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REVIEW ARTICLE

Review on Traditional Use of Nephroprotective Plants in Kerala

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Abstract

Our mother nature is an abundant treasure of medicinal plants. Many of the plants have active constituents like alkaloids, benzoquinones, catechols, carotenoids, flavonoids, glycosides, flavanol glycosides, steroid glycosides, glycoalkaloids, terpenoids, monoterpenoids, diterpenoids, triterpene saponins, sterols and polyphenols which are proved to be having tissue rejuvenation property. Which can be made use in critical conditions like nephropathy which can be curable only with kidney transplantation or dialysis, which are even unaffordable to common man. It will be very useful to isolate active ingredients from easily available medicinal plants which can be effectively used for conditions like Chronic Kidney Disease. India is a country which extensively follows different forms of medications like allopathy, Ayurveda, siddha and unani among them traditional system of medicine is considered to be pretty much important. The biodiversity of India helps traditional healers to explore vast possibility of it. Modern medicine gets ample support by evaluating and isolating natural, semisynthetic, and synthetic derivatives of effective phytoconstituents of herbs. The information's regarding such medicinal plants is exclusively possessed by certain tribal communities all over India. This article also points towards some plants used by traditional healers of different tribal communities of Kerala.

Keywords: *Nephroprotective, Herbal medicine, Tribal communities.*

Introduction

Nephropathy is a broad medical term used to denote disease or damage of the kidney, which can eventually result in kidney failure. The primary and most significant functions of the kidney are to excrete any waste products and to regulate the water and acid-base balance of the body. Therefore, loss of kidney function is a potentially fatal condition. Nephropathy is considered a progressive illness; in other words, as kidneys become less and less effective over time, the condition of the patient gets worse if left untreated. So, it is crucial to receive adequate diagnosis and treatment as early as possible [1].

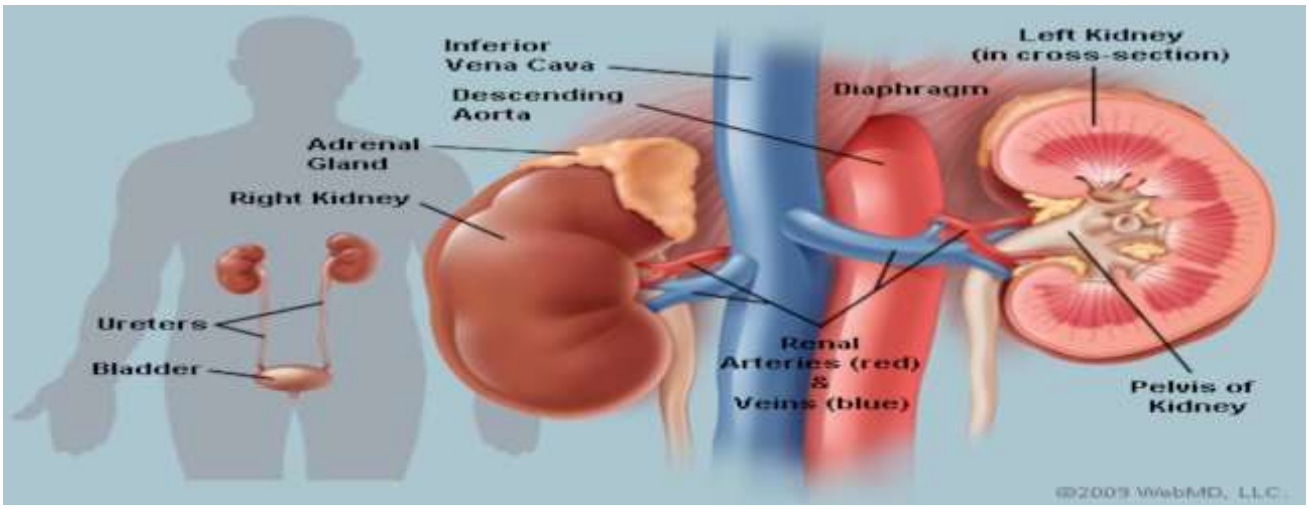

Fig. 1: Anatomy of kidneys

- The kidneys are a pair of bean-shaped organs on either side of your spine, below your ribs and behind your belly. Each kidney is about 4 or 5 inches long, roughly the size of a large fist.
- The kidney's job is to filter your blood. They remove wastes, control the body's fluid balance, and keep the right levels of electrolytes. All of the blood in your body passes through them several times a day.
- Blood comes into the kidney, waste gets removed, and salt, water, and minerals are adjusted, if needed. The filtered blood goes back into the body. Waste gets turned into urine, which collects in the kidney's pelvis -- a funnel-shaped structure that drains down a tube called the ureter to the bladder.
- Each kidney has around a million tiny filters called nephrons. You could have only 10% of your kidneys working, and you may not notice any symptoms or problems.
- If blood stops flowing into a kidney, part or all of it could die. That can lead to kidney failure.

