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VARIOUS PHYTOCHEMICALS AND HERBAL PLANTS EXPLORED IN THE TREATMENT OF RENAL FAILURE: A BRIEF REVIEW OF PRE-CLINICAL STUDIES

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ABSTRACT

Kidney is a important organ, with a million of nephrons performing vital functions of it. Some of the functions like filtration, electrolyte balance, and excretion and so on. So in order to make the kidney run all its vital functions adequately it is necessary to keep it healthy which can only be acquired with a healthy lifestyle. Herbal medicines proved as an efficient approach to treat various diseases and an affordable therapy to cure various kidney diseases. A lot of ways are known to have good effect on renal function, one of which is to use different phytoconstituents for the betterment of renal health. Many evidences from different studies are found which give support to the statement that phytochemicals are effective in keeping the renal functions intact. Ascorbic acid, lycopene, resveratrol, DL-α-lipoic acid, hesperidine are few important phytoconstituents for kidney. In past years, a number studies has been conducted in order to discover new ways/medicine/phytochemicals which can help to maintain a healthy renal function.

Keywords: Kidney, nephrons, phytoconstituents, taurine, lycopene, ginseng, ginkgo biloba

INTRODUCTION

Human kidneys are vital organs in maintaining the normal body functions. Maintaining fluids, electrolytes and acid-base balance are the main functions of the kidney. Other functions of kidney are water transport, conserving nutrients and excreting metabolic waste products. Kidney consists of an outer cortex and inner

medulla. Series of wedges that divided the medulla are known as renal pyramids. Nephrons are structural and functional unit of the kidney. There are approximately 1.2 million nephrons in the kidney which helps in the formation of the urine. Nephron consists of the afferent arteriole, efferent arteriole, loop of henle, collecting duct and the convoluted tubule. The other important function of kidney is to maintain the volume and composition of extracellular fluid within the normal limits **[1]**.

Diseases associated with kidney are acute kidney injury, chronic kidney disease, diabetes, polycystic kidney disease and kidney cancer. The pathogenesis of terminal renal failure includes decompensated benign nephrosclerosis, malignant nephrosclerosis, the ischemic contracted kidney, rapid progressive glomerulonephritis, diabetic nephropathy, renal amyloidosis, acute renal failure, myeloma kidney, acute interstitial nephritis, analgesic nephropathy, balkan nephritis, incomplete obstructive nephropathy and reflux nephropathy **[2]**. Drug induced kidney disease are pre renal failure, acute tubular necrosis, drug induced crystalluria, hypersensitivity angitis, thrombotic microangiopathy/ hemolyticuraemic syndrome, isolated proteinuria with nephrotic syndrome, chronic glomerulopathy , chronic tubulointerstitial disease and retroperitoneal fibrosis **[3]**. In madrid, spain a nine months study covering all ARF episodes encountered in the 13 tertiary-care hospital (covering 4.2 million people of over 14 years of age) shows that the serum creatinine level in normal individual was found to be more than 177µmol/liter. While sudden rise in normal creatinine level (50%or above) was seen in the patients with mild to moderate chronic renal failure (serum creatinine < 264µmol/liter). The mean age of the patients was 63±17 years. The most dominant causes of ARF was ATN (45%), obstructive ARF (10%), acute onset chronic renal failure (12.7%) and prerenal (21%). Mortality was higher in patients suffering from another diseases like coma, hypotension, jaundice and assisted respiration **[4]**.

Plants have been proved as important medicines from long time. Plants and their phytoconstituents known for the treatment of renal failure are thymoquine (*Nigella sativa*), ginsenosides (*Panax ginseng*), silymarin (*Silybum marianum*), gingerol (*Zingiber officinale*), polyphenols compounds (*Punica granatum*) and quercetin (*Ginkgo biloba*). Natural products mainly focus on oxidative stress and inflammation which are the main cause of renal failure **[5]**. For the health care 80% of world's inhabitants are mainly depend on traditional medicines systems according to World Health Organisation. Isolation of

quinine from the Cinchona bark for the treatment of malaria was great discovery in herbal medicines in 1820 **[6]**.

- **PHYTOCONSTITUENTS EXPLORED IN THE KIDNEY DISORDER**
  - **Ascorbic acid**

It is mainly found in the foods like tomatoes, broccoli and citrus fruits. It helps in the prevention of aging diseases like heart diseases, cancer and inflammatory diseases which could be produced by the free radicals. It provides its nephroprotective action by its free radical scavenging activity **[7]**. Asli Korkmaz *et al* (2009) has demonstrated that the Ascorbic acid shows nephroprotective action against ischemia-reperfusion injury in rats. This study shows that the biomarkers like urea and creatinine were restored when treated with 250 mg/kg dose which shows its action by its free radical scavenging properties **[8]**. Miriam A. Moreira *et al* (2013) has depicted that gentamicin-induced nephrotoxicity in rats can be treated with ascorbic acid. Ascorbic acid at a dose 100mg/kg helps in generation of nitric oxide and reduction of reactive oxygen species **[9]**.

