JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

A REVIEW ON INSIGHTS OF HERBAL NEPHROPROTECTIVE AGENTS

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Abstract: Nephrotoxicity is one of the most commonly reported kidney problems and occurs, when the body consumes a chemical or medication. Medication may be an NSAID, a chemotherapeutic agent, or an antibiotic. The adverse effect of a drug or another chemical on renal function is referred to as "nephrotoxicity." This explorative article was undertaken to provide a holistic review of known nephroprotective (NP) phytoconstituents along with their research-based evidences and mechanism. The present review aimed to provide in-depth and better evidences of the global burden of nephrotoxicity, pathophysiology of nephrotoxicity, nephroprotective plants and their phytoconstituents. By classifying and discussing the literature, we obtained many phytoconstituents, which were derived from herbal medicinal plants, from different origin. The mechanism of nephrotoxicity by several methods was proposed through discussing the literature. The occurrence and progression of Nephrotoxicity or AKI could be prevented by natural antioxidants through several pathways to prevent ROS accumulation and reduce renal cell injuries caused by excessive ROS formation. The plants which have – flavonoids, flavone, alkaloids, triterpenoids, glycosides, saponin, Gallic acid, β-Sitosterol, vitamin C, vitamin E etc. shows anti-oxidant and nephroprotective properties.

Keywords: Nephrotoxicity, Nephroprotective plants, Cisplatin, In silico.

I. INTRODUCTION

The kidneys, which comprise the most critical organs in human body, play a crucial role in supporting fluid equilibrium, erythrocyte production, regulate blood pressure, maintaining bone consistency, controlling hormonal balance, and filtering and eliminating nitrogenous and other waste products from the body **[1,2].** Additionally, they perform a role in the body's excretion of toxic waste and metabolic waste, as well as the metabolism of carbs, protein, lipids, and other nutrients. Human bodies are frequently exposed to toxic substances and agents in the environment, as well as a variety of physiological conditions, such as metabolic activity, an increase in the concentration of chemicals filtered in the tubular fluid, and heavy blood flow to the organs, all of which make people more vulnerable to toxins. The terminology "renal toxicity" is used to describe the quick loss of kidney function caused by the toxicity of medicines and other substances **[3,4]**. The Kidney and urinary tract disorders are rated 12th on the list of the main factor of mortality in the world; a significant issue in worldwide public health is kidney disease. Chronic kidney disease affects 10% of the world's population, and millions of people die every year due to economic reasons. 35 million of the 58 million illnesses that occurred in the world in 2005 were due to chronic kidney disease. According to a global perspective, over the past 15 years, the incidence of renal failure (or chronic kidney disease) has doubled **[5,6]** acute kidney damage is detected in 8%–18% or 22% of hospitalised patients, when the intensive care unit received new patients, the majority of them developed acute kidney injury within two days **[7]**. A sudden decline in kidney function, an increase in blood urea nitrogen and serum creatinine, and a decreased glomerular filtration rate are all symptoms of Acute Kidney Injury (AKI), a condition that can be reversed Glomerular Filtration Rate (GFR). Additionally, it can be claimed that AKI is specifically related to an oxygen and nutritional imbalance, which is brought on by reduced microcirculation to the nephrons and higher energy needs as a result of oxidative stress in the cells, but it's always intriguing to think of employing antioxidants to avoid AKI **[8,9].** This review focuses on plants that have been demonstrated to have nephroprotective action in vitro, in vivo, and in silico investigations.

II. *NEPHROTOXICITY OR RENAL TOXICITY*

The nephron which is known as the smallest unit of kidney as well as a functional and structural segment of the kidney. The average kidney structure contains millions of nephrons, and its primary job is to filter waste from the body while also maintaining the pH of the blood, the body's fluid balance, and the hormones that encourage the synthesis of red blood cells. Additionally, it controls blood pressure and bone health. The kidneys have three primary functions: renin and erythropoietin synthesis and secretion, clearance and accumulation of waste items from external metabolism, and plasma filtration and maintenance of whole-body electrolyte homeostasis **[10,11].** Nephrotoxicity refers to a detrimental impact on renal function by a drug or other substances. Numerous processes, such as renal tubular toxicity, glomerular injury, crystal nephropathy, and inflammation, contribute to nephrotoxicity. Hemodynamic alterations, direct cellular and tissue damage, tissue inflammation, and/or renal excretion blockage can all lead to nephrotoxicity or renal toxicity **[12]**. Various substances, including molds and fungus, cancer-causing medications like cisplatin, antibiotics like aminoglycosides, and metals like lead, arsenic, and mercury, can result in nephrotoxicity. Nephrotoxicants primarily affect the renal cells **[13,14]**. Depending on anatomical location and appearance of clinical it could be either acute or chronic renal damage due to the medication **[15]**. Nephrotoxicity damages the kidney, and the clinical manifestation of this is diminished renal function **[16]**. The medications that have a negative impact on the kidneys are taken off the market mostly due to nephrotoxicity. According to reports, acute kidney injury (AKI) episodes in hospitals are reportedly caused by a number of reasons, including drug-induced nephrotoxicity (8–60%). Nephrotoxicity is caused by a sudden reduction in the kidney's excretory systems, which increases the build-up of waste products from protein metabolism like urea, nitrogen, and creatinine **[17]**. Acute tubular necrosis—which results in acute kidney injury (AKI)—is frequently brought on by nephrotoxic damage to renal tissue **[18]**. Additionally, poor urinal drainage may be the cause [Rahman M, Shad F.et.al.2012]. In addition to lowering the glomerular filtration rate (GFR), decreased drainage raises intra-tubular pressure **[19].**

