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PLANT BASED NEPHROPROTECTION: *A Comprehensive Review*

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ABSTRACT :

Nephrotoxicity, a significant clinical issue resulting from the adverse effects of drugs, environmental pollutants, and metabolic waste products on kidney structure and function, necessitates the exploration of safer therapeutic alternatives. Traditional medicinal plants are good candidates since they are easy to find, not too harmful, and have a lot of phytochemicals in them. This review emphasizes the nephroprotective potential of five medicinal plants- Bergenia ligulata, Tribulus terrestris, Crataeva nurvala, Boerhavia diffusa, and Moringa oleifera—which exhibit protective effects through diverse mechanisms including antioxidant, anti-inflammatory, diuretic, and antiurolithiatic activities. These effects are largely attributed to active phytoconstituents such as flavonoids, alkaloids, glycosides, and saponins. Experimental validation using both in vitro (MTT assay, epifluorescence staining) and in vivo (cisplatin, acetaminophen, adenine-induced nephrotoxicity, and 5/6 nephrectomy models) methods has demonstrated significant renal protection offered by these plants. Furthermore, the paper discusses the pharmacological screening techniques and experimental models employed in nephroprotective research. Despite encouraging outcomes, challenges such as herbal-allopathic drug interactions, variability in phytochemical composition, lack of clinical standardization, and inadequate quality control limit the widespread application of herbal medicines. Overcoming these limitations through rigorous scientific evaluation, standardization, and integration of traditional knowledge with modern pharmacological approaches will be pivotal in developing effective plant-based nephroprotective therapies.

KEYWORDS:Nephrotoxicity,Nephroprotective agents,Medicinal plants, Herbal medicine, Bergenia ligulate, Tribulus terrestris, Crataeva nurvala,Boerhavia diffusa, Moringa oleifera,Phytochemicals, In vitro screening,In vivo models, Cisplatin-induced nephrotoxicity, Herbal drug interactions, Renal protection,Traditional medicine.

INTRODUCTION

One of the most important organs in the human body, the kidneys are principally in charge of eliminating hazardous chemicals and waste from metabolism. Apart from their excretory role, kidneys also contribute to the metabolism of essential molecules such as proteins, lipids, and carbohydrates. A critical renal function—*gluconeogenesis*—takes place in the *tubular epithelial cells*, which contribute to glucose production during fasting states. However, due to their unique physiology, kidneys are particularly susceptible to injury from both intrinsic and extrinsic factors. High renal blood flow, vigorous reabsorption and secretion processes, and a high concentration of chemicals in tubular fluid can all increase the kidney's sensitivity. Repeated or prolonged exposure to environmental toxins, pharmaceuticals, or metabolic byproducts can lead to *nephrotoxicity*, a condition marked by the rapid decline of kidney function. Nephrotoxicity is the term used to describe the harmful effects of various chemical agents on kidney structure and function. Several mechanisms contribute to nephrotoxicity, including *renal tubular toxicity*, *glomerular injury*, *crystal-induced nephropathy*, and *renal inflammation*. Mycotoxins, chemotherapeutic medications like cisplatin, antibiotics like aminoglycosides, and heavy metals like lead, arsenic, and mercury are examples of common nephrotoxic substances. Both internal and external factors can cause kidney disease. Extrinsic factors include systemic conditions like *cardiovascular disease, diabetes, obesity, sepsis, liver failure*, and *pulmonary dysfunction*. In contrast, intrinsic causes are related to direct renal impairment, such as *glomerulonephritis*, *polycystic kidney disease*, *tubular necrosis*, and *urolithiasis (kidney stones)*.The diagnosis and classification of kidney diseases fall under the domain of *renal pathology*, which focuses on structural and functional changes unrelated to tumours.Although the causes of nephrotoxicity and renal pathology are different—one is usually caused by drugs, while the other is caused by diseases—they have many characteristics in common. Both disorders affect the kidney's structural and functional units, the nephrons, which involve renal cell loss or injury...Key elements of the nephron, such as the glomeruli, tubules, interstitial tissue, and renal vasculature, are frequently damaged in nephrotoxic injury and renal disease. Millions of nephrons make up a normal human kidney, and each one is essential for waste removal, electrolyte and fluid balance, blood pH regulation, blood pressure control, bone health, and erythropoiesis (the synthesis of red blood cells) Whether kidney damage is caused by nephrotoxins or disease processes, same diagnostic frameworks are commonly used for its staging and characterisation. However, Making the distinction between nephrotoxicity and intrinsic renal pathology is crucial for the best treatment plan and outcome. [1]

NEPHROPROTECTIVE DRUGS:

