *Brassica rapa* (EBR) to ameliorate cisplatin-induced nephrotoxicity was studied in terms of oxidative stress, as characterized by lipid peroxidation, reactive oxygen species (ROS) production, and glutathione (GSH) depletion in LLC-PK1 cells. Pretreatment of cells with EBR prevented cisplatin-induced decreases in cell viability and cellular GSH content. The effect of EBR was then investigated in rats given EBR for 14 d before cisplatin administration. A single dose of cisplatin (7 mg/kg, i.p.) caused kidney damage manifested by an elevation in blood urea nitrogen (BUN), serum creatinine, and urine lactate dehydrogenase (LDH) levels. Also, renal tissue from cisplatin-treated rats showed a significant increase in malondialdehyde (MDA) production, and in the activities of aldehyde oxidase (AO) and xanthine oxidase (XO). A significant decrease in the activities of antioxidant enzymes, such as, glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase (CAT) was observed in cisplatin-treated rats versus saline treated normal group. In contrast, rats given EBR showed lower blood levels of BUN and creatinine, and of urinary LDH. Moreover, EBR prevented the rise of MDA production and the induction of AO and XO activities. This extract also recovered the reduced activities of GPx, SOD and CAT [13].

2.5. Bryophyllum calycinum

The aqueous extract of the leaves possessed potent nephroprotective activity in gentamycin-induced nephrotoxicity in rats. The plant hydroalcoholic extract was also found to exert significant diuresis and antiurolithitic activity when given by oral and ip route to rats [14-17].

2.6. Carum carvi

The renoprotective effect of aqueous extract of *Carum carvi* seeds was evaluated in experimentally induced diabetic nephropathy (DN) in rodents. The diabetic rats showed a variable increase in the serum levels of glucose, urea, creatinine, total urinary protein and microalbuminuric levels. Body weight decreased and urine volume increased in the diabetic groups. 30 and 60 mg/kg body weight of *Carum carvi* significantly decreased the levels of the biochemical parameters. High dose of *Carum carvi* aqueous seeds extract (60 mg/kg) showed renoprotection against STZ induced diabetic nephropathy in rats [124]. The renoprotective effect of C*arum carvi* essential oil (10 mg/kg of body weights orally) was also studied in diabetic rats. Diabetic rats showed an increase in the serum level of glucose, and decrease in glutathione peroxidase. 10 mg/kg body weight of *Carum carvi* oil significantly corrected these parameters. The morphological examination of untreated diabetic rats kidneys showed glomerular and tubular degeneration with massive cellular infiltration, hemorrhage in interstitial tissue and deformed renal tissue architecture. Whereas the kidney of C*arum carvi* essential oil treated rats showed marked improvement with minor pathological changes [18-19].

2.7. Cassia occidentalis

The nephroprotective activity of the 70% hydroalcoholic extract of *Cassia occidentalis*was tested against gentamicin induced nephrotoxicity in rats. The degree of protection was determined by estimating urinary creatinine, urinary glucose, urinary sodium, urinary potassium, blood urea, serum creatinine levels and body weight of the animals. The *in-vivo* antioxidant activity was determined by estimating the tissue levels of GSH, SOD, catalase and lipid peroxidation. The treatment with hydroalcoholic extract of *Cassia occidentalis*(200 and 400 mg/kg body weight) markedly reduced gentamicin induced elevation of urinary sodium, potassium electrolytes, urinary glucose, and blood urea and creatinine levels. It also increased the body weights. The comparative histopathological study of kidney exhibited almost normal architecture as compared to control group. The deterioration in the antioxidant parameter associated with gentamicin induced nephrotoxicity in rats was also attenuated by 70% hydroalcoholic extract of *Cassia occidentalis*. 70% hydroalcoholic extract of *Cassia occidentalis* showed a dose dependent increase in the level of GSH. However, 200 mg/kg showed 23.3% increase and 400 mg/kg showed 51.4.7% increase in GSH levels. Treatment with 70% hydroalcoholic extract of *Cassia occidentalis* significantly elevated the SOD ($p< 0.001$) and catalase ($p< 0.001$) [20-22].

