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A REVIEW ON NEPHROPROTECTIVE ACTIVITY OF HERBAL PLANTS

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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. Nephrotoxicity is one of the most common kidney problems and occurs when body is exposed to a drug or toxin. Nephroprotective agents are the substances which possess protective activity against nephrotoxicity. Medicinal plants have curative properties due to the presence of various complex chemical substances.

Keywords: Medicinal plants, Nephroprotective agents, Therapeutic agents

NEPHROTOXICITY:

Nephrotoxicity is the most common kidney problems and occurs when body is exposed to a drug or toxin. When kidney damage to occurs, body unable to ride of excess urine and wastes from the body and blood electrolytes (such as potassium and magnesium) will all become elevated. Nephrotoxicity is manifested functionally by decreased urine concentrating capacity, tubular proteinuria, lysosomal enzymuria and mild glucosuria, decreased ammonium excretion lowering of glomerular filtration rate, creatinine clearance and increase in serum BUN, serum creatinine level with kidney tissue morphological alteration.

Risk factors for nephrotoxicity:

- The elderly are more likely to overdose on antibiotics or analgesics.
- Kidneys already weakened by conditions such as diabetes can be particularly susceptible to nephrotoxicity.
- Severe dehydration.

- Prolonged exposure to heavy metals or solvents.
- Presence of diseases that cause the overproduction of uric acid.

Symptoms:

- Excess urea in the blood (azotemia).
- Anaemia.
- Increased hydrogen ion concentration in the blood (acidosis).
- Excess fluids in the body (over hydration).
- High blood pressure (hypertension).
- Serious symptoms of kidney failure may leads to seizures and coma.

Pathophysiology:

- Drugs produce nephrotoxicity by interfering with renal blood flow, increase in the kidney weight, glomerular function or tubular function.
- Many drugs are nephrotoxic because they are excreted from the body primarily by the kidneys.
- Most nephrotoxic drugs cause proximal renal tubular necrosis.

- If renal injury is severe, acute renal failure develops [1].

Kidney toxicity induced by nephrotoxic agents:

Renal failure:

Renal failure is a common clinical syndrome. It is defined as a rapid decline in renal function resulting in abnormal retention of serum creatinine and blood urea which must be excreted. The clinical manifestations of renal failure are the decline in glomerular filtration rate (GFR) and the inability of the kidney to excrete the toxic metabolic substances produced in the body. In addition, there is failure of regulation of fluids and electrolyte balance along with endocrine dysfunction. Depending up on the severity, it is divided as acute and chronic renal failure [2].

There are two types of renal failure:

1. Acute renal failure.
2. Chronic renal failure.
1. **Acute renal failure (ARF):** It is defined as a significant decline in renal excretory function occurring over hours or days. This is usually detected clinically by arise in the plasma concentration of the urea or creatinine. Acute renal failure may arise as an isolated problem, but much more commonly occurs in the setting of circulatory disturbance associated with severe illness, trauma, or surgery; transient renal dysfunction.

Figure 1: Schemating representation of the different causes of ARF

2. **Chronic renal failure (CRF):** It is the clinical syndrome of the metabolic and systemic consequences of a gradual, substantial and irreversible reduction in the excretory and homeostatic functions of the kidneys [3].

Causes of chronic renal failure:

- The most important causes of chronic kidney disease are diabetes, glomerulo nephritis, hypertension and other vascular disease.
- It can be difficult to recognize because the symptoms and clinical manifestations are non-specific Arteriopathic renal disease and hypertension
- Glomerulonephritis
- Diabetes
- Infective, obstructive and reflux nephropathies
- Congenital disease
- Familial or hereditary kidney disease, e.g. polycystic kidneys
- Hypocalcaemia
- Connective tissue diseases
- Neoplasm's
- Myeloma
- Reflux nephropathy
- Renal bone disease is a major cause of disability in patients with terminal renal failure.

DRUGS CAUSING NEPHROTOXICITY:

Drugs, diagnostic agents and chemicals are well known to be nephrotoxic. The following are the some of the important nephrotoxic agents [4, 5].

1. Antibiotics:

- Amino glycosides (10-15% incidences of ATN):- Gentamicin, Amikacin, Kanamycin, Streptomycin, Tobramycin, Neomycin.
- Quinolones:- Ciprofloxacin, Levofloxacin.
- Others:- Sulfonamides, rifampin, tetracycline, acyclovir, pentamidine, Vancomycin, amphotericin-B.

