Academic Sciences Asian Journal of Pharmaceutical and Clinical Research

Vol 5, Issue 4, 2012 ISSN - 0974-2441

Review Article

A REVIEW ON MEDICINAL PLANTS FOR NEPHROPROTECTIVE ACTIVITY

MOHANA LAKSHMI. S*, USHA KIRAN REDDY. T AND SANDHYA RANI. KS

Department of Pharmacognosy, Sree Vidyanikethan College of Pharmacy, Tirupati-517102, Andhra Pradesh, India,
Email:mohana_cog@yahoo.co.in

Received:23 july 2012, Revised and Accepted:3 September 2012

ABSTRACT

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

Keywords: Medicinal plants, nephroprotective agents, renal disorders.

INTRODUCTION

Nephrotoxicity is one of the most common kidney problems and occurs when body is exposed to a drug or toxin[1]. A number of therapeutic agents can adversely affect the kidney resulting in acute renal failure, chronic interstitial nephritis and nephritic syndrome because there is an increasing number of potent therapeutic drugs like aminoglycoside antibiotics, NSAID's, chemotherapeutic agents have been added to the therapeutic arsenal in recent years[2]. Exposure to chemical reagents like ethylene glycol, carbon tetrachloride, sodium oxalate and heavy metals such as lead, mercury, cadmium and arsenic also induces nephrotoxicity. Prompt recognition of the disease and cessation of responsible drugs are usually the only necessary therapy[3]. 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. Early literatures have prescribed various herbs for the cure of renal disorders[4]. Co-administration of various medicinal plants possessing nephroprotective activity along with different nephrotoxic agents which may attenuate its toxicity. The term renal failure primarily denotes failure of the excretory function of kidney, leading to retention of nitrogenous waste products of metabolism in the blood[5]. In addition to this, there is a failure of regulation of fluid and electrolyte balance along with endocrine dysfunction. The renal failure is fundamentally categorized into acute and chronic renal failure[6].

Acute renal failure (ARF) refers to the sudden and usually reversible loss of renal function which develops over a period of days or weeks. There are many causes for acute renal failure which mainly includes acute tubular necrosis that commonly accounts for 85% of incidence. Mostly acute tubular necrosis occurs either due to ischemia or toxins. The toxins may be exogenous or endogenous. The exogenous agents are radio contrast agents, cyclosporine, antibiotics, chemotherapeutic agents, organic solvents, acetaminophen and illegal abortifacients[5,6]. Chronic renal failure (CRF) is an irreversible deterioration in the renal function which classically develops over a period of years, leading to loss of excretory metabolic and endocrine functions. Various causes of renal failure has been recognized like hypertension, diabetes mellitus, antineoplastic agents like cyclophosphamide, vincristin and cisplatin etc.[5].

Agents Which Causes Nephrotoxicity

Drugs, diagnostic agents & chemical are well known to be nephrotoxic. The following are some of the important nephrotoxic agents[7].

A) Heavy metal: Mercury, arsenic, lead, bismuth

B) **Antineoplastic agents**
Alkylating agents: Cisplatin, cyclophosphamide
Nitrosoureas: Streptozotocin, Carmustine, Lomustine & Semustine
Antimetabolites: High dose Methotrexate, Cytosine Arabinose, high dose 6-thioguanine, 5-flurouracil
Antitumor antibiotics: Mitomycin, Mithramycin, Doxorubicin
Biologic agents: Recombinant leukocyte and interferon

C) Antimicrobial agents: Tetracycline, Acyclovir, Pentamidine, Sulphadiazine, Trimethoprin, Rifampicin, Amphotericin B

D) Aminoglycosides : Gentamycin, Amikacin, Kanamycin, Streptomycin

E) Miscellaneous
Radiocontrast agents: Non-steroidal anti-inflammatory agents (NSAID's): Ibuprofen, Indomethacin, Aspirin etc.

Nephropathies Caused Due To Different Toxic Mechanisms

Cisplatin Toxicity

Cisplatin is a potent antitumor drug, but its clinical use is limited due to renal toxicity. Cisplatin decreases antioxidants and anti oxidant enzymes leading to enhanced generation of reactive oxygen metabolites and lipid peroxidation[8, 9]. It is reported that many Indian medicinal plants show beneficial effects against renal injury[10]. An early report indicated that nephrotoxicity might occur in as many as 50 to 75% of patients receiving this drug, and is dose limiting[11]. It is used intensively in man, being effective in ovarian & bladder carcinoma, neuroblastoma, head and neck carcinoma, and lymphoma as well as thyroid endometrial neoplasm. However, the most significant activity is observed in testicular cancer. The clinical use of cisplatin is often complicated by nephrotoxicity, ototoxicity, gastrointestinal disturbances like nausea, vomiting and myelosuppression.

Early clinical trials of cisplatin in cancer patients showed a striking incidence of persistent azotaemia and acute renal failure. Experimental studies have shown that there is an abrupt fall in the effective renal plasma flow within 3 hrs of the i.p. dose of cisplatin. It is known to be filtered by the glomeruli and concentrated in the glomerular filtrate from which it is activated in the presence of a low intra cellular chloride concentration. The low intracellular concentration of chloride facilitates the displacement of chloride by the water molecule yielding a positively charged, hydrated and hydroxylated complex. Hydration of cisplatin induces formation of monochloro monoaquodiamino platin or diaquo diammineplatin. These agents alkylate the purine and pyrimidine bases of nuclear material[12]. Renal damage is seen in proximal tubular S_3 portion, the distal tubule and collecting duct.

Other proposed explanation of the nephrotoxicity of cisplatin include the possibility that it include generate reactive metabolites that bind covalently to tissue macromolecules. The nephrotoxic

effects might also be due to sulphydryl binding of heavy metal. A reduction in sulphydryl groups in the rat renal cortex has been demonstrated; this occurred before any significant change in renal function could be detected, suggesting that this biochemical change may be a primary event. Cell fractionations have shown that the greatest decline of sulphydryl groups occurs in the mitochondrial & cytosol fractions; these also had the highest concentrations of platinum[12]. A recent study found that cisplatin induced proximal tubule injury could be ameliorated by the administration of hydroxyl radical scavengers. In these studies cisplatin (5mg/kg BW) caused lipid peroxidation. The hydroxyl radical scavenger prevented acute renal failure by altering tubule damage & enhancing the regenerative response of damaged tubule cells protection from cisplatin toxicity has generally focused on providing free radical scavengers[13].

