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EVIDENCE-BASED NEPHROPROTECTIVE AYURVEDIC HERBAL FORMULATIONS: PHARMACOLOGICAL MECHANISMS AND CLINICAL IMPLICATIONS

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ABSTRACT

Kidney diseases, one of the increasing health burdens in the world today is kidney diseases such as acute kidney injury, chronic kidney disease, and diabetic kidney disease, which have few preventive and treatment measures. Although there is an improvement in traditional nephrology, currently used measures are not usually enough to prevent the development of disease or renal damage as a result of medications. In that regard, there is a growing interest in traditional medical systems, specifically Ayurveda, which is characterized by the focus on formulation-based, multi-target solutions to protect organs. This is an evidence-based review of nephroprotective Ayurvedic herbal formulations with emphasis on their pharmacological action mechanism and clinical implications. The experimental and translational research reveals that the reno protective effect of chosen Ayurvedic herbs and polyherbal preparations is manifested through the regulation of the major pathological processes, such as oxidative stress, inflammation, mitochondrial dysfunction, apoptosis, autophagy dysregulation, and renal fibrosis. In vivo, in vitro, and systems pharmacology studies demonstrate their ability to maintain renal architecture, positively change functional biomarkers and enhance cellular resilience in nephrotoxicity caused by drugs, diabetic nephrotoxicity and chronic kidney disease models. Similarities in mechanistic pathways have a comparative understanding of other non-Ayurvedic botanical studies, which support the unique formulation-based rationale of Ayurveda. Despite the promising outlook, the existing evidence base is predominantly preclinical in nature, which highlights the necessity of standardized preparations, lenient clinical trials, and biomarker-based assessment. All in all, Ayurvedic nephroprotective formulations can be viewed as potential adjunctive approaches in integrative nephrology, and thus, further studies are required to translate to their safe and effective clinical implementation.

KEYWORDS: Nephroprotection, Ayurveda, Diabetic Kidney Disease, Herbal Formulations, Pharmacological Mechanisms

1. INTRODUCTION

Kidney diseases are a major and increasingly popular health issue of global concern and comprise acute kidney injury (AKI) and chronic kidney disease (CKD) and disease-specific illness, including diabetic kidney disease (DKD). The conditions play a major role in the morbidity, mortality and the health care expenditure in the entire world. Renal failure is also an evolutionary process that not only causes end-stage kidney disease but also exposes the individual to cardiovascular risks and lowers the quality of life. The burden of the kidney disease has been growing, especially in the low- and middle-income countries where long term dialyses and renal replacement therapies are unaffordable, though the diagnostic modalities and the pharmacotherapy have been developed. The latter situation demonstrates the urgency of the effective preventive and nephroprotective interventions that may be implemented in everyday practice.

Contemporary medicine is mainly concerned with the control of the risk factors of hyperglycemia, hypertension, and proteinuria and the prevention of nephrotoxic agents which in the long run constitute the contemporary nephroprotective measures. The measures have been discovered to assist and, in most cases, it is not enough to stem out the development of the disease entirely. Nephrotoxicity caused by drugs, ischemia-reperfusion injury, oxidative stress, inflammation and fibrosis continue to be the major causes of renal damage in various clinical diseases. Furthermore, the adverse outcome and interactions with medications other than the inaccurate uptake of drugs by patients, can be explained by the chronic pharmacological interventions. These shortcomings are what have prompted a renewed concern in complementary and integrative methods of treatment with multi-targeted renal protection and acceptable safety.

The Ayurvedic medicine is a traditional system of medicine that has placed great significance to the management of the renal health and the prevention of urinary and metabolic diseases. The Ayurvedic texts present kidney related disorders to the entire system of *Srotas* known as *Mutravaha* and herbal preparations are given to bring the physiological processes back to normalcy. The Ayurvedic measures are suggested in the case of diabetic nephropathy as the supportive therapy to slow down the progression of the disease and the associated complications by holistically maintaining the metabolism and inflammatory activity [1]. They are also taking a new turn as it is possible to conduct the review of the traditional solutions with the help of modern research methods in the structured way.

The Ayurvedic herbs and formulations have been found to have more evidence of nephroprotective power through experimental studies. Indeed, as a case study, the prophylactic effect of bioherbal extracts like *Boerhavia diffusa* and *Tribulus terrestris* was observed against experimentally induced chronic kidney injury in the form of a change in haematological and biochemical parameters [2]. The results concur with the classical Ayurvedic philosophy, which prefers the use of formulation-based treatment to the use of single-compound treatment, of which more than one occurrence of a pathological target could be synergistically regulated.

More extreme pharmacological effects such as antioxidant, anti-inflammatory, diuretic and anti-fibrotic effects of Ayurvedic drugs, have also been emphasized by the extensive research conducted on Ayurvedic nephroprotective drugs and are currently highly relevant in the current models of kidney injury [3]. Other than the nephropathy, Ayurvedic herbs used in treating urinary disorders such as urolithiasis also have reno protective properties due to their ability to regulate the crystal formation, oxidative stress and renal epithelial cell injury [4]. Based on such evidence, the usage of the herbs through the sequence of diseases of the renal and urinary apparatus can be extended.

One of the individual botanicals, the *Tinospora cordifolia*, has been given quite a thorough coverage in terms of its nephroprotective effects, in the particular example. It has also been experimentally proven that it can reduce the results of gentamicin-caused nephrotoxicity by protecting the renal architecture and replenishing the biochemical markers to normalcy [5]. The potency of such herbs has also been accelerated through enhancing drug delivery and nano-encapsulation preparations be more functional in experimental models of diabetic complications like the renal involvement [6]. Such inventions show that the interface between conventional medicine and the new pharmaceutical science is changing.