2. Chemotherapy and immunosuppressant's:- Cisplatin, methotrexate, mitomycin, Cyclosporine, ifosphamide.

3. Heavy metals:- Mercury poisoning, lead poisoning, arsenic poisoning, bismuth, Gold, germanium, chromium, lithium.

4. Anti-hyperlipidemics:-

- Statin drugs- rhabdomyolysis
- Gemfibrozil (associated with ARF)

5. Miscellaneous: - Radioactive agents.

6. NSAIDS: - Paracetmol, ibuprofen, aspirin, etc.

7. Drugs of abuse:- Cocaine, Heroin, Methamphetamine

Nephrotoxic agents can produce damage either by directly reacting with cellular macromolecules and membrane components or from metabolism within the tubular cells to toxic products. The agents which cause

direct toxicity are heavy metals like Hg, Pb, which interact with sulfhydryl groups, organic cations such as spermine, cationic amino acids, amino glycosides which interacts with membrane phospholipids, polyene antibiotics like amphotericin-B which interacts with membrane cholesterol. Fluoride and oxalates produced by hepatic metabolism of metabolism of methoxyflurane intermediates of cisplatin, cystine conjugates, cephaloridine and acetaminophen induced damage by their metabolites. These toxic metabolites mainly include free radicals.

The nephrotoxins damage specific segment of the nephron to a greater extent than the other segments. The proximal tubule is the most commonly affected, because of the presences of inducible type of microsomal mixed function oxidises (cytochrome P 450) which have been implicated in the toxic activation of various agents. This segment is also rich in glutathione and glutathione metabolizing enzymes. The other common sites which can be affected are renal medulla, distal tubule and Loop of Henle. The renal medulla is affected mainly by polyene antibiotics and cyclosporine and that of distal tubule dysfunction is mainly due to non steroidal anti-inflammatory agents, cyclosporine, pentamidine, trimethoprim, sulphamethaxazole, amphotericin, amino glycosides, antibiotics, lithium and demeclocycline [6].

Mechanisms of drug induced renal damage [7]:

- a) Free radical production.
- b) Disturbance of renal tubule cell energy metabolism.
- c) Disrupted cell calcium homeostasis.
- d) Alteration of membrane phospholipids metabolism.
- e) Disruption of cellular monovalent cation volume and pH dependent degradation.
- f) Disruption of cytoskeleton.
- g) Abnormalities of protein and nucleic acid synthesis.
- h) Abnormalities of cell proteases.
- i) Disruption of lysosomal function.
- j) Death of tubular epithelial cells.
- k) Tubular cell necrosis.

In the present study acetaminophen induced nephrotoxic models have been adopted. Hence the mechanism of nephrotoxic injury caused by them is recorded [8, 9].

Diagnosis:

Damage to the kidneys is assessed through a combination of physical examination, blood tests, urine tests, and imaging procedures. Diagnosis of nephrotoxic injury as the underlying cause results from a thorough investigation of the patient's history.

Information regarding pre existing conditions, current prescriptions, and environmental exposures to toxins aid in determining the kidney malfunction by toxin.

Treatment:

- Treatment of nephrotoxicity takes place in the hospital and focuses on removing the toxin from the patient's system, while maintaining kidney function.
- Removal methods are targeted to specific toxins and may include the use of diuretics or chelates to enhance excretion of the toxin in urine, or, in extreme cases, the direct removal of toxins from the blood via haemodialysis or passing the blood over an absorbent substance such as charcoal.
- Support of kidney function depends on the extent of damage to the organs and ranges from monitoring fluid levels to dialysis.

Experimental models of nephrotoxicity:

- Acetaminophen induced nephrotoxicity
- Gentamicin induced nephrotoxicity
- Cisplatin induced nephrotoxicity
- Carbon tetrachloride induced nephrotoxicity
- Lead nitrate induced nephrotoxicity
- Cadmium induced nephrotoxicity
- Chromium-nickel induced nephrotoxicity
- Lead induced nephrotoxicity
- Hexachlorobutadiene induced nephrotoxicity
- Mercuric chloride induced nephrotoxicity
- Doxorubicin induced nephrotoxicity

Acetaminophen induced nephrotoxicity:

Acetaminophen also known Paracetmol, N-acetyl p-aminophenol. Acetaminophen is an OTC drug that produces analgesic and antipyretic effects belonging to the Para amino phenol class of non steroidal anti inflammatory drugs (NSAIDS) that is safely employed for a wide range of occurs in approximately treatments [10].

Renal insufficiency 1–2% of patients with acetaminophen over dose. The Pathophysiology of renal toxicity in acetaminophen poisoning has been attributed to cytochrome P-450 mixed function oxidize iso enzymes present in the kidney, although other mechanisms have been elucidated, including the role of prostaglandin synthetase and N-deacetylase enzymes.

An acute Paracetmol over dosage can lead to potentially liver and kidney failure in humans and experimental animals and in severe cases to death due to renal failure. Paracetmol is a Phenacetin metabolite. Phenacetin was considered one of the most nephrotoxic analgesics. A chronic nephrotoxic effect of therapeutic dosing of Paracetmol is suggested by case control

studies. It induces acute renal damage by elevating plasma creatinine levels and depleting glutathione levels. Tubular necrosis is observed histologically [11].

