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A Study on Nephrotoxicity of Nephron Protective Activity of Selective Plant Extracts

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Abstract – Nephrotoxicity is defining as rapid deterioration in the kidney function due to toxic effect of medications and chemicals. The treatment comes in a variety of ways, and certain medications might have several effects on renal function. Nephrotoxins are poisonous chemicals that have a negative impact on kidney function. The pharmacological therapy of the disease has been carried out using herbs for a considerable period. Plants have from the beginning of time been utilized as medicine. The Rig-veda allusions to the therapeutic qualities of certain herbs seem to be the oldest records of plant usage in medicine in India. Herbal medications were the earliest medicines for humanity, and they continue to play an important part in medicine and the study which discussed about different types of nephrotoxicity, Collection and authentication of the drug samples, Pharmacognostical evaluation of the drugs, Pharmacological evaluation of selected drugs.

Keyword – Nephrotoxicity, Drugs

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INTRODUCTION

The term "Nephrotoxicity" refers to kidney damage caused by medicines, toxic substances, or industrial or environmental toxins and pollutants. Nephrotoxicity is a kidney-specific condition in which excretion is disrupted by harmful substances or medicines. Drugs cause around 20% of Nephrotoxicity, but as the average life duration rises, so does the incidence of Nephrotoxicity in the elderly. The induction of renal failure is known to be caused by radio contrasting substances; cyclosporine, aminoglycoside (gentamicin); anticancer medications; and chemical compositions such As ethylene glycol; carbon tetrachloride; sodium oxalates; acetaminophen; heavy metals; pesticides.

With the development of civilization, people are becoming increasingly aware of the therapeutic qualities of herbal drugs and their products. Approximately 80% of the global population use herbal medication for their everyday routine, according to the World Health Organization. They must develop exceptional behaviour in relation to herbal medicines in order to maintain excellent health. Herbs and botanicals are becoming more important for human safety and health. Herbal medicines have a superior rationale and are recommended as a standard precaution for the treatment of specific illnesses. Diuretics are a kind of drug that works by increasing the volume of urine produced by the body and the amount of salt in the urine. Hypertension causes a number of heart problems, including stroke, coronary heart disease, peripheral artery disease, heart failure, and renal end-state disease. Inhibitors, beta blockers, calcium canal (or CCB) blockers, and diuretics of angiotensin-converting enzymes are all popular ways of lowering blood pressure. Most of these drugs reduce vascular resistance and decrease heart output. Actually, ACE inhibitors block angiotensin-I to angiotensin-II which reduces the constricting effect of angiotensin-arterial II, Beta receptors blocking the vascular and cardiac systems by inhibiting the stimulating characteristics of noradrenergic receptors. [1]

The severe fibrotic lesions that are affected by the harshness are related to end-stage renal illness (ESRD). Dietetic protein control, blood pressure management, and ACEIs are all used in the therapy of renal disease today (angiotensin-converting enzyme inhibitors). Renal fibrosis and chronic renal failure (CRF) are two of the most prevalent health issues in people throughout the globe. Diabetic nephropathy (28 percent), chronic glomerulonephritis (24 percent), chronic tubule interstitial nephritis (22 percent), obstructive uropathy (7.5 percent), diabetes mellitus, hypertension, and polycystic kidney disease are the main causes of CRF in India (4 percent). Kidney disease is the ninth largest cause of mortality in the United States, with about 19 million

people diagnosed with CRF each year. Diuretics are medicines that work in the kidneys and encourage fluid out of their bodies and at the same time cause salt loss. [2] This is accomplished by invasive substances via the reabsorption of water and ions by the walls of the renal tubules. Herbs and botanicals have risen to the top of the list of health benefits, attracting increasing attention. To back this up, an increasing number of studies has been published suggesting that plants and their products may act as mild diuretic agents.