- **Allicin**

Allicin (diallylthiosulfinate) is the main active component majorly found in the garlic. It provides its nephroprotective action by its antioxidant properties. Other than renal protection it also shows hypolipidemic, antiplatelet, antifungal and antibacterial effects. Recent studies has demonstrated that by the inhibition of cancer cells it shows its chemopreventive and anticancer properties **[10]**. Dalia H. El-Kashef, *et al* (2015) has illustrated that the gentamicin-induced nephrotoxicity in rats can be prevented by the administration of allicin. Oral administration of allicin at a dose 50mg/kg increases creatinine clearance, renal SOD activity and renal GSH content with decrease in creatinine levels, urea and renal MDA.Allicin helps in protecting the functional and structural damage in kidneys from gentamicin **[11]**. Hong Huang *et al* (2016) has depicted that streptozotocin-induced diabetic nephropathy in rats can be treated with the administration of allicin. This study has demonstrated that the oral administration of allicin at a dose 45mg/kg helps to decrease the serum creatinine and BUN along with decrease expression levels of collagen I, TGF-β1 and p-ERK1/2 **[12]**.

- **Caffeic acid phenylethyl ester**

Caffeic acid phenylethyl ester (CAPE) is well known for its anti-inflammatory, free radical scavenger and antioxidant properties. CAPE is an active constituent obtained from honeybee propolis and is being used from many years. It shows its antioxidant activity by inhibiting the production of ROS(Reactive oxygen

species) in human neutrophils and xanthine oxidase system **[13]**. CAPE also exhibit immunomodulatory, anticarcinogenic and antimitogenic properties. CAPE has potent action in blocking the nuclear transcription factor (NF-κB) activation **[14]**. H. Parlakpinar *et al* (2004) has depicted that the gentamicin-induced acute renal toxicity in rats can be treated with caffeic acid phenylethyl ester. CAPE with a dose 10 µmol/kg restores the levels of BUN, MDA and creatinine when administered intraperitoneally **[15]**. Nurettin Aydogdu *et al* (2004) has illustrated that the glycerol-induced acute renal failure can be treated with the administration of with caffeic acid phenylethyl ester **[16]**. Faruk O¨ ktem *et al* (2006) has demonstrated that the antioxidant activities of caffeic acid phenylethyl ester helps in treating methotrexate-induced renal oxidative stress. CAPE at a dose 10 µmol/kg decrease the levels of MDA (malondialdehyde) and increases the activity of SOD(superoxide dismutase), CAT (catalase) and GSH-Px(glutathione peroxidase) **[17]**.

- **Lycopene**

Lycopene is phytoconstituent mainly present is tomatoes and it is a naturally occurring carotenoid. Along with renoprotective it is also a chemoprotective agent. Recent studies has demonstrated that lycopene has ability to scavenge two reactive oxygen species which are peroxyl radicals and singlet molecular oxygen **[18]**. Consumption of tomato paste for 3 months can relief from sun injury due to U.V radiation **[19]**. Ahmet Atessahin *et al* (2005) has illustrated that cisplatin-induced nephrotoxicity and oxidative stress in rats can be treated with lycopene. Amelioration in the levels of plasma creatinine and urea concentration has been observed when treated with 4mg/kg of lycopene. More significant actions were observed in the groups pre-treated with lycopene. Lycopene also helps to decreasethe levels of MDA and increase the concentration of GSH with increased activities of GSH-Px and CAT **[20]**. Paula R. Augusti *et al* (2007) has depicted that lycopene could show nephroprotective action against mercuric chloride induced nephrotoxicity in rats **[21]**. I. Karahan *et al* (2005) has illustrated that the lycopene has protective action against the gentamicin-induced oxidative stress and nephrotoxicity in rats. Oral administration of lycopene at a dose 4 mg/kg shows amelioration in kidney MDA, GSH levels and GSH-Px and CAT activities **[22]**

- **Resveratrol**

Resveratrol (3,5,4′ -trihydroxystilbene) is a polyphenolic compound naturally present in red wine and grapes possess protective

action in renal and cardiovascular diseases. Resveratrol shows its antioxidant property by scavenging reactive oxygen species. It helps in managing multiple cellular functions like inflammation, apoptosis, mitochondrial biogenesis and adaptation to cellular stress **[23]**. Vikaschander *et al* (2006) has illustrated that glycerol-induced acute renal failure can be treated with the administration of Resveratrol in rats. Pre-treatment of Resveratrol at a dose (10mg/kg) helps to improve renal dysfunction, morphologic alterations and nitric oxide levels along with restoration of depleted renal antioxidant enzymes **[24]**. Goksel Sxener *et al* (2006) has demonstrated that the ischemia/reperfusion-induced oxidative renal injury can be improved when treated with Resveratrol. Resveratrol at a dose 30mg/kg helps to decrease serum creatinine, MDA, MPO and BUN and increase in GSH activity **[25]**. ANA I. MORALES *et al*(2002) has depicted that the trans-Resveratrol shows nephroprotective action against gentamicin induced nephrotoxicity. Trans- Resveratrol at a dose mg/kg increases GFR (glomerular filtration rate), RBF (renal blood flow) and urinary excretion of N-acetyl-beta-D-glucosaminidase **[26]**.