Overdose Acetaminophen is normally associated with several metabolic disorders including serum creatinine rearrangement. The Acetaminophen induced nephrotoxicity in animals and humans, increased concentration of serum urea and creatinine are considered. Acetaminophen undergoes deacetylation to p-aminophenol and bind to kidney proteins which distributed to mitochondria, microsomes, cytosol and associated proteins DNA, mitochondrial enzymes and Glucose-6-phosphatase. Renal tubular damage and acute renal failure can occur even in absence of liver injury and can lead to fatality in humans and experimental animals [12, 13].

Paracetmol is metabolized in both the liver and kidney nephrotoxicity may occur independently of hepatotoxicity depending on the balance of metabolism and glutathione stores within the kidney. Nitric oxide plays an important role in acetaminophen induced renal damage in rats. In administration of APAP to rats resulted in nephrotoxicity and development of oxidative stress damage in renal tissues. Nitric oxide plays an important role in acetaminophen induced renal damage in rats. Oxidative stress plays a role in Paracetmol induced liver damage and this contributes to the pathogenesis of Paracetmol induced renal damage, as evidenced by an increase in the lipid peroxidation and the depletion of intracellular glutathione (GSH). Because APAP can cause life-threatening renal damages, the antidote or treatment of APAP-induced nephrotoxicity has a toxicological importance. Although N-acetyl-Cysteine, a GSH precursor, protects against APAP hepatotoxicity in humans, it is not protective against APAP-induced renal damage [14].

Paracetmol given in increasing doses to male Wister rats depleted glutathione stores in the liver and kidneys, large amounts of oxidative radio labelled metabolite bound to a hepatic and kidney protein then lead to a dose dependent acute hepatic and renal necrosis [15].

Tubular cell loss is a characteristic feature of both acute renal failure and chronic renal disease and is observed when cell death predominates over mitosis. Apoptosis is an acute form of cell death that offers the opportunity for therapeutic intervention [16].

Pathophysiology:

The primary toxicity of acetaminophen is the result of drug metabolism in both the liver and extra hepatic tissues. Only 1% of the drug is excreted unchanged in

the urine. With therapeutic dosing in adults, approximately 63% of acetaminophen is metabolized via glucuronidation and 34% by sulfation. These phase II reactions occur primarily in the liver and result in water-soluble metabolites that are excreted via the kidney. At therapeutic doses, <5% percent of APAP is oxidized by the microsomal P-450 enzyme system to a reactive intermediate, N-acetyl-p-benzoquinone imine (NAPQI). In therapeutic dosing, this electrophilic metabolite is then reduced by glutathione and subsequently excreted as mercapturic acid, a relatively benign compound. In the setting of excess APAP, stores of sulphate and glutathione are depleted. This shunts more of the acetaminophen to the CYP-450 mixed function oxidase system, generating more NAPQI reactive intermediates. When large doses of drug are ingested, there is more severe glutathione depletion as well as massive production of metabolites, which compounds the toxicity, leaving large amounts of reactive species unbound. These electrophilic

intermediates then form adducts with sulfhydryl and glutathione moieties on cellular proteins. This process disrupts homeostasis, with subsequent activation of caspases and lysosomal enzymes that initiate apoptosis, or programmed cell death. This has been demonstrated in both liver and kidney tissue in animal models. The resultant cell death leads to tissue necrosis and ultimately organ dysfunction [17].

Mechanism of acetaminophen induced nephrotoxicity:

Acetaminophen is metabolized via conjugation with glucuronic acid and sulphate leading to excretion, before that a portion of APAP is metabolized by cytochrome P-450. Cytochrome P-450 oxidation of APAP results in the production of a chemically reactive metabolite, N-acetyl-p-benzoquinone imine (NAPQI), which then reacts with glutathione (GSH) to form an APAP-GSH conjugate. Depletion of reduced glutathione (GSH) and lipid peroxidation plays a crucial role in the development. GSH has an important function as a cellular protective mechanism against toxic metabolites. At therapeutic doses, NAPQI is removed by GSH; however, at overdoses of APAP, the GSH is exhausted and the NAPQI then binds to cellular proteins, including a number of mitochondrial proteins, which leads to cause nephrotoxicity. In addition, NAPQI leads to mitochondria dysfunction and reactive oxygen species (ROS) formation, which in turn leads to peroxynitrite and tyrosine nitration. The events in the mechanism, affects mitochondrial permeability transition, which leads to disturbances in the permeability transition, which leads to disturbances in the permeability of the inner mitochondrial membrane [18].

Adverse effects:

- Gastric irritation or bleeding tendencies
- Severe liver toxicity
- Skin rash
- Hypoglycaemia
- Neutropenia.