Traditional medications are quite beneficial in fundamental healthcare requirements. As per WHO, more than 80% of the population is using traditional medicines which provides complete health benefits, especially in developing countries. These are the main sources of novel compounds that have the

potential to be useful in the development of various medicines. Conventional functional medications are effective at preventing a number of illnesses. Numerous studies have recommended the consumption of these herbs due to their bioactive components. These plants have therapeutic benefits and offer illness prevention. Nephroprotective medicines are derived from plants and are used to treat various kidney disorders or to discover effective treatments for them. The issue of rising resistance and negative effects from pharmaceutical treatments has led to a search for safer and less expensive plant-based remedies. The awareness of herbal formulations has grown significantly in recent years, and people are now being compelled to use both natural and prescription treatments. This may create undesired effects due to the interaction between drugs and herbal drugs. Medicinal plants like herbs and form different parts of the plants consist of different variety of phytochemical constituents like alkaloids, glycosides, carotenoids, different phenolic compounds which has the antioxidant property. Because of their therapeutic properties, these plants are thought to be a healthy substitute for oxidative stress-related diseases, and as such, they can be used to treat a range of renal conditions. [2,3,4,5,6,7]

PLANTS RESPONSIBLE FOR NEPHROPROTECTION

1. BERGENIA LIGULATA WALL

Fig 1. Bergenia ligulata wall

Bergenia ligulata Wall. Known as the "stone breaker" or "stone flower," Bergenia ligulata Wall., a member of the Saxifragaceae family, has long been recognised for its ability to treat urolithiasis. It is also botanically recognized by the synonym *Saxifraga ligulata* Wall.
Synonyms: Bergenia ciliata (Haw.) Sternb., Megasea ciliata (Haw.), Saxifraga ciliata (Haw.) Royle., Saxifraga ligulata Wall., Saxifraga thysanodes Lindl

Chemical constituents responsible for nephroprotection:

- Bergenin
- Arbutin
- Catechin
- Gallic acid

Nephroprotective activities:

- Antiurolithic activity
- Antiviral activity
- Free radical scavenging activity
- Diuretic activity
- Antioxaluria activity.[8]

2. TRIBULUS TERRESTRIS

Fig 2. Tribulus terrestris

The plant, which is an annual herb and a member of the Zygophyllaceae family, has a weak, creeping, widely branched stem that can reach a maximum length of 95 cm. The leaves resemble chickpea leaves in that they are stipulate, paripinnate, compound, and sub-opposite.
Leaflets are arranged in 5–10 pairs, oblong to linear-oblong in shape, nearly equal in size, and display a *pubescent* texture on both surfaces. The apex of each leaflet is *mucronate*, and the leaflets are attached via short petioles.

Synonym: gokshura, bhakhdi, puncture vine, goat-head.[9]
Chemical constituents responsible for nephroprotection:

- Saponins (Protodioscin, Dioscin, Tribulosin)
- Flavonoids (kaempferol, Quercetin)
- Alkaloids (Harman)
- Tannins
- Glycosides
- Sterols (beta-Sitosterol, Stigmasterol).[10]

Nephroprotective activities:

- Anti urolithiasis activity
- Diuretic activity
- Antimicrobial property.[9]

3. CRATAEVA NURVALA

Fig 3. Crataeva nurvala

Crataeva nurvala (*Family: Capparidaceae*), commonly known as *Barna*, is an evergreen tree native to the Indian subcontinent (Patil et al., 2010; Suksamrarn et al., 2003; Khalid et al., 1986; Ghani, 2003). The species is widely distributed across various regions, including India, Bangladesh, Pakistan, the Philippines, South America, China, and Africa (Ghani, 2003). It thrives in dry, hot climates and prefers partially shaded environments for optimal growth (Kumar, 2012). *C. nurvala* is typically a moderate-sized deciduous tree with softwood. The inflorescences are dense and appear in terminal corymb formations, with minute bracts. Globe-shaped berries with a woody skin and seeds embedded in a golden pulp are produced by the tree. Characteristically, the bark is wrinkly, grey-white, and heavily speckled with lenticels.[11]

Synonym: Three leaved capers, Holy garglic pear, Lengam tree, Triune leaf tree, and Sacred Lingam tree.[12]

Chemical constituents responsible for Nephroprotection:

- Lupeol
- Betulinic acid
- Catechin

Nephroprotective activities:

- Antiurolithiatic activity
- Anti-inflammatory activity
- Antibacterial activity
- Antioxidant Activity
- Diuretic activity.[11]

4. BOERHAVIA DIFFUSA

Fig 3. Boerhavia diffusa

Boerhavia diffusa L. is classified under the family **Nyctaginaceae**, which comprises numerous herbaceous plants valued for their adaptability and medicinal uses. The actual meaning of Punarnava (hogweed) is "bring back to life" or "renewer." This creeper dries in the summer but grows wild all

year round in Brazil and India. It has very high medicinal value. [13,14]
Synonym: santhi, moto satado,ataki,sanadika,gonajali,sanadika,sothaghna, etc.[14]
Chemical constituents responsible for Nephroprotection:

- **Alkaloid:** Punarnavine
- **Flavonoids:** Quercetin
- **Retenoid:** Boeravinone B, C, Sitosterol.