Kidney Conditions

- Pyelonephritis (infection of kidney pelvis): Bacterial infection of the kidney, usually causing back pain and fever. A spread of bacteria from an untreated bladder infection is the most common cause of pyelonephritis.
- Glomerulonephritis: An overactive immune system may attack the kidney, causing inflammation and damage. Blood and protein in the urine are common problems that occur with glomerulonephritis. It can also result in kidney failure.
- Kidney stones (nephrolithiasis): Minerals in urine form crystals (stones), which may grow large enough to block urine flow. It is considered as one of the most painful conditions. Most kidney stones pass on their own, but some are too large and need to be treated.
- Nephrotic syndrome: Damage to the kidneys causes them to spill large amounts of protein into the urine. Leg swelling (edema) may be a symptom.
- Polycystic kidney disease: A genetic condition resulting in large cysts in kidneys that hinder their work.
- Acute renal failure (kidney failure): Dehydration, a blockage in the urinary tract, or kidney damage can cause acute renal failure, which may be reversible.
- Chronic renal failure: A permanent partial loss of working of kidneys. Diabetes and high blood pressure are the most common causes.
- End-stage renal disease (ESRD): Complete loss of kidney strength, usually due to progressive chronic kidney disease. People with ESRD require regular dialysis for survival.
- Papillary necrosis: Severe damage to the kidneys can cause kidney tissue to break off internally and clog the kidneys. If untreated, the resulting damage can lead to total kidney failure.
- Diabetic nephropathy: High blood sugar from diabetes progressively damages the kidneys, eventually causing chronic kidney disease. Protein in the urine (nephrotic syndrome) may also result.
- Hypertensive nephropathy: High blood pressure also causes kidney damage which may result in chronic kidney failure.
- Kidney cancer: Renal cell carcinoma is the most common cancer affecting the kidney. Smoking is the most common cause of kidney cancer.
- Interstitial nephritis: Inflammation of the connective tissue inside the kidney, often causing acute renal failure. Allergic reactions and drug side effects are the usual causes.
- Minimal change disease: A form of nephrotic syndrome in which kidney cells look almost normal under the microscope. The disease can cause significant leg swelling (edema). Steroids are used to treat minimal change disease.
- Nephrogenic diabetes insipidus: due to the action of some drugs the kidneys may lose the ability to concentrate urine. Even it may not be dangerous diabetic patient feels constant thirst and frequent urination.
- Renal cyst: Isolated kidney cysts often happen as people age, and they almost never cause a problem. Complex cysts and masses can be cancerous.[2]

Nephrotoxic Agents

There are a number of drugs, diagnostic agents and chemicals that cause nephrotoxicity. Some of the important nephrotoxic agents are

- Heavy metals - Mercury, Arsenic, Lead, Bismuth.
- Antineoplastic agents Alkylating agents - Cisplatin, Cyclophosphamide Nitrosoureas – Streptozotocin, Carmustine, Lomustine, Semustine. Antimetabolites-Methotrexate, Cytosine arabinose, high dose of 6-Thioguanine, 5-Flurouracil. Antitumour antibiotics – Mitomycin, Mithramycin, Doxorubicin.
- Biological agents – Recombinant leukocyte and Interferon.
- Antimicrobial agents – Tetracycline, Acyclovir, Pentamidine, Sulphadiazine, Trimethoprim, Rifampicin
- Aminoglycosides – Gentamicin, Amikacin, Kanamycin, Streptomycin. [3,4]

Mechanisms of Renal Toxicity

There are several mechanisms for toxicity caused by toxins like impaired lysosomal function, membrane changes and oxidative stress. Calcium homeostasis in the cell and calcium mediated cell functions are the targets for the various pathophysiological process and also cell death caused by toxicants. A number of pharmaceuticals and other chemicals impair the calcium messenger system.

The disturbances in the intracellular calcium cause cell death by disruption of the plasma membrane, cytoskeleton, endoplasmic reticulum and mitochondria. Chemicals produce toxicity by causing changes in the DNA or by apoptosis. The cellular accumulation of calcium causes generation of oxygen free radicals and damage cellular components especially mitochondrial membrane.