Acetaminophen Toxicity

Acetaminophen is also known as paracetamol[14]. It is a widely used analgesic and antipyretic drug that is safely employed for a wider range of treatments[15]. Overdose of acetaminophen in humans is fairly common and is often associated with hepatic[16-18] and renal damage[19-21]. Although nephrotoxicity is less common than hepatotoxicity in acetaminophen overdose, renal tubular damage and acute renal failure can occur even in the absence of liver injury[22-24] and can even lead to death in humans and experimental animals[25-26]. Studies are going on throughout the world in search of protective molecules that would provide maximum protection to the liver, kidney as well as other organs and practically very little or no side effects would be exerted during their function in the body[27-28]. A number of herbs are traditionally used in different countries during in response to drug or toxin induced hepatic and renal disorders[29].

There are three pathways for acetaminophen metabolism which includes conjugation with sulfate, glucoronide and metabolism by cytochrome p450 oxidase enzyme system[30-31]. 90% of ingested dose is metabolized through glucoronidation and sulfation pathway and 5% through cytochrome p450 oxidase enzyme system[32-34]. Metabolism by cytochrome p450 enzyme system produces a metabolite, *N*-acetyl-*p*-benzoquinone imine (NAPQI) which is toxic to liver and kidney. In therapeutic dose, this is rendered ineffective by reduced glutathione, an antioxidant compound in the liver and NAPQI-reduced glutathione is excreted by kidney[35-36]. In acetaminophen overdose, sulfation and glucoronidation pathways become saturated. The amount and rate of formation of NAPQI is greatly increased, depleting body's reduced glutathione stores and outstripping its capability to make new glutathione. NAPQI then binds covalently with cells causing their death, resulting in liver and kidney dysfunction[34]. Indeed several biological compounds with antioxidant properties proved effective in protecting the kidneys against deleterious effects of acetaminophen overdose[35].

Gentamicin Toxicity

Aminoglycoside antibiotics have been widely used for gram-negative bacterial infections. However, their nephrotoxicity and ototoxicity are the major limitations in clinical use. Among several aminoglycoside antibiotics, the grade of nephrotoxicity has been reported to be in the following order as, neomycin > gentamicin > tobramycin[36]. Gentamycin Nephrotoxicity occurs in about 15-30% of treated subjects, is manifested clinically as non-oliguric renal failure, with a slow rise in serum creatinine and hypoosmolar urinary output developing after several days of treatment[37]. Gentamicin is filtered through glomeruli into tubular urine, that binds with anionic phospholipids, such as phosphatidylinositol or phospholipdylserine, in brush border membrane of proximal tubular cells reabsorbed actively via pinocytosis process into tubular cells, taken up by lysosomes and thereafter produces phospholipidosis[36]. The drug enters into the cells by adsorptive/receptor mediated endocytosis after binding to acidic phospholipids and megalin and is found essentially in lysosomes. Animals treated with low, therapeutically relevant doses of aminoglycosides show both lysosomal phospholipidosis and apoptosis in proximal tubular cells[38].

The following are some of the medicinal plants for review which possess nephroprotective activity.

Table 1: List of Nephroprotective plants

	Botanical Name	Family	Part used	Chemical constituents	Screening method	References
1.	*Aerva lanata*	Rutaceae	Whole plant	Botulin,β-sitosterol, Amyrin, Hentriacontane, Campesterol, Stigma sterol, Kaempferol, Propionic acid, β-carboline-I, Aervoside and Aervolanine.	Gentamycin induced	Paller et.al., 1990[4]
2.	*Crataeva nurvula*	capparidaceae	Fruit	Kaemferol-3-O-a-D-glucoside, Quercitin-3-O-a-D-glucoside, Flavanoids, Glucosinolates, Steroids, Lupeol and Tannins.	Gentamycin induced	Kore et.al., 2011[4]
3.	*Orthosiphon stamineus*	Laminaceae	Whole plant	Flavanoids, Phenols, Carbohydrates, Steroids, Tannins, Glycosides, Terpins and Saponins	Gentamycin induced	Kannapan et.al.,2010[41]
4.	*Strychnos potatorum*	Loganiaceae	Seed	Flavanoids, Phenols, Saponins, Alkaloids, Steroids, Tannins, Glycosides, and Lignins.	Gentamycin induced	Ruby Varghese et.al., 2011[42]
5.	*Aerva javanica*	Amaranthaceae	Fresh roots	Isoquercetin, 5 methylmellein, 2-hydroxy-3-O-β-primeveroside naphthalene-1,4-dione, Apigenin7-Oglucoronide and Kaempferol	Cisplatin induced	Vinit movaliya et.al., 2011[43]
6.	*Carica papaya*	Caricaceae	Seed	Flavanoids, Phenols, Alkaloids, Protein, Sterols, Terpenoids, Carbohydrates, Steroids, Tannins, Glycosides, Terpins and Saponins.	Cisplatin induced	Subal debnath et.al., 2010[44]
7.	*Ficus religiosa L*	Moraceae	Latex	Flavonoids, Amino acids and Tannins.	Cisplatin induced	Yogesh chand yadav et.al., 2011[45]
8.	*Pedalium murex Linn*	Pedaliaceae	Dried fruits	Flavanoids, Flavones, Alkaloids, Triterpenoids, Carbohydrates, Glycosides and Saponins.	Cisplatin induced	Shelke et.al., 2009[46]
9.	*Vernonia cinerea*	Compositae	Aerial parts	Triterpenoids like α-amyrin, β-amyrin and lupeol.	Cisplatin induced	Sreedevi et.al., 2011[47]