III. PATHOPHYSIOLOGY OF CISPLATIN INDUCED NEPHROTOXICITY

Cisplatin is a platinum inorganic derivative. It is used to treat several kinds of cancer, including bladder, ovarian, lung, and testicular cancers **(20).** High-grade malignancies like osteosarcoma and soft tissue tumours like squamous cell carcinoma are also treated with cisplatin when used in combination therapy **(21,22)**. Depending on the amount of cisplatin used, there may be varying degrees of nephrotoxicity. A single cisplatin dose may cause reversible kidney damage in certain patients, whereas high doses or repeated rounds of therapy may result in irreversible renal failure **(23)**. According to pharmacokinetic studies, Nephrotoxicity is primarily caused by the long-time agglomerate of cisplatin in the kidney and the high volume of cisplatin dispersion**. [24]** The majority of pathogenic mechanisms that result in cisplatin-induced nephrotoxicity include ischemia or necrosis of the proximal renal tubular epithelial cells, as well as decrease in renal blood flow and glomerular filtration rate **[25,26]**. The dose of cisplatin is favourably linked with the histopathological alterations in cisplatin-induced nephrotoxicity. By first slowly entering kidney tubular cells through the organic cation transporter 2 and forming hydrates with water molecules, cisplatin continuously builds up in the kidneys **[27]**. The creation of cisplatin hydrate is reversible, and by splitting into cisplatin and water molecules, the substance can be expelled from cells. Damage of DNA, oxidative stress, autophagy and apoptosis occur as a result of cisplatin gets retains and accumulates in renal cells **[28].** (Fig. 1)

Cellular uptake and transport: The kidneys are the primary route of cisplatin excretion. During excretion, it gets concentrated, and the absorption in renal tubular epithelial cells is significantly higher than that in the blood. Renal cells take up cisplatin in the kidney through passive diffusion. During glomerular filtration, cisplatin and its components are released and reabsorbed in the renal tubules, causing a high concentration of the drug in the kidneys **[29]**. In addition, solute carrier family 47 member and multidrug and toxin extrusion 1 secrete cisplatin into the lumen **[30]**. Cisplatin-induced nephrotoxicity can be considerably decreased by oct2 gene knockdown **[31].**

DNA damage is caused by binding of cisplatin to DNA and creating DNA-damaging adducts, producing its cytotoxic effects **[32]**. The water molecules in a watery environment change the Cl^- ligand of cisplatin to create a positively charged hydrated complex ion, which is drawn to the nucleus by DNA electrostatic attraction. When this complex binds to DNA, it creates an adduct that prevents DNA replication and synthesis in rapidly growing cells by causing DNA cross-linking **[33]**. Less than 1% of platinum, including cisplatin, directly binds to nuclear DNA **[34]**. The hydrolysis of cisplatin results in the formation of positively charged metabolites that preferentially collect in negatively charged mitochondria. As a result, mitochondrial density and mitochondrial membrane potential in cells both affect how

sensitive cells are to the drug cisplatin **[35]**. The renal proximal tubule is the kidney area most vulnerable to cisplatin because it has areas with relatively high mitochondrial density **[36].**

Inflammation: The severity of cisplatin-induced acute renal failure and injury can be greatly reduced by TNF-inhibition or knockout suggests that elevated TNF-expression plays a crucial role in cisplatin-induced nephrotoxicity. TNF expression in the kidneys of a cisplatin-induced nephrotoxic mouse is increased, and this increased expression is associated with increased renal TNF-levels **[37].** TNF- causes oxidative stress by triggering proinflammatory cytokines and chemokines, which promotes kidney damage. By phosphorylating p38 mitogen-activated protein kinase (p38 MAPK) and controlling the generation of TNF, cisplatin hydroxyl free radicals ultimately cause the activation of nuclear factor kappa B. Dimethyl thiourea, an agent that neutralizes hydroxyl radicals, thereby prevents the activation of p38 MAPK and the production of TNF-mRNA in mice kidneys. Inhibiting p38 MAPK effectively protects the kidney damage caused by cisplatin by lowering TNF production **(38).** When the mitochondria fail, O_2 is produced; however, the inflammatory response of cisplatin causes the up regulating the direct NO-producers TNF, nicotinamide adenine dinucleotide phosphate oxidase, and inducible nitric oxide synthase (iNOS). NO^- and O^{2-} combine to form $ONOO^-$, which can oxidize, nitrate, and induce apoptosis and necrosis **[39]**

Oxidative stress: Recent research has demonstrated that the kidney damage caused by cisplatin is characterized by elevated levels of malondialdehyde , 4-hydroxy-8-hydroxydeoxyguanosine, and 3-nitrotyrosine and a reduction in the quality of the antioxidant enzymes catalase and superoxide dismutase is largely caused by oxidative and nitrosative stress. As a result, antioxidants and ROS scavengers have potent protective effects against nephrotoxicity **[40].** Adenosine triphosphate (ATP) depletion occurs when ROS disrupt the I-IV of the mitochondrial complex enzymes and stop the regular transmission of the oxidative respiratory chain **[41].**Then, elevated ROS cause lipid peroxidation, which modifies membrane permeability and structure, further impairs cellular function **[42].** Finally, ROS destroy proteins, carbohydrates, and amino acids, which encourage DNA damage and apoptosis. Furthermore, increased ROS levels can result in an increase in the synthesis of Fas- ligand (a cell membrane cytokine) and tumor necrosis factor alpha which accelerates apoptosis **[43].**