DIFFERENT TYPES OF NEPHROTOXICITY

- **Aminoglycoside Nephrotoxicity**

Aminoglycosides damage the proximal tubular cells preferentially. These agents are readily filtered by glomeruli and taken up rapidly by the proximal tubular epithel cells, where, following interactions with phospholipids on the brush border membranes, they are absorbed into lysosoms. By changing phospholipids metabolism, they have their primary harmful impact on the tubular cell. Aminoglycosides induce renal vasoconstriction, as well as their direct impact on cells. Dosage and duration of treatment are important variables in the development of AKI due to aminoglycoside nephrotoxicity. Taking the tubules with aminoglycosides is a saturable wonder, and after a single measurement, the taking is limited. [3] Therefore, an enormous measurement of over three doses each day is desired every day. A measurement every day is probably less likely to cause the cells to pile up after the point of immersion is achieved

- **Amphotericin B Nephrotoxicity**

In cell films, Amphotericin B links with sterols and therefore increases the penetration level of pores. This is the evidence for its nephrotoxicity, and it links with ergosterol in infectious cell dividers as well as cholesterol inside human cell films. Trademark modifications in electrolytes from the standard include wasting of the subsidiary potassium and magnesium in order to increase phone layer penetration. The hydrogen particle reverse rupture in the collection conduit leads to distal renal tubular acidosis (dRTA). [4] Lipid-based amphotericin B formulations decline in comparison to conventional Amphotericin B, but do not eradicate nephrotoxicity. This may be because the usual preparation has a direct nephrotoxic impact.

- **Contrast-Induced Nephropathy**

Even if it is still not fully understood that the pathology of contrast-induced nephropathy (CIN) is the result of renal vasoconstriction and the direct quality of toxic tubular renal epithel cells. Current CIN hazard theories include a combination of direct cytotoxicity with a harmful post-chemical reperfusion leading to radical oxygen-free generation leading to endothelial damage. Nephrotoxicity Calcineurin Inhibitor Active kidney damage is caused by cyclosporine and tacrolimus, due to the initiation of addictive and effective arteriolar vasoconstriction. Interstitial fibrosis may be damaged steadily. Tacrolimus has been shown to cause endothelial damage thrombotic microangiopathy.

- **Cisplatin Nephrotoxicity**

Cisplatin affects proximal tubules most of the time, with certain glomeruli and distal tubules being influenced optionally. Cisplatin has been released into the urine and produces extracted amounts of medicine that energetically disperse and dynamically absorb the phones. Cisplatin Cisplatin is constant in the circulatory system but in a chloride-poor cell state it is hydrolyzed. The metabolite hydrolysed links DNA, RNA, proteins and phospholipids to produce cytotoxicity it produces.[5]

- **Ifosfamide Nephrotoxicity**

The known cyclophosphamide simple is ifosfamide. Although cyclophosphamide is not nephrotoxic, ifosfamide is damaging to the tubular cells via its metabolite chloroacetaldehyde, and the proximal tubular association leads to Fanconi disease.

- **Foscarnet Nephrotoxicity**

Intensive interstitial nephritis and intratubular, precious stone arrangement are caused by foscarnet which is used to treat safe cytomegalovirus disease (SCD). This may include calcium salt, or sodium salt, despite the precious stone arrangement, calcium chelation by foscarnet leads to hypocalcemia.

- **Crystal-Forming Drug Nephrotoxicity**

Sulfa, acyclovir, methotrexate, ethylene glycol, and protease inhibitors such as indinavir, induce acute kidney damage (AKI) due to the precious tubular cell stone growth. Intratubular valuable stones may grow quickly and can appear as birefringent needle-molded jewels, which can lead to severe interstitial nephritis. [6]

- **Rhabdomyolysis**

Rhabdomyolysis is about skeletal muscle strands that are broken, causing the intracellular material to come into the course of potentially nephrotoxicity. The accompanying 3 devices cause acute kidney damage (AKI) in this environment: a. renal vasoconstriction b. Heme-interceded proximal tubular cell toxicity c. Intratubular cast arrangement