Chemicals produce nephrotoxicity by lipid peroxidation and cause membrane damage and cell death. Free radicals formed directly by metabolism of chemicals or from reduction of oxygen initiate lipid peroxidation by hydrogen abstractions from PUFA. This forms lipid per oxy radicals and lipid hydroxyl peroxides propagating chain reactions. Such chain reactions destroy cellular membranes which results in increased plasma membrane permeability or altered fluidity and cell death.

Lipid peroxidation also causes cell death by forming potent toxic lipid metabolites like hydroxyl alkenes. Proximal convoluted tubules are highly vulnerable to toxic action of chemicals owing to their high energy demand. Oxidative stress or reduction of oxidized glutathione (GSSG) to GSH by NADPH dependent GSSG reductase is lower than the rate of GSH oxidation. This leads to depletion of glutathione and cause oxidation of cellular enzymes, depletion of cellular ATP and loss of mitochondrial function. Super oxidase dismutase enzymes catalyze the dismutation of super oxide into oxygen and hydrogen peroxide.

It has been shown in animal experiments that the enzyme super oxidase dismutase and catalase can be used to prevent renal lesion [5]. Plants are a major source of new drugs since the inception of modern pharmacology. As per survey reports, one-third of all the newly approved compounds are derived from plants. Literature reviews reveals that different plants being effective in preventing/treating renal diseases very effectively.

Some renal conditions reported to respond to plant therapy are glomerulonephritis, IgA nephropathy, membranous nephropathy, glomerulosclerosis, immune complex nephritis, nephrotic syndrome, lupus, tubulointerstitial nephritis, chronic allograft nephropathy, kidney stones, etc. Plants which are having antiinflammation, anti-oxidation, diuresis, immunomodulation are proved to be working for prevention of acute allograft rejection and drug-induced nephrotoxicity, reduction in proteinuria, renal interstitial fibrosis, renal ischemia, tubular and mesangial cell proliferation, blood lipid levels, blood pressure, lipid peroxidation, apoptosis, renal necrosis, and calcium oxalate crystal aggregation, and stimulation of renal repair mechanisms, RNA and protein synthesis.

Continued efforts are required to identify and develop traditionally used medicinal plants in renal diseases so that more effective treatments are available from plants that have been known for their efficacy for hundreds of years [6, 7]. The present paper aimed to document the most common herbal medicines and their formulation used by

different tribal communities all over Kerala to treat renal disorders.

Natural Products and their Bioactive Compounds

Researchers identified several naturally occurring phytoconstituents through various research progammes for the treatment of nephrotoxicity. Phytochemicals are generally accepted to be safe with minimal side effects. Identification and charterization of new medicinal plants with active ingredients to cure renal diseases is being significant and increasing scientific interest in recent years.

There are hundreds of traditional medicines that are used for the treatment of Chronic Kidney Disease. Some of the plants shown promising activity are Tribulus terrestris, Pedalium murex Withania somnifera, Ficus recemosa, Piper cubeba, Aegle marmelos, Bauhinia variegate, Moringa olifera, Carica papaya, Eruca sativa, Allium sativum, Glycyrrhiza glabra, Pongamia pinnata, Solanum nigrum, Terminalia chebula, Tinospora cordifolia, Desmodium canfadens, Crataeva nurvala, Astragalus, Zingiber officinale, Ginkobiloba, Ephedra dystachia etc.

Here are some examples of nephroprotective activity studies of commonly available herbs done by inducing nephrotoxicity in animal models. G. Priyadarsini *et al.,* (2012) were studied the nephroprotective activity of Indigofera tinctoria (avuri kudineer) in Cisplatin induced renal damage in rats. Nephrotoxicity was induced in wistar albino rats by giving a dose of of Cisplatin 5mg/kg through intra-peritoneal administration. Decoction of Avuri kudineer was given at a dose of 500 mg/kg and 1000mg/kg were given for respective animal groups by oral route and the nephroprotective effect was evaluated by determining serum creatinine and blood urea and change in body weight of the animals.

