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ETHNO-PHARMACOLOGICAL INVESTIGATION OF SOME PLANTS FOR THE MANAGEMENT OF NEPHROTOXICITY

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Abstract
By 2040, kidney illnesses are anticipated to rank as the sixth greatest cause of mortality. Kidney injury is brought on by a number of physiological failures that are categorized as pre-, intra-, and post-renal causes. Pre-renal factors include things like diabetes, liver disorders, rhabdomyolysis, and intestinal microbiota, whereas post-renal causes include things like lithiasis, or blood clots in the ureters, prostate cancer, urethral blockages, prostate elongation, and urinary tract infections. Drug nephrotoxicity has also been identified as a significant contributor to kidney damage. Because certain medications have negative side effects, it is important to include additional therapy options for these disorders, such as nephroprotective agents. Plants are a rich source of nephroprotective compounds that can help at various stages of the physiological pathways that harm the kidneys. Plants are employed in traditional medicine for a variety of purposes, including as antioxidants, anti-inflammatories, diuretics, and anticancer agents. Scientific evidence is needed to substantiate some plants' nephroprotective properties because the mechanism of action of some of the plants that have been empirically employed is still unknown. The current study includes plants that reduce nephrotoxicity and phytochemicals that have nephroprotective effects.

Keywords: medicinal plant, phytochemicals, kidney disease, nephrotoxicity, nephroprotective.

Introduction

The kidney is the primary organ needed by the human body to achieve and carry out various crucial processes, such as detoxification, extracellular fluid management, homeostasis, and the excretion of harmful compounds. Nephrotoxicity, however, poses a serious threat to the public's health. According to a recent review of data from the US National Health and Nutrition Examination Survey, CKD, which comprises end-stage renal disease and the four phases of renal dysfunction that come before it, affects 19 million Americans. The expected number of people with end-stage renal illness increased globally. Different groups have significantly greater prevalence rates than other (Smith, 1951; Deray *et al*., 1989).

Nephrotoxicity is the term used to describe the harmful effects that chemicals can have on renal function. Examples of these compounds include molds and fungus, cancer treatments like cisplatin, antibiotics like aminoglycosides, metals like mercury, arsenic, and lead, as well as illicit drugs like cocaine. Changes in renal function as measured by the glomerular filtration rate (GFR), blood urea nitrogen (BUN), serum creatinine (sCr), or urine output are one sign of nephrotoxicity; however, nephrotoxicants can cause kidney damage without altering any recognized clinical marker of renal

function. Studies, for instance, have demonstrated that proximal tubule necrosis in male Sprague Dawley rats treated to gentamicin can reach up to 75% before any changes in BUN or sCr. (Perazella, 2009; Zhou et al., 2008).

Kidney damage, AKI, CKD

Even in the absence of initial changes in the GFR, kidney injury is defined as changes in the structure or function of the kidney. The fact that these modifications may eventually result in GFR declines is a key clarification to this definition. Proteinuria is the most noticeable sign of renal injury. AKI or CKD can also develop as a result of kidney injury. However, unlike the mechanisms causing renal cell injury, the mechanisms mediating kidney damage repair are not as well characterized (El Sabbahy and Vaidya, 2011).

In recent years, there have been several definition systems developed, reflecting changes in the definition of renal injury. These include the Risk, Injury, Failure, Loss, and End-Stage Renal Disease (RIFLE) designation and its adjustments (Makris and Spanou, 2016), as well as the Kidney Disease Global Outcomes (KDIGO) definition and staging study. The rate and length of time that kidney function declines differs between AKI and CKD in both of these criteria, with CKD being defined as lasting longer than 3 months based on structural and functional abnormalities (McManus and Wynter-Minott, 2017).

AKI, as opposed to CKD, is characterized by a sudden decrease in renal function and is frequently identified by variations in BUN (azotemia) and/or sCr. Also present will be proteinuria. AKI can persist for hours or weeks. Clinical indicators may recover to baseline levels once AKI resolves, or AKI may deteriorate, culminating in renal impairment and even multi-organ dysfunction. Although some studies employ BUN as an indicator, the assessment of AKI is mostly focused on changes in GFR, which are originally based on changes in sCr levels and urine output. New AKI biomarkers have been identified through extensive research, although it is unknown if a single biomarker could accurately describe AKI brought on by all stressors given that AKI is rarely caused by a single etiology. Even for GFR, this is valid since kidney injury can happen even in the absence of GFR declines (Hultstrom et al., 2018). This information highlights a problem in the industry.