- **Astaxanthin**

Astaxanthin is a dark-red pigment which is generally obtained from algae and aquatic animals. Astaxanthin is generally a carotenoid found in sea food including lobster, shrimp and salmon as well as in birds like quail and flamingo. Astaxanthin is known for its nephroprotective actions due to its strong antioxidant properties. Along with treatment of renal diseases it is also helpful in treating other diseases like cancer, diabetes, cardiovascular diseases, liver diseases, gastrointestinal diseases and eye diseases **[27]**. Astaxanthin protects fatty acids and biological membranes by scavenging lipid radicals and destroying peroxides **[28]**. P.R. Augusti *et al* (2008) has demonstrated that mercuric chloride induced kidney function impairment and oxidative stress can be treated by astaxanthin in rats. Oral administration of astaxanthin at a dose 50mg/kg helps to decrease lipid peroxidation and protein oxidation **[29]**. Gorkem Akca *et al* (2018) has illustrated that astaxanthin shows nephroprotective actions in cisplatin-induced nephrotoxicity in rats. This study shows that at a dose of 75mg/kg shows reduction in BUN, serum creatinine, total oxidant status and Caspase-3 and also improves degenerative proximal and distal tubules, edema and glomerular degeneration in kidney tissues **[30]**.

- **DL-α-lipoic acid**

DL-α-lipoic acid is a disulfide compound which acts as coenzyme in α-ketoglutarate

dehydrogenase and pyruvate dehydrogenase mitochondrial reactions which further leads to production of cellular energy (ATP). Dihydrolipoic acid is the reduced form of α-lipoic which reduce oxidative stress by increasing intercellular glutathione, scavenging free radical, by chelating transition metals in biological systems and by preventing membrane lipid peroxidation **[31]**. Asmma Hussein *et al* (2012) has illustrated that DL-α-lipoic acid improves the cisplatin-induced nephrotoxicity and cardiotoxicity in experimental animals. Lipoic acid at a dose 100mg/kg restored cisplatin-inducedbiomarkers which includes serum creatinine, blood urea nitrogen, tissue MDA, GSH , NO and SOD **[32]**. P. Sandhya *et al* (1995) has demonstrated that α-lipoic acid shows nephroprotective action against gentamicin-induced nephrotoxicity in rats. Lipoic acid at a dose 25mg/kg leads to increase the activity of ATPases, TCA cycle enzymes and glycolytic enzymes **[33]**.

- **Taurine**

Taurine is an intracellular free β-amino acid present in the mammalian tissues. Taurine plays various physiological roles like bile acid conjugation, cell proliferation, viability and prevention of oxidant induced injury in many tissues **[34]**. Ayse Erdem *et al* (2000) has depicted that taurine shows protective action against gentamicin-induced acute tubular necrosis. This study shows that the group treated with taurine found to be reduced accumulation of gentamicin in the kidney, normalization of Gpx and SOD activities and prevention of body weight due to gentamicin administration **[35]**. GH. Guz *et al* (2007) has illustrated that renal ischemia/reperfusion injury can be treated with administration of taurine. Taurine at a dose 7.5 mg/kg shows reduction in serum BUN, creatinine, tissue and serum MDA levels **[36]**. Lijun Wang *et al* (2008) has demonstrated that taurine shows nephroprotective action against streptozotocin induced diabetic rats by inhibition of renal LOX-1 mediated ICAM-1 expression. Administration of taurine helps to reduce serum BUN, creatinine and tissue MDA levels and also overcome the over expression of LOX-1 and ICAM-1in kidney cortices of diabetic rats **[37]**.

- **Hesperidine**

Hesperidine (5,7,3′-trihydroxy-4′-methoxyflavanone-7-rhamnoglucoside) belongs to flavanones which is generally a class of flavonoids mainly found in citrus fruits. Damaging effects induced by paraquat and peroxide hydrogen are protected with hesperidine which provides a strong cellular antioxidant protection **[38]**. Ramaswamy Anandan *et al*(2012) has

depicted that administration of hesperidine in male wistar albino rats provides nephroprotective action against gentamicin-induced acute nephrotoxicity. Hesperidine administration decreases triglycerides, serum cholesterol and free fatty acids while increses SOD, GPx activities and GSH content. Pre-treatment of hesperidine reduced the levels of creatinine, urea, uric acid, NO and MDA **[39]**. Bidya Dhar Sahu *et al* (2012) has illustrated that the cisplatin-induced acute renal injury can be treated by the administration of hesperidine in rats. Hesperidine at a dose 200mg/kg helps to provide nephroprotective action by decreasing inflammation, oxidative stress and DNA damage. Hesperidine also increase the expression of nitric oxide in the kidney and improve renal function **[40]**.