10.	*Acorus calamus*	Araceae	Aerial parts	Monoterpene, Sesquiterpene, Phenyl propanoid, Flavonoids, Quinone and basarone.	Acetaminophen induced	Palani et.al., 2010[48]
11.	*Boerhaavia diffusa*	Nyctaginaceae	Root	Flavonoids, Alkaloids, Steroids, Triterpenoids, Lipids, Lignins, carbohydrates, Proteins and Glycoproteins.	Acetaminophen induced	Surendra et.al., 2011[49]
12.	*Indigofera barberi L*	Fabaceae	Whole plant	Flavonoids, Phenolic acid and sterols.	Acetaminophen induced	Palani et.al., 2008[50]
13.	*Pimpinella tirupatiensis*	Apiaceae	Whole plant	Alkaloids, Flavonoids, Flavones, Volatile oils, β-Bisaboline, Δ-3-Carene, Cis-Carveol, Enemol, Δ-Carveol and Methylgeranate.	Acetaminophen induced	Palani et.al., 2009[51]
14.	*Curcuma longa*	Zingeberaceae	Rhizome	Curcumin, Turmeric oil, Terpenoids, Curcumin (Terpene), Starch and Albumnoids.	Cadmium induced	Eduardo Molina-Jijon et.al., 2011[52]
15.	*Drynaria fortune*	Polypodiaceae	Whole plant	Arsenic, Ca2+, Cu2+, Glucose, Iron, Mg, Mn, Hg, Naringin, K+, Na+, Starch and Zinc.	Silver chloride induced	Kore et.al., 2011[53]
16.	*Eruca sativa*	Crassulaceae	Seeds	Flavanoids	Mercuric chloride induced	Sarwar Alam et.al., 2007[54]
17.	*Moringa oleifera*	Moringaceae	Seeds	Vitamin A, Nicotinic acid, Ascorbic acid, Vitamin B, Fatty acid, Glucose, Sucrose, Citric acid, Malic acid, Succinic acid, Fumaric acid and Oxalic acid.	Fluoride induced	Ranjan et.al., 2009[55]
18.	*Tamarindus indica*	Caesalpinaceae	Fruit pulp	Polysaccharides, Balsamine, Catechin, Nasturtium, Tamarin, Phosphatidic acid, Phosphatidic choline, Ethanollamine, Serine, Inositol, Alkaloid, Citric acid, Tartaric acid and Pottasiumbitartrate.	Fluoride induced	Ranjan et.al., 2009[55]
19.	*Tectona grandis*	Verbanaceae	Bark	Lapachol, Dehydro-α-lapachone, Methyl quinizarin and Squalene.	Alloxan induced	Ghasias et. al., 2010[56]
20.	*Ginkgo biloba*	Ginkgoaceae	Whole plant	Flavonoids, Bilobalide, GingkolideA, Gingkolide B and Gingkolide CandBiflanoide.	Streptozotocin induced	Welta et.al., 2007[57]
21.	*Abutilon indicum*	Malvaceae	Whole plant	Saponins, Flavonoids and Tannins.	Gentamicin induced	Kakasaheb Khore et.al., 2011[58]
22.	*Euphorbia neriifolia*	Euphorbiaceae	Leaves	Saponins, Flavonoids and Tannins	N-nitroso dimethyl amine induced	Pracheta et.al., 2011[59]
23.	*Rubia cardifolia Linn*	Rubiaceae	Root	Purpurin, Manjistin, Garancin, Purpuroxanthin, Resin, Glucose, Sucrose, Triterpenes, Lucidine, Anthroquinine, Fattyacids and Gum.	Ethylene glycol induced	Kalyani Divakar et. al., 2010[60]
24.	*Punicagranatum* L	Puniaceae	Fruit peel	Ellagic acid, Ellagitannins and gallic acid.	Ferric nitrilo tri acetate induced	Mahgoub Mohammed AHMED et.al., 2010[61]

Aerva lanata

Aerva lanata is also called as Pasanabheda, Chaya, Gorakhganja belongs to the family Amaranthaceae[62]. The *Aerva lanata* plant is reported to have α-amyrin, campesterol, β-sitosterol, its palmitate, chrysin and flavonoid glucosides[63]. Canthin-6-one and β-carboline alkaloids were isolated from *Aerva lanata*[64]. Four new alkaloids viz., aervine, methylaervine, aervoside and aervolanine were isolated[65]. The plant was reported for various activities such as diuretic, hepato protective[66], antidiabetic[67], antimicrobial[68], anthelmintic and demulcent activity[69]. *Aerva lanata* also shows its effect on cisplatin and gentamycin model of acute renal failure [70].

The ethanolic extract of the entire plant of *Aerva lanata* was studied for its nephroprotective activity in cisplatin and gentamicin induced acute renal injury in albino rats of either sex. In the curative regimen, the extract at dose levels of 75, 150 and 300 mg/kg showed dose-dependent reduction in the elevated blood urea and serum creatinine and normalized the histopathological changes in tha cisplatin model. In the gentamicin model the rats in the preventive regimen also showed good response to the ethanol extract at 300 mg/kg. The results suggest that the ethanolic extract of *Aerva lanata* possesses marked nephroprotective activity with minimal toxicity and could offer a promising role in the treatment of acute renal failure caused by nephrotoxins like cisplatin and gentamicin[70].

Crataeva nurvala

Crataeva nurvala Buch-Ham belongs to the Family Capparidaceae commonly known as Varuna, is an evergreen tree indigenous to India[71]. Moreover, pharmacological study reveals the potentiality of *Crataeva nurvala* extract and its active principle, particularly lupeol as diuretic, anti-inflammatory, antioxidant, cardio-protective, hepatoprotective, lithonotriptic, anti-rheumatic, anti-periodic, contraceptive, anti-protozoal, rubifacient and vesicant[72].

The alcoholic extract of *Craaeva nurvala* 250 and 500 mg/kg for 10 days showed protective activity against cisplatin 5 mg/kg induced nephrotoxicicty. The results suggested, that the alcoholic extract has significantly altered the dysfunction of renal proximal tubule cells by decreasing the concentration of blood urea nitrogen, creatinine, lipid peroxidation, glutathione and catalase[73].

Administration of aqueous extract of *Crataeva nurvala* 200 and 400 mg/kg for 28 days showed protective activity against ethylene glycol induced nephrotoxicicty[74].

Orthosiphon stamineus

Orthosiphon stamineus Benth. is a medicinal herb belonging to the family Lamiaceae. The plant has extensively been exploited traditionally to treat several human ailments. Leaves of this plant have been used as diuretic, and to treat rheumatism, abdominal pain, kidney and bladder inflammation, edema, gout and hypertension[75]. Scientific studies have found that the leaves exhibit dynamic pharmacological properties such as, antioxidant, antibacterial, heptoprotective, anti-inflammatory, cytotoxic, diuretic, antihypertensive and vasodialative properties[76]. More than twenty phenolic compounds were isolated from this plant including lipophilic flavones, flavonol glycosides and caffeic acid derivatives such as rosmarinic acid and 2,3-dicaffeoyltartaric acid, were identified and quantified by HPLC[77].