Treatment:

Treatment should be started early within 16hrs of Paracetamol ingestion. Vomiting should be induced or gastric lavage done. Activated charcoal should be given orally to prevent further absorption. Drug treatment includes administration of N-acetylcysteine (I.V) or methionine (orally). Both have SH groups like glutathione. They replenish the stores of glutathione in liver and also they conjugate with this toxic metabolite and thus prevent its covalent bonding to hepatic and renal cellular protein [19].

Figure 2 Mechanism action of Acetaminophen induced nephrotoxicity.

Reasons for elevated BUN and serum creatinine:

BUN: BUN reflects the amount of nitrogen present in the body called urea and is used to determine extra nitrogenous wastes, filtered by kidneys. Kidney failure to filter as much urea leads to uraemia.

Serum Creatinine: The serum Creatinine provides energy to the muscles. The kidneys are normally able to filter out large amounts of creatinine on a daily basis. But in Kidney problems creatinine levels will increase.

Gentamicin induced nephrotoxicity:

Gentamicin is an amino glycoside antibiotic widely used for the treatment of bacterial infections, particularly against aerobic gram-negative bacteria. Nephrotoxicity and ototoxicity are serious side effects in the use of amino glycosides due to increased uptake of the antibiotic, mainly proximal tubules. Nephrotoxicity induced by amino glycosides manifest clinically as non-oliguric renal failure with a slow rise in serum creatinine and a hypo-osmolar urinary output developing after several days of treatment [20].

The toxicity of Gentamicin is due to generation of reactive oxygen species (ROS) in kidney. Several reports have documented the pathogenesis of amino glycosides -induced renal tubular cell injury such as derangement of lysosomal, mitochondrial and plasma membrane structure. Furthermore results of many studies have been shown that the altered concentrations of various biochemical indicators of oxidative stress in kidney tissue are due to Gentamicin because of the obvious medication of ROS in Gentamicin induced renal damage. Several antioxidant agents have been used to block Gentamicin nephrotoxicity [21].

Cisplatin induced nephrotoxicity:

Cisplatin is a potent antitumor agent, but its clinical use is limited due to renal toxicity. Cisplatin decreases antioxidants and antioxidant enzymes leading to enhanced generation of reactive oxygen metabolites and lipid peroxidation. Cisplatin produced dose limiting nephrotoxicity and high dose of CDDP produced the impairment of kidney, causes decreases in renal flow, GRF and increases urea and creatinine level in blood. Changes in urine volume, body weight, increases the products of lipid peroxidation and change renal clearances. Kidneys have some antioxidant enzymes like SOD, lipids peroxidise and glutathione (GSH) & catalase which protect kidney from free radicals like nitric acid and superoxide etc. Cisplatin is inhibited the activity of antioxidant enzyme in renal tissue like glutathione, SOD, GSH and catalase depletion and increase thiobarbituric acid- reactive substances. Cisplatin cytotoxicity in renal tubule cells including direct DNA damage, activation of caspase mitochondrial dysfunction formation of reactive oxygen species, effects on the endoplasmic reticulum and activation of TNF- α mediated apoptotic pathways [22].

Lead induced nephrotoxicity:

Lead is a potent neurotoxin, at higher levels of exposure causing symptoms of blindness, brain damage, kidney disease clinical manifestations of impairment, such as elevations in blood urea nitrogen (BUN) or serum creatinine, do not ordinarily become evident until 50-75% of the nephrons have been destroyed. Lead damage to the urine was evident from increase in the activity of g-glutamyl transpeptidase (g-GT), cathepsin D, alkaline phosphate (ACP), β -glucuronidase lactate dehydrogenation (LDH), N-acetyl-b-d-glucosaminidase (NAG) in urine along with some urinary constituents (urea, uric acid, creatinine, protein and phosphorus). Urinary excretion of nitrogenous waste products (urea and uric acid) and creatinine was increased significantly in lead poisoned rats coupled with phosphaturia. Elevation of urinary urea might be a consequence of impaired solute transport in the proximal tubules. Rejection of solutes in the proximal tubule would retard water reabsorption and ultimately enhance fluid delivery force for urea reabsorption. This would increase the driving force for urea reabsorption in the collecting duct [23].

Hexachlorobutadiene induced nephrotoxicity:

HCBD is a potent nephrotoxin which can cause degeneration, necrosis and regeneration in renal tubular epithelial cells. Toxicity is due to its conjugation with glutathione to form glutathione-S-conjugation, and finally to the related Cysteine conjugate. This metabolite is then actively taken up by kidneys and cleared through the renal tubular epithelial cells as a reactive thiol derivative by the enzyme lyase, which covalently binds to macromolecules. The S3 region (pars recta) of the proximal tubule of rat's kidney is the most susceptible organ to the nephrotoxicity induced by Cysteine-conjugates. Calcium has been shown to have an important role in cellular toxicity. As calcium homeostasis is precisely controlled, any alteration in intracellular calcium level could play an important role in the Cysteine-conjugate induced cell death. Calcium channel blockers like verapamil may affect the role of calcium in cellular toxicity [24].