2.8. Casuarina equisetifolia

The nephroprotective activity of methanolic extract of *Casuarina equisetifolia* leaves was studied in gentamicin induced nephrotoxicity in Wistar rats. Subcutaneous injection of rats with gentamicin (80 mg/kg body weight/day) for six consecutive days induced marked acute renal toxicity, manifested by a significant increase in serum urea, creatinine and uric acid levels, along with a significant depletion of serum potassium level. Also oxidative stress was noticed in renal tissue as evidenced by a significant decrease in glutathione level, superoxide dismutase, glutathione-S-transferase activities, with a significant increase in malondialdehyde and nitric oxide levels when compared to control group. Administration of plant extract at a dose of 300 mg/kg once daily for 4 weeks restored normal renal functions and attenuated oxidative stress. *Casuarina equisetifolia* leaves extract ameliorates gentamicin-induced nephrotoxicity and oxidative damage by scavenging oxygen free radicals, decreasing lipid peroxidation and improving intracellular antioxidant defense [23-24].

2.9. Citrullus colocynthis

The nephropathy protective effect of *Citrullus colocynthis* fruits extract was studied in streptozotocin induced diabetes in rats. The extract of *Citrullus colocynthis* fruit was given as (50mg/kg/day) orally for 50 days. *Citrulluscolocynthis* fruits extract caused significant decrease in blood glucose, urea, creatinine, microalbuminuria and uric acid, while, GSH, GPx and SOD were significantly increased in comparison with diabetic untreated group. The histopathological findings were coincided with biochemical findings in both diabetic and treated groups. Diabetic kidney showed atrophy of renal curpusle, shrinkage of capillary within increase Bowman's space while, diabetic rat received *Citrullus colocynthis* fruit extract showed partial protection of glumeruli and appeared nearly normal. The study clearly demonstrated that *Citrullus colocynthis* fruit exerted protective effects on the kidney functions and tissues. So it may play a role in prevent nephropathy as one of microvascular complications of diabetes mellitus [25-26].

The protective potentials of *Citrullus colocynthis* was evaluated against gentamicin induced nephrotoxicity. Toxic doses of gentamicin (80 mg/kg/day, i.m.) were administered alone and as co-therapy with the extract of *Citrullus colocynthis* (25 mg/kg/day, po). Physiological, biochemical and histological examinations were performed to compare the experimental and toxic groups with control group animals. Co-therapy of *Citrullus colocynthis* with gentamicin protected changes in the body weight, blood urea nitrogen, creatinine clearance, proteins and lactate dehydrogenase excretions. However, a significant rise in serum creatinine and serum uric acid with fall in serum calcium and serum potassium was observed, which were significantly different from control group animals. Necrotic and ruptured tubules were also found abundantly. This study revealed that co-theapy of *Citrullus colocynthis* with gentamicin for twenty one days, failed to protect renal injury associated by gentamicin in spite of its strong antioxidant properties [27].

2.10. Crocus sativus

The protective effects of saffron extract and crocin was evaluated in chronic - stress induced oxidative stress damage of the brain, liver and kidneys in rats. Rats were injected with a daily dose of saffron extract (30 mg/kg, ip) or crocin (30 mg/kg, ip) during a period of 21 days following chronic restraint stress (6 h/day). In order to determine the changes of the oxidative stress parameters following chronic stress, the levels of the lipid peroxidation product, malondialdehyde (MDA), the total antioxidant reactivity (TAR), as well as antioxidant enzyme activities glutathione peroxidase (GPx), glutathione reductase (GR) and superoxide dismutase (SOD) were measured in the brain, liver and kidneys tissues after the end of chronic stress. In the stressed animals that receiving saline, the levels of MDA, and the

activities of GPx, GR, and SOD were significantly higher (P<0.0001) and the TAR capacity was significantly lower than those of the non-stressed animals (P<0.0001). Both saffron extract and crocin were able to reverse these changes in the stressed animals as compared with the control groups (P<0.05). These observations indicate that saffron and its active constituent crocin can prevent chronic stress-induced oxidative stress damage of the brain, liver and kidneys [28-29].

The protective effect of *Crocus sativus* on gentamicin nephrotoxicity was investigated in rats. Male rats were treated with saffron (40 or 80 mg/k/day) for 10 days, or saffron (40 or 80 mg/ kg/day) for 10 days and gentamicin 80 mg/kg/day for five days, starting from day 6. At the end of treatment, blood samples were taken for measurement of serum creatinine (SCr) and BUN. The left kidney was prepared for histological evaluation and the right kidney for malondialdehyde (MDA) measurement. Gentamicin 80 (mg/k/day) increased SCr, BUN and renal tissue levels of MDA and induced severe histological changes. Saffron at 40 mg/kg/day significantly reduced gentamicin-induced increases in BUN and histological scores (p<0.05). Gentamicin-induced increases in BUN, SCr and MDA and histological injury were significantly reduced by treatment with saffron 80 mg/k/d (p<0.05, p<0.001, p<0.05, and p<0.001 respectively) [30].