The methanolic extract of *orthosiphon stamineus* benth was evaluated for its nephroprotective activity using rat model. Gentamycin is an extensively used aminoglycoside antibiotic. It has been reported to produce nephrotoxicity even at normal therapeutic dose level. The drug was administered intra peritonialy at a dose of 80mg/kg weight for 9 days. Histopathological sections showed marked glomerular, peritubular and blood vessel congestion. These increased levels of serum creatinine, blood urea, urinary protein and extent of renal damage were decreased by the methanolic extract of *Orthosiphon stamineus* at both dose levels that is 100 and 200 mg/kg body weight in rats[21].

Strychnos potatorum

Strychnos potatorum Linn commonly referred to as clearing nut belongs to the family Loganiaceae[78]. According to Ayurveda, the seeds are acrid, alexipharmic, lithotriptic and cure strangury, urinary discharges, head ailments etc[79]. Roots cure all types of leucoderma whereas fruits are useful in eye diseases, thirst, poisoning and hallucinations. The ripe fruit is emetic, diaphoretic, alexiteric, cures inflammation, anaemia, jaundice[78]. According to Unani system of medicine, seeds are bitter, astringent to bowels, aphrodisiac, tonic, diuretic and good for the liver, kidney complaints, gonorrhea, colic etc[80]. Since kidney is involved in the clearance of toxins and xenobiotics, it may be more prone to attack by various challenges. A large number of these agents may cause damage to these organs by oxidative stress.

The ethanolic extract of *Strychnos potatorum* seeds was evaluated for its nephroprotective effect by using rat models. Hence, the study concludes that the seeds of *Strychnos potatorum* possess marked nephroprotective activity and could have a promising role in the treatment of acute renal injury induced by nephrotoxins, especially gentamicin[42].

Aerva javanica

Aerva javanica Juss. ex Schult is medicinal plant belonging to the family Amaranthaceae[81]. Aerva javanica is reported as anthelmintic, diuretic, demulcent. It is used for the treatment of headache[82]. The decoction of the plant is administered to remove swellings, applied to acne like conditions of the face[83].

The aqueous extracts of *Aerva javanica* roots were studied for the scientific evaluation of nephroprotective activity. Various parameters like body weight, blood urea, serum creatinine, serum protein, total protein, serum albumin, urine volume and pH, tissue protein, GSH and TBARS level were compared with controls on 16th day after treatment. The study concludes that cisplatin injury was evidenced by the elevated biochemical markers and histopathological features of acute tubular necrosis. The aqueous extract at the dose level of 400 mg/kg body weight was found to normalize the elevated biochemical markers and bring about a marked recovery in kidneys as evidenced by using microscopy[43].

Carica papaya

Carica papaya Linn belonging to family caricaceae, is commonly known as papaya, Pawpaw, Melon tree[84]. *Carica papaya* is a rich source of phytoconstituents mainly carpaine ,dehydrocarpaines, pseudocarpaine. It has various traditional remedies and pharmacological activities like antioxidant, wound healing, hepatoprotective, anti inflammation, antibacterial, analgesic, heart tonic, anthelminitic and to treats ringworm, high blood pressure, stomachache, skin sores, fungal infections, cancer and prevents rheumatism, psoriasis[85].

The aqueous seed extract of *Carica papaya* Linn. has been evaluated by carbon tetrachloride induced renal injury in wistar rats as a dose and time-dependent study. The study showed that *Carica papaya* Extract has nephroprotective effect on Carbon tetr*a* chloride renal injured rats, an effect which could be mediated by any of the phytocomponents present in it via either antioxidant and/or free radical scavenging mechanism(s)[44].

Ficus religiosa

Ficus religiosa (L.), commonly known as pepal belonging to the family Moraceae. plants have been used in traditional Indian medicine for various range of ailments. Traditionally the bark is used as an antibacterial, antiprotozoal, antiviral, astringent, antidiarrhoeal, in the treatment of gonorrhea, ulcers, and the leaves used for skin diseases[86]. The leaves reported antivenom activity and regulates the menstrual cycle[87]. *Ficus religiosa* fruits contain flavonols namely kaempeferol, quercetin, and myricetin[88].

To evaluate the possible potential, nephroprotective and curative role of the methanolic extract of *Ficus religiosa* L. Latex was used against cisplatin (5mg/kg, i.p.) induced Nephrotoxicity. The blood was collected from the retro-orbital sinus of rats and determined for urea and creatinine levels in serum of each group after then rats were sacrificed for quantitative estimation of various enzymes and ATPases content in kidney tissue. A single dose of cisplatin induced shows the increased levels of urea & creatinine in serum and it was significantly recovered by 400mg/kg in curative and protective groups. The enzyme estimation in kidney tissue has found that increased malondialdehyde and decreased reduced glutathione (GSH). The results conclude that the study data confirmed nephrotoxicity induced by cisplatin due oxidative stress and methanolic extract of *Ficus religiosa* L. latex may have nephroprotective and curative activity[45].

Pedalium murex

Pedalium murex is used as herbal medicine belongs to the family Pedaliaceae. Fruit extract of this plant contains many phytochemicals such as carbohydrates, flavonoids, alkaloids, glycosides, steroids, phenols, saponins, tannins and fixed oils & fats[89]. The effects of these bioactive components showed diverse pharmacological properties such as antioxidant, anti-diabetic[90], antibacterial[91], aphrodisiac, anti-inflammatory activity[92] and nephroprotective property[93].

The ethanolic extract of dried fruits of *Pedalium murex* Linn was evaluated for its nephroprotective activity. Nephrotoxicity was induced in Wistar rats by intraperitoneal administration of Cisplatin 5mg/kg. Effect of concurrent administration of *Pedalium murex* ethanolic extract at a dose of 250 mg/kg given by oral route was determined using serum creatinine and blood urea and change in body weight as indicators of kidney damage. Cystone was used as standard drug. The extract significantly decreased the cisplatin induced nephrotoxicity. The results showed that the ethanolic extract of dried fruits of *Pedalium murex* has an excellent nephroprotective activity as compared to cystone[46].