Endoplasmic reticulum stress pathways: The apoptotic mechanism that is regulated by ERS can also be activated by cisplatin. When cisplatin enters cells, it interacts with the endoplasmic reticulum membrane's cytochrome P450 (CYP450) enzymatic system to cause oxidative stress and activate caspase-12, which causes apoptosis **[44]**. The endoplasmic reticulum phospholipase A2 enzyme, which inhibits downstream p53 and stimulates upstream caspase-3, is likewise activated by the ERS route. In the absence of mitochondrial malfunction, p53 and caspase-3 may be connected by the endoplasmic reticulum **[45].**

Apoptosis/Necrosis: According to the studies, cisplatin produces renal tubular epithelial apoptosis at low concentrations (8 μM) and necrosis at high concentrations (800 μM) **[46].** Cisplatin-induced apoptosis in renal tubular cells is predominately linked to ERS pathways, death receptor-mediated external pathways, and mitochondria-mediated endogenous pathways.

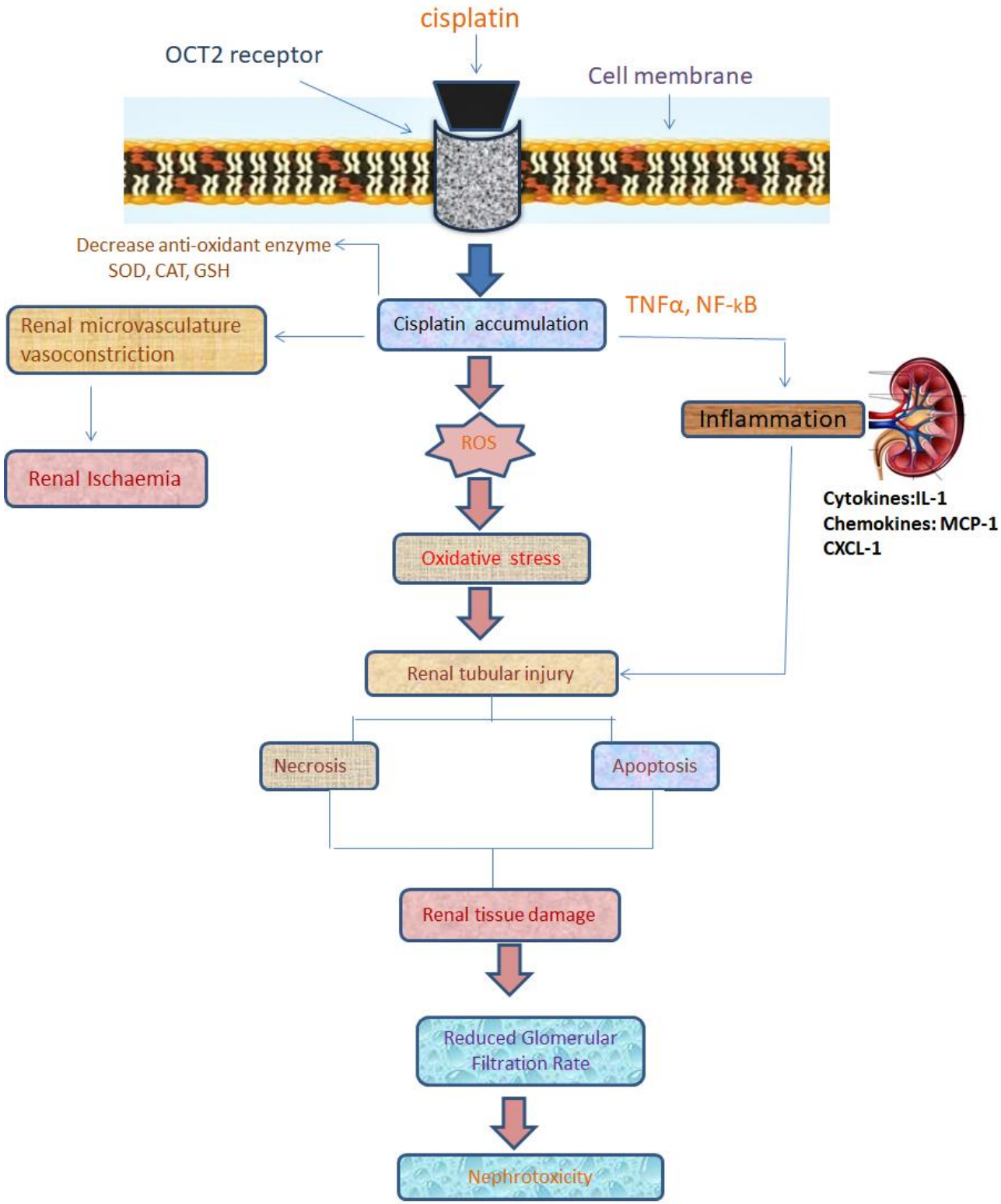


Fig.1 Illustrates the method by which cisplatin causes nephrotoxicity.

