

An update on administration of herbal drugs in renal failure patients

Fatemeh Dehghan-Shahreza*

Department of Clinical Science, School of Veterinary Medicine, Ferdowsi University of Mashhad, Mashhad, Iran

Correspondence to:

Fatemeh Dehghan-Shahreza;

Email:

F_dehghan66@yahoo.com

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Abstract

End-stage kidney disease is a condition that patients need dialysis or renal transplant and neither is completely able to compensate natural kidney function. They always suffer from unsatisfied situation. Hemodialysis receiver patients usually are susceptible to hemo-incompatibility induced oxidative stress due to interaction of patient blood and artificial kidney, which greatly reduce physical function and accelerate cardiovascular events. Oxidative injury related to chronic azotemia induces endothelial dysfunction and increases pro-inflammatory pathways. Therefore, recently much attention has been directed toward administration of natural antioxidant components to improve renal dysfunction and minimize complications in chronic kidney disease patients. The administration of medicinal plants due to containing various vitamins and bioactive substance is common in renal failure patients in the world, but they may aggravate unpredictably function and structure of kidney by interstitial fibrosis and tubular atrophy and also glomerulosclerosis. Therefore, it is crucial to evaluate attentively the possible side effects of various herbal drugs in end-stage renal disease and especially in dialysis patients.

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Introduction

Renal failure, as a common severe complication of several systemic disorders such as hypertension and diabetic mellitus, is not single event and reflects ongoing insults in multi-organs. It may lead to the failure of the kidney to eliminate waste metabolites and regulate fluid homeostasis correctly. Numerous agents can alter renal structure and induce pathogenic mechanisms in developing micro-vascular damage, which, reduce regenerative capacity of tubular cells, promote apoptosis and lead to tubular atrophy/interstitial fibrosis, and finally end-stage renal failure. End-stage kidney disease is a condition that patients need dialysis or renal transplant that neither is completely able to compensate natural kidney function. These patients always suffer from unsatisfied situation. Hemodialysis receiver patients usually are susceptible to hemo-incompatibility induced oxidative stress due to interaction of patient blood and artificial kidney, which greatly reduce physical function and accelerate cardiovascular events (1).

Materials and Methods

PubMed, EBSCO, directory of open access journals (DOAJ), Google Scholar, and Web of Science were searched with key words

Core tip

The administration of medicinal plants due to containing various vitamins and bioactive substance is common in renal failure patients in the world, but they may aggravate unpredictably function and structure of kidney by interstitial fibrosis and tubular atrophy and also glomerulosclerosis. Therefore, it is crucial to evaluate attentively the possible side effects of various herbal drugs in end-stage renal disease and especially in dialysis patients.

as diabetic mellitus, hypertension, herbal drugs, renal failure, oxidative stress, endothelial dysfunction, end-stage kidney disease, and hemodialysis and also aristolochic acid nephropathy.

Oxidative stress in diabetic mellitus and hypertension

In the United States, the diabetic mellitus and hypertension are main reasons of end-stage renal disease that induce oxidative stress and inflammatory processes are the most important mechanisms contributing to renal failure pathogenesis. Hyperglycemia in diabetic patients is originated from uncontrolled generation of reactive oxygen and nitrogen species throughout forming advanced

glycosylation end-products and disrupting electron transport chain in tubular and glomerular mitochondria that eventually make progressive alteration in structural and functional macromolecules, increase over expression of pro-inflammatory mediators such as chemokines and adhesion molecules, lead to infiltration poly-morphonuclear leukocyte enhancement to inflamed sites, and extensive induction of radical generation (2).

Likewise, the observations have indicated systemic hypertension can lead to enhanced reactive species production interactively, in microvascular renal tissue, by down-regulating super oxide dismutase enzymes activities and up-regulating NADPH oxidase activity. Furthermore, renal vascular involvement is the most major reason of secondary hypertension which will lead to accumulation of leukocytes and activated T cell in tubulointerstitial area. This phenomenon will result in progressive initiation of inflammatory and oxidative injury, deteriorate renal endothelial function that further aggravate the fibrosis processing in interstitial area with finally reduced glomerular filtration rate. Therefore, in end-stage kidney disease, there is no ability to fight efficiently against oxidative stress processes (3).