Similar to AKI, CKD can be divided into numerous categories based on the amount of urine produced, the presence or absence of kidney injury, hypertension, and variations in GFR. A number equal to or below 60 ml/min/1.73 m2 for more than three months serves as a typical reference point for GFR for staging CKD. It should be noted that a drop in GFR below this threshold simply indicates CKD and does not reveal whether the kidney damage was caused by nephrotoxic substances, renal disease, or extra-renal events (Barnett and Cummings, 2018).

Mechanism action of drug nephrotoxicity

The majority of medications that have been linked to nephrotoxicity do so through one or more well-known pathogenic pathways. These include rhabdomyolysis, inflammation, crystal nephropathy, and altered intraglomerular hemodynamics.

Glomerular hemodynamics

In healthy adults, the glomerular filtration rate (GFR) is 120 ml per minute. By controlling the blood flow in both the afferent and efferent arteries, the kidneys are able to maintain a steady filtration rate and the rate of urine output. This mechanism is driven by intraglomerular pressure, which is influenced by blood flow rate. Anti-prostaglandin medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs), medications with anti-angiotensin activity, such as angiotensin-converting enzyme inhibitors (ACEIs), or medications with angiotensin receptor blockers (ARBs), can cause nephrotoxicity in the glomerulus because prostaglandins and angiotensins are used to expand the afferent arteries (Blantz and Gabbai, 1989; Hostetter *et al*., 1981).

Tubular cell toxicity

Nephrotoxin, a toxin, is present in tubular cells. As medications are concentrated and reabsorbted through the glomerulus, they come into touch with renal tubules, particularly the proximal tubule cells, making them vulnerable to drug toxicity. Cytotoxicity is caused by damaged mitochondria in tubular cells, a dysfunctional tubular transport mechanism, and an increase in oxidative stress from the generation of free radicals. Antibiotics known to cause cytotoxicity include aminoglycosides, as well as antifungal, anti-retroviral, and anti-cancer medications (Baines and Brunskill, 2011).

Crystal nephropathy

Drugs and their metabolites can cause crystals, which can lead to renal function degradation. The production of the insoluble crystals is influenced by the urine's acidity. Antibiotics and antiviral medications can result in the formation of crystals (Yarlagadda and Perazella, 2008).

Rhabdomyolysis

The process through which muscle fiber contents are released into the circulation as a result of the breakdown of muscular tissue. This results in the breakdown of renal muscle cells, releasing myoglobin and serum creatine kinase into the blood. Myoglobin that has been released impairs kidney filtration, leading to acute tubular necrosis or renal failure. Typically, drug abuse, including that of heroin, methamphetamine, methadone, and alcohol, results in rhabdomyolysis (Sauret *et al*., 2002).

Inflammation

Nephrotoxins are capable of inducing inflammation. The tissue of the kidneys becomes fiberized as a result. As a result, both acute and chronic interstitial nephritis and glomerulonephritis are brought on. Nephrons, the functioning units of the kidneys, become inflamed when a person has nephritis. Antibiotics and NSAIDs both cause acute interstitial nephritis. The long-term use of several anti-cancer medications, analgesics, and calcineurin inhibitors is linked to chronic interstitial nephritis (Krane and Wanner, 2011).