Mercuric chloride induced nephrotoxicity:

Mercuric chloride is a wide spread environmental and industrial pollutant, which induces severe alterations in the tissues of both animals and men. Mercury is accumulated and expresses toxicity primarily to the kidney acute failure is a dramatically clinical syndrome. Toxic effects caused by mercury itself and by numerous secondary reactions in the body, reflect many biochemical parameters in the blood and kidney tissue. Mercuric chloride induced a nephropathy that is restricted primarily to the S3 segment of proximal tubule at the lowest doses of mercury. Transport

mechanism for binding protein appears to be important for the nephrotoxicity of metals. Toxic effects are related both to the proximal tubular cells and to changes at the level of glomerular basement membrane [25].

Potassium bromate induced nephrotoxicity:

Potassium bromate (KBrO_3) is an oxidizing agent causes infections in kidney and has been classified as 2B group toxic chemical a probable human carcinogen. KBrO_3 causes significant alterations in antioxidant enzymes and oxidative DNA damage in kidneys of rats [26].

Carbon tetrachloride induced nephrotoxicity:

Carbon tetrachloride induces acute and chronic renal injuries as well as oxidative stress in rats. CCl_4 caused the marked depletion of renal endogenous antioxidant enzymes. The pathogenesis of CCl_4 induced renal dysfunction is not completely known. It may be due to the function state of liver or renal injury may develop independently to hepatic events induces oxidative stress. High exposure to CCl_4 can cause liver, kidney and CNS damage, and liver is especially sensitive to CCl_4 because of its role as the body's principal site of metabolism. A number of endogenous and exogenous nephropathy risk factors generate oxygen free radicals. It enhances lipid peroxidation, reduces renal microsomal NADPH cytochrome p450, and renal reduced/oxidized glutathione ratio in kidney cortex as well as renal microsome and mitochondria [27].

Lead nitrate induced nephrotoxicity:

Lead is known to induce a broad range of physiological dysfunctions. Lead was reported to have pro-oxidant catalytic activity with respect to lipid peroxidation [28].

Cadmium chloride induced nephrotoxicity:

Cadmium is a well-known human carcinogen and a potent nephrotoxin. Metal toxicities might be associated oxidative tissue damage. Cadmium (Cd) can produce both acute and chronic tissue injury and can damage various tissues, including liver, kidney, lung and bone. In Cd exposure leads mainly to nephrotoxicity. Complex of Cd-metallothionein are released from necrotic hepatocytes and are delivered to the kidneys, where it appears that are taken up and induce proximal tubular injury and death [29].

Ferric-nitriloacetate induced nephrotoxicity:

Ferric nitrilotriacetate (Fe-NTA) induced renal oxidative stress. Iron is the most abundant metal in the human body and its overload may lead to various diseases. The iron complex of the chelating agent nitrilotriacetic acid is nephrotoxic. (Fe-NTA) enhances

renal lipid peroxidation with reduction in renal glutathione content, antioxidant enzymes, phase-II metabolizing enzymes, and glutathione -S- transferase [30].

Chromium-nickle induced nephrotoxicity:

Chromium and nickel are greater resulted in gastrointestinal, haematological, hepatic, renal and neurological effects. $K_2Cr_2O_7$ might be related to impairment of protein synthesis by chromium ions. It induced oxidative stress leading to deterioration of proteins in tissues. Nickel ions have higher affinity for proteins and amino acids and their binding to some chromatin proteins may result in oxidative and structural damage proteins. Renal tubular damage was observed in animal after exposure to nickel [31].

Nephroprotective activity review:-

Meliaazadirachta

Srinivasan Vet et al., 2014 investigate the Ethanolic extract of *Melia Azadirachta* against Acetaminophen induced Nephrotoxicity. The chemical constituents present in this plant such as Phytol, Squalene, Oleic Acid, 2-Piperidinone, N-[4-bromo-n-butyl]. The biochemical parameters are estimated by serum urea, creatinine, expect uric acid [32].

Pseudocedrelakotschy

OJewale AO et al., 2014 to evaluate the nephroprotective activities of ethanolic roots extract of *Pseudocedrelakotschy* against oxidative stress and nephrotoxicity in alloxan induced diabetic albino rats. The ethanolic roots extract of *Pseudocedrelakotschy* at a dose of 250 and 500 mg/kg body weight was administered at single dose per day to diabetes induced rats for a period of 28 days. Results of The ethanolic roots extract of *Pseudocedrelakotschy* can prevent renal damage from alloxan induced nephrotoxicity in rats [33].