Poly herbal preparations have taken centre stage in the Ayurvedic therapeutic procedures and are increasingly being tested on modern experimentation grounds, in an increasing manner. It was also discovered that hydroalcoholic polyherbal preparations possessed protective activity on drug-induced hepato-renal toxicity which has suggested that systemic activity of such preparations possesses protective potential [7]. Later on, in silico, in vitro and in vivo models of integrative research have clarified the nephroprotective multi-mechanistic effects of the traditional polyherbal preparations which further facilitates the use in contemporary nephrology studies [8]. The network pharmacological studies have also helped to enhance the understanding of complicated formulas like *Chandraprabha Vati* and their ability to act in the control of interrelated metabolic and inflammatory pathways that may be used in the case of the renal disease [9].

Simultaneously, the renal protective effects of the majority of the herbal agents in the diabetic nephropathy animal model have also been evaluated systematically as has the shortcomings in clinical translation [10]. These are all the good reasons to prove the point that Ayurvedic herbal preparations synthesis is evidence-based in the case of nephroprotection.

The current review has the purpose to discuss pharmacological supplementation of Ayurvedic nephroprotective herbal preparations critically and explain their mechanism of action and comment on whether they should be used or not in the treatment of kidney diseases. The review will provide the way forward on research in future and to enable rational inclusion into the contemporary practice of nephrology by integrating experimental and translational information on the Ayurvedic interventions. This review aimed:

1. To critically evaluate the experimental and translational evidence supporting the nephroprotective effects of Ayurvedic herbal formulations across acute kidney injury, chronic kidney disease, and diabetic kidney disease.
2. To elucidate the key pharmacological mechanisms underlying Ayurvedic nephroprotection and assess their potential clinical relevance as adjunctive strategies in contemporary nephrology practice.

2. Pathophysiology of Kidney Injury and Targets for Nephroprotection

2.1 Acute Kidney Injury (AKI)

Acute kidney injury is an acute injury of the renal system under the impact of different insults, the most apparent of which are ischemia-reperfusion injury and nephrotoxicity due to drugs. The consequences of ischemia-reperfusion are the endothelial dysfunction, ATP loss and excessive production of reactive oxygen species (ROS), leading to the death of tubular cells of the epithelium and microvasculature rarefaction. Nephrotoxic agents such as cisplatin, aminoglycosides and nonsteroidal anti-inflammatory drugs further enhance the impact of oxidative stress, mitochondrial damage, and inflammatory cascades on the effects of renal injury. A central position in the pathogenesis of AKI is played by mitochondrial dysfunction that disrupts energy metabolism and triggers the apoptotic and necrotic process. Various sources indicate that natural products can also regulate mitochondrial homeostasis and reduce ROS frequency and tubular integrity, making them possible to be nephroprotective in the treatment of AKI [11], as shown in Figure 1. Even traditional vegetal treatments have been cited to have the capability of inhibiting oxidative stress and inflammatory cascades during acute kidney injuries [12].

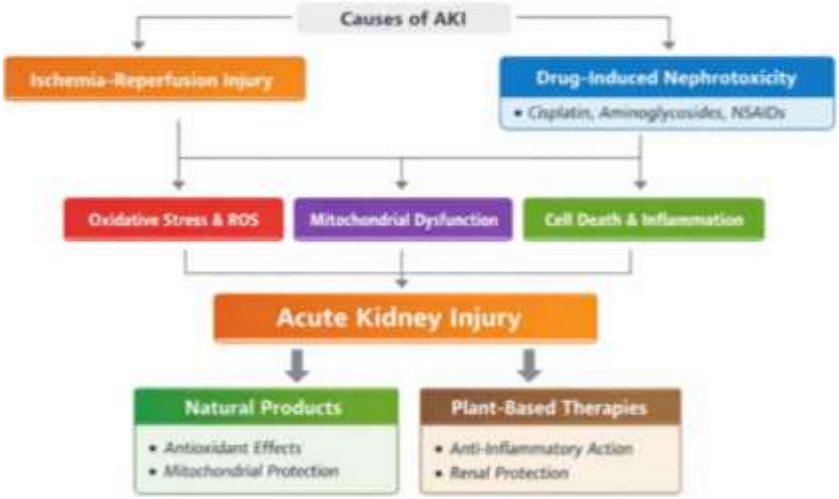

Figure 1. Schematic representation of the major pathogenic mechanisms involved in acute kidney injury (AKI) and the nephroprotective role of natural products.

2.2 Chronic-Kidney-Disease (CKD) Progression

Chronic kidney disease is a progressive disease that is marked by irreversible loss of nephrons and irreversible loss of glomerular filtration rate. Continuous oxidative stress, chronic inflammation and progressive renal fibrosis are also contributors to the progression of the advanced CKD after the initial renal injury. Excessive production of ROS activates pro-inflammatory transcription factors and pro-fibrotic mediators, which results in extracellular matrix and structural remodelling of renal tissue. Mitochondrial impairment also contributes significantly to the pathogenesis of CKD by supporting tubular energy deficiency, worsened fatty acid oxidation and increased susceptibility to apoptosis. Also, tubular epithelial damage and nonadaptive repair enhance interstitial fibrosis and capillary loss. This has resulted in medicinal phytochemicals of plants becoming promiscuous as an antioxidant, anti-inflammatory and anti-fibrotic agent in the amelioration of CKD [13]. Also, the existing conventional plant-based interventions have been tested with regard to their capacity to regulate a multiplicity of molecular pathways involved in renal degeneration, offering a multi-targeted method of delaying CKD progression.

2.3 Diabetic Kidney Disease

Diabetic kidney disease is a major cause of CKD in the global population and is due to long-term metabolic and hemodynamic abnormalities resulting from hyperglycemia. Persistent hyperglycemia encourages oxidative stress, advanced glycation product generation, and inflammatory pathways and leads to mesangial expansion and glomerulosclerosis. Additional dysregulations of the renin-angiotensin-aldosterone system promote intraglomerular hypertension and increase the pace of podocyte damage, resulting in proteinuria and progressive kidney failure. Recent experimental observations show that some medicinal plants and herbal preparations are capable of alleviating diabetic renal injury through the specific mechanisms of attacking oxidative stress, inflammation, and metabolic derangements. An example is that the gut microbiota and ferroptosis have been modulated as a new pathway of renoprotective action of *Orthosiphon aristatus* in diabetic nephropathy [14]. On the same note, *Phylanthus embplica* extracts are effective in preventing renal structures and function in diabetic models [15], and *Spilanthes filicaulis* has been found to protect streptozotocin-induced renal damages by its antioxidant and anti-inflammatory action [16], as represented in Table 1.