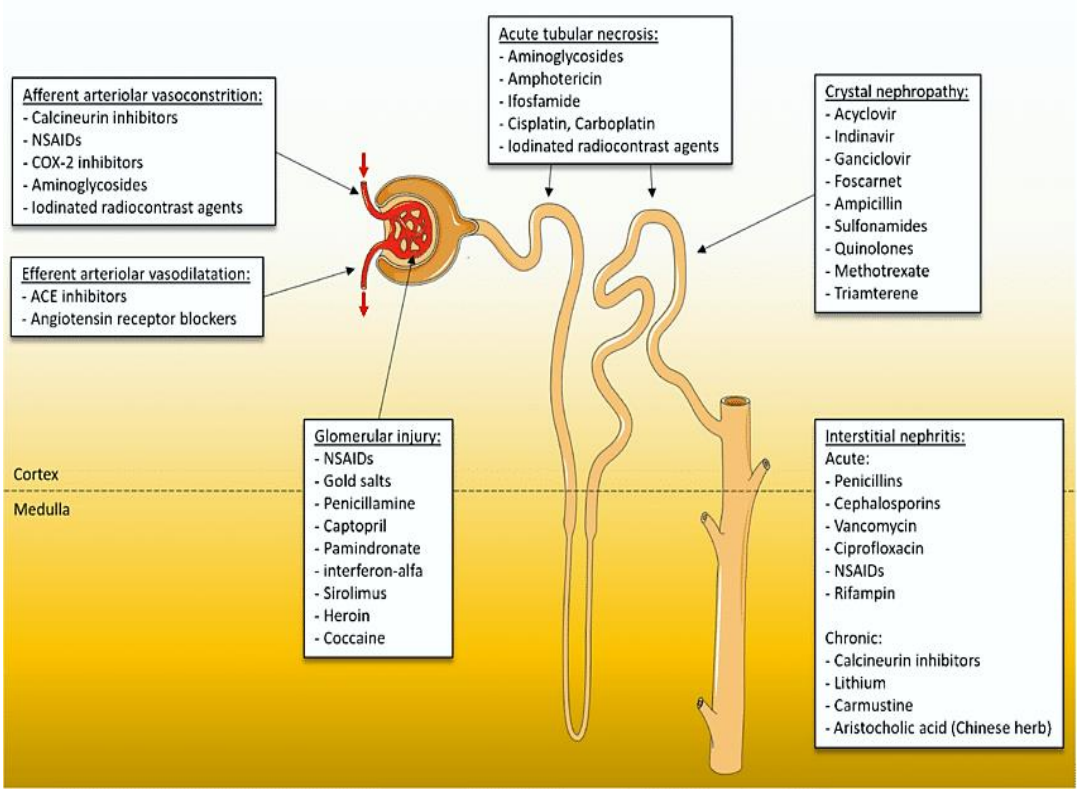

Figure: Drugs responsible for different type of nephrotoxicity

Diagnosis of nephrotoxicity

The primary measure in this condition is stopping and ceasing the offending medications because the majority of renal dysfunctions brought on by nephrotoxic medicines are reversible. Despite the fact that most nephrotoxic substances increase blood urea and serum creatinine, trimethoprim and cimetidine may cause an increase in serum creatinine prior to the onset of nephrotoxic effects because they compete with creatinine for secretion from the renal tubules. Since serum creatinine is unaffected by food, it is a more accurate marker of renal function than blood urea. Therefore, a 50% increase in creatinine or a rise of more than 2 mg/dL above baseline is considered an early indicator of acute renal failure. Additionally, a review of the patient's entire prescription regimen is necessary to determine the offending nephrotoxic substance (Elsby *et al*., 2017).

Biomarkers used for detecting nephrotoxicity

Biomolecules that indicate a connection between a chemical and a disease are known as biomarkers. They often allow for the early diagnosis of health problems brought on by exposure to exogenous toxins. They also offer a foundation for comprehending the onset's mechanics. The discovery of biomarkers has advanced significantly. Novel nephrotoxicity biomarkers include:

- Alanine aminopeptidase (AAP)
- N-acetyl-glucosaminidase (NAG)
- Gamma-glutamyl transpeptidase (GGT)
- Kidney injury molecule 1 (KIM-1)
- Lactate dehydrogenase (LDH)
- Glutathione-s-transferase (GST)
- (Boudonck *et al*., 2009).

Medicinal plants as an alternative approach to treat nephrotoxicity

The use of plants and their extracts as wholesome substitutes in food supplements, herbal medications, natural health products, phytomedicine, or nutritional supplements has increased during the past 20 years. It is now widely accepted that plants and the phytochemicals they contain have unique therapeutic effects for various medical conditions, working, among other things, as antioxidants, antimicrobials, anti-inflammatories, diuretics, and anticancer agents. A plant-based diet has shown to be beneficial for renal pathophysiology, especially in a patient with mild proteinuria and diabetic nephropathy. Similar to how herbal treatments lessen the need for dialysis by treating the root causes of renal failure, improving its symptoms, and reducing its adverse effects. Therefore, the present method of using plants as a complementary therapy has a twofold benefit because they aid in the battle against the illness and also function as nephroprotective agents (McGraw *et al*., 2016; Moorthi, *et al*., 2017).