- **Silymarin**

Silymarin derived from milk thistle is a polyphenolic compound extracted from *silybum marianum* and *cynara cardunculus* seeds and fruits. These seeds consists of potent antioxidant flavonolignans. Silymarin has its renal protective action in animals due to its antioxidant properties. Silymarin protects kidney by showing protective action against damaging free radicals and by stimulating the protein and RNA synthesis which is an important step in renal repair mechanism **[41]**. Flavonolignans which are majorly present in silymarin are isosilybin, dehydrosilybin ,silydianin and few flavonoids mainly taxifolin. The active component of silymarin is silybin. Silybin and Silychristin both stimulates the biosynthesis of protein and DNA, proliferation rate and activity of lactate dehydrogenase **[42]**. Out of silicristin, silidianin, and isosilibinin pure silybin is more effective. Proliferation rate increased upto 23% in Vero kidney cells as compare to control cells when the cells were treated with silybin. Other than kidney silybin has its positive effects on liver cells like RNA, DNA and protein biosynthesis. Faruk Turgut *et al* (2008) has illustrated that the silymarin shows both antioxidant and protective effects on the kidney tissues of rats injured by the ischemia and reperfusion. As compared to I/R group the serum and tissue antioxidant enzymes levels were significantly high in I/R + silymarin group. This study has demonstrated that the group treated with silymarin has low levels of creatinine, urea and cystatin C in serum as compared with I/R group **[43]**.

Mustafa Cengiz *et al* (2018) has depicted that silymarin shows its renoprotective effect against the renal injury induced by thioacetamide. Administration of silymarin before TAA (thioacetamide) could protect the renal tissues from the nephrotoxicity produced by TAA. This study shows that the group

which was treated with both silymarin and TAA has reduced tubular damage and normal renal cortex. This group has decreased levels of BUN and uric acid. Increase in the dose of silymarin shows more protective action[44]. Chuanpit Ninsontia *et al* (2011) have demonstrated that Cisplatin-induced renal cell injury can be protected by silymarin. This study shows that the human renal tubular HK-2 cells which are damaged by cisplatin-induced apoptosis are selectively protected by silymarin. Due to the antioxidant property of silymarin it protects the renal cells from the intercellular ROS produced by cisplatin **[45]**. Samah S. Oda *et al* (2012) has illustrated that the silymarin has protective action against the nephrotoxicity induced by mercury in rats. Silymarin not only protects the kidney but also helps to bring malondialdehyde and glutathione back to their respected levels. Silymarin also protects the hepatic cells along with renal cells **[46]**.

Table 1: List of phytoconstituents with their nephroprotective actions against renal failure

Phyto-constituents	Dose	Route of administration	Animal used	Model used/Injury Induced by	Observations/ Outcomes	References
Ascorbic acid	100mg/kg	Intraperitoneal	Wistar rats	Gentamicin	Generation of nitric oxide and reduction of reactive oxygen species	[9]
Allicin	45mg/kg	Oral	Sprague–Dawley (SD) rats	Streptozotocin	Decrease in serum creatinine and BUN along with decrease expression levels of collagen I, TGF-β1 and p-ERK1/2	[12]
Caffeic acid phenylethyl ester	10 µmol/kg	Intraperitoneal	Male wistar albino rats	Methotrexate	Decrease in levels of MDA and increases the activity of SOD, CAT and GSH-Px	[17]
Lycopene	4mg/kg	Oral	Male Sprague–Dawley rats	Cisplatin	Decreased urea, creatine and MDA + increase in CAT activities	[20]
Resveratrol	120mg/kg	Oral	Male wistar rats	Gentamicin	Increased GFR (glomerular filtration rate), RBF (renal blood flow) and urinary excretion of N-acetyl-beta-D-glucosaminidase	[26]
Astaxanthin	75mg/kg	Intraperitoneal	Male Sprague Dawley rats	Cisplatin	Reduction in BUN, serum creatinine, total oxidant status and Caspase-3 + improved degenerative proximal and distal tubules, edema and glomerular degeneration in kidney tissues	[30]

α-lipoic acid	**25mg/kg**	**Oral**	**Male Wistar rats**	**Gentamicin**	**Increased activity of ATPases, TCA cycle enzymes and glycolytic enzymes**	**[33]**
Taurine	**7.5mg/kg**	**Intraperitoneal**	**Male Wistar albino rats**	**Ischemia/ reperfusion**	**Reduction in serum BUN, creatinine, tissue and serum MDA levels**	**[36]**
Hesperidine	**200mg/kg**	**Oral**	**Male wistar rats**	**Cisplatin**	**Decreased inflammation, oxidative stress and DNA damage + increased expression of nitric oxide in kidney**	**[40]**
Silymarin	**100mg/kg**	**Oral**	**Male albino wistar rats**	**Thioacetamide**	**Less tubular damage + decrease BUN and uric acid**	**[44]**

Note: BUN(Blood urea nitrogen), MDA (Malondialdehyde), SOD (Superoxide dismutase), CAT (Catalase), GPx or GSH-Px (Glutathione peroxidase)

- **HERBAL PLANTS EXPLORED IN KIDNEY DISORDER**
  - **Garlic**

Garlic (*Allium sativum*) which comes under family Amaryllidaceae is an important and valuable herb. It was originated in central asia. Garlic is an herb used for treating ulcers, respiratory problems, colic and flatulence. For ear ache garlic oil drops are used for treatment (Thomas, 2001). The first isolated and biologically active compound of garlic was Allicin which is effective against fungi, bacteria and parasites. Organosulfur compounds which act as antioxidant are active components of garlic. Allicin which act as flavonoid, germanium which act as trace element (immunostimulant and normalizer) and selenium (for the optional function of the antioxidant enzyme glutathione peroxidase), sulfur compounds present in volatile oil and amino acids are other bio-active compounds **[48]**. In human lymphocyte chromosome garlic play a protective role against genotoxicity produced by cisplatin **[49]**. From the previous reports it is also suggested that garlic has protective effect against nephropathy **[50]** and renal reperfusion injury **[51]**. N. Anusuya *et al*. (2013) reported that the ethanolic extract of garlic shows protective action against the nephrotoxicity induced by cisplatin in male wister rats. Elevated kidney weight with reduction in the activities of kidney antioxidants, increased lipid peroxidation with serum kidney markers like BUN (blood urea nitrogen), urea, uric acid and creatinine has been seen in cisplatin induced nephrotoxicity. Gradual increase in the level of antioxidants and taking back the markers to their normal levels has been reported when treated with the ethanolic extract of garlic which shows a protective effect. There is no important biochemical effect was seen when the rats were treated