LITERATURE REVIEW

Shamna (2018) a kidney is especially prone to nephrotoxin activity since it gets 25% of the heart rate. Nephrotoxins may release toxic components and cause harm in the presence of metabolic activities in kidney tube cells. A simple blood test may be used to detect nephrotoxicity. The blood assessment comprises blood urea nitrogen (BUN) measures, serum creatinine concentration and glomerular filtration rate as well as creatinine clearance. The majority of renal illnesses stay undetected until they develop into phases where the standard treatment procedures are not adequate to fully heal them. In this research, biomarkers which are more sensitive than the known indicators and are more suggestive of pre-renal impairment were identified. The research also focuses on the identification of biomarkers that may show the nature of the relevant processes. The sensitivity and selectivity needed for nephrotoxicity to be determined at the early stage of nephrotoxicity tests such as measuring the blood creatinine or BUN levels is not present. Recent biomarkers reported in this study may offer valuable information for the earlier and more selective diagnosis of nephrotoxicity.

Azade sari (2019) Study on the nephrotoxic effects of the medication has been performed. Drugs may lead to mild to severe nephrotoxin issues, resulting in immediate or chronic renal impairment, depending on the outcomes. Many medications with prescription and non-prescription may harm the kidneys. A few fundamental properties should be taken into consideration before beginning therapy, such as medical history, age and weight, pharmacological risk and nephrotoxicity combinations. Biomarkers must be closely monitored and often utilized if nephrotoxic medications are necessary. Before therapy, basic kidney functions should be assessed. As many patients recover when the therapy stops, early diagnosis and implementation of adequate treatment methods are important for drug-induced nephropathies.

Md. Anzar Alam (2016) As one of the body's most essential organs, the kidneys play several responsibilities in keeping everything running as it should. Urine production, water and salt balance, and hormone release are some of its most important functions. NSAIDS, antibiotics, and anti-tubercular medications can all harm kidneys if used in excess. Renal failure is a condition in which the body's ability to process metabolic products decreases. Dialysis, kidney transplantation, or chemotherapy are the primary treatment options now available. This kind of treatment is quite pricey, therefore it is out of reach for most people. When it comes to finding a cure, there are several unorthodox medicines described in the Unani literature of Mawalide Salasa, such as those derived from natural sources like plants, minerals, and animals, all with minimal side effects and easy access. This study aimed to shed light on the function of the Unani Medicine medication repertory used to treat amraze kuliya/zofe kuliya, which has been clinically proven to be effective in the treatment of renal diseases.

Lillie MA, et al. (2018) a recent review was given on nephrotoxicity and renal pathogenesis. The present situation of nephrotoxicity research is addressed by this review. It underlines that our understanding of nephrotoxicity must be combined with renal failure induced by pathology. Such methods are required to address significant issues such as acute and chronic renal illness diagnosis, prediction and therapy, and acute renal damage to chronic renal disease.

Joanne YC, et al. (2018) A review was conducted on advances in vitro drug-inducing model nephrotoxicity. In vitro Tests for nephrotoxicity in humans are currently unreliable toxicity predictors. While nephron tubule functional protein is well recognized and medically sensitive, current in vitro cell models do not properly imitate the form and function of the kidney tubule such that in-vivo damage response is not seen. A novel approach to this problem has been stimulated by our knowledge of renal development, the regenerating of humans in pluripotent stem cells, and improved 3D culture platforms. The primary aim is to produce cell models showing better functional maturity and therefore higher harms and productivity for both known and uncovered nephrotoxicity.

Mark AP, et al. (2018) Review of the Common Drug Nephrotoxicity Pharmacology presented. The prescribed and consumed drugs are widespread among patients. The cause of the kidney is still reasonably frequent. Nephrotoxicity of medicines is a complex process, comprising the inherent nephrotoxicity of medicinal products, its underlying features as a result of improving their risk of renal damage, and the metabolism and removal from the possible offending agent by the kidney.

