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Herbal medicine in the management of renal disease: A comprehensive review of its potential for acute kidney injury, chronic kidney disease, diabetic nephropathy, and hypertension

Ali Rastegar-Kashkouli[1*], Mohsen Jafari[1], Pourya Yousefi[1], Shahrzad Alimohammadi[2,3], Hoda Miranzadeh Mahabadi[1], Shiva Toumaj[1], Zahra Taheri[4], Kamran Shirbache[5], Ali Shirbacheh[6], Hossein Mardanparvar[7], Hamid Nasri[1*]

Abstract

Each year, a considerable number of individuals are diagnosed with potentially life-threatening renal failure, encompassing acute kidney injury (AKI) and chronic kidney disease (CKD). New natural herbal compounds, whether used in isolation or combined with medical treatments and an appropriate regime, have been suggested for the management of renal failure. The etiology of AKI remains uncertain; nevertheless, several factors have been proposed as potential causative agents that can lead to renal failure, including renal ischemia-reperfusion injury (IRI), nephrotoxicity, sepsis, administration of radiocontrast agents, and exposure to heavy metal ions. Several commonly utilized herbs with anti-diabetic and antihypertensive properties, known for their antioxidant, anti-inflammatory, and vasorelaxant effects, have been recognized as efficacious therapeutic agents in the management of CKD. The management of renal failure typically involves treating the underlying diseases, such as IRI, sepsis, and diabetes. However, if addressing the root cause is not possible, the focus shifts to managing complications like hypertension and proteinuria.

Keywords: Herbal medicine, Acute kidney injury, Chronic kidney disease, Diabetic nephropathy, Hypertension

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Introduction

Each year, a considerable number of individuals are diagnosed with potentially life-threatening renal failure, encompassing acute kidney injury (AKI) and chronic kidney disease (CKD). They are closely linked disorders that are risk factors for each other and cardiovascular disease (CVD) (1). Figure 1 depicts the categorization of renal failure.

The treatment of AKI and CKD requires significant efforts, often involving the utilization of herbal medicine as an alternative therapeutic approach encompassing various plant-based components and extracts. Presently, this method has emerged as a highly effective and safe treatment modality. Plants serve as rich reservoirs of bioactive compounds characterized by potent antioxidant properties and significant anti-inflammatory activity. As a result, the utilization of herbal drugs for disease prevention and therapeutic purposes has been consistently evolving globally. Therefore, in recent years, new natural herbal compounds, whether used in isolation or combined with medical treatments and an appropriate regime, have been suggested for the management of renal failure (2). The primary objective of this review is to present an array of effective herbal products aimed at the treatment of AKI and CKD.

Acute kidney injury

AKI is characterized by a rapid decline in renal function, indicated by an abrupt increase in serum creatinine (Cr) and blood urea nitrogen (BUN) levels. The etiology of

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[1]Nickan Research Institute, Isfahan, Iran. [2]Department of Immunology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary. [3]Doctoral School of Molecular Medicine, University of Debrecen, Debrecen, Hungary. [4]Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran. [5]Independent researcher, 40 Av de Charles de Gaulle, 79000 Niort, France. [6]Niort Hospital, Niort, France. [7]Department of Nursing, Faculty of Nursing and Midwifery, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.
***Corresponding Authors:** Ali Rastegar-Kashkouli, Email: Ali.rastegar.med@gmail.com; Prof. Hamid Nasri, Email: hamidnasri@yahoo.com, Email: hamidnasri@med.mui.ac.ir

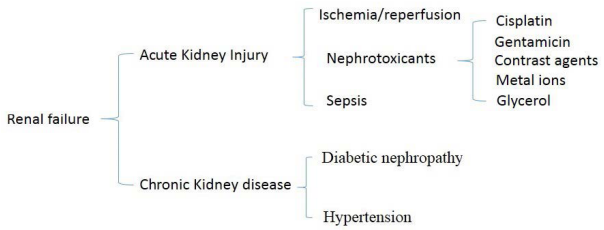

Figure 1. The categorization of renal failure.

Implication for health policy/practice/research/ medical education

A literature review demonstrated that medicinal plants have been applied as therapeutic agents for treating renal diseases alone or in combination with conventional treatments and appropriate regimens. Also, the treatment of underlying disease and reducing kidney disease risk factors are two key points in the management of these patients' treatment.

AKI remains uncertain; nevertheless, several factors have been proposed as potential causative agents that can lead to renal failure, including renal ischemia-reperfusion injury (IRI), nephrotoxicity, sepsis, administration of radiocontrast agents, and exposure to heavy metal ions (Table 1) (3).