Table 1. Experimental Evidence Supporting Nephroprotection in Diabetic and Fibrotic Kidney Injury Models

Plant/Extract	Experimental Model	Key Renal Target	Major Mechanism	Reference
Cannabis oil extract	Folic acid–induced renal fibrosis (rat)	Renal fibrosis	Anti-fibrotic, anti-inflammatory	[17]
Malva sylvestris extract	Gentamicin-induced nephrotoxicity (rat)	Tubular injury	Antioxidant, anti-inflammatory	[18]
CKD–OA comorbidity model	Chronic kidney disease mouse model	Renal–systemic interaction	Disease-modifying signaling	[19]
Date palm seed extract (polyherbal)	Gentamicin-induced renal injury (mouse)	Renal inflammation	PARs/RXR-α modulation	[20]
Thymelaea microphylla extract	Drug-induced renal injury (rat)	Oxidative stress	Flavonoid-mediated antioxidant effect	[21]

3. AYURVEDIC CONCEPTUAL FRAMEWORK OF RENAL PROTECTION

The Ayurveda describes the kidney mechanism under the name of *Mutravaha Srotas*, which is a physiological mechanism that takes part in the generation, transportation, and excretion of urine. It is considered that the integrity of such a system is critical in making sure that there are an internal homeostasis, fluid balance and elimination of metabolic waste. It has

been described that metabolic disturbances, toxic injury and impaired tissue nutrition are causes of derailment of *Mutravaha Srotas* that ultimately result in a reduction in urine secretion, characteristic urine and systemic complications. Such notions are quite close to the existing concepts regarding renal tubular impairment, renal filtration impairment, and the formation of structural damage, yet they rely on classical definitions.

The translational relevance concept is observed where Ayurvedic concepts are used to the present biomedical concepts. The processes which are associated with processes of kidney injury in the modern models are oxidative stress, inflammation and accumulation of toxins and can be traced back to Ayurvedic ideas of *ama* or *dosha* imbalance in the renal channels. This finding is also informed by increasing volumes of experimental nephrology research findings that suggest that plant-based interventions can alleviate biochemical and histopathological signs of kidney injury through antioxidant and anti-inflammatory action [22]. These results provide a scientific point of interface between the outdated understanding of renal protection and the evidence-based nephroprotective processes.

A tendency towards polyherbal rather than single-compound, formula-based therapy is also one of the typical features of Ayurveda. The principle of the approach is that multi-target interventions are required, given that complex diseases such as kidney disorders involve a complex of pathways. The objective of polyherbal formulations is to achieve the synergies, enhanced bioavailability, and low toxicity. This plan is also supported by the recent metabolomic and phytochemical research studies that reveal the existence of diverse bioactive profiles in pharmaceutical plant extracts in terms of their capacity to select multiple targets of metabolism and cellular activity simultaneously [23]. The Ayurvedic paradigm, when criticized in terms of translation, has offered a systematic, systems-based account of nephroprotection that can happily be adjusted to the existing multi-mechanistic biomedical view of treatment, as shown in Table 2.

Table 2. Evidence Base Supporting Multi-Target Nephroprotection (Translational Rationale for Formulation-Based Therapy)

Agent (plant/compound)	Kidney injury model	Key protective target	Dominant mechanism	Reference
Ipomoea aquatica (ethanolic leaf)	Cisplatin nephrotoxicity (rat)	Tubular injury	Antioxidant / anti-inflammatory	[24]
Medicinal plants (overview)	Cisplatin nephrotoxicity	Multi-pathway injury	Oxidative stress + inflammation + apoptosis	[25]
Pyxinol (lichen constituent)	Cisplatin nephrotoxicity	DNA injury	DNA-damage response modulation	[26]
Leonotis ocymifolia (aqueous extract)	Cisplatin nephrotoxicity	Inflammation + DNA injury	Anti-inflammatory + anti–DNA damage	[27]
Vitamin E + silymarin	Gentamicin nephrotoxicity	Oxidative tissue damage	ROS suppression / antioxidant defense	[28]

4. Evidence-Based Nephroprotective Ayurvedic Herbal Formulations

4.1 Formulations Studied in Acute Kidney Injury

Acute kidney injury (AKI) is a frequent, acute clinical complication that transpires due to drug toxicity, ischemia and systemic disease. Experimental works on herbal preparations have been conducted where they have provided mechanistic insight into nephroprotection in acute renal injuries. It has been demonstrated that cases of nephrotoxicity induced by paracetamol can be prevented using cases of herbal extracts such as *Eurycoma longifolia* which is evidenced by reversal of serum creatinine, urea, and normal histopathological structure of renal tubules [30]. The findings indicate the suppression of oxidative stress and the reduced epithelial injuries of the tubules, which are the major pathologic features of AKI.

Bioactive phytoconstituents have been reported to regulate apoptotic pathways, mitochondrial dysfunction and inflammatory pathways on a molecular level. Tetramethylpyrazine is a traditional herbal medicine-based active substance that has therapeutic potential in AKI that improves renal microcirculation, suppresses proinflammatory cytokine release, and causes oxidative damage [29]. The given type of multi-target effects is particularly relevant to AKI, whereby an injury is formed in a short period, and it is anchored in the concerted action. All these facts indicate the logic behind the herbal interventions as the adjunctive nephroprotective intervention to acute renal injury especially in cases where the renal damage is drug-induced or toxin-mediated.

4.2 Formulations in Diabetic Kidney Disease

It is chronic hyperglycemia-induced diabetic kidney disease that is persistent proteinuria, oxidative stress, inflammation, and progressive fibrosis-based. The effect of herbal compounds has been discovered to be effective in controlling these interconnected pathways. *Yiqi Yangyin Huayu Tongluo* was found to possess reno protective effect on both nephropathy in experimental diabetic nephropathy, as the formula reduces albuminuria, improves glomerular arrangement and suppressing oxidative stress and cytokine release. These effects underscore metabolic and renal injury as two pathways which can be attacked using multi-component formulations.