Costus afer

Uboh FE et al., 2014 effect of *Costus afer* leaves Juice on nitrocellulose Thinner induced nephrotoxicity in rats. The increased levels of parameters such as BUN, creatinine, uric acid, and serum urea, MDA, GP_x and SOD were treated with *Costus afer* leaves than the levels are decreased. The results suggest that the *Costus afer* leaves have the potential in preventing the nitrocellulose thinner induced nephrotoxicity [34].

Maytenusemargints

Pathan MM et al., 2013 had evaluated the nephroprotective activity of *Maytenusemargints* ethanolic extract. The inducing method of Paracetmol

for oral rought. The rats were treated with plant extract of *Maytenusemargints* at different dose levels. Histopathological examination and elevation of biochemical marker enzymes serum creatinine and BUN confirmed the kidney injury produce by Paracetmol. Treatment of rats with *Maytenusemargints* extract showed that the reduction in levels of serum creatinine near to normal on a dose dependent manner. The shows that the *Maytenusemargints* extract proved that the potent nephroprotective effects against the Paracetmol induced nephrotoxicity [35].

Solanum xanthocarpum

Qumrealam et al., (2013) to investigate the Nephroprotective effect of alcoholic extracts of fruits of *Solanum xanthocarpum* against Cisplatin-induced nephropathy in rats. The nephroprotective activity parameters are estimated by the urine and creatinines are related. The ethanolic extract 400 mg/kg treated rat group showed significant elevation in body weight with a significant increase in urine volume output. *Solanum xanthocarpum* showed nephrotoxicity activity in a dose dependent manner compared to standard drug of cystone [36].

Ipomea aquatica

Saleh Alqasoumi., 2013 to evaluated protective effect of water spinach *Ipomea aquatica* ethanol extract (IAE) against gentamicin (GM)-induced nephrotoxicity in Wistar albino rats. The induction of gentamicine is produced by the renal failure characterised by significant increase in serum and urine creatinine urea, uric acid, and gamma-glutamyl transferase and protein levels. The elevations of MDA, reduced concentration of TP and NP-SH in kidney tissues, are indicators of oxidative stress in the kidney [37].

Triphala

Monojit Mitra et al., 2013 investigation of the nephroprotective effects of *triphala-an* ayurveda formulation in experimental models of nephrotoxicity. The gentamicin treated rats had significantly reduced the body weight, urinary sodium, potassium and creatinine while significantly elevated values of urinary glucose, serum urea (BUN) and creatinine , kidney weight and lipid peroxidation when compared to rats. The results of this study provide the experimental evidence for claiming the nephroprotective effect of *triphala* [38].

Peucedanum grande

Aslam M et al., 2013 investigation of the Nephroprotective Effects of Methanolic Extract of *Peucedanum grande* against Acute Renal Failure Induced by Potassium dichromate in Rats. Potassium

dichromate is induced the nephrotoxicity. The rats were given pre-treatment of *P. grande* orally at a different dose levels. The biomarkers estimated by lipid peroxidation, serum kidney toxicity markers and histopathological estimation of kidney. The result plant is proved that the nephroprotective activity [39].

Vernoniaamygdalina

Iwaraet al., 2013 to evaluation of the nephroprotective effect of combined extract of *Vernonia amygdalina* and *Moringaoleifera* in diabetes induced kidney injury in albino Wister rat. The inducing method using streptozotocine. Significant increase in K^+ , Na^+ , Cl^+ and urea concentration in groups treated with V.A and M.O. the results shows that the synergistic effect of the plant in amelioration of nephrotoxicity associated with diabetes mellitus [40].

Cucumismeli

Nazeem Fahamiya et al., 2012 to evaluate nephroprotective activity of methanolic extract of *Cucumismeli* seed in gentamicine induced nephrotoxicity. Gentamicine treated showed increased the levels of blood urea nitrogen and serum creatinine, were significantly treated with methanolic extract of *Cucumismeli* seed. The antioxidants are estimated by the levels of SOD, CAT, GP_x and reduced GSH were increased with decreased in MDA content in methanolic extract of *Cucumismeli* seed pre-treated group when compared with gentamicine alone treated group. The histopathological and biochemical parameters proved that the protective nature of ME-CM in gentamicine induced renal damage [41].

Garlic (Allium sativum)

Anusuyaet al., 2013 investigate the in vivo antioxidant and nephroprotective potential of ethanolic extract of *garlic (Allium sativum)* against cisplatin induced nephrotoxicity in male Wister rats. The animals were treated with the ethanolic extract of *Allivum sativum* at two dose levels .the effect of the higher dose (300 mg/kg b.w) of extract on normal rats was also studied. The induction of cisplatin is resulted in a decrease in the activities of kidney antioxidants with a concomitant increase in kidney weight, lipid peroxidation along with serum kidney markers like urea, uric acid, creatinine and BUN. Treatment with ethanolic extract of *Garlic* posses a potential nephroprotective property with no after effects. So the plant proved that the nephroprotective activity [22].