Nephroprotective activities:

- Diuretic Activity
- Antioxidant
- Anti Inflammatory
- Antimicrobial
- Treat Kidney Swelling, Nephritis, UTIs.[13]

5. MORINGA OLEIFERA LAM

Fig 5. Moringa oleifera lam

Moringa oleifera Lam. is a small to medium-sized deciduous tree widely cultivated in home gardens and as hedges due to its nutritional and economic value. The bark is thick, soft, and corky, marked by deep fissures, while the younger parts of the plant are covered with fine, soft hairs (tomentose). The leaves are typically tri-pinnate, with elliptic leaflets. The seeds are three-angled (trigonous), each bearing wings along the edges.[15]
Synonym: Haritashaka,Dirghaka,Laghupatraka,Shobhanjana,Tikshanagandha,Mukhabhanga,Saubhanjana,Shigru.[16]

Chemical constituents responsible for Nephroprotection:

- Flavanoids
- Isothiocyanate
- vitamin C (Ascorbic acid) [17,18]

Nephroprotective activities:

- Antiurolithiatic activity
- Antioxidant activity
- Anti-inflammatory activity
- Antimicrobial activity
- Diuretic activity.[19]

SCREENING METHODS

Drug screening processes are critical in determining the therapeutic efficacy and safety of both synthetic and natural medicines. These procedures are essential for identifying potentially harmful effects as well as therapeutic benefits, thus supporting the rational development of new drug candidates. The capacity to screen herbal extracts and extracted phytochemicals has been substantially improved by contemporary molecular pharmacological approaches. However, classical pharmacological screening continues to hold significant value. In vitro testing is the initial step in this traditional method, followed by in vivo testing in animal models such as mice and rats, and, if necessary, higher-order species. Many currently approved therapeutic agents have been discovered and validated using this well-established framework. The process of developing new drugs requires close collaboration between medicinal chemists and pharmacologists. Together, they work to evaluate novel chemical entities (NCEs), understand their mechanisms of action, and identify active constituents, particularly from natural sources. Many of the pharmacotherapeutic drugs used today have their origins in herbal sources. In the treatment of a variety of ailments, such as cancer, endocrine and metabolic disorders, and other chronic diseases, these bioactive chemicals have demonstrated significant promise. As such, the integration of traditional knowledge with contemporary pharmacological screening methods continues to be a valuable strategy in the discovery of new, effective treatments.[20]

I-IN-VITRO MODELS

A. EPIFLUORESCENCE STAINING

A dual-staining protocol using epifluorescence microscopy was used to identify viable and non-viable renal cells in vitro, allowing the nephroprotective potential of chosen plant extracts to be assessed. Normal kidney epithelial cells (Vero cells) were suspended in 10 mL of phosphate-buffered saline (PBS).

Two hundred microliters of the suspension were given to each treatment group. To induce cellular toxicity, gentamicin was added to each aliquot. The test groups subsequently received 50 µL of the selected plant extract at a concentration of 500 mg/mL, while the positive control group received 50 µL of vitamin E, a known antioxidant. Untreated cells served as the normal control. To all treatment and control samples, 50 µL of acridine orange and 50 µL of ethidium bromide were added. Samples were then incubated at room temperature for 1 hour in the dark. After incubation, the cells were studied using an epifluorescence microscope. Acridine orange absorption caused viable cells to glow green, while ethidium bromide intercalation caused non-viable cells with damaged membranes to glow red. This method provided a direct visual means of assessing cellular integrity and viability, enabling comparative evaluation of the protective effects of the plant extract in mitigating gentamicin-induced nephrotoxicity.

B. CYTOPROTECTIVE ASSAY

The cytoprotective capability of test substances was assessed using the MTT assay, a well-known colorimetric technique for determining cell viability. This test is based on the fact that in metabolically active cells, mitochondrial succinate dehydrogenase may change the yellow tetrazolium salt 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) into an insoluble purple formazan product.Vero cells were seeded at a density of 0.1×10^6 cells per well in 100 µL of phosphate-buffered saline (PBS) in 96-well flat-bottom plates. To induce cytotoxicity, cells were incubated with gentamicin, while treatment groups received gentamicin along with the test compound. After incubation, 50 µL of MTT solution (1 mg/mL) was added to each well, and the plates were incubated at 37°C for 48 hours. Following incubation, 150 µL of dimethyl sulfoxide (DMSO) was added to each well to solubilize the formazan crystals formed by viable cells. A microplate spectrophotometer was used to test the coloured solution's absorbance at 630 nm. The intensity of the colour directly correlates with the number of viable cells, thus allowing quantification of cytoprotective effects.[21]