The decoctions at a dose of 500 and 1000mg/kg of body weight markedly decreased the cisplatin induced nephrotoxicity. The acute toxicity of Avuri kudineer was not occurred at 2000mg/kg on mice but toxic symptoms like aggressiveness, tremors, mild diarrhoea, dyspnoea and abdominal writhing were observed after 48 hours of oral drug treatment at the dose level of 5000 mg/kg and total duration of study was 14 days. Hence, one-tenth and one twentieth dose was selected as therapeutic dose from maximum tolerable dose by toxicity study. Rajneesh kumar singh *et al.,* (2014) studied the nephroprotective effect of Mentha arvensis on cisplatin-induced nephrotoxicity in Sprague-Dawley rats. The hydroalcoholic extract of Mentha arvensis was administered orally at dose levels 200 mg/kg and 400 mg/kg of body weight. The effectiveness of the drug was assessed by conducting kidney function test, lipid peroxidase, oxidative stress study and histological studies. The hydroalcoholic extract of Mentha arvensis significantly reduced cisplatin-induced elevated serum levels of creatinine, total protein, blood urea nitrogen, while increase in superoxide dismutase activity, glutathione content, and lipid peroxidase in oxidative stress.

The histological findings also supported the nephroprotective action of the extract. Krishna Mohan Chinnala *et al.,* (2017) had conducted nephroprotective activity study of ethanolic extract of Allium cepa in Sprague Dawley rats by gentamycin induced nephrotoxicity. Treatment with the Allium cepa at the dose level of 200 mg/kg and 400 mg/kg of body weight given for 14 days shown significant reduction in serum creatinine and total protein in comparison with the toxic group.

Patel Mahipal *et al.,* (2017) studied Nephroprotective effect of Murraya koenigii on cyclophosphamide induced nephrotoxicity in male Wistar rats. Methanolic and aqueous extracts of M. koenigii extracts at doses of 100 mg/kg and 200 mg/kg body weight was given through intraperitoneal route. The effectiveness was measured by assay methods like blood urea nitrogen, creatinine and parameters like superoxide dismutase, glutathione and lipid peroxide. The study revealed the nephroprotective effect of Murraya koenigii extracts against cyclophosphamide induced nephrotoxicity. Venugopala Rao Konda *et al* (2016).

Were studied Nephroprotective effect of ethanolic extract of Azima tetracantha root in glycerol induced acute renal failure in Wistar albino rats. Doses of 250 and 500 mg/kg of body weight were administered, amongst 500 mg/kg is found to have significant nephroprotective action. Nephroprotective activity was assessed by the levels of serum creatinine, blood urea nitrogen, total proteins, albumin and urine output as well as

histopathological studies. Ruby Varghese *et al*., had conducted Nephroprotective Effect of Ethanolic Extract of Strychnos Potatorum seeds in adult rats of both Albino & Wister strains. The doses given were 5, 50,300 and 2000 mg/kg body weight. The alcoholic extract of Strychnos potatorum at a dose level of 200mg/kg body weight was found to normalize the raised blood urea, blood protein and serum creatinine caused by gentamycin induced nephrotoxicity.

Histopathological evaluation revealed that only gentamicin treated animals showed tubular necrosis with interstitial inflammatory infiltrate and congestion of blood vessels. Whereas, the gentamicin along with ethanolic extract of Strychnos potatorum treated animals showed normal tubules and blood vessels with no congestion. Ethanolic extract of Strychnos potatorum in a dose of 200mg/kg body weight showed better normalizing of the renal tissues, when compared to the other dose levels. Nitin M *et al*., (2012) studied the Nephroprotective activity of Vigna mungo on gentamicin-induced renal damage in albino rats. The seed powder of Vigna mungo was successively extracted with methanol and water.

By invitro study method biochemical parameters such as blood urea nitrogen, serum creatinine, and serum uric acid were checked among groups treated with only rifampicin as compared to the normal control group, on the other hand groups treated with cystone and alcoholic extract of Vigna mungo showed significantly low values. The normal control group showed normal histology of rat kidney when treated with alcoholic extract of Vigna mungo after inducing nephrotoxicity by giving rifampicin.