Ischemia-reperfusion injury

IRI plays a crucial role in the development and progression of kidney failure. When blood flow to the kidneys is temporarily disrupted, as in cases of renal artery occlusion or low blood pressure, ischemia occurs, leading to an inadequate supply of oxygen and nutrients to renal tissues. Subsequently, during the reperfusion phase, the sudden restoration of blood flow can trigger a cascade of events, including the generation of reactive oxygen species, inflammation, and activation of immune cells. These processes contribute to cellular damage, oxidative stress, and impaired renal function, ultimately leading to kidney failure (4).

AKI induced by nephrotoxicants

Nephrotoxicants constitute a significant etiological factor contributing to the occurrence of AKI. Clinical studies have identified various agents, including cisplatin, gentamicin, glycerol, radiocontrast agents, and heavy metal ions such as mercury, as known nephrotoxic substances (1).

Cisplatin

Cisplatin is an antineoplastic chemotherapeutic agent employed in the treatment of various malignancies, encompassing cancers of the head and neck, lung, ovary, and breast. Cisplatin toxicity is dose-dependent and is accompanied by a significant mortality rate. Following the administration of doses exceeding 50 mg/m^2 of body surface area, a decline in glomerular filtration rate (GFR) is observed (5). Furthermore, cisplatin-induced nephrotoxicity may arise due to various factors including low blood calcium and erythropoietin levels, elevated plasma uric acid and aldosterone concentrations, renal tubular acidosis, isosthenuria, temporary proteinuria, thrombotic microangiopathy, and the development of CKD (5).

Gentamicin

Gentamicin, an aminoglycoside antibiotic, is commonly administered as the first-line treatment for some severe infections that pose a significant risk of nephrotoxicity. The precise mechanisms underlying gentamicin-induced AKI have yet to be fully elucidated. However, anticipated mechanisms encompass the provocation of oxidative stress, apoptosis, necrosis, elevation of endothelin I levels, and the accumulation of monocytes/macrophages within the renal tissue. Several studies have demonstrated that a range of herbal antioxidants have the ability to control gentamicin-induced AKI (6).

Glycerol

Glycerol, a component present in triglycerides, finds extensive application in food processing and pharmaceutical formulations due to its inherent properties as a sweetening agent and hygroscopic substance. The pathogenesis of glycerol-induced AKI involves toxic effects

Table 1. Herbal drugs which prevent AKI

Causative gents of AKI		Plants/Pure herbal compounds				
Ischemia/reperfusion		*Brassica rapa L* (1)	*Cuscuta Chinensis* (1)	*Glycyrrhiza glabra* (1)	Salvia miltiorrhiza (1)	Crocus Sativus (1)
Nephrotoxicants	Cisplatin	Soybean (1)	*Scutellaria Barbata* (1)	*Lepidium sativum* (1)	Zingiber officinale (1)	Panax Ginseng (1)
	Gentamicin	*Tephrosia purpurea* (1)	*Momordica dioica* (1)	*Andrographis Paniculata* (1)	*Casuarina equisetifolia* (1)	*Allium sativum* (1)
	Contrast agents	Aconitum (1)	*Silybum marianum* (1)	*Azima tetracantha* (1)	*Zingiber officinale* (1)	Silymarin (11)
	Metal ions	Green tea (12)	Dongchongxiacao (Cordyceps) (13)	Grape seed (14)	Silymarin (15)	Vitamin E (16)
	Glycerol	*Juglans Sinensis* (1)	*Rheum palmatum* (1)	*Drynaria fortune* (1)	*Curcuma Longa* (17)	*Drynaria Fortune* (18)
Sepsis		*Salvinia auriculata* Aubl (19)	*Salviae miltiorrhiza* (20)	*Oregano* (21)	Phyllanthus acidus (22)	Alpinetin (23)

on renal tubular cells, oxidative stress, inflammation, and IRI (7).

Radiocontrast agents

Radiocontrast plays a significant role in the occurrence of reversible AKI and accounts for approximately 10% of all cases of hospital-acquired AKI. It reduces renal blood flow and results in postoperative AKI. The mechanisms underlying contrast agent-induced AKI appear to involve multiple factors, including direct toxicity on renal tubular epithelial cells, renal medullary hypoxia, and imbalances in vasodilator and vasoconstrictor factors. These factors encompass the activities of nitric oxide, prostaglandins, endothelin, and reactive oxygen species (ROS) (8).

Heavy metal ions

Heavy metal ions, such as mercury (e.g., mercuric chloride or methylmercury), chromium, and cadmium have been identified as sources of free radicals that have the potential to induce nephrotoxicity. Renal damage caused by mercury primarily manifests in the kidney, where direct toxic effects and the accumulation of mercury complexes in the proximal straight tubules of the nephrons are observed. Additionally, chromium intoxication has been recognized as a potential inducer of both AKI and CKD (9).