with the higher doses of garlic extract **[52]**. Segoviano-Murillo *et al* (2008) has depicted that the S-allylcysteine which is an antioxidant present in garlic shows protective effect in renal injury and oxidative effect induced by reperfusion and ischemia **[53]**. Mahmoud Rafiein-Kopaei *et al* (2013) has shown the levels of serum BUN and creatinine increased tremendously after the injection of gentamycin. Metformin, garlic or their combination could lower the BUN and creatinine levels after the administration of Gentamicin (GM) (high doses). To elevate the antioxidant potency for improving GM-tubular toxicity Garlic extract along with Metformin could be safely use **[54]**. Levent Kabasakal *et al* (2005) has depicted that ischemia/reperfusion induced nephrotoxicity can be reversed by aqueous extract of garlic. Ischemia/reperfusion results in decrease in GSH (glutathione), increase in MDA (renal malondialdehyde) and MPO (myeloperoxidase) activity which led to the formation of free radicals. Levels of GSH, MDA and MPO activity were restored back to their normal levels when treated with aqueous garlic extract (1mL/kg) in rats, it decreases free radical formation. Aqueous garlic extract not only improves the renal function but also repair the damage at microscopic level **[55]**. Tae Won Lee *et al* (2019) has reported that acute kidney injury in rats induced by colistin can be improved by the aqueous extract of aged black garlic. Functional and structural renal damages along with the production of ROS (reactive oxygen species) which led to oxidative stress and protein oxidation (involves in inflammation) has been observed during colistin administration. Aged black garlic extract used with potent antioxidant effects can indirectly lower the protein oxidation and oxidative stress and directly have anti-inflammatory properties **[56]**. Jose´ Pedraza-Chaverri *et al* (2008) has illustrated that garlic powder have potency to show protective action against potassium dichromate-induced nephrotoxicity and oxidative stress. A diet containing 2% of garlic powder has ability to improve potassium dichromate induced renal injury with its antioxidant and ROS scavenging properties **[57]**. Hanaa A Hassan *et al*(2009) has reported that garlic oil (at dose 5ml/kg body weight) has reno-protective action against oxidative stress induced by sodium nitrate. Garlic oil has antioxidant properties which leads to reduce the levels of lipid peroxidation and nitric oxide by scavenging free radicals **[58]**.

- **Rhubarb**

In countries like china and japan Rhubarb is well known for its treatment in chronic renal failure. Root and rhizome of rhubarb contains Anthraquinones which are their active component have nephroprotective

and other pharmacological effects. Different ingredients (rhein, emodin, aloemodin) isolated from rhubarb root has different pharmacologic actions, nowadays is used to slow down the progression of chronic kidney disease. Recent, animal studies has illustrated that biological activity of squaleneepoxidase, which is key enzyme of cholesterol synthesis can be inhibited by the galloylproanthocyanidins obtained from the rhubarb. Rhubarb caused increased excretion of waste products (including amino acids, serum creatinine and urea nitrogen) through intestine which is confirmed from early experiments **[59]**.

It has been evaluated from the invitro studies of emodin that the emodin has effect on both growth and metabolic changes of renal mesangial and tubular epithelial cells. Ingested extract of rhubarb (containing emodin) present in serum obtained from rat has ability to suppress the growth of both mesangial and tubular cells. Rhubarb plays a crucial role by lowering the triglyceride and cholesterol levels in the patients suffering from CRF **[60]**. Through experimental studies it has revealed that the rhubarb shows effects on renal fibrosis, which was thought to relieve SCr (serum creatinine) and proteinuria through down regulating gene expression of growth factors in glomeruli from diabetic rats. There can be inhibition of proliferation of mesangial cells, decreasing the monocyte infiltration and reduction in high renal metabolism plays a crucial role **[61]**.