Additionally, hemodialysis patients are highly susceptible to cardiovascular dysfunction that is the main cause of their mortality. Oxidative injury related to chronic azotemia induces endothelial dysfunction and increases pro-inflammatory pathways. This situation looks to be in part associated to mitochondrial dysfunction that initiates an elevated electron leakage which is originated from oxidative phosphorylation reaction with a resultant reactive species production. Therefore, anti-inflammatory/oxidative modality can prevent/reduce hemodialysis complications (4). Vegetables and fruits have been known as a source of natural components with chemoprotective properties, feasible availability and low cost. Recently much attention has been directed toward administration of natural antioxidant components to improve renal dysfunction and minimize complications in chronic kidney disease patients. In this review, we have summarized the therapeutic effects of herbal chemoprotective constituents on ameliorating and slowing renal failure related complications, and secondly, to imply current knowledge on occurrence of unpredictable side effects herbal remedies in renal failure patients.

Herbal antioxidant components and renal failure

In the studies of Chander & Chopra and Giovannini et al, the protective effects of resveratrol on rats' kidney structure and function with ischemia/reperfusion injury was investigated. They found that resveratrol, as a stilbene polyphenol found mostly in grapes, is responsible for preventing ischemia and reperfusion induced tubulointerstitial lipid peroxidation by activating a nitric oxide-dependent processes. Ischemia could be an initiating condition in acute renal damage which aggravates the process of chronic rejection following kidney transplantation. Likewise, the study regarding influence of grape powder supplementation on antioxidant enzyme levels and inflammatory in-

dices in hemodialysis patient have showed that patients receiving 12 g grape powder supplementation plus grape jelly daily are enhanced glutathione peroxidase activity and reduced inflammatory indices such as C-reactive protein, after supplementation, in comparison with hemodialysis patients receiving only grape jelly (5,6). Moreover, Chen et al have found, dialysate containing herbal antioxidants such as epigallocatechin gallate are able to reduce hemodialysis associated oxidative complications. They detected that, large amount generation of reactive species by polymorphonuclear cells decreased during supplementation of dialysate fluid with epigallocatechin gallate. They also detected a favorable procedure that is able to enhance enhance total antioxidant capacity and prevent chronic cardiovascular dysfunction mediated by chronic azotemia in hemodialysis receiver patients (7).

In addition, Tavafi found that rosmarinic acid and *Satureja khuzestanica* (Savory) essential oil consumption could preserve glomerular function and structure in diabetic rats. In another study administration of *Aster koraiensis*, rosmarinic acid, savory, coenzyme Q10 and *Lindera strychnifolia* root extract were capable to reduce the process of glomerulosclerosis in diabetic kidney disease rodents (8).

Study regarding the efficacy of pomegranate juice in preclinical investigations has detected promising results. To found the improving potency of pomegranate juice for inhibiting oxidative stress and pro-inflammatory status in hemodialysis patients, Shema-Didi et al conducted a study on 101 chronic hemodialysis patients, which divided randomly in two groups — one pomegranate juice receivers and placebo receivers as control group — during each dialysis session at three times a week for one year. They found that pomegranate juice consumption resulted in a significant time response diminution in systolic blood pressure, protein and lipid oxidation, blood lipid level, polymorphonuclear cell preparing and pro-inflammatory mediator levels. Pomegranate juice receivers are hospitalized for shorter time than hemodialysis patients which enrolled in control group. These promising results determined prolonged pomegranate juice consumption decreases the accelerated cardiovascular disorders, alleviates oxidative damage induced atherosclerosis and improves efficacy of the innate immunity against infection pathogens and therefore increases quality of life in hemodialysis patients (9,10). Also, polyphenol components in various fruits, vegetables and nuts are potential natural antioxidants which have chemoprotective activity in living systems. Ellagic acid, a phenolic constituent, has been extremely investigated in various experimental researches. Their results have been shown, this substance is potent anti-inflammatory agent through inhibiting nuclear factor-kappa B pathways, antioxidant and anti-diabetic substance that prevents diabetic mellitus associated end-stage renal failure and attenuates chronic kidney disease complications such as cardiovascular events by promoting overexpression of endothelial antioxidant enzymes. Additionally, *Curcuma longa*, a member of *Zingiberaceae* family, contains yellow pigment with high potent antioxidant

efficiency, is called curcumin. This chemoprotective pigment is able to reserve cardiovascular normal function in nephrectomy rats due to maintain from normal oxidative phosphorylation reaction in cardiac mitochondria during uremic induced oxidative imbalance. It also augments indirectly antioxidant capacity by activating protein kinase C phosphorylate nuclear factor erythroid 2-related factor-2, thereby; alleviate cardiotoxicity of excess reactive species generation in uremic rats (11).