Autophagic dysregulation has turned out as one of the key contributors to diabetic renal injury that influences podocyte survival and tubular homeostasis. It has also been demonstrated that the Chinese herbal medicine and the active components can restore autophagic balance thereby and reducing the destruction of renal cell in the diabetic models and grading the course of the ailments [30]. The latter is emphasized by the doubled control of metabolic load and the quality-

control processes of the insiders, which reflect the hyperdiabetic nephropathy into herbal preparations. Formulation-based approaches offer a safe nephroprotective approach that involves correction of glycemic-related harm and intrinsic cellular dysfunction of the kidney that has potential clinical utility in the treatment of diabetic kidney disease (Figure 2).

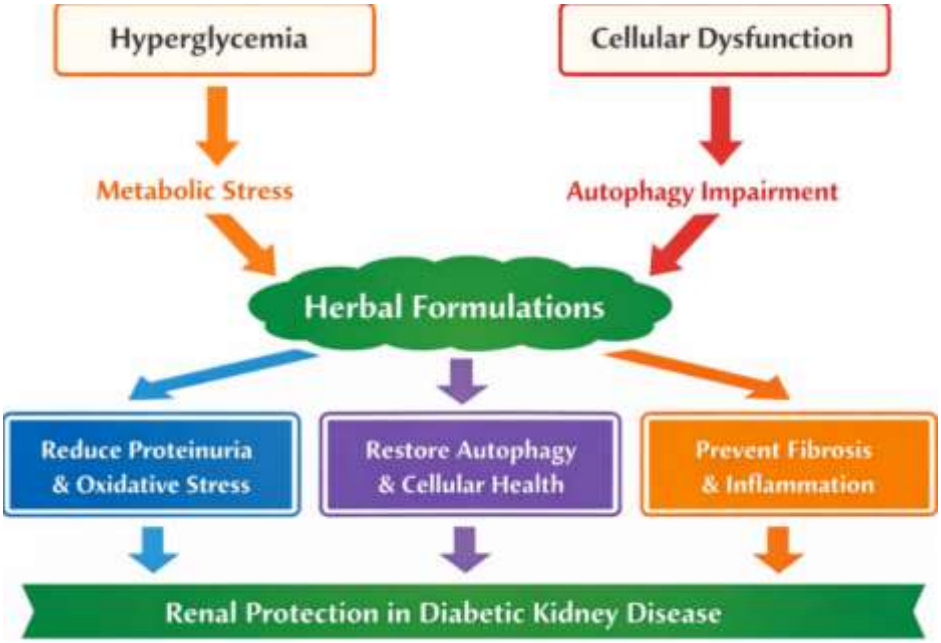

Figure 2. Herbal Formulations in diabetic Kidney-Diseases

4.3 Formulations in Chronic Kidney Disease and Fibrosis

Long-term inflammation, immune dysregulation and calcium deposition, and gradual fibrosis of the kidney lead to the development of chronic kidney disease that ultimately leads to permanent loss of nephrons. The remedies may be phytochemicals and herbal preparations that are able to prevent these processes being anti-inflammatory agents and antifibrotic agents. The CKD pathogenesis is primarily immunological in nature, and the induction of an innate and adaptive immune reaction is the aspect of the process chronic inflammation and tissue remodelling [31]. The assault on such immune reactions is a major technique of therapeutic outcome of long-term renoprotection.

The quercetin (flavonoid compounds) and other such compounds that are prevalent in pharmaceutical plants have been shown to protect diverse kidney disease models via inhibition of oxidative stress, prevention of profibrotic signalling pathways and immune response regulation. The exercises result in reduced extracellular matrix deposition and renal conservation. The synthesis of these compounds in the formulation-based therapies would act synergistically and lead to higher renal resilience in the long-term. Overall, it can be said that herbal preparations could be considered as potential supplements in delaying CKD and decreasing renal fibrosis by delivering the effects of long-term anti-inflammatory and immunomodulatory actions.

5. PHARMACOLOGICAL MECHANISMS UNDERLYING NEPHROPROTECTION

5.1 Regulation of Autophagy and Cellular Homeostasis

The autophagy may be involved in the centrality in the preservation of cellular integrity of kidneys in the clearing of damaged organelles and misfolded proteins especially when an incidence of metabolic and oxidative stress takes place. Dysregulated autophagy also leads to the podocyte loss, impaired and damaged epithelial tubular structures and the progressive dysfunction of the kidney in diabetic kidney disease. There is a little novel data that herbal medicines and their bioactive factors would be capable of replenishing autophagic equilibrium that will maintain renal structure and performance. It is established that the Chinese herbs preparations can regulate the critical signaling pathways of autophagy such as AMPK-mTOR, Beclin-1-LC3 which leads to cellular resistance to hyperglycemia-induced stress [32].

These mechanisms make it possible to maintain the quality control of the state of mitochondria and to block the apoptotic signal by supporting adaptive autophagy and avoiding the overload and pathological autophagic flow. The development of autophagy process also suppresses inflammatory response and fibrotic remodelling that are also critical in the pathogenesis of chronic kidney disease. The fact that herbal compounds have an effect on autophagic reactions, but with different efficacies, is a pointer to a mechanistically distinct nephroprotective modality that can be used to augment conventional metabolism and haemodynamic modes of therapy. This multi-level homeostatic control over the activity of cells suggests a high degree of translationality of the formulation-based therapies in complex renal diseases where the uni-targeted approaches are likely to be ineffective.