OCT2 receptor- organic cation transporter **SOD-** superoxide dismutase, **CAT-** catalase, **GSH-** glutathione **TNFα-** tumor necrosis factor alpha, **NF-kB-** nuclear factor kappa B

Figure 1 The primary molecular pathways responsible in the development of cisplatin causing acute kidney disease (AKD) are depicted in a pathophysiological diagram. Cisplatin accumulation increases the tumour necrosis factor alpha (TNF-alpha) production **(47,48)** and reactive oxygen species, both of which promotes inflammation **[49],** oxidative stress **[50],** and vascular injury **[51],** and apoptotic pathways which causes renal tissue damage and reduced glomerular filtration rate as a result nephrotoxicity occurs **[52].**

Nephroprotective Plants - It has been demonstrated that when medications and nephroprotective plants are taken simultaneously, the toxicity of the drugs is reduced **(53).** Numerous researches have been conducted to formally establish that plants can be utilized to treat renal illness. Plants exhibit

nephroprotective effect as a result of a variety of complex chemical compounds **(54).** Plant's secondary metabolite chemicals known as flavonoids, notably nephroprotective flavonoids, have a critical impact on kidney physiology **(55).** According to recent research on the effects of flavonoids on renal function and the mechanisms of action involved, flavonoids have a crucial role in renal physiology, possess diuretic and natriuretic properties, and protect against Reno degeneration in Acute kidney Inflammation (AKI) and Chronic kidney disease (CKD) caused by a variety of etiologies, including hypertension, diabetes, nephrotoxicity, and stress oxidative agents **(56).** Numerous studies have been done to give a scientific basis for the use of herbs in treating a variety of diseases, including chronic kidney disease, because of the wide range of benefits they provide for treating different human disorders.

It has been demonstrated by Gaikwad et al.2012, that when medications and nephroprotective substances are taken at the same time, the toxicity of the drugs is reduced. Nephroprotectors are substances that can reduce nephrotoxic effects. Due to a variety of complex chemical compounds, plants provide nephroprotective properties. Many researches have been performed to demonstrate scientifically that plants can be applied to cure renal illness. Flavonoids are plant secondary metabolite chemicals that have important effects on kidney function, including nephroprotective properties.[**57]**

Zhang et al. have found in the recent study that Rhubarb has shown remarkable effects in preventing kidneys from the oxidation, inflammation, autophagy, and fibrosis. Rhubarb's primary active components of anthraquinones. They dramatically decreased blood urea nitrogen (BUN), UA, SCr, superoxide dismutase (SOD), and malondialdehyde (MDA) levels as well as normal renal weight. In rats with diabetic nephropathy, they also reduced interleukin-6 (IL-6) and tumor necrosis factor (TNF) production and turned on the PI3K/Akt/glycogen synthase kinase-3 (GSK-3) signaling pathway. However, inappropriate excessive quantity and usage of rhubarb can seriously impair renal function causing nephrotoxic effects. These effects have gained more attention of many researchers **[58]**

Abelmoschus moschatus is a popular herbal remedy used in Ayurvedic medicine to treat kidney-related illnesses. It is available as tea, medicated oil, medicated wine etc. Amarasiri et al have recently found that it has promising effect against adriamycin-mediated acute kidney injury by antioxidant, anti-inflammatory, and anti-apoptosis pathways [**59]**

The nephroprotective activity of ***Combretum Micranthum*** has been demonstrated by Kpemissi et al.2019. and was tested in mice for 14 days study, followed by a single intraperitoneally CP injection at dose of 200-400 mg/ kg on the fifth day. At both doses, CM normalizes renal function by correcting markers of serum and urine renal damage, transaminases, and oxidative stress markers.[**60]**

Nephroprotective effectiveness of ***Homonoia riparia*** has been demonstrated by Xavier et al.2017. The MTT test demonstrated that H. riparia fractions of butanol and water (200 g/ml) exhibited significant nephroprotective activity against cisplatin-induced cell damage in HEK-293 cells.[**61]**

A gentamicin-induction approach in rats was used to assess nephroprotective efficacy by Wu et al.2012. ***Macrothelypteris oligophlebia*** extracts at 200 and 400 mg/kg inhibited the elevated BUN and Cr levels, according to the findings. The influence on renal tissue enzymes also suggested activity, with a considerable drop in MDA and NO and a rise in SOD, CAT, and GSH-Px. The Histopathological examination results revealed that a dosage of 500 mg/kg provided the highest histological protection against gentamicin-induced renal tubule damage.[**62]**

An *in vivo* investigation utilizing gentamicin-induced mice revealed nephroprotective efficacy by Hussain et.al.2012, that ***Solanum xanthocarpum*** extracts at 200 and 400 mg/kg provided protection against increased renal weight ratio. It gives optimal protection against the index of kidney organs and enhanced urine production at 400 mg/kg and also, plasma and urine test results showed a significant decrease in urea and creatinine concentrations. *S. xanthocarpum* was also tested on kidney antioxidants, and it showed that it can prevent the decreased activity of SOD, CAT, and GSH. Surprisingly, 400 mg/kg provided the best protection, practically identical to a conventional control. Histopathological examinations at 200 mg/kg revealed minimal degenerative and necrotic tubular modification compared to 400 mg/kg, showing tubular epithelial cell regeneration.[**63]**

In vivo and *in vitro* nephroprotective efficacy of ***Ceiba pentandra*** has been demonstrated by Abouelela *et* al. 2020. The increased blood creatinine, BUN, cysteine, micro albuminuria, urine KIM-1, TNF-, and CRP were considerably reduced by 400 mg/kg of C. pentandra ethyl acetate in in-vivo testing on MTX-induced nephrotoxic rats. In addition to a decline in renal MDA and NO levels, there was an increase in SOD, CAT, and GSH activity.[**64]**

The nephroprotective efficacy of ***Eurycoma longifolia*** has been demonstrated *by* Chinnappan et al.2019. The extract was examined in animal models of Paracetamol intoxication at doses of 100, 200, and 400 mg/kg. The results showed that albumin levels that were near normal and a reduction in total protein

levels were both stopped by extracts at 200 and 400 mg/kg. The urea and creatinine levels decrease significantly with the same dose, and the dose-dependent creatinine clearance is also increased. According to the histological analysis, a dosage of 400 mg/kg provided the highest protection while maintaining a kidney look that was nearly normal.[**65]**