Vernonia cinerea

vernonia cinerea less belonging to family Asteraceae[94]. Mainly it consists of 38%fatty oil.plant contains β–amyrin acetate, β-amyrinbenzoate;lupeol and its acetate, β-sitosterol,stigmosterol,a-spinasterol, kcl and also contains flavonoids,glycosides,tannins and carbohydrates[95]. The different parts of vernonia cinerea less has been possess Hypoglycemic and anti-diabetic activity[96], anti-pyretic activity[97], anti-bacterial activity[98], diuretic and anti-diuretic activity[99], anti-inflammatory activity[100], free radicals and No

scavenging activity[101],Analgesic activity[102]. The alcoholic extracts of aerial parts of vernonia cinerea has been examined for the effect of petroleum ether, ethyl acetate on cisplatin-induced nephrotoxicity at a dose of 6mg/kg, i.p. in albino rats. The alcoholic extract showed pronounced curative activity and the ethyl acetate extract has exhibited good prophylactic activity and petroleum ether extract showed moderate protection for both curative and prophylactic models against cisplatin-induced toxicity[47].

CONCLUSION

From this study, it is clear that the medicinal plants play a prominent role against various diseases. A variety of medicinal plants and plants extracts have been reported for its significant nephroprotective activity in animal models. The nephroprotective activity is probably due to the presence of Flavanoids in all the few medicinal plants. The results of this study indicate that extracts of leaves and plants of some medicinal plants have good potentials for use in kidney damage. The present review study give evidential explore mechanism of action of medicinal plants against experimentally induced nephrotoxicity. Hence, the review of the study is concluded that the herbal drug possesses nephroprotective activity and it has been proven by different animal models which gives many links to develop the future trials.

REFERENCES

1. Porter GA and Bennett WM. Nephrotoxic acute renal failure due to common drugs American journal of Physiology, 1981; 241(7): F1-F8.
2. Hoitsma AJ, Wetzels JF and Koene RA. Drug induced nephrotoxicity. Aetiology, clinical features and management, Drug Saf, 1991; 6 (2): 131-147.
3. Paller MS., Drug induced nephropathies Med Clin North Am,1990; 74 (4):909-917.
4. http://farmacists.blogspot.com
5. Herfindal, Gourley. Text book of therapeutic drug and disease management. 7th Edn. Charcil Livingstone, London; 2000; 425-36.
6. Barry M, Brenner, Floyd C, Rector. The kidney 6th Ed. Vol I, W.B. Saunders Company, Philadelphia; 2000; 3-67.
7. Schrier RW, Gottschalk CW. Disease of kidney, 5thed, 2, Published by Little Brown & Co,1993; 1031-1165.
8. Baumann,K and Hannemann. J.Toxicology, 1988; 51: 119- 132.
9. Sadzuka,Y., Shoji, T. and Takino,Y. Toxicol. Lett., 1992; 62: 293-300.
10. Ali,B.H. andAlMoundhri,MS. Food Chem. Toxicol.,2006; 44: 1173-1183.
11. Balchley, J.D. and Hill, J.B. Renal and electrolyte disturbances associated with cisplatin. Ann. Intern. Med., 1981; 95, 628-632.
12. Davison A M, Cameron J S, Grunfeld J P,and Kerr D N S. Oxford Textbook of Clinical Nephrology 2nd ed. 3, Published by Oxford University Press, 1988; 2650-53.
13. Brenner B M, The Kidney, 6th edn, Published by W B Saunders Co. USA pp:1563-1564
14. Yapar K, Kart A, Karapehlivan M, Atakisi O, Tunca R, Erginsoy S, Citil M. Hepatoprotective effect of l-carnitine against acute acetaminophen toxicity in mice. *Exp and toxicolo pathology*, 2007; 59,121-128.
15. Nelson SD. Mechanisms of the formation and disposition of reactive metabolites that can cause acute liver injury. (1995)*Drug Metab. Rev*,27,147-177.
16. Boelsterli UA. Specific targets of covalent drug-protein interactions in hepatocytes and their toxicological significance in drug-induced liver injury. (1993), *Drug Met. Res*. 25, 395-451.
17. Holtzman JL. The role of covalent binding to microsomal proteins in the hepatotoxicity of acetaminophen. (1995), *Drug Metab. Rev,* 27, 277-97.
18. Placke ME, Wyand DS, Cohen SD. Extrahepatic lesions induced by acetaminophen in the mouse. (1987) *Toxicol. Pathol*,15, 381-387.
19. Trumper L, Monasterolo LA, and Elias MM. Probenecid protects against in vitro acetaminopheninduced nephrotoxicity in male Wistar rats. (1998), *J. Pharmacol. Exp. Therapeat*, 283, 606-10.
20. Ghosh A, Sil PC. Anti-oxidative effect of a protein from Cajanus indicus L. against acetaminophen-induced hepato-nephro toxicity. (2007), *Biochem Mol Biol,* 40,1039-49.
21. H.Gulnaz, M. Tahir, B. Munir, W. Swami. Protective effects of garlic oil on acetaminophen induced Nephrotoxicity in male albino rats. (2010), Biomedica Vol.26, 9-15.
22. Carpenter, H.M., Mudge, G.H. Acetaminophen nephrotoxicity:studies on renal acetylation and deacetylation. (1981), *J. Pharmacol. Exp. Ther*. 218, 161-167.
23. Jones AF, Vale JA. Paracetamol poisoning and the kidney. (1993), *J. Clin. Pharm. Ther*,18, 5-8.
24. Eguia L, Materson BJ. Acetaminophen related acute renal failure without fulminant liver failure. (1977), *Pharmacotherapy*;17,363-70.
25. Ray SD, Mumaw VR, Raje RR, Fariss MW. Protection of AAPinduced hepatocellular apoptosis and necrosis by cholesteryl hemisuccinate pretreatment. (1996),*J. Pharmacol. Experiment. Therapeutics,* 279, 1470-1483.
26. Webster PA, Roberts DW, Benson RW, Kearns GL. Acetaminophen toxicity in children diagnostic confirmation using specific antigen biomaker. 1996, *J. Clin. Phamacol*, 36, 397-402.
27. Montilla P, Barcos M, Munoz MC, Bujalance in streptozotocin-induced diabetic rats.(2005), *J. Biochem. Mol. Biol*. 38, 539-544.
28. Mansour HH, Hafez HF, Fahmy NM. (2006),Silymarin modulates Cisplatin-induced oxidative stress and hepatotoxicity in rats. *J. Biochem. Mol. Biol*, 39, 656-661.
29. El-Beshbishy HA. Hepatoprotective effect of green tea [Camellia sinensis] extract against tamoxifen-induced liver injury in rats.(2005), *J. Biochem. Mol. Biol*. 38, 300-306.
30. Slitt A.M.L, Dominick P.K, Roberts J.C, Cohen S.D. Effects of ribose cysteine pretreatment on hepatic and renal Acetaminophen Metabolite formation and glutathione depletion. Basic Clin Pharmacol Toxicol 2005; 96: 487-494.
31. Gamel el-din AM, Mostafa AM, Al-Shabanah O, Al- Bekairi AM, Nagi MN. Protective effect of Arabic gum against acetaminophen induced hepatotoxicity in mice. Pharmacol Res 2003; 48: 631-635.
32. Presscott L. Oral or Intravenous N-Acetylcysteine for Acetaminophen poisoning? Ann Emerg Med 2005; 45: 409-413.
33. Mugford CA, Tarloff JB. The contribution of oxidation and deacetylation to acetaminophen Nephrotoxicity in female Sprague-Dawley rats. Toxicol Lett 1997; 93: 15-22.
34. Melo DAS, Saciura VC, Poloni JAT, Oliveria CSA, Filho JCFA, Padilha RZ, et al. Evaluation of renal enzymeuria and cellular excretion as a marker of acute nephrotoxicity due to an overdose of acetaminophen in Wistar rats. Clin Chem Acta 2006; 373: 88-91.
35. Liebert JJ, Matlawska I, Bylka WM, M Marek. Protective effect of Aquilegia vulgaris (L) on APAP-induced oxidative stress in rats. J Ethanopharmacol 2005; 97: 351-358.
36. Hu J J, J.S.H. Yoo, M. Lin, E-J Wang, C.S Yang. Protective effects of diallyl disulfide on Acetaminophen induced toxicities. Food Chem Toxicol 1996; 34: 963- 969.
37. Abdel-Zaher AO, Abdel-Hady RA, Mahmoud MM, Farrag MMY. The potential protective role of alphalipoic acid against acetaminophen- induced hepatic and renal damage. Toxicol 2008; 243: 261-270.
38. Suzuki, S.S., Takamura, J., Yoshida, Y., Shinzawa, Niwat, Tamatani, S R., 1995. Comparison of gentamicin nephrotoxicity between rats and mice. Camp. Biochem. Physiol. 1, 15-28.
39. Ali, B.H., 2003. Agents ameliorating or augmenting experimental gentamicin nephrotoxicity: some recent research. Food and Chemical Toxicology 41, 1447–1452.
40. Servais, H., Ortiz, A., Devuyst, O., Denamur, S., Tulkens, P.M., Mingeot-Leclercq, M.P., 2008. Renal cell apoptosis induced by nephrotoxic drugs: cellular and molecular mechanisms and potential approaches to modulation. Apoptosis 13, 11-32.