II-IN-VIVO MODELS

1. CHEMICAL TECHNIQUES

A. CISPLATIN INDUCED NEPHROTOXICITY

Cisplatin is a popular platinum-based chemotherapeutic drug used as both a first-line treatment and adjuvant therapy in a variety of solid tumours. Cisplatin (cis-diamminedichloroplatinum (II)) enters cells primarily via the copper transporter 1 (Ctr1), which results in cytotoxicity. Once inside the cell, it undergoes aquation—a process in which the chloride ligands are replaced by water molecules—activating the platinum complex for interaction with intracellular targets. One of the critical interactions occurs with glutathione (GSH), a major intracellular antioxidant. Cisplatin also binds to surface enzymes on renal proximal tubular cells, including gamma-glutamyl transpeptidase (GGT) and aminopeptidase N. The conjugation of cisplatin with GSH produces reactive cisplatin-GSH intermediates, which, rather than being detoxified, contribute to kidney damage. These intermediates concentrate in the proximal tubules, depleting intracellular GSH and increasing oxidative stress. This redox imbalance is a key contributor to the nephrotoxic effects of cisplatin, ultimately resulting in tubular cell damage and impaired renal function. A total of 32 male rats were randomly assigned to four experimental groups (n = 8 per group) based on body weight to evaluate the nephroprotective potential of the test extract against cisplatin-induced renal injury. Group I (Normal Control): For ten consecutive days, animals were given normal saline orally. On day 5, 0.5 mL of normal saline was injected intraperitoneally (i.p.). After ten days of oral saline, Group 2 rats received a single dosage of cisplatin on day five. Rats in Group III were given an oral dose of plant extract at a rate of 200 mg/kg/day for 10 days. On Day 5, one hour after the test compound dose, a single cisplatin injection (7.5 mg/kg, i.p.) was administered. Group IV: Similar to Group III, but with a higher plant extract dose of 400 mg/kg/day. Throughout the experimental period, body weight was recorded daily. On Day 11 (i.e., 5 days post-cisplatin administration), urine samples were collected by placing the rats on a clean plastic surface and collecting spontaneously voided urine. The samples were centrifuged at 1500 rpm for 5 minutes, and the supernatant was stored at −20 °C until biochemical analysis. The collected blood was allowed to clot at room temperature for 20 minutes and then centrifuged at 4000 rpm for 10 minutes at 4 °C. Serum was separated and stored at −20 °C for subsequent biochemical evaluation. Rats were euthanized using an overdose of thiopentone sodium. The left kidney was fixed in 10% neutral buffered formalin for histological examination, whilst the right kidney was left intact for biochemical testing. [22,23]