5.2 Antioxidant and Anti-Inflammatory Mechanisms

In acute and chronic kidney diseases, oxidative stress and inflammation form the basic components of renal injury. Overproduction of reactive oxygen species triggers lipid peroxidation, DNA damage and pro-inflammatory transcription

factor activation, culminating into tubular and glomerular damage. Isoquercitrin, one of the flavonoid compounds with extensive occurrence in medicinal plants, has been shown to have great nephroprotective effects in the cisplatin-induced nephrotoxicity by inhibiting oxidative stress and inflammatory responses [33]. Its protective effects involve suppression of the increase in ROS, inhibition of pro-inflammatory cytokines, and maintenance of the activity of antioxidant enzymes. There are strong relations of these effects with the inhibition of apoptotic signals and renal cellular membrane stabilization. Synchronous inhibition of oxidative and inflammatory cascades of action makes the plant-derived antioxidants offer a multifaceted protective effect, which is not confined to symptom relief. This multi-mechanistic modulation may be of particular value in nephrotoxic injury, in which oxidative stress and inflammation mutually enhance each other in a self-perpetuating cycle. The antioxidant and anti-inflammatory of herbal constituents are thus a primary pharmacological foundation to nephroprotection and underpin their inclusion into wider renal injury mitigating approaches.

5.3 Modulation of Apoptosis and Cell Death Pathways

Apoptotic and necrotic cell death pathways have played an important role in the pathogenesis of acute kidney injury, particularly in nephrotoxicity caused by drugs. The pathophysiology of cisplatin-induced AKI encompasses the apoptosis of tubular epithelial cells, the dysfunction of the mitochondria and the increase in inflammation. The comprehensive research on cisplatin nephrotoxicity has been able to establish the involvement of the intrinsic apoptotic pathways, including mitochondrial membrane depolarization, caspase activation, and DNA damage response signalling.

Apoptotic cascades may be blocked with pharmacological interventions that can significantly reduce tubular cell loss and renal function. Plant-based products have been proven to counter pro-apoptotic mediators and activate the cytoprotective signal pathways. These effects owe their contribution to the increased cell survival in the case of toxic insults and decreased renal injury. It is worthwhile to note that the modulation of apoptosis does not occur in vacuo, but it is coincidental with oxidative stress, inflammation, and mitochondrial integrity, as also presented in Figure 3. This specific feature of herbal agents convinces the necessity to use them to work out nephroprotective approaches based on formulations, particularly in the acute and toxin-induced kidney failure scenario.

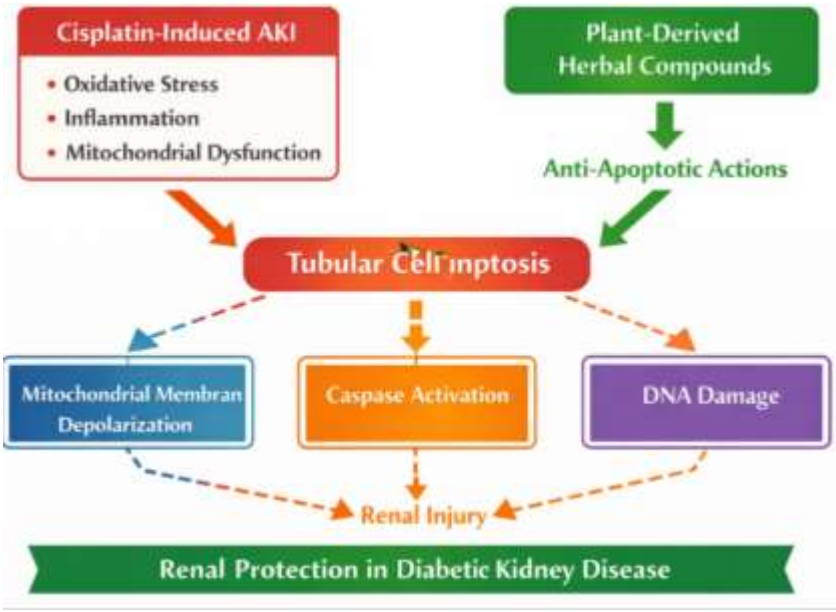

Figure 3. Modulation of Apoptosis and Cell Death Pathways

5.4 Mitochondrial and NAD^+-Dependent Metabolic Protection

One of the main pathological mechanisms of kidney damage is mitochondrial dysfunction, as renal tubular cells are very reliant on oxidative metabolism to generate energy. Interfering with the redox homeostasis, the depletion of NAD^+ pools, and impaired mitochondrial respiration are the reasons why cisplatin causes nephrotoxicity. NAD^+ dependent enzymes, such as sirtuins and poly (ADP-ribose) polymerases, are involved in the regulation of mitochondrial biogenesis, oxidative stress responses, and DNA repair. The malfunction of these pathways increases the renal damage and promotes the impairment of functioning.

Natural products of plant origin are observed to regulate NAD^+ dependent metabolism, which increases mitochondrial resistance and ameliorates oxidative stress in renal tissue. These compounds maintain the energy metabolism and redox balance, which preserves the tubular cell survival and functional recovery of the cells after toxic insults. A promising approach to nephroprotection is as a mitochondrial and metabolic integrity, especially in environments with less protection in conventional therapies. The ability of the herbal agents to induce these basic cellular functions even further justifies their translational application in the prevention and management of kidney diseases.

6. CLINICAL EVIDENCE AND TRANSLATIONAL RELEVANCE

6.1 Human Studies and Clinical Trials

There is still a paucity of direct clinical data on nephroprotective Ayurvedic and plant-based interventions, with most of the available data being based on experimental and preclinical studies. Nonetheless, these studies give mechanistic insights that would give a powerful basis to the translation research. To illustrate, linalool has been shown to exert potent renoprotective properties in nephrotoxicity induced by cisplatin by regulating the effects of inflammatory and oxidative stress, such as inhibition of the HMGB1/TLR4/NF-KB signaling and activation of the Nrf2/HO-1 antioxidant pathway [34]. These pathways have a high relevance to human kidney damage since they are involved in chemotherapy-related AKI and inflammatory renal damage. These findings justify the need to develop preclinical trials in the first phase to assess the safety, dosage, and renal effects of a chosen herbal compound in at-risk groups of patients, such as those receiving nephrotoxic treatments.