Achillea millefolium (Asteraceae)- The nephroprotective activity of ***Achillea millefolium*** in humans have been done, in randomized controlled experiment, 31 individuals with chronic renal disease were enrolled; 16 of them received 1.5 g powdered of *A. millefolium* flower three times per week for two months, while 15 received a placebo during that time. In order to determine the impact of a millefolium on plasma nitric oxide metabolites (nitrite and nitrate), plasma samples were taken before and after the research period. After two months, plasma nitrite and nitrate concentrations reduced. (**66**)

Acacia Gum (Fabaceae) - The nephroprotective activity of ***Acacia Gum*** in humans have been done, eight adult patients with asymptomatic non-terminal renal failure who consumed Lipidol and took 50 g of Acacia Gum daily had lower serum urea, larger faeces, and excreted more nitrogen from their stools than the eight control patients who took pectin supplementation in place of acacia.[**67]**

Avena sativa L. (Poaceae)-The nephroprotective activity of ***Avena sativa L*** in humans have been done, With 97 individuals, a prospective, interventional, randomized, single-blind, placebo-controlled experiment was conducted. The subjects received a 250 mg stevia pill twice day, combined with either an ARB or CCB (angiotensin-II receptor blocker or calcium channel blocker). First follow-up appointments were made three months after the break. The biochemical testing required the collection of blood and urine samples. The baseline examination was conducted using a standardized questionnaire. Each subject gave their informed consent.[**68]**

Salacia chinensisa (Celastraceae)-The nephroprotective activity of ***Salacia chinensisa*** in humans have been done, Randomization was used to divide 30 stable diabetic CKD patients into two groups, A and B, each with 15 patients. Group B received a placebo while Group A received the experimental medicine Salacia chinensisa 1000 mg twice day. Renal function evaluations: Serum creatinine and creatinine clearance, lipid profile, interleukin-6, serum homocysteine, and indicators of endothelial dysfunction were all assessed at baseline and over the course of a six-month follow-up period. (**69**)

Panax ginseng (Araliaceae) -The nephroprotective activity of ***Panax ginseng*** in humans have been done, 197 individuals with early CKD (stage 2 or 3) were enlisted, and they were then randomly assigned to either PG (500 mg orally every day) or a placebo for a period of six months. Analysis of renal function (creatinine and urea clearance), oxidative stress, inflammation assessment, and lipid profile were performed at baseline, the end of the treatments, and six months after the treatments, From the 177 patients who finished the research. (**70**)

Curcuma longa (Zingiberaceae)-The nephroprotective activity of ***Curcuma longa*** in humans have been done, a 100 patient, double-blind, placebo-controlled research on pruritus. Curcuma longa or a placebo group was randomly assigned to the patients (mean age, 53.3 years). The two groups pruritus scores and biochemical markers, such as high-sensitivity C-reactive protein (hs-CRP), were compared before and after the study. (**71**)

TABLE 1: THE POTENTIAL OF MEDICINAL PLANTS AS NEPHROPROTECTIVE IN DIFFERENT ANIMAL MODEL

S. N	Plant	Comman Name	Family	Part Used	Chemical Constituent	Renal Effect	Subjects involved	Ref.
1	*Allium sativum*	Garlic	*Amaryllidaceae*	Bulb	Allicin ,Allin, Fatty acids, and Essential amino acids	Renal protection	Wistar rats	72
2	*Ocimum sanctum*	Tulsi	*Lamiaceae*	leaves	Ursolic acid	Nephroprotective	Wistar albino rats	73
3	*Punica granatum*	Pomegranate	*Lythraceae*	Rind	Urolithins ,Ellagic acid	Renal protection	Wistar rats	74

4	*Trigonella foenum graecum*	Fenugreek	*Fabaceae*	leaves	VitaminC, minerals, alkaloids, flavonoids, fiber, saponins, steroidal saponins, proteins, carbs, and lipids	Nephroprotective	Wistar rats	75
5	*Suaeda vermiculata*	Seablite	*Amaranthaceae*		Vanillin, gallic acid, cinnamic acid, coumaric acid, and catechin. Acids Amino	AKI protection	Male Sprague Dawley rats	76
6	*Aerva lantana*	Gorakhdi, ni Bur	*Rutaceae*	whole plant	Botulin,ervoside, Aervolanine, βSitosterol, Stigmasterol, Kaempferol, Campesterol, Propionic acid	Nephroprotective, Protect against tubular cell toxicity	Wistar rats	77
7	*Coleus aromaticus*	Mexican Mint	*Lamiaceae*		carvacrol, thymol, 8eugenol, chavicol, ethyl salicylate	Nephroprotective	Wistar rats	78
8	*Sphaeranthus indicus*	Gorakh mundi	*Asteraceae*	Fruits	chavicol, α-ionon,e, dcadinene, p-methoxycinnamadehyde a-terpinene,, Lactone, Sterol Glycoside, Flavanoids and Essential oil citral, geraniol, geranyl acetate, βionone, alkaloids	Nephroprotective' Protect acute tubular necrosis	rats	79
9	*Pedalium murex*	Bara Gokhuru	*Pedaliaceae*	Dried Fruit	flavonoids, Flavones, Alkaloids Tri-terpenoid, Carbohydrate	Renal protection, antioxidant activity	Wistar rats	80