Dan gao *et al* (2016) has illustrated that the acute renal failure induced by the mercuric chloride in rats can be treated by the rhubarb anthraquinones. For checking the nephroprotective effect of rhubarb anthraquinones against mercuric chloride in rats total rhubarb extract (TR) was separated into three parts, anthraquinones extract (TA), total tannins (TT) and remaining components extract (RC) so that individual effects of total rhubarb extract parts can be seen. From the results it is seen that TA and TR plays protective role in mercuric chloride induced ARF in rats while TT and RC has no effects **[62]**. Lingna Zeng *et al* (2013) has depicted that tannins present in the rhubarb shows protective actions against the nephrotoxicity induced by the potassium dichromate in rats. Hydroxyl radicals, which are dominant lesion product generated by hexavalent chromium are scavenge by the total tannins (TT). TT has less ability to transform toxic high valence chromium ions into non-toxic low valence ions. Chromium ions can further be precipitated by TT. Tannins present in rhubarb has metal precipitation, reductant and radical scavenger properties **[63]**. Takako Yokozawa *et al* (1994) has demonstrated that oral administration of rhubarb extract shows the protective action

against the chronic renal failure induced by adenine diet in rats. Administration of rhubarb extract in rats shows positive results in treating the hypocalcemia by increasing the serum calcium level. This study has shown that there is gradual decrease in the levels of urea nitrogen and creatinine when the rats were treated with the higher doses of rhubarb extract which was administered orally **[64]**. Tokako Yokozowa *et al* (1991) has illustrated that the different tannins obtained from rhubarb has shown positive action against the uremic toxins. (-)-Epicatechin 3-0-gallate which is one of the tannin obtained from rhubarb helps to decrease the levels of methylguinide (MG), guanidinosuccinic acid (GSA) and urea nitrogen in blood. Creatinine level of rats treated with this compound was also decreased. Similarly Procyanidin B-2 3,3'-di-O-gallate which is another tannin obtained from rhubarb helps to decrease GSA, MG and urea nitrogen **[65]**.

- **Ginseng**

Korean red ginseng is one of the widely prescribed and intensively studied herbal medicine obtained from the root of Panax ginseng C.A. Meyer (Araliaceae). KRG (korean red ginseng has wide range of physiological and pharmacological actions. It not only protects the kidneys but also pharmacological uses in brain, immune system and liver functions. It also have preventive action against tumor, pain, antidiabetics effects, regulation of blood pressure, antifatigue, antioxidant and antiaging effects **[66]**. Several studies have shown that the ginseng has anti-diabetic effect, such as enhancement in energy expenditure, absorption of glucose in intestine, better sensitivity to insulin and increase in sugar metabolism **[67]**. Yildiray Kalkan *et al* (2012) has depicted that the apoptosis in rat kidneys induced by gentamicin sulphate can be treated by panax ginseng. This study has shown that the group treated with gentamicin sulphate has increased levels of creatinine, serum urea and BUN. The group treated with panax ginseng and gentamicin sulphate has decreased levels of BUN, serum urea and creatinine. Panax ginseng contains antioxidant properties which helps to scavenge free radicals **[68]**.

Eun Jin Kim *et al* (2013) has illustrated that adenine-induced renal failure in rats can be treated by the saponins of heat processed ginseng. Sun ginseng improves the renal functioning by excreting out the urea nitrogen and creatinine thus helps to decrease the serum urea nitrogen and creatinine levels **[69]**. William C.S.Cho *et al* (2012) has demonstrated the streptozotocin-induced diabetic rats can be treated by Ginsenoside Re which is active compound in Panax ginseng. Antioxidant and antihyperlipidemic are the main

properties of Ginsenoside Re. Blood glucose, total cholesterol and triglyceride levels could lower down with the use of Ginsenoside Re of Panax ginseng. Not only the kidney but in eye glutathione and malondialdehyde are also restored with the use of panax ginseng **[70]**.

- **Ginger**

In most of the areas of asia and africa Ginger (*Zingiberofficinale*) is widely used from long time as a popular food spice. The main active constituents present in ginger are vitamins, phenolic, volatile oil, proteolytic enzymes and trace elements **[71]**. Due to the strong antioxidant activity it protects biological tissues and cell membrane lipids from various toxicants by scavenging the free radicals **[72]**. Various studies have shown that the ginger has nephroprotective effects against various drug-induced nephrotoxicity. Sami A. Gabr *et al* (2017) has demonstrated that ginger has protective action against cadmium-induced renal toxicity. Restoration of renal functions biomarkers, total antioxidants status and molecular DNA through free radical scavenging and regenerative mechanism was seen when treated with ginger. Through the complexation mechanism ginger behaves like ligand and stop the accumulation within kidney due to presence of oxygen group in ginger constituents **[73]**. S. Maghsoudi *et al* (2010) has depicted that the renal ischemia reperfusion-induced injury can be prevented by the administration of ginger. I/R-induced elevated creatinine was prevented by the pretreatment with ginger. Administration of the ginger in I/R+ginger group weaker the water intake, restore urinary K + and Na +.Superoxide anion and hydroxyl radicals are two ROS which are mainly scavenged by the ginger **[74]**.

K R Shanmugam *et al* (2010) has illustrated that alcohol induced renal damage in male albino rats can be treated by the use of ginger. This study shows that ginger shows its antioxidant effect by enhancement of GSH level, decreasing lipid peroxidation and maintaining normal levels of antioxidant enzymes **[75]**. EbruUz *et al* (2009) has depicted that ginger shows its nephroprotective effects on renal ischemia/reperfusion injury in rat kidneys. When compared to I/R group levels of serum urea creatinine and plasma cystatin C (CYC) remains unchanged in ginger+I/R group **[76]**.