6.2 Safety and Tolerability

Clinical translation of herbal nephroprotective agents requires a critical prerequisite that is safety evaluation. More comprehensive biochemical, histopathological, and toxicological evaluations are being more widely used in experimental studies to put renal safety profiles in place. The use of sophisticated forms of analysis including phytochemical profiling using LC/MS has allowed the characterization of herbal extracts in more detail and minimized the possibility of variability and contamination [35,36]. These are used to control quality and standardize, which is required to be reproducible and accepted by regulation. The dose-dependent toxicity, long-term effects of exposure, and the possibility of the presence of potentially nephrotoxic constituents must be considered in particular in nephrology practice. To promote the safe use of herbal preparations as adjunctive therapeutic agents to prevent renal diseases, it will be necessary to establish standardized extraction procedures and reliable safety markers.

6.3 Herb–Drug Interactions in Nephrology Practice

Interaction between herbs and drugs is also a major clinical factor especially to patients with kidney disease who may be taking a number of medications. The compounds found in plants which can alter the inflammatory, oxidative and metabolic pathways can also affect the drug metabolizing enzymes and transporters that have a potential to change the pharmacokinetics of the traditional therapies. Pathway-level modulation, including NF- $B and Nrf2 signaling, is proven experimentally and indicates that the interaction with antihypertensive, antidiabetic, and immunomodulatory drugs can occur [37,38]. Moreover, complicated phytochemical profiles revealed by metabolomic analyses highlight the necessity to focus on the assessment of the risk of interaction. Careful implementation of herbal interventions is needed in transplant patients and complicated CKD patients as the immunosuppressants and narrow therapeutic index drugs should be used in these states with the help of clinical surveillance and evidence-based recommendations.

7. ROLE OF AYURVEDIC FORMULATIONS AS ADJUNCTIVE NEPHROPROTECTIVE THERAPIES

Plant-based and Ayurvedic preparations are increasingly becoming a topic to examine as a complementary intervention to support the usual nephrology therapy particularly in the cases where conventional interventions are not able to protect the environment completely. Such interventions are more appropriately described as add-on therapies to reduce renal harm, enhance cellular resilience, and improve the overall tolerability of the treatment instead of replacing evidence-based medical treatment. Experimental evidence suggests that some phytochemicals do have the potential to be utilized in the targeted therapy of specific molecular pathways that cause nephrotoxicity and therefore provide a mechanistic synergistic effect to those already considered in the pharmacological interventions. An example is using linalool to reduce the cisplatin-induced renal damage by simultaneously inhibiting pro-inflammatory HMGA1/TLR4/NF-KB signalling and consequently inducing Nrf2/HO-1 antioxidant defence pathway which is equally broadly applicable to chemotherapy-related kidney damage [39].

Adjunctive nephroprotective strategies could be useful, particularly in relation to the high-risk clinical groups such as patients undergoing contrast-enhanced imaging or undergoing nephrotoxic chemotherapy. Such environments that contain a given antioxidant and anti-inflammatory effect on herbal preparations toward the reduction of her subclinical renal injury and functional reserve could be viewed as a viable alternative. This possibility in translational applications is also supported by the establishment of phytochemical profiling, in which the quality and characterization of herbal extracts that can be achieved via the LC/MS permit standardization, quality control, and rational selection of doses in [40]. The therapies based on formulations offer a multi-targeted intervention approach that is appropriate to a multifaceted pathophysiology of kidney disease, and such methods are not harmful to add to the streamlined renal care routes, hence their application should be recommended as a preventive and individual treatment of nephrology.

8. RESEARCH GAPS AND FUTURE DIRECTIONS

Since there is increasing experimental evidence indicating that Ayurvedic and herbal preparations have a nephroprotective effect, several gaps need to be tackled before they can become more widely incorporated in the clinical nephrology practice. First among them is the absence of sufficiently powered, properly designed randomized controlled studies that can assess clinically meaningful renal outcomes including the decline in estimated glomerular filtration rate, reduction in proteinuria and occurrence of acute kidney damage. Majority of the available data are based on models of animals which, though informative in terms of its mechanistic aspects, are incapable of addressing the heterogeneity of diseases and responses to treatment in human populations.

The other significant unmet necessity is to develop biomarker-based nephroprotection measures. The inclusion of tested biomarkers of oxidative stress, inflammation, tubular injury, and fibrosis may allow an early identification of renal damage and select the nephroprotective interventions individually. These strategies would contribute to the increase in translational relevance and enable objective assessment of therapeutic response.

The aspect of standardization is still a challenge, especially in the formulation-based therapies. Unreliable results of phytochemicals, variable source of plants, extraction techniques, and phytochemical makeup makes it hard to replicate and be approved by regulators. It will be necessary to establish stringent quality control systems, standardized manufacturing processes and transparent safety records in order to be accepted by the global community. The population-specific issues, regulatory settings, and health system integration should also be considered in future studies in order to guarantee that evidence-based herbal nephroprotective strategies may be utilized safely and efficiently under different clinical conditions.

9. CONCLUSION

The review summarizes the existing evidence that Ayurvedic herbal formulations have a nephroprotective potential using evidence-based and translational approaches. Both experimental and mechanistic research has shown that the chosen herbs and polyherbal preparations have an ability to reduce kidney damage by targeting major pathological events such as oxidative stress, inflammation, mitochondrial dysfunction, apoptosis, dysregulated autophagy, and kidney fibrosis. These multi-target interventions are especially topical in the light of the intricate mechanisms that contribute to the acute injury of kidneys, chronic progression of kidney diseases, and diabetic kidney disease. Together, these data have indicated the existence of pharmacological plausibility and clinical potential of formulation-based nephroprotection. Meanwhile, there are crucial drawbacks that should be considered. Much of the existing information is obtained by preclinical prototypes and standardized formulations and validated clinical trials with renal endpoints are limited. The differences in phytochemical contents, dosage and quality assurance remain a problem in reproducibility and regulatory transferability. The safety concerns, such as the interactions of the herbs and the drugs used along with the long-term adherence, are particularly important in the nephrology groups where polypharmacy is often necessary. In the future, this field will have to evolve in terms of integration of high-quality clinical trial design, biomarker-driven evaluation, and standardised manufacturing practices. Ayurvedic preparations provide potentially useful multi-mechanistic renal protective systems to be studied research-wise and clinically as an adjunct measure to augment current treatments. Nephroprotective herbal formulations can play a significant role in the prevention and personalized kidney care of the future with cautious evidence-based generation and sensible application.