AKI induced by sepsis

Septic shock, being the predominant etiology of AKI, is significantly associated with elevated rates of morbidity and mortality. Sepsis-induced AKI, in particular, exhibits a mortality rate of 70%, representing a substantial increase compared to the overall mortality rate observed in AKI cases. Approximately 35% of individuals admitted to the intensive care unit (ICU) experience AKI, with nearly half of these cases arising secondary to sepsis (10). Table 1 provides a summary of herbal compounds that have been documented for their potential in preventing AKI induced by the aforementioned factors. Herbal compounds have exhibited potent properties and hold promise as therapeutic agents and/or protective agents against conditions associated with oxidative stress and inflammation. For instance, certain herbs possessing antioxidant, vasodilatory, and diuretic properties have demonstrated nephroprotective effects in cases of glycerol-induced AKI. Moreover, herbs with antimicrobial and anti-inflammatory properties can be employed in the management of sepsis-associated AKI (1,11-14).

Chronic kidney disease

While CKD frequently contributes to the progression towards end-stage renal disease (ESRD), it serves as a distinct and substantial risk factor for the development of CVD and represents the leading cause of mortality among individuals with CKD (1).

An underlying commonality that encompasses all these syndromes is the presence of inflammation and oxidative stress. Two pivotal components play a crucial role in the progression of CKD: the primary etiology, particularly diabetes; and secondary contributing factors such as elevated blood pressure and proteinuria (1).

Diabetic nephropathy

Insulin resistance promotes the proliferation and division of renal cells, facilitates the production of various growth factors such as transforming growth factor beta, upregulates the expression of receptors such as angiotensin II type 1 receptor in mesangial cells, and reduces the synthesis of nitric oxide by endothelial cells. These variations develop diabetic nephropathy (DN) which often contributes to CKD.

Diabetic nephropathy constitutes a significant etiology of renal failure and ESRD. Oxidative stress might play an important role in the pathogenesis of DN. The first laboratory irregularity is a positive albuminuria test. Risk factors associated with the progression of DN include suboptimal blood glucose control, prolonged duration of diabetes, concomitant presence of other microvascular complications, and familial history of DN and hypertension (2).

Diabetic nephropathy-related herbal medicines

In recent decades, herbal medicines have gained significant recognition, and there is a growing global demand for the utilization of natural products in the treatment of diabetes. Controlling blood glucose levels can decrease complications in diabetic patients, avoid oxidative stress problems, and improve recovery. Herbs possessing antioxidant properties have demonstrated effectiveness in controlling diabetes mellitus (DM) and improving DN (24, 25). In Table 2, some curative plants against DM and DN are shown with the recommended mechanism of action (24,25).

Non-diabetic CKD

Hypertension

Hypertension is the most prevalent comorbidity in CKD. Hypertension is characterized by systolic blood pressure (SBP) of ≥140 mm Hg and diastolic blood pressure (DBP) of ≥90 mm Hg (26). Experimental studies have shown that CKD patients without hypertension have greater GFR than similar patients with hypertension (27,28). Several studies have reported associations between a reduction in proteinuria with antihypertensive treatment and slower progression of renal disease (29).

A substantial body of scientific evidence has underscored the efficacy of herbal interventions in managing hypertension and CVD (30). Frequently used antihypertensive herbs with properties such as antioxidant, vasorelaxant, and anti-inflammation are listed in Table 3.

Use of diuretic herbs in patients with CKD

Diuretics play a significant role in the control of

Table 2. Herbals which improve DN with their suggested mode of action (24,25)

Herb	Anti-diabetic mode of action
Terminalia arjuna	Down-regulation of mitogen-activated protein kinases (phospho-ERK1/2, phospho-p38) and NF-κB (p65). Arjunolic acid may prevent hyperglycemia-induced oxidative stress
Curcuma longa	Adjusting aldose reductase, ATPases, superoxide dismutase, catalase, glucose-6-phosphate dehydrogenase, glutathione, transaminases, lactate dehydrogenase, and membrane polyunsaturated fatty acid/saturated fatty acid ratio
Trigonella foenum-graecum	Hypoglycemic, hypocholesterolemic, and hyperinsulinemic effects
Psidium guajava	Decreasing malate dehydrogenase and ROS levels
Zingiber officinale	Adjusting cytosolic and mitochondrial enzymes like glucose-6-phosphate dehydrogenase, lactate dehydrogenase, sorbitol dehydrogenase, malate dehydrogenase, and glutamate dehydrogenase
Aloe vera	Adjusting fasting blood sugar and plasma insulin, antioxidant activity
Cladophora glomerata	Improving hyperglycemia, hypertriglyceridemia, insulin resistance, and renal morphology, and preventing DN through protein kinase C