					s, Glycosides and Saponin			
10	*Combretum micranthum*	kinkeliba	*Combretaceae*	Leaf	Isovitexin, gallic acid, cianidanol, and epicatechin	Nephroprotective	in vivo, in vitro rats	81
11	*Homonoia riparia lour*	**Kalire** (Batek)	*Euphorbiaceae.*	All Parts Of The Plant	Gallic acid	Nephroprotective	In-vitro rats	82
12	*Solanum xanthocarpum*	Yellow-fruit nightshade	*Solanaceae*	Fruits	Protoapigenone, 5,7-dihydroxy-6,8-dimethyl flavanone, naringenin, naringenin-4′-Oglucoside, and matteucinol	Renal protective	Mice rodents	83
13	*Ceiba pentandra*	Kapok, java cotton, java kapok	*Malvaceae*	Aerial	Glochidiobos ide, cis- and trans-clovamide, cinchonains 1a and 1b, and quercitrin	Nephroprotective	In vitro , Rat	84
14	*Sonchus oleraceus*	Common sow thistle, Sow thistle, Soft thistle	*Asteraceae*	Aerial	villosol, ferulic acid, chicoric acid, ursolic acid, caftaric acid, -sitosterol,Taraxasterol, luteolin, apigenin, rutin,	Nephroprotective	Wistar rats	85
15	*Dendropanax morbifera*	Korean dendropanax	*Araliaceae*	Leaf And Stems	rutin, syringin, chlorogenic acid, and neochlorogenic acid	Renal protection	In vitro in vivo diabetic rat	86
16	*Carica papaya*	Papaya, Papaw, pawpaw	*Caricaceae*	Leaf And Sead	Cysteine,p-cumarellamic dimethoxy phenol, and l-glutamic acidtocopherol, ascorbic acid, carpaine, and deoxycempfe	Nephroprotective, Increase glomerular congestion, tubular necrosis, and peritubular necrosis	In silico in vivo mice	87

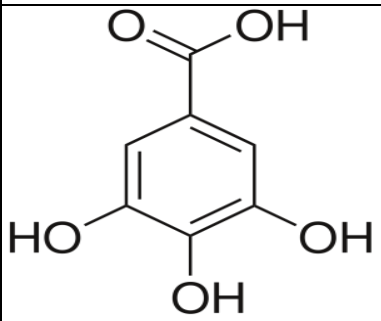
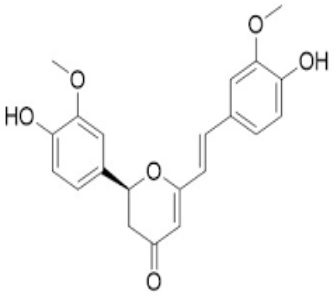
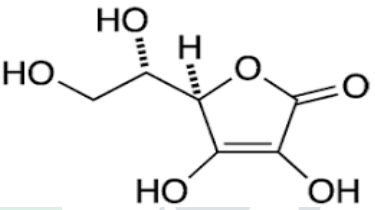
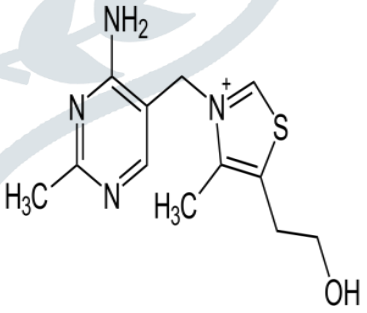
					rol homocysteine.			
17	*Boesenbergia rotunda*	Finger root Chinese ginger	*Zingiberaceae*	Rhizome	Panduratin A	AKI protection	In vitro, in vivo mice	88
18	*Abelmoschus esculentus L*	Bhendi	*Malvaceae*	Fruit, Seed, Root	Thiamine riboflavin, carotene, folic acid, and tocopherol, palmitic acid	nephroprotective	In vivo mice	89
19	*Acorus calamus*	sweet flag	*Acoraceae*	Roots	flavonoids, Monoterpene, Sesquiterpene, Phenyl Propanoid and Quinone	Renal antioxidant activity	male albino rats	90
20	*Aerva javanica*	kapok bush, desert cotton	*Amaranthaceae*	Whole Plant	Aervoside, Aerolanine, Kaempferol, Propionic Acid, -Carboline-I, Stigmasterol, Kaempferol, Hentriacontane, and Aervoside	protect acute tubular necrosis of proximal renal tubules	Wistar rats	91
21	*Andrographis paniculata*	*Creat, green chiretta*	*Acanthaceae*	Leaves	Flavonoid and Polyphenolic compounds	Significant reduction of necrosis in proximal tubules of kidneys	male albino rats	92
22	*Aristolochia indica*	Isharmul	*Aristolochiaceae*	Leaves	Flavonoids, Alkaloid, Saponin	Enhance free radical scavenger activity in kidney	Wistar rats	93
23	*Asparagus racemosus*	Satawar	*Liliaceae*	Roots	Saponins, polyphenols, flavonoids, phytosterols, and ascorbic acid	Protect renal necrosis and oxidation activity	Wistar rats	94
24	*Avuri kudineer*	Black heena	*Fabaceae*	Leaves	glycoside indican, indigotine, indirubin, flavanoids, rich source of potash	Decoction inhibit the binding by alkylating DNA and triggers transcription inhibition and renal apoptosis	albino rats	95
25	*Azima tetracantha*	Bee Sting Bush	*Salvadoraceae*	Roots	Flavonoids, Terpinoids, Alkaloids, Tannins,	Glomerular damage and tubular necrosis	Wistar albino rats	96