2.11. Cuminum cyminum

The effect of *Cuminum cyminum* (Cumin) on kidney exposed to profenofos was evaluated in female swiss albino mice. The results showed that cumin was effective in normalizing the uric acid and creatinine level [31-32].

Depression in growth, hepatotoxicity and nephrotoxicity were observed in rats that had been given paracetamol at 500 mg/kg orally for 4 weeks. These findings were accompanied by leucopenia, macrocytic normochromic anemia and alterations of serum aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase activities and concentrations of cholesterol, urea and other serum constituents. Serum bilirubin did not change. In rats given the mixture of paracetamol 500 mg/ kg plus 6% *Cuminum cyminum* fruit for 4 weeks, the recovery of paracetamol hepatotoxicity was evidenced by increase in body weight, absence of hepatocellular fatty vacuolation and significant improvement of serbiochemical and hematological parameters [33-34].

2.12. Cymbopogon schoenanthus

The effects of *Cymbopogon schoenanthus* was investigated in experimental induced kidney stones in male Wistar albino rats. Oxalate nephrotoxicity was experimentally induced by 200 mg single dose of glycolic acid given orally (gavage). The rats were divided into three groups: positive control (glycolic acid), test (glycolic acid plus *Cymbopogon schoenanthus*), and negative control (drinking water). Urine analysis of blood urea nitrogen (BUN), creatinine, and calcium revealed significant differences in induction groeupcompared to control. In addition, significant pathological changes were found in the kidney revealed by histopathological studies. Daily oral treatment with the *Cymbopogonschoenanthus* (1 ml of the extract) significantly corrected the incidence of nephrotoxicity (BUN, creatinine and calcium level differences). Moreover, a highly potent diuretic activity was recorded for *Cymbopogon schoenanthus*. After three days of experiments, five treated rats with the glycolic acid only died. The rest of animal survived and looked healthy. The author concluded that the *Cymbopogon scheonanthus* extract has prophylactic effect in oxalate stone formation [35-36].

2.13. Cynodon dactylon

The effect of hydroalcoholic extract of *Cynodon dactylon* was evaluated in ethylene glycol-induced nephrolithiasis in a rat model. *Cynodon dactylon* extract reduced the levels of calcium oxalate deposition especially in medullary and papillary sections from of the kidney of the treated rats [37].

The beneficial effect of different fractions of *Cynodon dactylon* was studied in ethylene glycol-induced kidney calculi in rats. Male Wistar rats were randomly divided into control, ethylene glycol, curative, and preventive groups. The control group received tap drinking water for 35 days. Ethylene glycol, curative, and preventive groups received 1% ethylene glycol for induction of calcium oxalate (CaOx) calculus. Preventive and curative subjects also received different fractions of *Cynodon dactylon* extract in drinking water at 12.8 mg/kg, since day 0 and day 14, respectively. After 35 days, the kidneys were removed and examined for histopathological findings and counting the CaOx deposits in 50 microscopic fields. In curative protocol, treatment of rats with *Cynodon dactylon* n-butanol fraction, significantly reduced the number of the kidney CaOx deposits compared to ethylene glycol group. In preventive protocol, treatment of rats with *Cynodon dactylon* ethyl acetate fraction significantly decreased the number of CaOx deposits compared to ethylene glycol group [38-39].

2.14. Daucus carota

The renoprotective activity of *Daucus carota* root extract was studied in renal ischemia reperfusion injury in rats. Renal pedicles of rats were occluded for 45 minutes followed by 24 hours reperfusion. Six days prior to induction of I/R, groups of rats received petroleum ether extract, fractional methanolic extract and methanolic extract of *Daucus carota* root (250 & 500 mg/kg, orally). Renal ischemia reperfusion caused significant impairment of kidney function. Six day administration of *Daucus carota*, minimized this effect. Rats with renal I/R only showed significantly decreased activity of superoxide dismutase, catalase, and reduced glutathione compared with the sham operated rats. These declining trends were significantly less in the group treated with petroleum ether, fractional methanolic and direct methanolic extract of *Daucus carota* root compared with those in I/R group. Renal I/R produced a significant increase in malondialdehyde level, while pretreatment with *Daucus carota* extracts was associated with a significantly lower malondialdehyde level. Accordingly, *Daucus carota* extracts exerted renoprotective activity probably by the free radical scavenging activity [40-41].