41. Kannappan N., Madhukar., Mariymmal., Uma sindhura P., Mannavalan R.,"Evaluation of nephroprotective activity of *Orthosiphonstamineus*Benth extract using rat model", International Journal of PharmTech Research, 2010; 2 (3):209-215.
42. Ruby Varghese.,Mohammed Moideen M., Mohammed Suhail MJ., Dhanapal CK.,"Nephroprotective effect of ethanolic extract of *Strychnospotatorum*Seeds in Rat Models", Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2011; 2 (3): 521-529.
43. VinitMovaliyaa.,DevangKhamarb&ManjunathSetty M.,"Nephroprotective activity of aqueous extract of*AervaJavanica*roots in cisplatin induced renal toxicity in rats", Pharmacologyonline, 2011;1:68-74.
44. SubalDebnath, NileshBabre, Manjunath Y.S., Mallareddy.,PabbaParameshwar and Hariprasath K.,"Nephroprotective evaluation of ethanolic extract of the seeds of papaya and pumpkin fruit in cisplatin-induced nephrotoxicity", Journal of Pharmaceutical Science and Technology, 2010; 2 (6):241-246.
45. Yogesh Chand Yadav., Srivastava D.N., VipinSaini., SaritaSinghal., Seth A.K.,Sharadkumar., Tejas K., Ghelani., Anujmalik.,"Nephroprotective and curative Activity of methanolic extract of *Ficusreligiosa*L. latex in Albino Rats Using Cisplatin Induced Nephrotoxicity", Pharmacologyonline, 2011;1:132-139.
46. Shelke T. T., Kothai.R.,Adkar. P. P., Bhaskar.V.H.,Juvale. K.C., Kamble B.B and Oswal R. J.,"Nephroprotective activity of ethanolic extract of dried fruits of *Pedalium murex* Linn", Journal of Cell and Tissue Research, 2009; 9(1):1687-1690.
47. Sreedevi. A., Bharathi K., Prasad K.V.S.R.G.,"Effect of *Vernoniacinereaa*erial parts against Cisplatin-induced nephrotoxicity in rats", Pharmacologyonline, 2011;2: 548-555.
48. Palani S., Raja S, Praveen Kumar R.,Parameswaran P., Senthil Kumar B., "Therapeutic efficacy of *Acoruscalamus*on acetaminophen induced nephrotoxicity and oxidative stress in male albino rats", ActaPharmaceuticaSciencia, 2010;52: 89-100.
49. Surendra K.,Pareta., Kartik., Patra C., RanjeetHarwansh., Manoj Kumar., Kedar Prasad., Meena.,"Protective effects of *BoerhaaviaDiffusa*against Acetaminophen-Induced nephrotoxicity in Rats",Pharmacologyonline, 2011;2:698-706.
50. PalaniS., SenthilkumarB.,Praveen Kumar R., Devi K., Venkatesan D, Raja Sathendra E.,"Effect of the ethanolic extract of *Indigoferabarberi (L)* in acute Acetaminophen - Induced Nephrotoxic Rats", Advanced Biotech, 2008;(9):28-31.
51. Palani S., Raja S., Praveen Kumar R., SoumyaJayakumar., Senthil Kumar B.,"Therapeutic efficacy of *Pimpinellatirupatiensis* (Apiaceae) on acetaminophen induced nephrotoxicity and oxidative stress in male albino rats", International Journal of PharmTech Research, 2009; 1 (3):925-934.
52. Eduardo Molina-Jijon., Edilia Tapia., Cecilia Zazueta., Mohammed El Hafidi., Zyanya Lucia Zatarain-Barron., Rogelio Hernandez-Pando., Omar Noel Medina-Campos Guillermo Zarco-Marquez., Ismael Torres., Jose Pedraza-Chaverri., "Curcumin prevents Cr (VI)-induced renal oxidant damage by a mitochondrial pathway", Food and Chemical Toxicology, 2011; FRB-10747: (1-15).
53. Kore KJ*., Shete RV and Jadhav PJ.,"Nephroprotective role of *A. MARMELOS* extract", International Journal of Research in Pharmacy and Chemistry, 2011; 1(3): 617-623.
54. SarwarAlamM.,GurpreetKaur.,ZoobiJabbar.,KaleemJaved.,Moh ammadAthar.,"*Erucasati va* seeds possess antioxidant activity and exert a protective effect on mercuric chloride induced renal toxicity", Food and Chemical Toxicology, 2007;45:910–920.
55. Ranjan R., swarup D., Patra R C., Chandra., Vikas., "*Tamarindusindica* L. and *Moringaoleifera* M. Extract administration ameliorates fluoride toxicity in rabbits", Indian Journal of Experimental Biology, 2009; 47 (11):900-905.