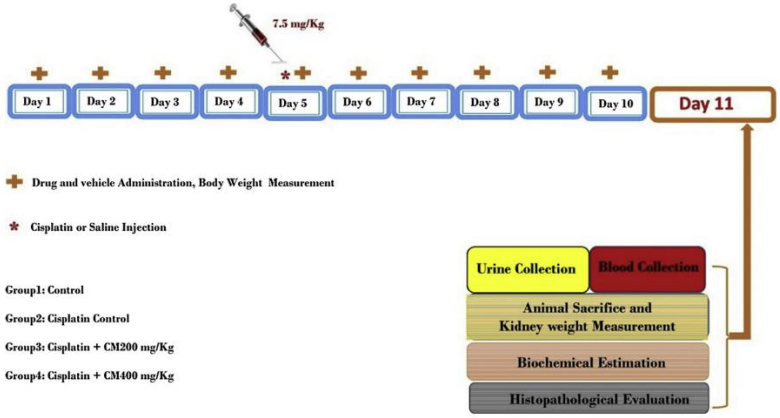

Fig 6. Experimental design of cisplatin-induced nephrotoxicity

B. ACETAMINOPHEN INDUCED NEPHROTOXICITY

Paracetamol (PCM), often known as acetaminophen, is a popular pain reliever and fever reducer. Although therapeutic amounts are normally regarded safe, an overdose can result in severe hepatotoxicity and nephrotoxicity. When taken orally, approximately 63% of paracetamol is metabolized in the liver by glucuronidation and 34% through sulphation pathways. The resulting water-soluble conjugates are excreted through the kidneys. However, a significant proportion of paracetamol (approximately 5–10%) is oxidized by the cytochrome P450 enzyme system to form the highly reactive intermediate, N-acetyl-p-benzoquinone imine (NAPQI). Under normal physiological conditions, NAPQI is rapidly detoxified by intracellular glutathione (GSH). In cases of overdose, glutathione stores become depleted, leading to accumulation of NAPQI, which induces oxidative stress, cellular necrosis, and ultimately nephrotoxicity. In this study, forty male rats were randomly assigned to five groups (n = 8) to determine the preventive effects of a test chemical against PCM-induced kidney injury. Group I (Controls): Normal saline (10 mL/kg, p.o.) was administered once day for 14 days. Group II (PCM Control): Received normal saline (10 mL/kg, p.o.) daily for 14 days along with intraperitoneal injections of paracetamol (200 mg/kg/day). For 14 days, Group III (Test Compound Control) received the test compound (200 mg/kg/day, p.o.) and oral normal saline (10 mL/kg/day). Group IV (PCM + Test 100 mg/kg): Treated with the test compound (100 mg/kg/day, p.o.) followed one hour later by paracetamol (200 mg/kg/day, i.p.) for 14 days. Group V (PCM + Test 200 mg/kg): Treated similarly to Group IV but with a higher dose of the test compound (200 mg/kg/day, p.o.). On the 15th day, all animals were fasted and then euthanized under ketamine anaesthesia (100 mg/kg, i.m.). Blood samples were taken from the retro-orbital plexus using heparinized tubes, and plasma and serum were separated by centrifugation. Both kidneys were removed, rinsed with cold distilled water then isotonic saline, blotted dry, and weighed. Tissue homogenates were prepared in 0.1 M Tris-HCl buffer (pH 7.4) for biochemical analysis. To assess the antioxidant defence response, oxidative stress markers such as glutathione (GSH), catalase (CAT), and superoxide dismutase (SOD) were measured in kidney tissue homogenates. [22,24]

C. ADENINE INDUCED NEPHROTOXICITY

Adenine-induced nephrotoxicity is a well-accepted non-surgical paradigm for researching chronic kidney disease (CKD), first proposed by Yokozawa in 1982. In this experimental model, male Wistar rats (9–10 weeks old) are fed a powdered diet supplemented with adenine at a concentration of 0.75% w/w to induce nephrotoxicity. Rats are randomly assigned into seven groups, with various treatment protocols extending up to 16 weeks. While the control group receives a standard powdered rat diet, the test group is administered the adenine-enriched diet. In certain studies, test chemicals are co-administered for the full 16-week period or for the final 8 weeks at a 0.25% adenine concentration to investigate potential Reno protective effects. Adenine and its metabolite, 2,8-dihydroxyadenine, accumulate in the renal tubules, causing crystal formation that obstructs tubular flow and causes severe degeneration in both the tubules and the interstitial tissue. These alterations result in delayed excretion of nitrogenous waste, closely resembling the biochemical and morphological characteristics of CKD in humans. At the end of the treatment period, renal function is assessed through 24-hour urine collection using metabolic cages to measure urinary protein, creatinine, and urea nitrogen levels. Histopathological evaluations further confirm kidney damage consistent with chronic renal impairment. The adenine-induced model offers several advantages over surgical models of CKD. It is non-invasive, relatively easy to implement, and associated with low inter-individual variability. Moreover, it allows for a consistent and reproducible degree of renal function decline, making it an ideal model for preclinical studies on CKD pathogenesis and therapeutic evaluation.[22]

2. METABOLIC OR IMMUNOLOGICAL TECHNIQUES

A. AGING

Aging is naturally associated with progressive structural and functional changes in the kidney, including glomerulosclerosis, interstitial fibrosis, tubular atrophy, and a decline in glomerular filtration rate (GFR). These age-related alterations render the elderly population more susceptible to renal impairment. Animal studies have shown that naturally aging rats, particularly those older than 24 months, serve as valuable models for investigating nephrotoxicity due to the spontaneous development of renal scarring and functional decline. Among the available rodent models, male Sprague–Dawley rats exhibit a higher vulnerability to renal damage compared to females and other strains. This sex-specific predisposition is evidenced by the earlier onset and greater severity of glomerular and interstitial lesions. Notably, proteinuria—a key marker of renal dysfunction—emerges in approximately 25% of male Sprague–Dawley rats by 3 months of age. This prevalence increases progressively with age, affecting 38% by 6 months, 56% by 12 months, and reaching 94% by 24 months [36,39,40]. According to these results, aging male Sprague-Dawley rats are a valid and physiologically appropriate model for researching chronic kidney injury and assessing nephroprotective measures. [25,26]

B. SPONTANEOUSLY HYPERTENSIVE RATS

The main cause of hypertension is alterations in vascular smooth muscle function, and renal dysfunction is mainly linked to elevated vasoconstrictor activity. Because of its close pathophysiological similarities to human essential hypertension, the spontaneously hypertensive rat (SHR) is a well-established animal model for researching this condition. In SHRs, hypertension typically develops during the early postnatal period, with systolic blood pressure (SBP) rising to 180–200 mm Hg by 5–6 weeks of age. Notably, this model also displays early-onset renal alterations. Nephrotoxic biochemical and histological indicators, including tubular damage and glomerular injury, can be observed as early as the sixth week of birth. Because of these features, SHRs are a useful model for examining how hypertension and progressive kidney injury interact, as well as for assessing possible nephroprotective measures. [27,28]