The major astringency component in green tea leaf is catechins. It is reported this phenolic constituent is responsible to decrease cardiovascular risk factors, blood pressure, inflammatory indices like fibrinogen and serum amyloid A. In experimental studies, in animal models, it is an angiotensin II inhibitor, thereby diminishing angiotensin II induced oxidative damage to renal and cardiac micro-vascular cells. More recently an investigation has been found, the green tea reduces property of pro-inflammatory proteins such as fibrinogen, attenuate inflamed condition and also is a prevention strategy of microvascular dysfunctions in end-stage renal disease patients. Likewise, it can stop activated signaling pathways induced oxidative injury, such as p22^{phox} protein, as a subunit of NADH/NADPH oxidase in vascular endothelial cells and leukocytes in hemodialysis patients (12).

According to these findings, the administration of herbal remedies may enhance anti-oxidative, anti-inflammatory efficacies in dialysis.

In fact, a delay in progression of chronic kidney disease through control of hypertension, diabetes management, improvement of metabolic acidosis, may attenuate the acceleration of chronic renal disease course, or even may ameliorate some of the hemodialysis associated complications. However, the beneficial properties of herbal antioxidants in kidney disease have been shown in experimental *in vivo* and *in vitro* studies; therefore, it is crucial to determine safety limitation of herbal medicines in renal failure patients may be regarded to abnormal herb pharmacokinetic behavior. In fact, large amount of substances existed in medicinal plants, usually are excreted into renal tubules and may lead to accumulation of toxic herbal components in renal tissue and blood in hemodialysis patients that conversely may cause to loss kidney function. Additionally, inappropriate administration of medicinal plants in hemodialysis patients may result in various side effects due to their body accumulation in hemodialysis individuals.

Herbal remedies and their possible side effects

End-stage renal disease patients and kidney transplant receiver should be attentive of herbal medicines containing antioxidants components due to consuming concurrently herbal medicines and their specific medications may cause their intervention. Some medicinal plants can alter cytochrome P450 enzymatic system activity leading to change of other medications concentrations (13). For instance, administration of immunosuppressant medications, such as cyclosporine which is necessary for prevention of transplanted organ rejection, is rapidly metabolized and deplet-

ed by iso-enzymes of CYP450 that have interaction with herbal remedies. Conversely, corn silk, as a traditional Chinese herbal medicine, reduces potentially creatinine level in kidney disease patients. It has anti-diabetic, antimicrobial, hypoglycemic, hypolipidemic and diuretic function. It contains alkaloids, tannins, stigmasterol, flavonoids, saponins and various vitamins. However, it has been found that corn silk extract is capable of decreasing obviously hyperglycemia in diabetic rats by enhancing insulin release as well as recuperating the injured β -cells of Langerhans islets. It also can interact with other antidiabetic medications such as statins which usually are consumed by chronic renal disease patients (14). Similarly, celery, as reducer hypertension, and parsley, as inhibitor of platelets aggregation, can inhibit CYP450 enzyme activity and induce drug intervention. Parsley, *Petroselinum crispum*, is a member of *Apiaceae* family which is native in central Mediterranean area. It has potency to inhibit diabetes and platelet aggregation by polyphenolic constituents in its extract. Uremic patients are susceptible to bleeding due to uremia-associated platelet dysfunction and administration of heparin during hemodialysis. Also, this herb can diminish Na-K ATPase pump activity in collecting duct and act as diuretic agent in kidney failure patients (15).

Furthermore, herbal remedies may influence directly on residual function on injured kidney. Aristolochia plant is used extensively in traditional Chinese herbal medicine as diuretic and also has blood pressure regulating effect. The plant is a member of the *Aristolochiaceae* family comprises aristolochic acid which is an apoptotic substance for kidney epithelial tubular cells, activates caspase-3 pathway and enhances mitochondrial permeability. Tubular proteinuria, tubular atrophy, progressive interstitial fibrosis, and finally small kidneys are features of aristolochic acid nephropathy. Various cytokines and mediators such as transforming growth factor, vascular endothelial growth factor, epidermal growth factor and connective tissue growth factor are responsible for nephropathy of aristolochic acid (16). Moreover, metabolites of this substance are carcinogenic factors that have high affinity to react with DNA adenine residues which result in over expressing of tumor protein p53, as a cell cycle regulator protein, and finally lead to urothelial carcinoma (17).