REFERENCES

1. Payal G, Kumar MP, Anamika S. Ayurvedic Approach For The Management Of The Diabetic Nephropathy. Journal of Ayurveda. 2017 Apr;11(2).
2. Raval SK, Patel SG, Dhami AJ, Bhavsar SK. Prophylactic effect of biherbal extracts of Boerhavia diffusa and Tribulus terrestris in Wistar rats against adenine induced chronic kidney disease: haemato-biochemical profile.
3. Kulkarni EG, Pal SH, Phadke JJ. Critical review and analysis of nephro-protective drugs in Ayurveda. J Bio Innov. 2020;9(5b):39-50.
4. Ahmed S, Hasan MM, Mahmood ZA. Globally used antiurolithiatic plants of family Asteraceae: Historical background, mechanism of action, therapeutic spectrum, formulations with doses. Journal of Pharmacognosy and Phytochemistry. 2017;6(3):394-402.
5. Sharma M, Pundir J, Vishwakarma P, Goel RK, Saini M, Saxena KK. Evaluation of nephroprotective activity of Tinospora cordifolia against gentamicin induced nephrotoxicity in albino rats: an experimental study. International Journal of Basic & Clinical Pharmacology. 2019 Jun;8(6):1179.
6. Ambalavanan R, John AD, Selvaraj AD. Nano-encapsulated Tinospora cordifolia (Willd.) using poly (D, L-lactide) nanoparticles educe effective control in streptozotocin-induced type 2 diabetic rats. IET nanobiotechnology. 2020 Dec;14(9):803-8.
7. Srivastava AK. Acetaminophen-induced hepato-and nephrotoxicity and amelioration by hydroalcoholic polyherbal formulation in experimental rodents. International Journal of Green Pharmacy (IJGP). 2018;12(04).
8. Gaurav, Sharma I, Khan MU, Zahiruddin S, Basist P, Ahmad S. Multi-mechanistic and therapeutic exploration of nephroprotective effect of traditional ayurvedic polyherbal formulation using in silico, in vitro and in vivo approaches. Biomedicines. 2023 Jan 9;11(1):168.
9. Dongre P, Majumdar A. Network pharmacology analysis of Chandraprabha Vati: A new hope for the treatment of Metabolic Syndrome. Journal of Ayurveda and Integrative Medicine. 2024 May 1;15(3):100902.
10. Putra IM, Fakhrudin N, Nurrochmad A, Wahyuono S. A review of medicinal plants with renoprotective activity in diabetic nephropathy animal models. Life. 2023 Feb 16;13(2):560.
11. Shahin DH H, Sultana R, Farooq J, Taj T, Khaiser UF, Alanazi NS, Alshammari MK, Alshammari MN, Alsubaie FH, Asdaq SM, Alotaibi AA. Insights into the uses of traditional plants for diabetes nephropathy: a review. Current issues in molecular biology. 2022 Jun 29;44(7):2887-902.
12. Rahman MA, Akter S, Dorotea D, Mazumder A, Uddin MN, Hannan MA, Hossen MJ, Ahmed MS, Kim W, Kim B, Uddin MJ. Renoprotective potentials of small molecule natural products targeting mitochondrial dysfunction. Frontiers in Pharmacology. 2022 Jul 15;13:925993.