Some important nephro-protective plant

***Eurycoma longifolia*:**

Long-leaved Eurycoma The herbal remedy "Jack" is sometimes referred to as "Tongkat Ali" in popular culture. belongs to the Simaroubaceae family. In experimental mice, the herbal extract Eurycoma longifolia (EL) exhibits nephroprotective efficacy against paracetamol-induced nephrotoxicity. Serum creatinine, BUN, total protein, albumin, and creatinine clearance were all tested on the fifteenth day. There has been histopathological investigation of all groups. Due to nephrotoxicity, there was a significant (p0.05) increase in blood urea and serum creatinine levels in the paracetamol alone group compared to the therapy groups. The biochemical profiles of the serum and urine as well as the kidney's histological analyses show that EL extract has nephroprotective potential against paracetamol-induced nephrotoxicity. (Chinnappan *et al*., 2019).

***Sphaeranthus amaranthoides*:**

The procumbent herb *Sphaeranthus amaranthoides*, also known as sivakaranthai, is a member of the Asteraseae family. Acute kidney injury (AKI) can be effectively treated with the aqueous extract of

Sphaeranthus amaranthoides burm f., which also prevents kidney damage from gentamicin-induced nephrotoxicity. Animals pre-treated with varying concentrations of Sphaeranthus amaranthoides exhibit normal levels of LDH, GGT, creatinine, BUN, and electrolytes in both serum and urine; however, higher levels of these parameters were seen in the gentamicin-treated group (Rethinam *et al*., 2021).

Plectranthus amboinicus:

Popular medical plant *Plectranthus amboinicus* is a member of the Lamiaceae family. a medicinal plant that may be found all over India and is used as traditional medicine to treat epilepsy, bronchitis, and the flu. The aqueous leaf extract of *P. amboinicus* exhibits notable nephroprotective effect against acute nephrotoxicity brought on by Adriamycin. The increased levels of blood creatinine concentration in the extract-treated group are significantly reduced when compared to the nephrotoxic control group after co-administration of the aqueous leaf extract of *P. ambonicus* at a dose of 400 mg/kg. When compared to the ADR-induced control group, the group treated with plant extract exhibits less acute tubular necrosis according to histopathological study of kidney tissues (Amarasiri *et al*., 2018).

Alstonia scholaris

Alstonia Scholar Linn, commonly known as the devil's tree or dita bark, is a member of the Apocynaceae family. *Alstonia scholaris* extract in dichloromethane demonstrates At doses of 200 and 400 mg/kg, gentamycin (80 mg/kg)-induced experimental rats exhibited nephroprotective action. Animals treated with extract of Alstonia scholaris linn show a significant reduction in serum and urine urea, uric acid, and creatinine due to the presence of terpenoids, alkaloids, or flavonoids in the herb. However, animals treated with gentamycin are at risk for severe nephrotoxic because of high levels of serum urea, creatinine, uric acid, total protein, and urine urea, uric acid, and creatinine (Kanase and Mane, 2018).

***Tamarindus indica* Linn:**

The Fabaceae family, which includes the important medicine *tamarindus indica*, is primarily found in tropical regions. Drug used in the unani system; works well as an antiseptic, stomachic, laxative, and heart tonic in addition to treating dysentery.The fruit pulp of *Tamarindus indica* Linn has an ethanolic extract that exhibits nephroprotective efficacy against cisplatin-induced nephrotoxicity in experimental mice. Histopathological studies also show reversal of kidney damage and restoration of the normal kidney structure, which supports its Nephroprotective activity because of the presence of flavonoids. The evaluation of renal parameters on nephrotoxic rats with EETI showed significantly elevated the attenuated body weight, urine volume, creatinine clearance, and significant reduction in elevated serum creatinine level (Balakrishna *et al*., 2020).

Combretum micranthum

The Combretaceae family includes the medicinal herb *Combretum micranthum*. Human embryonic kidney cells (HEK-293) used as an in vitro model for diabetic nephropathy were reported to be sensitive to glucose nephrotoxicity. According to the final findings, kidney cells exposed to high glucose (100 mM) for a period of 72 h had significantly less viability, which led to morphological changes like cell shrinkage, rounded cell shape, and cytoplasmic vacuolation. Cell viability was significantly increased when treated with CM extract at 10 and 25 g/mL compared to the high glucose control, going from 10 to 23%. Therefore, research suggests that *C. micranthum* may have nephroprotective effects (Kpemissi *et al*., 2019).