Table: 1 documented nephroprotective phytoconstituents from different medicinal plants and their methods of screening

Botanical Name	Family	Part Used	Chemical constituents	Screening method
Crataeva nurvula[15]	capparidaceae	Fruit	Botulin, ß-sitosterol, Amyrin, Hentriacontane, Campesterol, Stigma sterol, Kaempferol, Propionic acid, ß-carboline-I, Aervoside and Aervolanine..	Gentamycin induced
Carica papaya[15]	Caricaceae	Seed	Flavanoids, Phenols, Alkaloids, Protein, Sterols, Terpenoids, Carbohydrates, Steroids, Tannins, Glycosides, Terpins and Saponins.	Cisplatin induced
Boerhaavia Diffusa[15,17]	Nyctaginaceae	Root	Flavonoids, Alkaloids, Steroids, Triterpenoids, Lipids, Lignins, carbohydrates, Proteins and Glycoproteins.	Acetaminophen induced
Pedalium murex Linn[15]	Pedaliaceae	Dried fruits	Flavanoids, Flavones, Alkaloids, Triterpenoids, Carbohydrates, Glycosides and Saponins.	Cisplatin Induced
Eruca sativa[15]	Crassulaceae	Seeds	Flavanoids	Mercuric chloride induced
Moringa oleifera [15]	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
Ginkgo biloba [17]	Ginkgoaceae	Whole plant	Flavonoids, Bilobalide, GingkolideA, Gingkolide B	Streptozotocin induced
Rubia cardifolia[17]	Rubiaceae	Root	Purpurin, Manjistin, Garancin, Purpuroxanthin, Resin, Glucose, Sucrose, Triterpenes, Lucidine, Anthroquinine, Fatty acids and Gum.	Ethylene glycol induced
Uphorbia Neriifolia[17]	Euphorbiaceae	Leaves	Saponins, Flavonoids and Tannins	N-nitroso dimethyl amine induced
Abutilon Indicum[17]	Malvaceae	Whole Plant	Saponins, Flavonoids and Tannins.	Gentamicin induced
Tribulus terresteris[16]	Zygophyllaceae	Fruits	Saponine, diosgenine, gitogenine, Flavonoids, alkaloids	Gentamicin induced
Withania somnnifera[16]	Solanaceae	Roots	Alkaloids(somniferon), withaminon, wasamin, sugars, Glycosides, amino acids, essential oils, withaniol, hexatriacontane, phytosterol and oils	

Piper cubeba[16]	Piperaceae	Fruit	Sesquiterpene hydrocarbons, cubebine, cubebinine, and kinokinin, cubebic acid. The oxygenated cyclohexanes, piperenol A&B together with (+)-crotepoxide and (+)-zeylenol	Cisplatin and Gentamicin induced
Ficus recemosa[9]	Moraceae	Fruit	Gluacol, beta-sitosterol, lupeol acetate, friedelin, higher hydrocarbons and other phytosterols	Cisplatin induced
Aegle marmelos[16]	Rutaceae	Leaves and fruits	Aegeline, Aegelinine, rutin, sterol, bete-sitosterol, beta-D-glucoside, mamesinine, lupeol, tannins, phlobatannins, flavonoids, umbelliferon, quercetine, and volatile oils.	gentamycin
Bauhinia variegate[16]	Fabaceae	Flowers	Stigmasterol, flavone, glycosides, lupeol, kaempferol-3-glucoside, Bete-sitosterol	cisplatin
Cassia auriculate[16]	Fabaceae	flower, leaves, stem, root, and unripe fruit	Tannins, Di-(2-ethyl) hexyl phthalate, alkaloids, resins, Ca2+ and phosphorous	
Allium sativum[16]	Liliaceae	leaves, flowers, and cloves	Flavonoids, anthocyanins, polyphenols, and diallyl disulfide, allicin	
Glycyrrhiza glabra[16]	Fabaceae	Rhizome	Glycyrrhizin, glyciyrrhinic acid, glycosides, steroids, glucose, sucrose, resin, starch and essential oil	gentamicin
Pongamia pinnatta[16]	Fabaceae	Fruits and sprouts	Pongamol, protein, alkaloids, tannins, sugar, resin and fatty oil	Cisplatin and gentamicin
Solanum nigrum[16]	Solanaceae	Whole plant juice and root juice	Alkaloids, reducing sugars, glycosides, saponins, steroids,l eutein, lycopene, vitamin C, glucose, fructose, caffeicsolasodine, tamatidenol, solamarginetrigogenin, potassium, Sulphur, calcium and phosphorous	
Terminalia chebula[16]	Combretaceae	Fruits	Palmitic stearic oleic linoleic, astringent, tannic acid	

The traditional knowledge about the plant wealth is a vibrant and valuable aspect of Ethnobotany. The practice of herbal healing has been evolved as a part of Indian culture since antiquity. The ethnobotanical practices in India provide a spectrum of variation such as Ayurveda, Unani and Siddha. Parallel to the development of these classical systems of medicine, folk or tribal medicines are also succeeded in the rural and tribal habitats. But as the time went on, and those healers who practiced the theorized and codified system were considered superior to those who practiced the folk methods of healing. There are large numbers of folk or tribal practitioners across the villages of India who was abandoned a lot because of their illiteracy and low social status. The toxicity and adverse reactions of allopathic medicines, has led to increased renaissance of public interest towards the herbal treatment of native healers. A number of herbal medicines have been used effectively to prevent and even reverse some of the kidney damage [18].