3. SURGICAL TECHNIQUES

A. 5/6 NEPHRECTOMY

Subtotal nephrectomy, commonly referred to as 5/6 nephrectomy, remains one of the most established and widely used experimental models for mimicking progressive renal failure following the loss of renal mass in humans. This model reliably reproduces key pathological features observed in chronic kidney disease (CKD), including glomerulosclerosis and tubulointerstitial fibrosis. There are two principal approaches to performing 5/6 nephrectomy: the ligation model and the ablation model. In the ablation model, the upper and lower poles of the remaining kidney are surgically removed, usually 1-2 weeks after the initial uninephrectomy. In the ligation model, branches of the renal artery are selectively ligated to infarct specific regions of

the remaining kidney, a technique that is technically feasible in rats but technically problematic in mice because of their limited renal arterial branching. This technique is suitable for use in both rats and mice. A hybrid method combining arterial ligation with partial excision has also been described to induce a complete 5/6 nephrectomy in mice, offering greater flexibility in achieving desired levels of renal impairment. Despite its utility, the success and reproducibility of the 5/6 nephrectomy model are highly dependent on surgical expertise and infrastructure. Variability in the extent of renal tissue infarction or removal contributes to significant inter-individual and inter-laboratory differences, which must be carefully controlled to ensure experimental consistency. [29,30]