Descurania sophia

Descurania sophia is a dicot annual weed that is a member of the Brassiaceae family, which includes the cruciferae. It is a type of conventional Chinese medicine that treats a variety of illnesses. Due to its abundance in phytoconstituents, the seeds of this plant are used to relieve cough,

asthma, reduce edema, improve urine production (diuresis), and have other pharmacological advantages. *Descurania sophia* hydroalcoholic extract exhibits a protective effect against gentamicin-induced nephrotoxicity in test animals. Consequently, a significant and dose-dependent decrease in serum levels of BUN, creatinine, cholesterol, triglycerides, sodium excretion, and the rate of cell death (apoptosis) was found (Askari *et al*., 2021).

Miscellaneous Phytoconstituents for Nephroprotective Activity

Lycopene

Lycopene is a vivid red carotene and carotenoid pigment that derives from the Neo-Latin word lycopersicum, which refers to the tomato species. According to a preliminary study, eating tomato paste for three months reduces sunburn caused by ultraviolet light by 30 minutes due to lycopene. Research on lycopene has revealed that it also has nephroprotective properties (Atessahin *et al*., 2005).

Caffeic acid phenylethyl ester

Propolis from bee hives contains a potent chemical molecule called caffeic acid phenylethyl compound. It is well known for having immunomodulatory, antimitogenic, and anticarcinogenic characteristics. It prevents nuclear transcription factor (NF-B) activity in a powerful and targeted manner. Recent research has shown that it also has nephroprotective properties (Murtaza *et al*., 2014).

Xanthorrhizol

Curcuma xanthorhiza may contain a sesquiterpenoid chemical called xanthorrhizol. It has unquestionably been discovered to have antibacterial, anticancer, and anti-inflammatory effects in the past. Additionally, postpartum uterine hemorrhage caused by inflammation has been treated with the stem. Recent investigations have also demonstrated that it has nephroprotective properties (Ali and Al Moundhri, 2006).

DL-α- Lipoic acid

Octanoic acid is the source of the associated organosulfur molecule known as lipoic acid (LA). The majority of foods contain lipoic acid, with traces also present in kidney, heart, liver, spinach, broccoli, and yeast extract. In clinical trials, lipoic acid is used to speed up the healing of chronic wounds, lower levels of asymmetric dimethylarginine (ADMA) in diabetic patients with end-stage urologic disease receiving hemodialysis, and stop or slow the progression of Alzheimer's disease (Holmquist et al., 2007). According to studies, DL-- Lipoic Acid also has nephroprotective properties (Sundararajan *et al*., 2014).

Ascorbic acid (Vitamin C)

Because vitamin C is a vitamin, the body cannot keep it. Foods including citrus fruits, broccoli, and tomatoes contain it. It is an inhibitor that reduces some of the damage done to deoxyribonucleic acid by free radicals, which are harmful molecules. Free radical accumulation over time may speed up the aging process and lead to the emergence of diseases like cancer, heart disease, and inflammatory illness. Research has shown that ascorbic acid also exhibits nephroprotective properties (Saleem *et al*., 2012).

Pyridoxamine

The B-complex vitamin family, which includes pyridoxamine and B-complex vitamins, includes the vitamin pyridoxamine. Through the B-complex vitamin salvage pathway, pyridoxamine is converted to the physiologically active form of B-complex vitamin, B-complex vitamin 5-phosphate. According to alternative diagnosis research, pyridoxamine is also useful in treating kidney stone disease, diabetic retinopathy, and diabetic neuropathy. Pyridoxamine has nephroprotective effect, according to studies (Srivastava *et al*., 2020).

Lupeol

The main component of eatable fruits and vegetables is lupeol, a triterpene. Lupeol has been discovered to have a wide range of medicinal characteristics, including those for treating cancer, diabetes, renal disease, liver toxicity, arthritis, diabetes, inflammation, and other health issues. Research has shown that lupeol exhibits nephroprotective properties (Nagraj *et al*., 2000).