The nephroprotective effects of ethanolic root extract of *Daucus carota* (200 mg/kg and 400 mg/kg. po) was studied against gentamicin-induced nephrotoxicity in Albino Wistar rats. Nephrotoxicity was induced in rats by intraperitoneal administration of gentamicin (100 mg/kg/day) for 8 days. Gentamicin intoxication induced elevated serum urea, BUN, uric acid, and creatinine levels which was found to be significantly ($P < 0.01$) decreased in a dose-dependent manner in groups received *Daucuscarota.* The nephroprotective effects of *Daucus carota* were further confirmed by histological observations [42].

2.15. Foeniculum vulgare

The nephroprotective effects of different oral doses of aqueous extract of *Foeniculum vulgare* seeds 250 mg/kg, *Solanum nigrum* 500 mg/kg fruit and their mixture (of 250 and 500 mg/kg/oral respectively) were studied in gentamicin induced nephrotoxicity in albino rabbits. All the treatments were continued for 21 days. Blood samples were taken from all groups at day 21 to determine serum urea, creatinine, albumin, plasma malondialdehyde and catalase. Histopathological parameters of kidneys were also examined at day 21. Gentamicin induced oxidative stress and caused structural changes in the kidneys. The aqueous extract of *Foeniculum vulgare* seeds, *Solanum nigrum* fruit and their mixture significantly prevented renal damage by normalizing increased levels of renal markers. Mixture of both plants at high doses exhibited improved nephroprotective and antioxidant activities [43].

The renoprotective effect of the aqueous extract of *Foeniculum vulgare* (150 mg/kg bw) was studied in experimental PCOS female rats. The mean values of blood urea nitrogen in PCOS rats treated with low dose of extract of *Foeniculum vulgare* and estradiolvalerate and non-treated, was significantly ($p<0.05$) increased compared with non-PCOS and PCOS rats treated with high dose of extract of *Foeniculum vulgare*. Moreover, histopathological changes of kidney samples were comparable in PCOS rats with respect to treated groups with extract of *Foeniculum vulgare* [44]. The protective effect of fennel essential oil (250, 500, and 1000 mg/kg/day, for 10 days) as a phytoestrogen source was studied against cisplatin -induced nephrotoxicity in rats. The serum levels of blood urea nitrogen (BUN) and creatinine (Cr), kidney tissue damage score (KTDS), and kidney weight (KW) and body weight changes in CDDP-treated groups increased significantly ($P< 0.05$). Fennel essential oil did not reduce the levels of BUN and Cr, KTDS, and KW and body weight changes. Also, the serum and tissue levels of nitrite were not altered significantly by fennel essential oil [45].

2.16. Glycyrrhiza glabra

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 (200 mg/kg/day) administration restored the expression of aquaporin 2 with paralleled changes in urine output. The changes in renal functional parameters (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 [46].

Glycyrrhizic acid (GA) also alleviated sepsis-induced acute kidney injury (AKI) by improving the pathological changes, decreasing the levels of blood urea nitrogen, creatinine, and increasing the survival rate of rats with AKI significantly. The production of inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, was markedly inhibited by GA. Furthermore, GA inhibited the production of nitric oxide and prostaglandin E2 and expression levels of induced nitric oxide synthase and cyclooxygenase-2 in kidney tissues. GA also suppressed the apoptosis in kidney tissue induced by AKI and inhibited the activation of NF-κB signaling pathway [47].

2.17. *Juglans regia*

The modulatory effects of walnut extract on the toxicity of an anticancer drug, cyclophosphamide (CP) was evaluated in mice. Plant extract+CP group animals showed restoration in the level of cytochrome P450 (CYP) content and in the activities of glutathione S-transferase (GST), glutathione peroxidase (GP) and catalase (CAT) in both liver and kidneys. But plant extract restored the activity of superoxide dismutase (SOD) and the level of reduced glutathione (GSH) in the kidneys only when compared with CP-treated animals. Plant extract treatment alone caused significant reduction in the content of CYP in the kidneys mainly. The extract showed a significant increase in the level of GSH and in the activities of GP in both the tissues and CAT in liver only, whereas no significant change was observed in the activities of GST and SOD. The extract+CP showed a significant decrease in the LPO in liver and kidneys when compared with the CP-treated group [48-49].

3. Conclusion

The current review discussed the nephroprotective effects of medicinal plants against gentamicin, paracetamol, profenofos, D galactosamine (D-GalN), chronic-stress, sepsis and cytotoxic drugs induced kidney injury as well as streptozotocin induced diabetic nephropathy, in addition to chemically induced nephrolithiasis. The review showed that many medicinal plants can attenuate the biochemical, functional and structural renal toxicities of a wide range of drugs and toxins representing effective nephroprotective alternatives.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest. The authors shared equally and their interest was equal

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