- ***Punica granatum***

Punica granatum belongs to family Punicaceae commonly known as pomegranate is widely used in treating various disease. Pomegranate consists antioxidant of polyphenolic class which generally contains tannins, anthocyanins and flavonoids **[77]**. It is used antiviral, antifungal, antibacterial and carcinogenic agent. Ellagic acid, punicic, flavones,

flavanols and flavone glycosides. It posses its hypoglycemic activity due to the presence of constituents like gallic , ursolic and oleanolic acids, these all acids provide antidiabetic effects **[78]**.

Previous studies has reported that the free radical scavenging activity of *P.granatum* is due to the ellagic acid. Leaves of *P.granatum* also posses strong antioxidant activity along with antihyperlipidemic effect which are helpful in treating nephrotoxicity **[79]**. El-Sayed M. El-Habibi *et al* (2013) has reported that the Punicagranatum shows renoprotective action against chronic renal failure induced by adenine in male rats. This study shows that the pomegranate peel methanolic extract exert antioxidant and anti-inflammatory effects on renal failure. High phenolic content in pomegranate is responsible for antioxidant activity by scavenging ROS and induction of various antioxidant enzymes **[80]**. Nidhal AK Mohammed Ali *et al* (2012) has demonstrated that gentamicin-induced nephrotoxicity in rats could be prevented by the administration of *Punica granatum*. Alteration in serum levels of urea, creatinine uric acid, sodium, potassium and chloride can be protected by the aqueous extract of *Punica granatum*. Mild tubular necrosis can also be reversed by *Punica granatum* aqueous extract **[81]**. Ahmed E. Abdel Moneim *et al* (2013) has shown that *Punica granatum* juice has potent nephroprotective effect against carbon tetrachloride-induced nephrotoxicity in rats **[82]**.

- **Ginkgo biloba**

Ginkgo biloba (Ginkgoaceae) is a chinese herbal plant, its leaves and extract are prescribed worldwide as medicine for the treatment of various diseases. Its standard extract contains 5% - 7% of terpenes and 22% - 27% of flavone glycoside **[83]**. Diabetic nephropathy is caused by the reduced GFR and increased albuminuria. Treatment of early stage diabetic nephropathy can be done with Gingko biloba extract which helps to improve kidney function and albuminuria **[84]**. Recent studies has demonstrated that the ginkgo biloba extract prevents the glucose-induced accumulation of extracellular matrix in rat mesangial cells **[85]**. Mukaddes Gulec *et al* (2006) has demonstrated that the cisplatin-induced nephrotoxicity in rats is treated by the administration of ginkgo biloba extract. Adenosine deaminase (AD) activities was significantly decreased in the group treated with cisplatin + GBE (ginkgo biloba extract). GBE has no significant effect on malondialdehyde (MDA), myeloperoxidase (MPO) activities and nitric oxide levels (NO). **[86]**. M. U. R. Naidu *et al* (2000) has illustrated that ginkgo biloba extract shows potent effect against the

nephrotoxicity induced by gentamicin in rats. This study shows that 177% raised plasma and 374% raised kidney tissue MDA (malondialdehyde) were restored back to their normal levels when treated with the ginkgo biloba extract. Ginkgo biloba extract shows its action by neutralization of peroxyl and hydroxyl radicals **[87]**. H. Akdere *et al* (2014) has depicted that Ginkgo biloba EGb 761 has protective action against renal ischemia-reperfusion injury in rats. EGb761 is standardized and real ginkgo extract. Antioxidant, anti-allergic and anticarcinogenic properties of ginkgo biloba extract is due to the presence of vanillic, hydroxykynurenic and kynurenic acid. Tissue damage could be decreased by the use of ginkgo biloba extract EGb761 before renal ischemia-reperfusion **[88]**.

- ***Nigella sativa***

Nigella sativa (Ranunculaceae) commonly known as black cumin along with its components shows protective action in curing renal diseases like nephrolithiasis and other renal damages. Antioxidant activity of *nigella sativa* is due to the presence of thymoquinone which is an active quinone, this quinone has ability to scavenge free radicals and superoxide anion.[89]. It not only protects the kidneys but also protects the livers by stopping the leakage of renal enzymes into the circulation **[90]**. Recent studies has shown that the nigella sativa oil protects kidneys from acetaminophen-induced renal injury in rats **[91]**. Ethanolic extract of N.sativa helps to prevent both formation and deposition of calcium oxalate **[90]**. I˙hsan Yaman *et al* (2010) has demonstrated that gentamicin-induced nephrotoxicity in rats can be prevented by the administration of *nigella sativa*. Renal damage and oxidative injury is prevented by the free radical scavenging and antioxidant properties of *nigella sativa* **[92]**. Mousa-Al-Reza Hadjzadeh *et al* (2012) has depicted that cisplatin-induced renal injury in rats can be prevented by the alcoholic extract of *nigella sativa*. Histology of kidney of cisplatin group showed renal injury but the group treated with *nigella sativa* had well-preserved shape.