Phytoconstituents from medicinal plants for nephroprotective activity

Name of plants	Major constituent	Specific constituents	Ref
Aerva lanata	Flavonol glycoside	Kaempferol-3- rhamnoside & kaempferol- 3-rhamnogalactoside	(Shirwaikar *et al*., 2004)
Camellia sinensis	Flavonoids	Epicatechin, epicatechingallate, epigallocatechin, epigallocatechingallate	(Bhattacharya *et al*., 2013)
Crocus sativus	Carotenoid	crosin	(Naghizadeh *et al*., 2010)
Nigella sativa	Benzoquinones	Thymoquinone	(Aftab *et al*., 2013)
Phoenix dactylifera L.	Flavonoids	Quercetin	(Abdel *et al*., 2009)
Ramulus mori	Flavonoids, flavonol, Diglucoside	Rutin, quercetin, morin, mulberroside A	(Zhu *et al*., 2004)
Satureja khuzestanica	Monoterpenoid	Carvacrol	(Tavafi *et al*., 2011)
Solanum xanthocarpum	Glycoalkaloid	Solasodine	(Patel *et al*., 2012)
Zingiber officinale	Catechols	Gingerols	(Ajith *et al*., 2008)
Andrographis paniculata	Diterpenoid	Andrographidoids	(Rao, 2006)
Berberis vulgaris	Alkaloids	Berberine	(Jyothilakshmi *et al*., 2013)
Cassia auriculata	Flavonoids	Quercetin & Rutin	(Annie *et al*., 2005)
Curcuma longa	Terpenoid	Curcumin	(Venkatesan *et al*., 2000)
Panax ginseng	Steroid glycosides, triterpenesaponins	Ginsenosides Rh4 & Rh3	(Kiefer and Pantuso, 2003)
Picrorhiza kurroa	Glycosides	Picroside I and Kutkoside	(Yadav & Khandelwal, 2009)
Polyporus umbellatus	Alkaloids	Ergone	(Zhao, 2013)

Conclusion

From this study, it is obvious that the active components of several herbal plants protect against nephrotoxicity brought on by a variety of agents (drugs, chemicals, etc.).The nephroprotective activity is most likely caused by the presence of a variety of active ingredients, including alkaloids, benzoquinones, catechols, carotenoids, flavonoids, glycosides, flavonol glycosides, steroid glycosides, glycoalkaloids, terpenoids, monoterpenoids, diterpenoids, triterpene saponins, sterols, and polyphenols in a select few herbal plants. The findings of this study suggest that some medicinal plants' leaves and other parts may be used to treat renal injury.

References

1. Smith HW. The kidney: structure and function in health and disease. Oxford University Press, USA; 1951
2. Deray G, Martinez F, Katlama C, Levaltier B, Beaufils H, Danis M, Rozenheim M, Baumelou A, Dohin E, Gentilini M, Jacobs C. Foscarnet nephrotoxicity: mechanism, incidence and prevention. American journal of nephrology. 1989 Oct 28;9(4):316-21.
3. Perazella MA. Renal vulnerability to drug toxicity. Clinical Journal of the American Society of Nephrology. 2009 Jul 1;4(7):1275-83.
4. Zhou Y, Vaidya VS, Brown RP, Zhang J, Rosenzweig BA, Thompson KL, Miller TJ, Bonventre JV, Goering PL. Comparison of kidney injury molecule-1 and other nephrotoxicity biomarkers in urine and kidney following acute exposure to gentamicin, mercury, and chromium. Toxicological sciences. 2008 Jan 1;101(1):159-70.
5. Sabbahy ME, Vaidya VS. Ischemic kidney injury and mechanisms of tissue repair. Wiley Interdisciplinary Reviews: Systems Biology and Medicine. 2011 Sep;3(5):606-18.
6. Makris K, Spanou L. Acute kidney injury: definition, pathophysiology and clinical phenotypes. The clinical biochemist reviews. 2016 May;37(2):85.
7. McManus MS, Wynter-Minott S. Guidelines for chronic kidney disease: Defining, staging, and managing in primary care. The journal for Nurse practitioners. 2017 Jun 1;13(6):400-10.
8. Hultstrom M, Becirovic-Agic M, Jönsson S. Comparison of acute kidney injury of different etiology reveals in-common mechanisms of tissue damage. Physiological genomics. 2018 Mar 1;50(3):127-41.
9. Barnett LM, Cummings BS. Nephrotoxicity and renal pathophysiology: a contemporary perspective. Toxicological Sciences. 2018 Aug 1;164(2):379-90.
10. Blantz RC, Gabbai FB. Glomerular hemodynamics in pathophysiologic conditions. American Journal of Hypertension. 1989 Nov 1;2(11_Pt_2):208S-12S.
11. Hostetter TH, Troy JL, Brenner BM. Glomerular hemodynamics in experimental diabetes mellitus. Kidney international. 1981 Mar 1;19(3):410-5.
12. Baines RJ, Brunskill NJ. Tubular toxicity of proteinuria. Nature Reviews Nephrology. 2011 Mar;7(3):177-80.
13. Yarlagadda SG, Perazella MA. Drug-induced crystal nephropathy: an update. Expert opinion on drug safety. 2008 Mar 1;7(2):147-58.
14. Sauret JM, Marinides G, Wang GK. Rhabdomyolysis. American family physician. 2002 Mar 1;65(5):907-13.
15. Krane V, Wanner C. Statins, inflammation and kidney disease. Nature Reviews Nephrology. 2011 Jul;7(7):385-97.
16. Elsby R, Chidlaw S, Outteridge S, Pickering S, Radcliffe A, Sullivan R, et al. Mechanistic *in vitro* studies confirm that inhibition of the renal apical efflux transporter multidrug and toxin extrusion (MATE) 1, and not altered absorption, underlies the increased metformin exposure observed in clinical interactions with cimetidine, trimethoprim or pyrimethamine. *Pharmacol Res Perspect.* 2017;5:1–13.
17. Boudonck KJ, Mitchell MW, Német L, Keresztes L, Nyska A, Shinar D, Rosenstock M. Discovery of metabolomics biomarkers for early detection of nephrotoxicity. Toxicologic pathology. 2009 Apr;37(3):280-92.
18. McGraw, N.J.; Krul, E.S.; Grunz-Borgmann, E.; Parrish, A.R. Soy-based renoprotection. *World J. Nephrol.* **2016**, *5*, 233–257.
19. Moorthi, R.N.; Vorland, C.J.; Gallant, K.M.H. Diet and Diabetic Kidney Disease: Plant Versus Animal Protein. *Curr. Diabetes Rep.* **2017**, *17*, 15.
20. Chinnappan SM, George A, Thaggikuppe P, et al. Nephroprotective effect of herbal extract Eurycoma longifolia on paracetamol-induced nephrotoxicity in rats. Evidence-Based Complementary and Alternative Medicine. 2019:1-6.