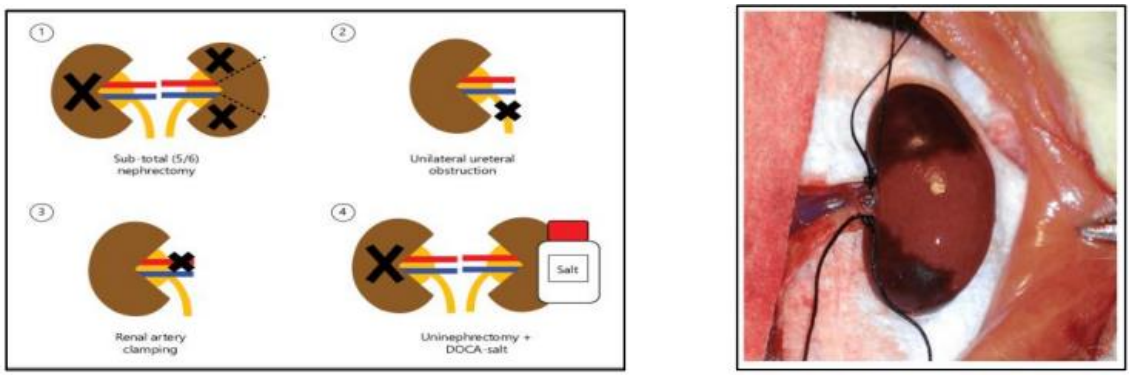

Fig 7. Surgical procedure of 5/6 Nephrectomy

B. RADIATION NEPHROPATHY

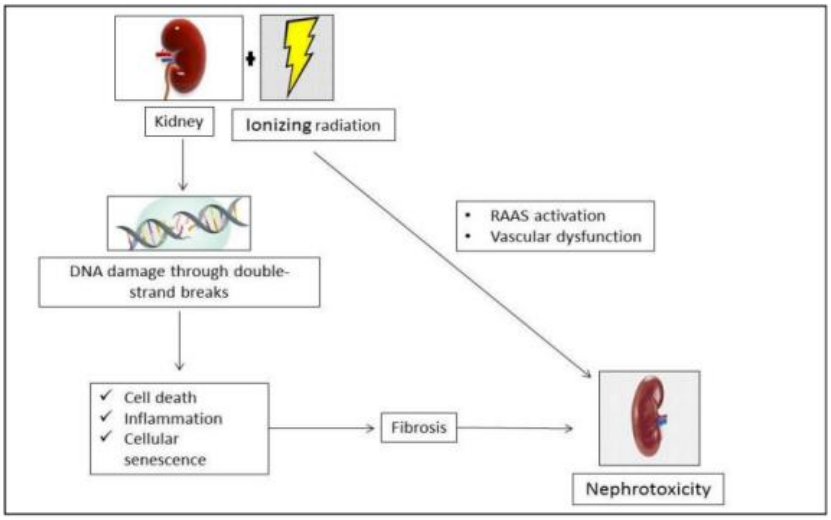

Fig 8. Radiation nephropathy

In the treatment of solid cancers, radiation therapy (RT) is still a mainstay and is frequently used either by itself or in conjunction with chemotherapy and/or surgery. The usage of RT keeps growing as the worldwide incidence of cancer rises as a result of longer life expectancies and higher exposure to carcinogenic risk factors. Even though RT is very good at reducing tumour growth and increasing patient life, its negative effects on nearby healthy tissues usually limit its therapeutic efficacy. One of the principal challenges in radiation oncology is the difficulty of achieving precise tumour targeting while sparing normal tissues. The unintended irradiation of healthy organs limits the maximum permissible RT dose, which can compromise tumour control and treatment outcomes. At the molecular level, DNA is the primary target of ionizing radiation. Radiation directly damages cellular components by breaking chemical bonds and displacing electrons. Furthermore, it results in indirect harm through the production of reactive oxygen species (ROS), which trigger oxidative stress. Radiation-induced nephrotoxicity is the result of structural and functional damage caused by the buildup of ROS in renal tissue. When RT encompasses the abdominal or pelvic areas, where the kidneys may be unintentionally exposed, this oxidative process is a serious problem. [31,32,33,34,35]

CHALLENGES IN NEPHROPROTECTIVE RESEARCH OF HERBAL DRUGS

1. CHALLENGES IN CLINICAL RESEARCH OF HERBAL MEDICINES:

There are unique challenges in the fields of ethics, quality control, study design, economics, and legislation for clinical research in herbal medicine. The World Health Organisation (WHO) published guidelines in 2005 to facilitate the scientific assessment and regulation of herbal products in order to promote more comprehensive clinical trials. Double-blind designs are particularly difficult to implement in herbal medicine research, though. The key reasons for this include the distinct flavour, aroma, and appearance of herbal remedies, as well as the holistic approach used by many of them, which

sometimes includes additional components such as diet and lifestyle suggestions. These factors can make it difficult to create indistinguishable placebos, which could jeopardise blinding integrity. Single-blind designs, in which the researcher is told of the treatment allocation, but the participant is not, might be a more feasible option in these situations.

- *Control Selection*: Identifying appropriate placebos or comparators that adequately mimic the sensory characteristics of herbal products (e.g., the pungent aroma of ginger) remains a significant obstacle.

Addressing these problems is critical for expanding the research base and better incorporating herbal medicines into modern healthcare paradigms. [36,37,38]

2. CHALLENGES RELATED TO HERBAL-ALLOPATHIC DRUG INTERACTIONS:

Numerous active phytoconstituents, each with distinct pharmacological activities, metabolic routes, and binding qualities, make up herbal remedies. These complex profiles may cause interactions with conventional (allopathic) drugs, especially through pharmacokinetic and pharmacodynamic pathways. When the traditional medication has a limited therapeutic window, these interactions are especially concerning. For instance, herbs like garlic and ginger have antiplatelet effects that can enhance the risk of bleeding in patients taking anticoagulants such as warfarin. Therefore, it is important to carefully consider and observe when combining allopathic and herbal medicine. [39]

3. CHALLENGES IN MONITORING SAFETY OF HERBAL MEDICINES:

With the growing global consumption of herbal products in recent decades, efforts have intensified to evaluate not only their therapeutic benefits but also their potential risks. Integrative healthcare has made establishing scientific proof of herbal medicines' safety and effectiveness a top priority. Nonetheless, it is intrinsically difficult to track negative consequences associated with herbal medicines. The most frequent causes of these problems include the use of the inappropriate plant species, adulteration etc. Several variables can affect the safety profile of herbal medicines, including the plant's geographical origin, harvesting and handling techniques, route of administration, and potential interactions with prescription drugs. Additionally, proper identification and authentication of herbal materials are frequently hindered by limited taxonomic knowledge or inadequate documentation practices among manufacturers. One significant issue is the confusion caused by common or vernacular names of herbs, which can lead to misidentification and inappropriate use. To ensure the safety of herbal medications, correct botanical nomenclature (including synonyms), identification of the plant section used, and thorough manufacturer information are required. Adverse reaction reporting systems should also be strengthened for herbal products. Ultimately, safeguarding public health in this area requires a collaborative effort among botanists, phytochemists, pharmacologists, clinicians, and regulatory bodies to establish rigorous standards for quality, identification, and safety monitoring. [40,41,42,43,44,45]

4. CHALLENGES IN QUALITY CONTROL OF HERBAL MEDICINES:

Assuring the quality of herbal medications remains a significant challenge due to the complexity and diversity of raw plant components. The purity and effectiveness of herbal components are influenced by a number of factors, including genetics, farming practices, environmental conditions, and adherence to good farming and collection procedures (GACP), which include appropriate crop selection, growing, and harvesting processes. It may be challenging to maintain consistent quality control if any of these characteristics are variable. Standard operating procedures (SOPs) must be followed at every stage, from raw material identification and procurement to storage and sanitation, in accordance with Good Laboratory Practices (GLP) and Good Manufacturing Practices (GMP), in order to preserve quality. More difficulty arises when it comes to guaranteeing the quality of final herbal products, particularly multi-herb mixtures. There are still technical challenges in identifying and confirming the existence and amount of each component.