Awdishu L, et al. (2017) Evaluated Nephrotoxicity was caused by the 6R medication. Our present understanding of medicinally caused kidney disease is restricted by different definitions of renal damage, inadequate evaluation of concomitant risk variables and a lack of long-term results. This review provides a 6-R framework in which the risk, identification, reaction, renal supports rehabilitation and research of drug-induced renal damage is recognised and managed.

Krishna M, et al. (2017) Evaluated Ethanolic Extract of Allium Cepa Linn nephroprotective activity. Kidney illnesses are an important global issue in Gentamicin induced nephrotoxicity in Rats. Renal injury is frequent because the kidney may discharge harmful chemicals. The objective of this research was an evaluation of the protection effect of ethanolic extract of Allium cepa Linn (EEAC). In

measures comprising serum creatinine, total protein, kidney weight and bodily weights, the nephroprotective effect was seen in the EEAC therapy comparing the standard group (vitamin E–250 mg/kg) to the control group versus toxic control animals. The protective effect of EEAC was also shown in histopathological investigations.

Akanksha Sharma,et al, (2017) A pharmacological assessment of SDDCT, as a nephroprotective potential in rats, was evaluated in this research. Material and procedures: In this research, the pharmacological potential of SDDCT in rats caused nephrotoxicity in Gentamicin was assessed. In order to prevent nephrotoxicity the SDDCT proved helpful. In gentamicin, nephrotoxicity of 100 mg/kg was tested in rats for seven days by i.p. administration and by a higher dosage (100 mg/kg b.w. p.o.) and lower dose at a different dose level. Pharmacology potential was evaluated by i.p. administering rats for a period of seven days. Different factors were studied: physical, biochemical, and antioxidants. In those receiving SDDCT with Gentamicin gentamicin was shown to decrease glomerular damage, inflammatory cell build up, epithelial desquamation, and necrose in sections of the medulla. Gentamicin caused rise in serum creatinine (0.40 ± 0.15), serum urea (30.33 ± 2.21), serum uric acid (1.80 ± 0.27), and blood urea (16.06 ± 1.5) nitrogen levels. The results include the normalisation of gentamicin. Histopathological investigations also demonstrate this. Outcome and debate: Due to the improvement of high biomarker concentrations, such as; BUN, creatine, uric acid, decreased level of MDA and rise of level of SOD, catalase, and GSH the nephroprotective activity of SDDCT was evaluated by comparing sick group and treatment group with reference and standard. Finally, a high dosage of SDDCT (100 mg/kg) was found in the assessment of general biological parameters and histopathologic activities to be more substantially effective compared to a lower dose (50 mg/kg).

OBJECTIVE OF STUDY

- To study of Pharmacognostical profile of the herbal drugs.
- To study and Determination of physicochemical parameters.
- To study Assessment of in-vitro nephron protective activity of the extracts through.
- To study of Screening of nephron protective activity of selective plant extracts.
- To study Histopathological examination

RESEARCH METHODOLOGY

Gallic acids, Quercetin, reference standard were purchased from Sigma Aldrich (USA). Cisplatin was purchased in the form of cisteen injection by (Miracalus Pharm, Mumbai India), Gentamicin sulphate was purchased in the form of Ranbiotic injection (Ranbaxy Pharmaceuticals New Delhi), and mesna was purchased in the form of Uromitexan injection (Baxter Oncology Germany). GGT (gama gutamyl transpeptidase) purchased from Reckon diagnostic Pvt. Ltd. 5, 5'-dithiobis-2- nitrobenzoic acid (DTNB), thibarbituric acid (TBA), trichloroacetic acid (TCA), and tris buffer were purchased from S.D. Fine Chemical Limited, India.