Phyllanthus acidus

Vidya S et al., 2013 reported the nephroprotective activity of methanolic extract of *Phyllanthus acidus* leaves against gentamicine induced nephrotoxicity in experimental rodents. Nephrotoxicity was induced in

albino rats by intraperitoneal administration of gentamicine 100mg/kg/day for 10 days and methanolic extract of leaves of *Phyllanthus acidus* at different dose levels for 14days by oral route. The result of study is proved that the methanolic leaf extracts of *phyllanthus acidus* possesses nephroprotective activity against gentamicine induced nephrotoxicity in albino rats [20].

Moringa pterygosperma

Lakshmana G et al., 2013 reported that the determination of Nephroprotective Activity of Ethanolic Leaf Extract of *Moringa pterygosperma* on Paracetmol induced Nephrotoxic Rats. Furosemide was taken as standard drug. The parameters estimated are RBC content, haemoglobin content, urea and creatinine levels. The extract showed nephro-protective activity by significantly reducing the levels of blood urea, serum creatinine, increasing the red blood cell count and haemoglobin content [3].

Varunadiloha

Chaudhari Hiteshet al., 2013Theexperimental appraisal of nephro-protective activity of *Varunadiloha*. The Iron is nephrotoxic, causing various urinary diseases which when untreated results in fatal condition like renal failure. But *Ayurveda*, after subjecting to various *Samskaras* (processing), has used *Loha* (Iron) in *bhasma* (Calx) form in numerous formulations to treat urinary diseases. Significant decrease in serum creatinine and serum urea in curative group was suggestive that the drug *Varunadiloha* was delivering its best to improve the lost kidney function [42].

Indigoferatinctoria

Priyadarsini G et al., 2012 To report that thenephroprotective activity of decoction of *Indigofera tinctoria* (avurikudineer) against cisplatin-induced nephropathy in rats. The nephrotoxicity induced by cisplatin than damage kidney. The administration of AKL and AKRL *Avurikudineer* at a dose different dose levels by oral rought. The decoctions significantly decreased the cisplatin induced neurotoxicity. Remarkable changes were observed in body weight, serum creatinine and urea levels. *Avvurikudineer* proved that the nephroprotective activity against cisplatin induced nephrotoxicity [42].

Ficus Racemosa

Shivalinge Gowda KP et al., 2012 Study of Nephroprotective Activities of Stem Bark Extracts of *Ficus Racemosa* in Gentamicin Induced Acute Renal Failure in Rats. Gentamicin is enhancing the generation of superoxide anion and hydrogen peroxide by renal cortical mitochondria. The

List of medicinal plants for Nephroprotectivity

S.No	Plant name	Part used	Screening method	References
1.	<i>Ficus religiosa</i> L (Moraceae)	Latex	Cisplatin	Yogesh C <i>et al.</i> , 2011 [47]
2.	<i>Tectonagrandis</i> (Verbanaceae)	Bark	Alloxan	Ghasiaset <i>et al.</i> , 2010 [48]
3.	<i>Crataevanurvula</i> (Capparidaceae)	Fruit	Gentamicine	Shelkea T <i>et al.</i> , 2011 [49]
4.	<i>Spathodea Campanulata</i> (Bignoniaceae)	Bark	Gentamicine	Shanmukha I <i>et al.</i> , 2010 [50]
5.	<i>Lepidium sativum</i> L (Brassicaceae)	seeds	cisplatin	Yogesh Chand <i>et al.</i> , 2009 [51]
6.	<i>Ipomoea digitata</i> (Convolvulaceae)	Root	Gentamicine	Kalaiselvan A <i>et al.</i> , 2010 [52]
7.	<i>Brideliaretusa</i>	Bark	Ccl ₄	Cordeiro M <i>et al.</i> , 2011 [53]
8.	<i>Ficus hispida</i> (Moraceae)	Fruit	Cisplatin	Swathiet <i>et al.</i> , 2011 [54]
9.	<i>Vignamunga</i> (Fabaceae)	Seeds	Rifamycin	Nitin M <i>et al.</i> , 2012 [55]
10.	<i>Anthoxanthum Odorum</i> (Poaceae)	Aerial parts	Acetaminophen	Dheeraj V <i>et al.</i> , 2010 [56]
11.	<i>Solanum nigrum</i> (Solanaceae)	Whole plant	Amphotericin B	Geo A <i>et al.</i> , 2011 [57]
12.	<i>Plectranthus Amboinicus</i> (Lamiaceae)	Leaves	Acetaminophen	Palani S <i>et al.</i> , 2010 [58]
13.	<i>Merremia Emarginata</i> (Convolvulaceae)	Whole plant	Cisplatin	Sudhavani V <i>et al.</i> , 2010 [59]
14.	<i>Canarium Schweinfurthii</i> (Poaceae)	Stem Bark	Acetaminophen	Okwosa C <i>et al.</i> , 2009 [60]
15.	<i>Andrographis paniculata</i> (Acanthaceae)	Root	Gentamicin	Pratibha S <i>et al.</i> , 2009 [61]
16.	<i>Vernonia cinerea</i> (Compositae)	Aerial parts	Cisplatin	Sreedevi <i>et al.</i> , 2011 [62]
17.	<i>Pedaliium murex</i> Linn (Pedaliaceae)	Dried fruits	Cisplatin	Shelke <i>et al.</i> , 2009 [63]
18.	<i>Abutilon indicum</i> (Malvaceae)	Whole plant	Gentamicin	Kakasaheb Khore <i>et al.</i> , 2011 [64]
19.	<i>Punica granatum</i> (Punicaceae)	Fruit peel	Ferric nitrilo tri acetate induced	Mahgoub Mohammed Ahmed <i>et al.</i> , 2010 [65]
20.	<i>Rubi cardifolia</i> Linn (Rubiaceae)	Root	Ethylene glycol	Kalyani Divakare <i>et al.</i> , 2010 [66]