Processing and Harvesting Issues: Inadequate farming techniques, poor propagation, unregulated harvesting, and a lack of processing technologies often contribute to substandard herbal products. Inconsistent or inappropriate post-harvest treatment degrades product quality.

Adulteration: Adulteration: Another significant issue with herbal medication quality monitoring is adulteration. It may be intentional or accidental and includes:

- *Use of toxic substances* (e.g., lead shot in opium, limestone in asafoetida),
- *Powder adulteration* (e.g., olive stone powder in *Cinchona*),
- *Heavy metal contamination* (lead, arsenic, mercury),
- *Spiking with synthetic drugs* such as sildenafil, warfarin, or alprazolam—cases that have been flagged by the U.S. FDA.

To make sure herbal medicines are safe, effective, and properly marketed, India follows the *Drugs and Cosmetics Act of 1940*. This law, especially *Chapter IVA***,** lays down rules for how Ayurvedic, Siddha, and Unani (ASU) medicines should be made, packaged, labelled, and sold. Over time, the Act has been updated. The addition of Schedule 'T' in 2000 was one significant modification. In order to guarantee the quality of traditional medicines, this lays forth the Good Manufacturing Practices (GMP) that must be adhered to. Key regulatory bodies include the Ayurveda, Siddha, and Unani Drugs Technical Advisory Board (ASUDTAB) and the Drugs Consultative Committee (ASUDCC), both of which help harmonize implementation across India. Further requirements include proper labelling with scientific names, documentation of raw materials, disclosure of additives, heavy metal testing, and expiry dates.

Quality Assurance Infrastructure. In India, a number of important organisations collaborate to ensure that herbal remedies are authentic, safe, and efficient. Organizations like the *Pharmacopoeial Laboratory of Indian Medicine (PLIM)***,** the *Central Council for Research in Ayurveda and Siddha (CCRAS)***,** the *Central Council for Research in Unani Medicine (CCRUM)***,** and various labs under *CSIR* play an important role. They concentrate on developing standard operating procedures (SOPs), monographs, and pharmacopoeial standards. Overall, quality control in the production of herbal

medications requires coordinated efforts across disciplines, including botany, pharmacognosy, pharmacology, and regulatory science, to ensure reliable and secure medicines for patients.[46]

CONCLUSION

Nephrotoxicity is still a prevalent and dangerous medical condition. This usually occurs as a result of prolonged exposure to toxic substances in the environment, certain drugs, or waste products from the body's own metabolism. The kidneys' structure and function may be changed by these harmful substances. Research on plant-based alternatives has accelerated significantly because existing medicines are still constrained by adverse effects and expensive prices. Traditional medicinal systems, enriched with centuries of empirical knowledge, offer a treasure trove of botanicals with promising nephroprotective potential. This review focuses on the healing potential of five well-known medicinal plants—**Bergenia ligulata, Tribulus terrestris, Crataeva nurvala, Boerhavia diffusa**, and **Moringa oleifera**. It explores what makes these plants effective, looking at their natural compounds, how they work in the body, and how they've been tested in both lab (in vitro) and animal (in vivo) studies related to kidney damage.These plants offer a wide range of kidney-protective benefits, including **antioxidant, anti-inflammatory, diuretic**, and **anti-stone (antiurolithiatic)** effects. These effects are mostly caused by potent natural compounds such phenolic acids, alkaloids, flavonoids, and saponins. Scientists have used modern research tools like MTT cell viability tests, epifluorescence staining, and other animal models utilizing drugs such as acetaminophen, adenine, and cisplatin, as well as surgery such as a 5/6 nephrectomy, will be used to collect convincing evidence that these plants can help protect the kidneys from injury. Despite these promising findings, the integration of herbal nephroprotective agents into mainstream medicine faces several obstacles. Some key challenges still need to be addressed when it comes to using herbal medicines. The difficulty of standardizing herbal products with a large number of natural ingredients is one of the primary issues. Where the plant was grown, how it was collected, and how it was processed can all affect the quantity and quality of these chemicals. There's also the *risk of herbs interacting with other medicines***,** which can affect how well they work or cause side effects. Furthermore, robust clinical investigations that unequivocally demonstrate the safety and efficacy of numerous herbal remedies in people are still lacking. Moving forward, a multidisciplinary approach involving pharmacologists, botanists, toxicologists, clinicians, and regulatory authorities is essential to bridge the gap between traditional wisdom. These natural remedies have the potential to significantly improve kidney care worldwide if used properly.

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