13. Alam S, Sarker MM, Sultana TN, Chowdhury MN, Rashid MA, Chaity NI, Zhao C, Xiao J, Hafez EE, Khan SA, Mohamed IN. Antidiabetic phytochemicals from medicinal plants: prospective candidates for new drug discovery and development. Frontiers in endocrinology. 2022 Feb 24;13:800714.
14. Zhou Z, Niu H, Bian M, Zhu C. Kidney tea [Orthosiphon aristatus (Blume) Miq.] improves diabetic nephropathy via regulating gut microbiota and ferroptosis. Frontiers in pharmacology. 2024 Jun 19;15:1392123.
15. Lin CH, Shih CC. The ethyl acetate extract of Phyllanthus emblica L. alleviates diabetic nephropathy in a murine model of diabetes. International Journal of Molecular Sciences. 2024 Jun 18;25(12):6686.
16. Ojo OA, Ogunlakin AD, Akintayo CO, Olukiran OS, Adetunji JB, Ajayi-Odoko OA, Ogwa TO, Molehin OR, Ojo OO, Mothana RA, Alanzi AR. Spilanthes filicaulis (Schumach. & Thonn.) CD Adams leaves protects against streptozotocin-induced diabetic nephropathy. Plos one. 2024 Apr 19;19(4):e0301992.
17. Bylan D, Khalil A, Shebaby W, Habchy C, Nasser S, Faour WH, Mroueh M. Lebanese cannabis oil extract protected against folic acid-induced kidney fibrosis in rats. PloS one. 2024 Dec 12;19(12):e0311790.
18. Yarijani ZM, Najafi H, Shackebaei D, Madani SH, Modarresi M, Jassemi SV. Amelioration of renal and hepatic function, oxidative stress, inflammation and histopathologic damages by Malva sylvestris extract in gentamicin induced renal toxicity. Biomedicine & Pharmacotherapy. 2019 Apr 1;112:108635.
19. Julovi SM, Dao A, Trinh K, O'Donohue AK, Shu C, Smith S, Shingde M, Schindeler A, Rogers NM, Little CB. Disease-modifying interactions between chronic kidney disease and osteoarthritis: a new comorbid mouse model. RMD open. 2023 Aug 1;9(3):e003109.
20. Sohaim S, Mohammed S, Amin E, Ali HM, Abdelbakky M. Date palm seed extract and herbal mixture mitigate gentamicin-induced renal injury in mice: Role of protease-activated receptors (PARs) and retinoid X receptor alpha (RXR-α). Journal of Herbmed Pharmacology. 2022 Apr 1;11(2):286-95.
21. Bencheikh N, Ouahhoud S, Cordero MA, Alotaibi A, Fakchich J, Ouassou H, Assri SE, Choukri M, Elachouri M. Nephroprotective and antioxidant effects of flavonoid-rich extract of Thymelaea microphylla Coss. et Dur aerial part. Applied Sciences. 2022 Sep 15;12(18):9272.
22. Bencheikh N, Bouhrim M, Kharchoufa L, Al Kamaly OM, Mechchate H, Es-Safi I, Dahmani A, Ouahhoud S, El Assri S, Eto B, Bnouham M. The nephroprotective effect of Zizyphus lotus L.(desf.) fruits in a gentamicin-induced acute kidney injury model in rats: a biochemical and histopathological investigation. Molecules. 2021 Aug 8;26(16):4806.
23. Sharma C, Rani J, Kapoor M, Kaur N, Gawdiya S, Pradhan SK. Comparative metabolomics-based screening of fruit extracts of less-known melon (Cucumis melo var. agrestis) accessions collected from dry terrain of North India by using HPLC–DAD. Natural Product Research. 2024 Oct 30:1-9.
24. Bokolo B, Adikwu E. Ethanolic leaf extract of Ipomoea aquatica Forsk abrogates cisplatin-induced kidney damage in albino rats. Journal of Nephropharmacology. 2018 Nov 6;8(1):e02-.
25. Hooshyar N, Sedighi M, Hooshmand M, Valizadeh R, Ebrahimi S, Khosravifarsani M, Ghasemi B, Nowrouzi N, Nasri P. Mechanistic impact of medicinal plants affecting cisplatin-induced nephrotoxicity; an overview. Immunopathologia Persa. 2019 May 5;5(1):e07-.
26. Yang Y, Zhu X, Yu G, Ma J. Protective effect of pyxinol, one active ingredient of Lichenes on cisplatin-induced nephrotoxicity via ameliorating DNA damage response. Frontiers in pharmacology. 2021 Sep 6;12:735731.
27. Mufti A, Feriani A, Ouchari W, Mandour YM, Tlili N, Ibrahim MA, Mahmoud MF, Sobeh M. Leonotis ocymifolia (Burm. f.) Iwarsson aerial parts aqueous extract mitigates cisplatin-induced nephrotoxicity via attenuation of inflammation, and DNA damage. Frontiers in Pharmacology. 2023 Aug 1;14:1221486.
28. Georgiev T, Nikolova G, Dyakova V, Karamalakova Y, Georgieva E, Ananiev J, Ivanov V, Hadzhibozheva P. Vitamin E and silymarin reduce oxidative tissue damage during gentamycin-induced nephrotoxicity. Pharmaceuticals. 2023 Sep 27;16(10):1365.
29. Wang FL, Wang YH, Han L, An HY, Zhang JH, Zhang XY, Chen ZQ, Qin JG. Renoprotective effect of Yiqi Yangyin Huayu tongluo formula against diabetic nephropathy in diabetic rats. Evidence-Based Complementary and Alternative Medicine. 2018;2018(1):4276052.
30. Chinnappan SM, George A, Thaggikuppe P, Choudhary Y, Choudhary VK, Ramani Y, Dewangan R. Nephroprotective effect of herbal extract Eurycoma longifolia on paracetamol-induced nephrotoxicity in rats. Evidence-Based Complementary and Alternative Medicine. 2019;2019(1):4916519.
31. Liu P, Zhu W, Wang Y, Ma G, Zhao H, Li P. Chinese herbal medicine and its active compounds in attenuating renal injury via regulating autophagy in diabetic kidney disease. Frontiers in endocrinology. 2023 Mar 3;14:1142805.
32. Chen J, Liu Q, He J, Li Y. Immune responses in diabetic nephropathy: Pathogenic mechanisms and therapeutic target. Frontiers in Immunology. 2022 Aug 15;13:958790.
33. Li J, Gong X. Tetramethylpyrazine: an active ingredient of Chinese herbal medicine with therapeutic potential in acute kidney injury and renal fibrosis. Frontiers in Pharmacology. 2022 Jan 25;13:820071.
34. Chen YQ, Chen HY, Tang QQ, Li YF, Liu XS, Lu FH, Gu YY. Protective effect of quercetin on kidney diseases: From chemistry to herbal medicines. Frontiers in pharmacology. 2022 Sep 2;13:968226.
35. Liu P, Zhu W, Wang Y, Ma G, Zhao H, Li P. Chinese herbal medicine and its active compounds in attenuating renal injury via regulating autophagy in diabetic kidney disease. Frontiers in endocrinology. 2023 Mar 3;14:1142805.
36. Wang H, Xia W, Long G, Pei Z, Li Y, Wu M, Wang Q, Zhang Y, Jia Z, Chen H. Isoquercitrin ameliorates cisplatin-induced nephrotoxicity via the inhibition of apoptosis, inflammation, and oxidative stress. Frontiers in pharmacology. 2020 Dec 18;11:599416.

37. McSweeney KR, Gadanec LK, Qaradakhi T, Ali BA, Zulli A, Apostolopoulos V. Mechanisms of cisplatin-induced acute kidney injury: pathological mechanisms, pharmacological interventions, and genetic mitigations. Cancers. 2021 Mar 29;13(7):1572.
38. Iskander A, Yan LJ. Cisplatin-induced kidney toxicity: Potential roles of major NAD+-dependent enzymes and plant-derived natural products. Biomolecules. 2022 Aug 5;12(8):1078.
39. Mohamed ME, Abduldaium YS, Younis NS. Ameliorative effect of linalool in cisplatin-induced nephrotoxicity: the role of HMGB1/TLR4/NF-κB and Nrf2/HO1 pathways. Biomolecules. 2020 Oct 28;10(11):1488.
40. Prasanth D, Reddy LS, Dasari T, Bhavanam PR, Ahmad SF, Nalluri R, Pasala PK. LC/MS-Based profiling of hedyotis aspera whole-plant methanolic extract and evaluation of its nephroprotective potential against gentamicin-induced nephrotoxicity in rats supported by in silico studies. Separations. 2023 Oct 30;10(11):552.