56. Ghaisas M.M., Navghare V.V., Takawale A.R., Zope V.S., Phanse M.A., "Antidiabetic and Nephroprotective effect of*Tectonagrandis* L in alloxan induced diabetes", Arspharmaceutica, 2010; 51 (4):195-206.
57. Welta K., Weissa J., Martinb R., Hermsdorfc T., Drewsa S., Fitzla G., "Ginkgo biloba extract protects rat kidney from diabetic and hypoxic damage", Phytomedicine, 2007; 14:196–203.
58. Kakasaheb J. Kore, Dr. Rajkumar V.Shete. Effect of Abutilon indicum extract in gentamicin induced nephrotoxicity, IJPRD,2011;Vol 3(7): October 2011 (73-79).
59. Pracheta P., Veena Sharma., Lokendra Singh., RituPaliwal., Sadhana Sharma., SachdevYadav., Shatruhan Sharma.,"Chemopreventive effect of hydroethanolic extract of *Euphorbia neriifolia*leaves against DENA-Induced renal carcinogenesis in mice", Asian Pacific J Cancer Prev, 2011;12:677-683.
60. KalyaniDivakar., Pawar A.T., Chandrasekhar S.B., Dighe S.B., GoliDivakar.,"Protective effect of the hydro-alcoholic extract of *Rubiacordifolia* roots against ethylene glycol induced urolithiasis in rats", Food and Chemical Toxicology, 2010; 48: 1013–1018.
61. Mahgoub Mohammed AHMED and Safaa Eid ALI.,"Protective effect of pomegranate peel ethanol extract against ferric nitrilotriacetate induced renal oxidative damage in rats", Journal of Cell and Molecular Biology, 2010; 7(2) & 8(1):35-43.
62. Vaidyaratnam PS Variers, Arya Vaidya Sala. Indian Medicinal Plants, a compendium of 500 species Orient Longman pvt. Ltd, 3-6-752, Himayatnagar, Hyderabad 500029 (A.P.), India 1994; (1)67-69.
63. Khare CP. Encyclopedia of India Medicinal Plants, Rational Western Therapy, Ayurvedic and other traditional Usage. Botany, Springer-Verlag Berlin Heidelberg, New York 2007; 29-30.
64. Zapesochnaya G, Kurkin V, Okhanov V, Miroshnikov A. Canthin-6-one and β-carboline alkaloids from *Aerva lanata,* Planta Med 1992; 58(2):192-6.
65. Vaidyaratnam PS Variers, Arya Vaidya Sala. Indian Medicinal Plants, a compendium of 500 species Orient Longman pvt. Ltd. 3-6-752, Himayatnagar, Hyderabad 500029 (A.P.), India 1994; (3)19.
66. Majumdar FI, Shah MB, Patel KN, Shah BK. *Aerva lanata*-Its diuretic and hepatoprotective activity, Indian J. Nat. Prod 1999; 15(1):9-12.
67. Vetrichelvan T, Jegadeesan M. anti-diabetic activity of alcoholic extract of *Aerva lanata* (L) Juss. Ex Schultes in rats. J Ethnopharmacol 2002; 80(2-3):103-7.
68. Chowdhury D, Sayeed A, Islam A, Shah ABM, Astaq MKGR. Antimicrobial activity and cytotoxicity of *Aerva lanata,* Fitoterapia 2002; 73(1):92-4.
69. Guhabhakshi DN, Sensarma P, Pal DC. A Lexicon of Medicinal Plants in India, Naya prakash 206 Bidhansarani Calcutta India 1999; (1):61-2.
70. Shirwaikar A, Issac D, Malini S. Effect of *Aerva lanata* on cisplatin and gentamicin model of acute renal failure. J Ethnopharmacol 2004; 90 (1):81-6.
71. Shumaia Parvin, Md. Abdul Kader, Md. Ajijur Rahman, Mir Imam Ibne Wahed and Md. Ekramul Haque. antibacterial activities and brine shrimp lethality bioassay of the chloroform extract of stem bark of crataeva nurvala buch ham, IJPSR, 2012; Vol. 3(3): 830-834.
72. Farjana K, Md. Amran H, Apurba SA, Stesh CB, Nazmul Q. evaluation of analgesic and antidiarrhoeal property of the ethanolic extract of *Crataeva nurvala* Buch. Ham leaves. *Int J Pharm Sci Rev Res* 2012; 12(2): 5-8.
73. Shelkea TT, Bhaskarb VH, Adkara PP, Jhaa U, Oswala RJ. Nephroprotective activity of ethanolic extract of stem barks of *Crataeva nurvala* Buch Ham. *International Journal of Pharmaceutical Sciences and Research* 2011; 2(10): 2712-17.
74. Sridhar N, Venkataraman S, Mishra M, Ravikumar R, Sam Jeeva KE. Antinephrolithiatic effect of *Crataeva magna* lour. Dc. root on ethylene glycol induced lithiasis. *Int. J. Pharm & Ind. Res* 2011; 1(2): 135–7.
75. Hegnauer R. Chemotaxonomie der pflanzen In. 1966; Verlag SB (ed), 314-316.