21. Rethinam G, Duraiswamy A, Reddy GD, Elankani P, Srinivasan SK. Nephroprotective effect of Sphaeranthus amaranthoides Burm f.: Sivakaranthai (a Siddha Kayakalpa drug) against gentamicin induced nephrotoxicity. Advances in Traditional Medicine. 2021; 20:1-10.
22. Amarasiri AM, Attanayake AP, Jayatilaka KA, Mudduwa LK. Acute nephroprotective and antioxidant activities of aqueous leaf extract of Plectranthus amboinicus (Roxb.) grown in Sri Lanka. J. Pharmacogn. Phytochem. 2018;7(4):155-61.
23. Kanase V, Mane DJ. A pharmacognostic and pharmacological review on Alstonia scholaris. Asian J Pharm Clin Res. 2018;11(12):22-6.
24. Balakrishna V, Kumar DS, Lakshmi T. Tamarindus indica L.(Fabaceae): Extent of explored use in traditional medicine. Asian J Pharm Clin Res. 2020; 13:28-32.
25. Kpemissi M, Eklu-Gadegbeku K, Veerapur VP, *et al*. Antioxidant and nephroprotection activities of Combretum micranthum: A phytochemical, in-vitro and ex-vivo studies. Heliyon. 2019 ;5(3):1-35.
26. Askari H, Enayati N, Ahmadian-Attari MM, Bakhtiyari M, Alirezaei A. Protective Effects of Descurainia sophia against Gentamicin Induced Nephrotoxicity in Rats. Iranian Journal of Pharmaceutical Research. 2021;20(1):40-52.
27. Atessahin A, Yilmaz S, Karahan I, Ceribasi AO, Karaoglu A. Effects of lycopene against cisplatin-induced nephrotoxicity and oxidative stress in rats. Toxicology. 2005 Sep 1;212(2-3):116-23.
28. Murtaza G, Karim S, Akram MR, Khan SA, Azhar S, Mumtaz A, Bin Asad MH. Caffeic acid phenethyl ester and therapeutic potentials. BioMed Research International. 2014 May 29;2014.
29. Ali BH, Al Moundhri MS. Agents ameliorating or augmenting the nephrotoxicity of cisplatin and other platinum compounds: a review of some recent research. Food and chemical toxicology. 2006 Aug 1;44(8):1173-83.
30. Sundararajan R, Bharampuram A, Koduru R. A review on phytoconstituents for nephroprotective activity. Pharmacophore. 2014 Jan 1;5(1):160-82.
31. Saleem U, Ahmad B, Rehman K, Mahmood S, Alam M, Erum A. Nephro-protective effect of vitamin C and Nigella sativa oil on gentamicin associated nephrotoxicity in rabbits. Pakistan journal of pharmaceutical sciences. 2012 Oct 1;25(4).
32. Srivastava AK, Kaushik D, Lal VK, Behera BR. Chapter-2 Prospectives of Indian Nephroprotective Medicinal Plants. Chief Editor. 2020:15.
33. Nagaraj M, Sunitha S, Varalakshmi P. Effect of lupeol, a pentacyclic triterpene, on the lipid peroxidation and antioxidant status in rat kidney after chronic cadmium exposure. Journal of applied toxicology: an international journal. 2000 Sep;20(5):413-7.
34. Shirwaikar, A; Issac, D; Malini, S (2004), "Effect of Aerva lanata on cisplatin and gentamicin models of acute renal failure", Journal of Ethnopharmacology, 90 (1), 81– 86
35. Bhattacharya S, Gachhui R, Sil PC. Effect of Kombucha, a fermented black tea in attenuating oxidative stress mediated tissue damage in alloxan induced diabetic rats. Food and chemical toxicology. 2013 Oct 1;60:328-40.
36. Naghizadeh B, Mansouri SM, Mashhadian NV. Crocin attenuates cisplatin-induced renal oxidative stress in rats. Food and chemical toxicology. 2010 Oct 1;48(10):2650-5.
37. Ahmad A, Husain A, Mujeeb M, Khan SA, Najmi AK, Siddique NA, Damanhouri ZA, Anwar F. A review on therapeutic potential of Nigella sativa: A miracle herb. Asian Pacific journal of tropical biomedicine. 2013 May 1;3(5):337-52.
38. Abdel-Raheem IT, Abdel-Ghany AA, Mohamed GA. Protective effect of quercetin against gentamicin-induced nephrotoxicity in rats. Biological and Pharmaceutical Bulletin. 2009 Jan 1;32(1):61-7.
39. Zhu JX, Wang Y, Kong LD, Yang C, Zhang X. Effects of Biota orientalis extract and its flavonoid constituents, quercetin and rutin on serum uric acid levels in oxonate-induced mice and xanthine dehydrogenase and xanthine oxidase activities in mouse liver. Journal of ethnopharmacology. 2004 Jul 1;93(1):133-40.