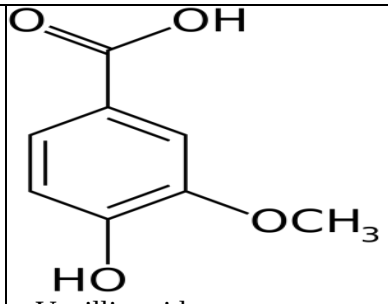
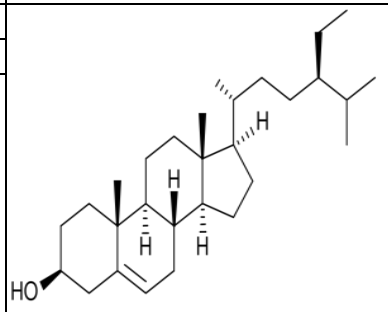
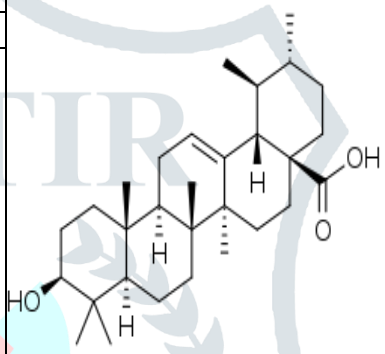
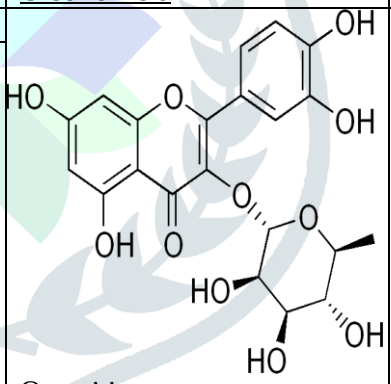
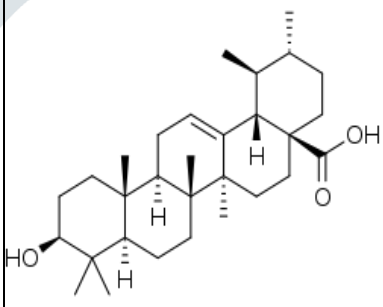
					Saponins & Glucosinolates			
26	*Bauhinia variegatea*	Orchid tree	*Orchidaceae*	Stems	Lupeol, Kaempferol3-Glucoside, Stigmasterol, Flavone Glycosides, and -Setosterol	Protect glomerular and tubular arrangements with normal Bowmen's capsule	rats	97
27	*Benincasa Hispida*	Fuzzy Gourd, Ash Gourd	*cucurbitaceae*	Leaves	Asparagines, mannitol, proline, arginine, aspartic acid, glucose, and vitamin B and beta-sitosterol.	Protect against lipid peroxidation, oxidative stress, and renal DNA damage.	rats	98
28	*Benincasa hispida*	Winter Melon, Wax Gourd	*cucurbitaceae*	Fruits	Volatile substances, fats, proteins, carotenoids, glycosides, saccharides, vitamins, minerals, -sitosterone, and uronic acid	Elevated tissue GSH levels significantly and decreased lipid peroxidation levels	rats	99
29	*Boerhaavia diffusa*	Punarnava	*Nyctaginaceae*	Fruits	Alkaloids, steroids, and flavonoids Triterpenoids, Lipids, Glycoproteins, Carbohydrates, and Lignins	Inhibit the xenobiotic induced nephrotoxicity due to their potent antioxidant effects	rats	100
30	*Calotropis procera*	Apple of sodom, calotrope	*Apocynaceae*	Flowers	Glycosides, Flavonoids, Tannins and Triterpenes	prevents the kidney's release of reactive oxygen species	albino rabbits	101
31	*Caralluma umbellata*	Caralluma	*Asclepiadaceae*	Stems	Phenols, Flavanoids, Alkaloids, Steroids, Terpenoids and Glycosides	Increase glomerular filtration rate , decrease the generation of free radicals production by renal cortical mitochondria	albino rats	102

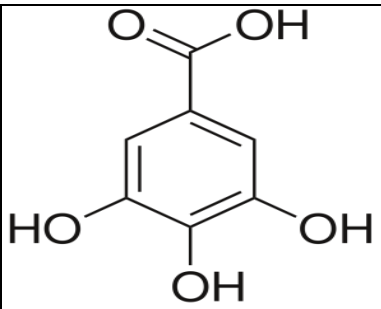
32	*Cassia fistula*	golden shower tree	*Fabaceae*	Fruits	Phenolic Derivatives anthraquinones, Xantho-Nes, Phenolic acids, Phenolic Diterpenes, Flavonoids, Volatile Oil, Waxy and Resinous Derivatives	Improve tubule interstitial lesions & the s3 segment in the outer medulla, which is a part of the proximal tubules, is damaged	albino rats	103
33	*Cissampelos pareira*	velvetleaf	*Menispermaceae*	Whole Plant	Glycoside, Alkaloids, Tannins (Phenolic Compounds), Flavonoids	Enhancing the levels of glutathione and decreasing the lipid peroxidation	rats	104
34	*Curuma longa*	Turmeric	*Zingiberaceae*	Roots	Polyphenol (Curcumin), Termeric oil, Terpenoids, Curcumen, Starch, Albumnoids	Improve renal tubular damage	rats	105
35	*Zingiber officinale*	zinger	*Zingiberaceae*	Rhizomes	flavonoid	Keep the proximal convoluted capsule and bowman's capsule intact to protect the glomeruli.	rats	106
36	*Vitex negundo*	Chinese chaste tree	*Verbenaceae*	Bark	Phenylpropnoids or Polyphenolic and Flavonoids	Protect tubular brush borders	rats	107
37	*Vernonia cinerea*	Little ironweed	*Compositae*	Aerial Parts	fatty acids, Steroids Flavonoids, 39Tri-terpenoids: α-Amyrin and βAmyrin	impact that serves to protect the S3 section of the proximal tubule	rats	108
38	*Tribulus terrestris*	Gokharu	*Zygophyllacea*	Fruits	Harmine, Harman, Saponins, Steroidal Sapogenins, Lavonoids, Kaemferol, Tribuloside, Alkaloids and Resins	Protect renal tubular cell necrosis	albino rats	109