Table 3. Frequently used antihypertensive herbs with antioxidant, vasorelaxant, and anti-inflammatory properties (30)

Herb	Antioxidant	Vasorelaxant	Anti-inflammation
Allium sativum	Scavenges ROS, Increases antioxidants, Reduces NADPH activity	Increases NO and H2S, Inhibits ACE and eNOS uncoupling	Inhibits NF-κB and VCAM-1
Andrographis paniculata	Scavenges ROS, Increases antioxidants	Increases NO, Inhibits ACE and Ca^{2+} channels	Inhibits NF-κB
Apium graveolens	Increases antioxidants	Blocks Ca^{2+} channels	-
Camellia sinensis	Scavenges ROS, Increases antioxidants, Reduces NADPH activity	Increases flow-mediated dilation (FMD) and NO, Blocks AT1 receptor and eNOS uncoupling	Inhibits NF-κB, VCAM-1, and TNF-α
Coptis chinensis	Increases antioxidants, Reduces NADPH activity	Inhibit EMP, eNOS uncoupling, and Ca^{2+} channels	Inhibits NF-κB and VCAM-1
Coriandrum sativum	Scavenges ROS, Increases antioxidants	-	Inhibits NF-κB
Crataegus spp.	Scavenges ROS	Inhibits eNOS uncoupling	Inhibits TNF-α and IL-6
Crocus sativus	Scavenges ROS, Increases antioxidants	Blocks Ca^{2+} channels and eNOS uncoupling	Inhibits NF-κB
Hibiscus sabdariffa	Scavenges ROS, Increases antioxidants	Increases NO, Blocks Ca^{2+} channels	-
Panax	Increases antioxidants	Inhibits eNOS uncoupling	Inhibits NF-κB, TNF-α, and IL-6
Salviae miltiorrhizae	Scavenges ROS, Increases antioxidants	Opens K_{ATP} channels Increases NO, Inhibits ACE and Ca^{2+} channels	Inhibits NF-κB, VCAM-1, and TNF-α
Zingiber officinale	Scavenges ROS, Inhibits lipid peroxidation		-
Nigella sativa	-	Blocks Ca^{2+} channels	-
Cymbopogoncitratus	-	Increases NO, Blocks Ca^{2+} channels	-
BidenspilosaL.	-	-	Inhibits NF-κB and TNF-α

hypertension through an adjustment of the urine volume. Non-diabetic individuals with CKD commonly necessitate the administration of multiple antihypertensive medications in order to achieve optimal blood pressure levels. Furthermore, the elevation in extracellular fluid volume constitutes a primary underlying factor in the development of hypertension among patients with CKD, thereby necessitating the prominent inclusion of diuretics as a key component in the antihypertensive regimen for the majority of affected individuals. Multiple studies have indicated that patients typically required two to three antihypertensive drugs on average to achieve their target blood pressure. It is noteworthy that a substantial proportion of these patients, ranging from 70% to 80%, were prescribed diuretics as an additional treatment for improved blood pressure management (2). Medicinal herbs have gained recognition as potent sources of diuretic agents, with numerous studies confirming their diuretic effects. The use of herbal plants as diuretics (*Phyllanthus amarus, Bixa Orellana, Tropaeolum majus L, Taraxacum officinale, Viscum articulatum Burm, Allium sativum, Mangifera Indica, Elettaria cardamomum, Lepidium sativum,* and *Lepidium latfolium*) has seen a recent increase and holds promise in the treatment of hypertension (31,32).

Conclusion

Medicinal plants hold significant therapeutic potential

in the management of diverse conditions including AKI, CKD, DN, and hypertension. The management of renal failure typically involves treating the underlying diseases, such as IRI, sepsis, and diabetes. However, if addressing the root cause is not possible, the focus shifts to managing complications like hypertension and proteinuria.

Authors' contribution

Conceptualization: ARK, SA, HN.
Methodology: HN, ARK, SA.
Validation: HN, SA, HM, ARK.
Investigation: SA, ARK, MJ, PY, HN.
Resources: ARK, HN, HM.
Data curation: HN, ARK.
Writing–original draft preparation: HN, ARK.
Writing–review and editing: SA, HM, ZT, KS, AS, HMM, MJ, PY, ST.
Visualization: HN.
Supervision: ARK, HN.
Project administration: HN, ARK.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

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