76. Chung WG, Roh HK, Kim HM, Cha YN. Involvement of CYP3A1, 2B1, and 2E1 in C-8 hydroxylation and CYP 1A2 and flavin-containing monooxygenase in N-demethylation of caffeine; identified by using inducer treated rat liver microsomes that are characterized with testosterone metabolic patterns. Chem Biol Interact 1998;113:1–14.
77. Sumaryono W, Proksch P, Wray V, Witte L, Hartmann T. Qualitative and Quantitative Analysis of the Phenolic Constituents from Orthosiphon aristatus. Planta Med 1991; 57:176–180.
78. Gupta RS, Kanwar N, Rehwani H, Verma SK, Dobhal MP. Asian J Exp Sci 2006; 20(1): 181-187.
79. Agharkar SP. Medicinal plants of Bombay presidency. Pbl. Scientific Publishers, Jodhpur, India, 1991, pp. 203-204.
80. Oudhia P. *Strychnos potatorum* Linn. Society for Parthenium Management (SOPAM), Raipur, India, 2004.
81. Soliman, M. A.: Cytogenetical studies on Aerva javanica (Amaranthaceae) — Fl. Medit. 16: 2006; 333-339.
82. Chopra RN, Nayar IC, Chopra IC. Glossary of Indian Medicinal Plants. New Delhi. Council of Scientific and Industrial Research. 1956:4-8.
83. Gaze AT. The vegetation of the district of Minbu in Upper Burma, Rec. Bot. Surv. India. 1940; 3:139.
84. Mabberly DJ. The Plant Book. New York, NY: Cambridge University Press ; 1987.
85. Doughari JH, Elmahmood AM, and Manzara S (2007) Studies on the antibacterial activity of root extract of carica papaya L. *African journal of microbiology Research* 1(3): 037-041.
86. Kalpana G, Rishi RB. Ethnomedicinal Knowledge and healthcare practices among the Tharus of Nwwalparasi district in central Nepal. For Ecol Manage 2009;257:2066-72.
87. Chopra RN, Chopra S.Indigenous Drugs of India.2 nd ed. Calcutta: Dhur and Sons; 1958. p. 606.
88. Bushra S, Farooq A. Flavonols (kaempeferol, quercetin, myricetin) contents of selected fruits, vegetables and medicinal plants. Food Chem 2008*;* 108:879-84.
89. Thamizh Mozhi M, Mulaicharam A R, Murugesh S, Phytochemical and Pharmacognostical studies on Pedalium murex Linn. International Journal of Research in Ayurveda and Pharmacy, 2(1), Jan-Feb 2011, 253-258.
90. Ravi Kumar R, Krishnamoorthy P, Antidiabetic effect of Pedalium murex: Effect on Lipid Peroxidation in Alloxan induced diabetes. International Journal of Research in Ayurveda & Pharmacy, 2(3), 2011, 816-821.
91. Gunasekaran Balamurugan, Muralidharan P, Satyanarayana Polapala, Aphrodisiac activity and curative effects of Pedalium murex (L.) against ethanol-induced infertility in male rats. Turk J Biol 34, 2010, 153-163.
92. ParimalaDevi B, Davidraj C, TamilChelvan N, Ramasubramaniaraja R, Evaluation of Anti-Inflammatory activity of Methanol Extract of Abutilon indicum and Pedalium murex- A comparative study. Journal of Pharmacy Research, 3(10), 2010, 2425-2426.
93. Shelke TT, Kothai R, Adkar P P, Bhaskar V H, Juvale K C, Kamble B B, and Oswal R J, Nephroprotective activity of ethanolic extract of dried fruits of Pedalium murex Linn. Journal of Cell and Tissue Research. Vol. 9(1), 2009, 1687-1690.
94. Oriental legman, Indian Medicinal plants,1994;vol.(5).
95. Rajashekar. m Bhande, P. kalyani, S. Ramachandra Setty, H. Ramesh and K. Sreenivasa Rao. Pharmacognostical evaluation of leaves of Vernonia cinerea Less,Biomedical and pharmacology Journal, 2010; vol.3(1):p.g.no. 87-91.
96. G.Y.sy,A.cisse,R.B.Nongonierma,M.Sarr,N.A.Mbodj,B.Faye.Hypo glycemic and antidiabetic activity of acetonic extract of Vernonia colorata leaves in normoglycaemic and alloxan-Induced diabetic Rats,Journal of etanopharmacology,2005;98:pp.171-175.
97. MalyaGuptha*.U.K.Mazumder.L.Manikandan,S.Bhattacharya,P. K.Haldar and S.Roy.Evaluation of Antipyretic Potential of Vernonia cinerea Extract in rats.Phytotherpy Research phytother.Res.2003;17:804-806.
98. .MalyaGuptha.U.K.Mazumder.L.Manikandan, S.Bhattacharya, C.C.Kandar. Antibacterial activity of Vernonia cinerea, Fitoterapia,2003;74:148-150.
99. J.O.Adeboye,W.Asije and S.O.Awe.Diuretic and Antidiuretic Activity of the leaf extracts of vernonia cinerea(Less)(Fam.Compositae),Phytothrapy Research,1997;vol.11:454-456.
100. U.K.Mazumder, M.Guptha.L. Manikandan,S. Bhattacharya,P. K.Haldar and S.Roy.Evaluation of Antiinfammatory activity of vernonia cinerea less.extract in rats.Phytomedicine,2003;10:185-188.
101. P.Pratheesh kumar and Girija Khuuttan.Vernonia cinerea L.scavenges free radicals and regulates nitric oxide and proinflammatory cytokines profile in carrageenan induced paw edema model.Immunopharmacology and immunotoxicology,2009;31(1):94-102.
102. E.O.Iwalewa,O.J.Iwalewa,J.O.Adeboye.Analgesic,antipyretic,ant i-inflammatory effects of methanol, chloroform and ether extracts of vernonia cinerea less leaf.Journal of Ethanopharmacology,2003;86:229-234.