40. Tavafi M, Ahmadvand H, Tamjidipoor A, Delfan B, Khalatbari AR. Satureja khozestanica essential oil ameliorates progression of diabetic nephropathy in uninephrectomized diabetic rats. Tissue and Cell. 2011 Feb 1;43(1):45-51.
41. Patel PK, Patel MA, Vyas BA, Shah DR, Gandhi TR. Antiurolithiatic activity of saponin rich fraction from the fruits of Solanum xanthocarpum Schrad. & Wendl.(Solanaceae) against ethylene glycol induced urolithiasis in rats. Journal of ethnopharmacology. 2012 Oct 31;144(1):160-70.
42. Ajith TA, Aswathy MS, Hema U. Protective effect of Zingiber officinale roscoe against anticancer drug doxorubicin-induced acute nephrotoxicity. Food and chemical toxicology. 2008 Sep 1;46(9):3178-81.
43. Rao, NK, "Anti-hyperglycemic and renal protective activities of Andrographis paniculata roots chloroform extract", Iran Journal of Pharmacology and Therapeutics. 2006, 5, 47–50.
44. Jyothilakshmi V, Thellamudhu G, Kumar A, Khurana A, Nayak D, Kalaiselvi P. Preliminary investigation on ultra high diluted B. vulgaris in experimental urolithiasis. Homeopathy. 2013 Jul;102(03):172-8.
45. Annie S, Rajagopal PL, Malini S. Effect of Cassia auriculata Linn. root extract on cisplatin and gentamicin-induced renal injury. Phytomedicine. 2005 Aug 2;12(8):555-60.
46. Venkatesan N, Punithavathi D, Arumugam V. Curcumin prevents adriamycin nephrotoxicity in rats. British journal of pharmacology. 2000 Jan;129(2):231-4.
47. Yadav N, Khandelwal S. Therapeutic efficacy of Picroliv in chronic cadmium toxicity. Food and chemical toxicology. 2009 Apr 1;47(4):871-9.
48. Zhao YY. Traditional uses, phytochemistry, pharmacology, pharmacokinetics and quality control of Polyporus umbellatus (Pers.) Fries: a review. Journal of ethnopharmacology. 2013 Aug 26;149(1):35-48.
49. Kiefer D, Pantuso T. Panax ginseng. American family physician. 2003 Oct 15;68(8):1539-42.