nephrotoxicity in rat was induced by administration of gentamicine. The parameters are estimated by the kidney weight, urine volume, serum urea, serum creatinine and antioxidant parameters such as lipid peroxidation, catalase and glutathione. The ethanol extract of this plant can be as a nephroprotective agent [43].

Phyllanthus amarus

Syed Asad Bakhtiar *et al.*, 2012 evaluated the Hepatoprotective and nephroprotective activity of *Phyllanthus amarus* Schum & Thonn. Nephroprotection was assessed by measuring serum creatinine, blood urea nitrogen (BUN) and kidney weight. Histopathological analysis of liver samples also confirmed the Hepatoprotective activity of methanolic extract of the seeds, which was comparable to the standard silymarin. The results obtained in this study indicate that the methanolic extract has significant effect than aqueous extract when compared to silymarin and cysteine, respectively. Hence, the *Phyllanthus amarus* seed possesses a potent protective effect against thioacetamide-induced hepatic damage, and gentamicine-induced renal damage [44].

Colpomenia sinuosa

Lekameera Ramarajan *et al.*, 2012 To Investigate the Nephroprotective effects of *Colpomenia sinuosa* (Derbes & Solier) against carbon tetrachloride induced kidney injury in Wistar rats. The results shows significantly decreased ($P < 0.01$) level of TC, the cholesterol and urea levels shows significantly increased ($P < 0.05$) in CCl₄ treated groups when compared to control groups. The *Colpomenia sinuosa* is proved that they have nephroprotective activity [45].

Vitex negundo

Guguloth *et al.*, 2011 to investigated the nephrotoxicity of methanolic extracts of *Vitex negundo*. Linn bark (VBE) against chemical induced kidney damage. Kidney damage was induced by single oral administration of Paracetamol 750 mg/kg. Methanolic extracts of *Vitex negundo*. Linn bark was orally administered to the animals once daily for 14th

days. The results shows that the methanolic extracts of *Vitex negundo*. Linn bark has protected the kidney from Paracetamol toxicity [46].

Aegle marmelos

Kore KJ *et al.*, 2011 evaluated the Nephroprotective activity of an aqueous extract of Leaves of *Aegle marmelos* in Wistar rats. The aqueous extract of *Aegle marmelos* leaves (AEAM) was administered at three doses (250, 500, and 750 mg/kg, p.o.) to Wistar

rats in Gentamicin (GM)-induced nephrotoxicity GM increased serum creatinine, urea and blood urea nitrogen level, while AEAM reduced serum creatinine, urea and blood urea nitrogen level in gentamicin toxicity indicating a nephroprotective effect. The aqueous extract of *Aegle marmelos* leaves possess the Nephroprotective activity y model [21].

CONCLUSION:

Nephrotoxicity is the one of the most common kidney problems occurs when body is exposed to drug or toxin. When kidney damaged occurs body is unable to ride of excess of urine and waste from the body. A number of therapeutic agents can adversely affect the kidney resulting in acute renal failure and intestinal nephritis and nephritic syndrome. From the study clear that the medicinal plant play a prominent role against were as disease. Many plants having use for the treatment of kidney failures in traditional system of models. Throughout world because number of chemicals and drugs available in the market are producing drug adverse effect and drug interactions. Due to this the use of available drugs reduces in use. A second alternative drug as herbal drugs having polyphenols includes flavonoids, tannins and phenols. Which have better antioxidant activity play a drastic effect in urinary tract as well as kidney disorders. Hence the review of study is concluded that the herbal drug posses nephroprotective activity and it has been proven by different animal models.

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