Table: 2 Medicinal plants for kidney diseases used by different tribal communities in Kerala

Wayanadu(kurichya, kuruma,Adiyan,paniya, kattunaika) [19,20]	Hygrophila schulli (Buch.-Ham.)	Leaf, Root	The root paste mixed with goat milk is taken internally for kidney stone. The leaf paste is applied externally against ectoparasitesin cattle.	Kidney stone
	Momordica dioica Roxb.ex.Willd	Leaf	The leaf juice mixed with goat milk is taken internally to remove kidney stone	Kidney stone
	Scoparia dulcis L	root	Hot infusion of ground root is taken orally for kidney stone	Kidney stone
	Rotula aquatica Lour Root	Leaf	Decoction is taken for treating kidney stone. The leaf paste is diluted and drunk for controlling menstrual bleeding in women	Kidney stone

	Nymphaea stellata Burm. f	Stem Flower Tuber	It is used in many poly herbal formulations for anti-ageing and menstrual irregularities. Flowers used as a remedy for kidney problems.	Kidney diseases
Malayali and Narikuravar communities[21]	Achyranthes bidentata Blum., Amaranthaceae	Whole plant	Powder for oral use	Kidney disease
	Terminalia bellirica(Gaertn.) Roxb.	fruit	Powder for oral use	Kidney disease
	Pedalium murex L	fruit	Powder for oral use	Kidney disease
	TribulusterrestrisL.,	fruit	Powder for oral use	Kidney disease
	Aerva lanata (L.)	Whole plant	Powder for oral use	Kidney disease
Irula Tribes of Dhoni forest[22]	Cheilocostus speciosus	rhizome	Decoction of rhizome	Kidney disease
	Aerva lanata (L.)	Leaf	Decoction of leaf juice	kidney stone inflammation
Kani tribes of Kottoor reserve forest[23]	Arenga wightii Griff	stem	Mixed with large quantity of water	Painful urination
	Ensette superbum Roxb	Seed powder	Mixed with 1 glass water or milk	Kidney stone and leucorrhoea
Irula tribes of Idukki District[24]	Scopariadulcis L.	Seeds	An infusion of the seeds, obtained by soaking them in water overnight	Cure kidney stone.
	Strychnos potatorumL.f.	Whole plants, Young fruits, seeds	Extract of seeds	Urinary and Kidney diseases
	Hemidesmusindicus L.	Roots	Syrup extracted from roots	Refrigerant for kidney and urinary disorders
Tribal people in Attapady,Kerala[25]	Aervalanata (L.)Juss.	Leaves	Herb Leaves Salt Cooked	Urinary stone
	AsparagusracemosusWilld.	Tuber	Decoction	Urinary stone
	Macaranga peltata	Tree Bark	Bark is used to cure back pain and also use for kidney	Back pain, Kidney stones
Mullu kuruma tribes of Wayanadu[26]	Ichnocarpus frutescens (L.) Parvalli	Root	Root juice is used internally in the treatment of anaemia and kidney stone.	Kidney stone
	Indigofera tinctoria Neelamari	Root	Root decoction is given internally in decoction for kidney stone	Kidney stone
Malayaraya tribes of vannapuram village in Idukki[27]	*Eclipta alba L. Hassk. Kayyonni*	Whole plant	Decoction	Rejuvenate hair, kidney and liver

Conclusion

This review article points towards the knowledge and usage of herbal medicine for the treatment of kidney disorders among tribes. They use forest plants, weeds, fruits, vegetables, spices, ornamental plants, ferns and many other plant parts as traditional medicine. Forests are abundant source of medicinal plants. It is difficult to enlist all of them under a common heading. The information gathered here is useful for further a researcher who seeks information about plants used for kidney disorders. This paper is aimed to record medicinal folk-lore for curing nephrotoxicity that exists in

threatening stage. In ayurvedic system and siddha system several herbs are prescribed for reducing renal damage and to avoid kidney related complications. This paper refers to use our best endeavors of indigenous herbs to alternative medicine of renal damage.

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