1. Collection and authentication of the drug samples:

The drug Kaunch (seeds of Mucuna pruriens), Kurpha (seeds of Portulaca oleracea) and Jadvar (roots of Delphenium denudatum) were procured from a local Indian market and were identified by Dr. H.B. Singh (Chief Scientist & Head, Raw materials Herbarium & Museum, NISCAIR, New Delhi). A voucher specimen (Ref. RHMD/1704/04) has been deposited in the Department of Pharmacognosy and Phytochemistry,

2. Macroscopical evaluation:

The plant material was subjected to macroscopical evaluation for its physical appearance, shape, size, taste, color and odor etc.

3. Microscopy of drug:

The plant material kaunch (seeds), khurpha (seeds) and jadwar (roots) were subjected to microscopical evaluation. The cleaned plants sample were prepared for sections cutting and fixed in fixing solution consisting of formalin (5.0 mL) + acetic acid (5.0 mL) + ethyl alcohol 90 mL 70%. The specimens were dehydrated after 24 h of fixing with tertiary butyl alcohol and were casted in to paraffin blocks (Sass, 1940). The specimens were sectioned (10-12 µm) with the help of Microtome and slides of the transfer section were prepared and stained with different staining reagents to ascertain the presence of particular type of microscopical structure

DATA ANALYSIS

Pharmacognostical Evaluation of the Drugs

The kaunch seeds are about 4 cm to 5 cm long, enclosed in free orange hairs that cause strict itching if they get in touch with skin. The exterior of seeds are shiny black or brown in color along with characteristic odor and astringent taste. The seeds

can be identify and authenticate by these morphological characters.

Fig : 1 pruriens character of Macroscopical M. seeds

Microscopical characters

The microscopic and anatomical features are often so diagnostic that they are now commonly used in routine identification of traded herbal materials. Beneath the micropyle many trachied elements were monitor it was loosely fitted with thin walled parenchyma. The calcium oxalate crystals were plain and prism shape while yellow color resinous material well spread in parenchymatus region. The dome shaped twisted rim aril present at the hillar region which compile of tightly bunged parenchyma filled with resinous material. It is possible that this sort of research may lead to the authentication of herbal medications purchased from marketplaces in order to identify the medicinal plant correctly and to check for adulteration

Phytochemical screening

The methanolic extract of pruriens was subjected to a variety of chemical assays, including alkaloid testing, glycosides, tannins, sugar, carbohydrates, saponins, proteins, amino acids, resins, lipids/fats, phenolic compounds and flavonoids as discussed by the reported method. The screening of methanolic extract exposed the presence of flavonoids, terpenoids, saponins, phenolic compounds, proteins and amino acids. Analyses of the plant's phytochemical composition indicated the existence of compounds with medicinal and physiological properties. Tannins bind to proline rich protein and interfere with protein synthesis. Flavonoids' power comes from their capacity to interact with proteins both extracellular and soluble, as well as the bacterial cell wall. They also are effective antioxidant and show strong anticancer activities.

Table 1.1: Result of heavy metals and drugs used in this study

Standard heavy metals	Tested herb		
	Species	Family	Part used
Cadmium (Cd)			
Lead (Pb)	M. pruriens	Fabaceae	Seed
Arsenic (As)	D. denudatum	Ranunculaceae	Root
Mercury (Hg)	P. oleracea	Portulacaceae	Seed

Table 1.1: Contamination levels of heavy metals in different herbs (mg kg-1) obtain from atomic absorption spectrophotometer (AAS)

PHARMACOLOGICAL EVALUATION OF SELECTED DRUGS

A. In-vivo antioxidant and nephroprotective activity

Effect of aqueous extract of M. pruriens on blood urea concentrations in cisplatin induced nephrotoxicity in rats