- ***Aerva javanica***

Aerva javanica belongs to family Amaranthaceae is worldwide well known for treating kidney diseases. This plant is used as Pasanabheda which means breakdown of kidney stones. Along with nephroprotective drug it is also act as diuretic, demulcent and anthelmintic **[93]**. Recent studies have shown the presence of phytoconstituents like phenolics, flavonoids, alkaloids, saponins, triterpenoids, steroids, carbohydrates, saponins, glycosides and tannins **[94]**. Vinit Movaliya *et al* (2011) has depicted that the aqueous extract of *Aerva javanica* roots

shows nephro-protective action against cisplatin induced renal toxicity in rats. This study shows that the elevated biochemical markers of kidneys was normalized with the use of aqueous extract at a dose 400mg/kg weight **[95]**. Vinit Movaliya *et al* (2014) has illustrated that alcoholic extract of root of *Aerva javanica* shows nephroprotective action against cisplatin-induced renal toxicity in albino rats. Biomarkers like urea, creatinine and total protein were restored back to their normal levels when treated with alcoholic extract of aervajavanica. Alcoholic extract of aervajavanica at dose 400mg/kg shows nephroprotective action against acute renal injury in rats **[96]**.

- ***Tephrosia purpurea***

Tephrosia purpurea belongs to the family fabaceae not only helpful in treating renal diseases but also known for its wound healing action. It is also used as liver tonic. *Tephrosia purpurea* is used in the treatment of drug induced renal tubular necrosis **[97]**. *Tephrosia purpurea* also possess other biological activities like antiviral, antibacterial, anti-asthmatic, antiulcer and hepatoprotective. The *in vitro* antioxidant activity was done on hydroalcoholic extract of roots of *Tephrosia purpurea* which was studied by the super oxide free radical activity, DPPH (diphenylpicrylhydrazyl) free radical scavenging activity and nitric oxide scavenging activity **[98]**. Avijeetjain *et al* (2009) has illustrated that the *Tephrosia purpurea* has nephroprotective effects on gentamicin model of acute renal failure. *Tephrosia purpurea* at a dose 200mg/kg body weight shows antioxidant activity through Cox-2 expression and inhibition of overproduction of NO. Tephrosiapurpurea shows its renal protective activity without any toxicity **[99]**. Ravuri Halley Gora *et al* (2014) has depicted that *Tephrosia purpurea* helps to ameliorates the arsenic-induced nephro-toxicity in rats. *Tephrosia purpurea* at a dose 500mg/kg helps to reduce blood urea nitrogen and creatinine levels in the kidney **[100]**. Naghma Khan *et al* (2000) has illustrated that the N-diethylnitrosamine and Potassium bromate mediated renal oxidative stress and toxicity can be treatment with the use of Tephrosiapurpurea in wister rats. This study has shown that the N-diethylnitrosamine and Potassium bromate mediated renal oxidative stress and toxicity can be ameliorated when treated with *Tephrosia purpurea* at doses 5mg/kg and 10mg/kg body weight **[101]**.

Table 2: List of herbal plants with their nephroprotective actions against renal failure

Plants	Dose (mg/kg)	Route of Administration	Animal used	Model used/Injury induced by	Observations/ Outcomes	References
Garlic	300	Oral	Male wistar rats	Cisplatin	BUN and Creatinine levels were decreased + increased activity of antioxidants	[102]
Rhubarb	55	Oral	Male albino rats	Adenine	Decreased urea and creatinine + increased calcium levels	[64]
Ginseng	200	Intraperitoneal	Sprague–Dawley rats	Gentamicin sulphate	Reduction in kidney damage, BUN and creatinine	[68]
Ginger	200	Oral	Male albino rats	Alcohol	Activities of renal XOD and GST were restored	[75]
Punicagranatum	200	Oral	Male rats	Adenine	Activity of antioxidant enzymes was elevated + increased urine volume	[80]
Ginkgo biloba	300	Oral	Male wistar rats	Gentamicin	Elevated plasma and kidney tissue MDA were restored	[87]
Nigella Sativa	100	Intraperitoneal	Albino male rats	Gentamicin	Decreased MDA + NO generation	[92]
Aervajavanica	400	Oral	Albino wistar rats	Cisplatin	Decreased urea, creatinine and albumin + recovery in kidney	[95]
Tephrosiapurpurea	500	Oral	Wistar Rats	Arsenic	Decreased Urea and creatinine + reduced lipid peroxidation and glutathione levels	[100]

Note: BUN(Blood urea nitrogen), MDA (Malondialdehyde), XOD (Xanthine oxidase), GST (Glutathione-s-transferase), NO (Nitric oxide)

DISCUSSSION

Kidney plays a vital role in maintaining fluids, electrolytes and acid-base balance. Malignant nephrosclerosis, the ischemic contracted kidney, rapid progressive glomerulonephritis and diabetic nephropathy are some of kidney diseases which may leads to renal failure if not treated on time. Plants and their phytoconstituents helps to fight against various renal diseases. These plants provide nephroprotective action against various drugs and chemicals. They possess their nephroprotective activity due to the presence of sterols, saponins, triterpenes, diterpenoids, monoterpenoids, glycosides, polyphenols, flavonol glycosides, flavonoids, carotenoids and alkaloids. These active constituents have been reported for their significant

nephroprotective activity in animal models. Plants and phytoconstituents like garlic, rhubarb, ginseng, *punica granatum*, ginger, *tephrosia purpurea*, resveratrol, astaxanthin, lycopene, allicin and ascorbic acids have shown their nephroprotective actions when experimented on various animal models. These plants/phytoconstituents may be used in the future for treatment of various kidney disorders.

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