On the other hand, it has been reported that some medicinal plants contain heavy metals such as mercury, cadmium, lead and arsenic, high level of minerals, like phosphorus and potassium and also pesticides which are intrinsically nephrotoxic through accumulating in renal interstitial and tubular cells and enhancing generation of reactive species that finally induce functional and structural alterations in kidney tissue. For example, *Arctostaphylos uva-ursi* is identified as bearberry, because bear eat its fruit that has been consumed as diuretic, anti-microbial and anti-inflammatory agent for urinary tract complications. Its leaves contain tannins that have antioxidant, anti-inflammatory properties and are responsible for shriveling mucous membranes in the body. This herb contains toxic metals, progress extremely renal failure (18). Accordingly,

recent investigations have been detected Chinese herbal medicine containing cadmium is a causative factor of an uncertain etiology of chronic kidney disease in developing countries. Heavy metals such as selenium, cadmium, arsenic and lead were analyzed in urine and blood samples of chronic kidney disease of patients with uncertain etiology. Interestingly, the assessment of urine cadmium level in these patients showed a nephrotoxic range of this element. Additionally, the study examined the foods for other heavy metals which consequently discovered toxic levels of various heavy metals containing arsenic and cadmium. In fact, the results showed chronic exposure to low levels of cadmium via the food chain lead to higher cadmium urinary level and make a significant correlation between cadmium level of urine and stage of kidney disease in patients with uncertain etiology of chronic renal disease. Therefore, chronic cadmium nephrotoxicity may be one of responsible factors of unknown etiology of chronic kidney disease pathogenesis (19). On the other hand, some researchers found an association between the aggravations of chronic kidney disease and various environmental substances. They found that improvement of health standards can slow the progression of chronic kidney disease especially, in the developing country.

In addition, nettle is an herbaceous flowering herb that is grown mostly in Asia, northern Africa and Europe, commonly uses for diabetes and other endocrine disorders, urinary tract inflammation, infection and urination insults. The previous studies have shown nettle extracts have cytotoxic and anti-inflammatory activity by cytotoxic mechanism can prevent lipopolysaccharides stimulated NF- κ B pathway triggering (20). However, it contains too much phosphorus and potassium that are dangerous because these individuals suffer hyperkalemia which is made by abnormal kidney filtration of excess electrolytes and waste metabolites. Therefore, these herbal drugs may aggravate complications triggered kidney insufficiency and develop to complete kidney failure (21).

Likewise several herbal medicines are served as diuretics could be irritants for renal structure including parsley and juniper berries which possess volatile oil, and damage to tubular cells.

However, herbal medicines are consumed to alleviate renal failure complication, but inappropriate administration of them sometimes progress chronic renal disease and hemodialysis related complications such as hypertension and anemia. For example, licorice (*Glycyrrhiza glabra*) is a sweet flavor that is the most commonly member of traditional Chinese herbal plants, and is used for treatment of various increases like gastritis. The most important component of licorice root is glycyrrhetic acid which can inhibit enzyme 11 β -hydroxysteroid dehydrogenase and subsequently, decrease serum potassium level. While, in patient with renal failure, hyperkalemia is a common condition that causes cardiac arrhythmia and also muscular constriction, hence, this remedial modality in renal failure may lead to critical electrolytes imbalances. Also, licorice may cause retention of water and sodium, that results in

blood pressure elevation that is harmful for renal failure or dialysis patients (22). In addition, *Ginkgo biloba* leave is a common modality in traditional Chinese herbal medicine which administers for various conditions such as improvement blood flow to various organs and Alzheimer disease. It has been detected that its leave extract is a source of antioxidant components, including terpene lactones, polyphenols and flavonoids which are able to scavenge reactive species in biological systems. Also, it is a relaxing factor for vascular muscle cells and inhibitor of platelet aggregation; thus, it can keep normal micro-circulation into injured kidney. Prolong administration of this herbal medicine increased hemorrhagic episodes in elder patients with chronic renal failure. However, it is possible that these side effects may be age-associated of this herbal drug and also duration of prescription (23). However there was not increasing of bleeding tendency during co-administration of anticoagulant therapy and *Ginkgo biloba*.

However, most conducted investigations are experimental studies and few human studies on administration of herbal drugs in dialysis have been conducted, yet. Indeed, most studies have been investigated the beneficial effect of herbal medicines on healthy individuals. Therefore, there are the unpredictable side effects of herbal medicine. Importantly, administration of herbal drug requires determining therapeutic dose while natural antioxidant have limited therapeutic dose and they have bidirectional role.

Conclusion

The administration of medicinal plants due to containing various vitamins and bioactive substance is common in renal failure patient throughout the world, but they may aggravate unpredictably function and structure of kidney by interstitial fibrosis and tubular atrophy and also glomerulosclerosis. Therefore, it is crucial to consider attentively the possible side effects of various herbal drugs in end-stage renal disease and especially in dialysis individuals.

Author's contribution

FDS was the single author of the manuscript.

Ethical considerations

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

Conflicts of interest

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