The Cisplatin exhibited clear indications of nephrotoxicity and significant renal impairment, as seen in the blood urea increase in comparison with control groups. The AEMP was shown to correct the increased blood urea and lead to a significant recovery in renal tissue at a dosage of 800 mgkg-1 body weight. Concentrations of blood urea in the group of toxicants (group II) of an animal were substantially elevated in comparison with the normal control group, which induced serious nephrotoxicity ($p<0.05$). Treatment with the AEMP showed significant ($p<0.01$) decrease in the (Group IV, V and VI) concentrations of serum urea compared to the toxicant group. The results showed significant inhibition of raised blood urea level in test drugs. AEMP at a dose of 800 mgKg-1 significantly inhibited the rise of blood urea level. The mean score were 33.70 ± 1.38 in normal control group, 99.57 ± 1.62 in toxicant group, 39.50 ± 1.51 in group V AEMP (800 mgKg-1), 53.51 ± 0.85 in group IV AEMP (400 mgKg-1) and 93.88 ± 1.61 in group III AEMP (200 mgKg-1) (Fig 49, Table 63). The overall percent reversal of toxicity inhibition of AEMP was 91.91% in group V at higher dose of 800 mgKg-1 with respect to normal control (100%) and toxic control (0%).

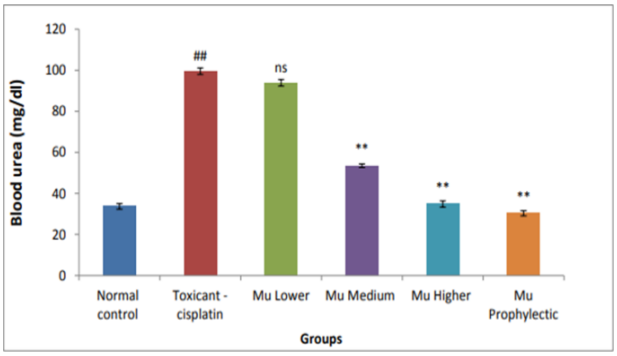

Fig 2: Effect of aqueous extract of M. pruriens on blood urea

CONCLUSION

Nephrotoxicity of cisplatin and gentamicin was observed after administration of 5 mgkg-1 b.w, ip and 40 mg kg-1 b.w, sc for 15 and 13 days respectively as evident from biochemical and histopathological changes. The cisplatin and gentamicin -treatment showed significant elevation in the blood urea nitrogen, uric acid and serum creatinine level indicative renal damage, increase in tissue TBARS level and decrease in the level of SOD, catalase and GSH level together with rise in the level blood urea nitrogen, uric acid and serum creatinine due to oxidative damage as compared to control group, which confirms nephrotoxicity induced by cisplatin and gentamicin, Cisplatin and Gentamicin were used to induce nephrotoxicity in the present study. These are the most widely used drugs in the treatment of cancer and gram negative infections respectively with the common side effect of nephrotoxicity. To treat this induced nephrotoxicity, ethanol and ethyl acetate extract of Mimosa pudica root, A. salvifolium stem bark and A. viridis root were used. A wealth of important information has been obtained using these models. The photochemical screening of the above extracts supported the presence of flavonoids, Phenols, alkaloids and tannins which were responsible for the treatment of induced nephrotoxicity

When the body is exposed to a medication or toxin, one of the most prevalent side effects is nephrotoxicity. An estimated 80,000 people with chronic renal failure are identified each year in India due to kidney disease, which is the tenth most common cause of mortality. Renal replacement therapy has been the only treatment option up to this point for those with end-stage renal disease. If you don't have access to a kidney, your only option is dialysis, which has a number of drawbacks, including the high cost. The kidney can be negatively affected by powerful therapeutic medicines such aminoglycoside antibiotics and chemotherapy treatments like cisplatin, leading in acute renal failure and chronic interstitial nephritis.

The nephroprotective study was carried out with the plants A.viridis, M. pudica (root) and A. salvifolium (stem bark) due to the following reasons: local availability, easy identification and its other medicinal values

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