39	*Trianthema portulacastrum*	Giant Pigweed, Black Pigweed	*Aizoaceae*	Whole Plant	3,4-Dimethoxy Cinnamic acid, Cyanin,Dimethylflavone, Ecdysterone Trianthenol, and 3,2'-Acetylaleuritolic Acid	Protect proximal tubular necrosis	albino rats	110
40	*Thespesia populnea*	portia tree, Milo	*Malvaceae*	Leaves	Tannins, Terpenes, Saponins, Flavonoids, and Quinine Alkaloids	Preventing necrosis of proteins in the renal tubules	Wistar albino rats	111
41	*Salviae officinalis*	Kamrkash, *Sage Weed*	*Lamiaceae*	Whole Plant	Salvinolic acids A–G, Rosmarinic, Isoferul, Tanshine–I, Cryptotanshine–V–VI, and Lithospermic acids	Antioxidant action	albino rats	112
42	*Panax ginseng*	Ashwagandha	*Araliacea*	Root	Panaxosides, Chikustsu saponin, Ginsenosides (Dammarol), and saponin (Oleanolic acid)	Protect the renal dysfunction, inflammatory cytokine expression and apoptosis of kidney	Wistar albino rats	113
43	*Momordica tuberosa*	Kakrol, Karchikai	*Cucurbitaceae*	Tubers	saponins, Cardiac Glycosides, Triterpenoids saponins, Triterpenoid and Bitters	Alter the generation of nitric oxide	albino rats	114
44	*Lantana camara*	ghaneri	*Verbenaceae*	Roots	Pentacyclic triterpenoids, Linaroside, Oleanolic acid, Octadecanoic acid, Ursonic acid	Inhibit renal nitric oxide generation and mitochondrial hydrogen peroxide generation	sprague-dawley rats	115

TAB.2 DOCKING SCORE OF BIO-ACTIVE COMPOUNDS OF NEPHROPROTECTIVE MEDICINAL PLANTS AGAINST NF-κB

S.n	Plant	Bio-active compound		Chemical structure	Activity	ref.
1	*Combrethum Micranthum G (Combretaceae)*	Gallic acid	*−21.167*	 Gallic acid	has been performed in male Wistar rats	116
		β-Sitosterol	*−6.859*			
		Linolenic acid	*−10.761*			
2	*Curcuma longa (Zingiberaceae)*	Curcumin	*−8.94*	 Cyclocurcumin	has been performed in gentamicin nephrotoxic rats	117
		Cyclocurcumin	*− 6.77*			
		Stigmasterol	*− 2.28*			
3	*Carica Papaya (Caricaceae)*	Ascorbic acid	*−6.0*	 Ascorbic acid	has been performed in In-vivo mice	118
4	*Abelmoschus Esculentus L (Malvaceae)*	Riboflavin	*− 7.7*	 Thiamine	has been performed in In-vivo mice	119
		Thiamine	*−6.0*			
		Folic Acid	*− 7.9*			
5	*Abutilon Indicum (Malvaceae)*	Coumaric acid	*−6.8*		has been performed in diabetic nephrotoxic rats	120
		Riboflavin	*− 7.7*			
		Vanillic acid	*−36.471*			

				 Vanillic acid		
6	*Aerva Lantana (Rutaceae)*	β-Sitosterol Stigmasterol Botulin	*−6.859* *− 2.28* *−8.4*	 β-Sitosterol	has been performed in Wistar rats	121
7	*Sonchus Oleraceus (Asteraceae)*	Rutin Ursolic Acid Chicoric Acid	*−314.35* *−4.10* *-8.63*	 Ursolic Acid	has been performed in Wistar rats	122
8	*Ceiba Pentandra (Malvaceae)*	Quercitrin Cinchonains	*−247.11* *−37*	 Quercitin	has been performed in Wistar rats	123
9	*Ocimum Sanctum (Lamiaceae)*	Ursolic Acid	*−11.8*	 Ursolic Acid	has been performed in Wistar rats	124
10	*Suaeda Vermiculata (Amaranthaceae)*	Gallic acid Cinnamic Acid Coumaric Acid	*−21.167* *−6.66* *−6.8*		has been performed in Male Sprague Dawley rats	124

				 Gallic acid		

CONCLUSION

Many drugs when administered for a long period have been known for inducing AKI; however, the use of medicinal plants to prevent the nephrotoxicity is always interesting to be discussed. Various types of plants that are often used traditionally as nephroprotective agents have been mentioned in this study. This review supports and confirms the usefulness of ethno-medicine, most of which have potential nephroprotective flavonoids. Most of the plants have nephroprotective-related antioxidant activity. The plants which have – flavonoids, flavone, alkaloids, triterpenoids, glycosides, saponin, Gallic acid, β-Sitosterol, vitamin C, vitamin E etc. shows anti-oxidant and nephroprotective properties.

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