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Plants used to decrease serum creatinine levels and contrast-induced nephropathy: A review article

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Review Article

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Abstract:

Background and aims: Contrast-induced nephropathy (CIN) is one of the most common reasons for acute kidney failure. Because of the increasing use of contrasts for computed tomography and angiography and coronary interventions, the incidence of CIN is on rise. CIN is a serious and common side effect ofthe use of contrasts. Despite taking of preventative measures, around 30-70% of patients are at risk of CIN. Researchers thus are seeking out appropriate approaches to prevent CIN. Positive effects of many medicinal plants, with antioxidant and anti-inflammatory properties and high efficiency and safety, in decreasing serum creatinine levels have been demonstrated. This study was conducted to collect evidence on the medicinal plants that are effective in decreasing serum creatinine levels and CINdevelopment

Methods: For this purpose, the key words contrast media, herbal, acute kidney injury, and nephropathy were used to retrieve relevant articles indexed in Google Scholar, Magiran, Elsevier, and PubMed. Then, the eligible articles were included in the review.

Results: The results of studies are reported in Table

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Conclusion: Although some studies have suggested that some herbs have a toxic effect on kidney function, in the present review, most plants could help decrease serum creatinine levels and improve renal function

Keywords: Contrast media, Nephropathy, Herbal, Contrast-Induced Nephropathy.

INTRODUCTION

Contrast-induced nephropathy (CIN) is one of the most common reasons for acute kidney failure(1-3) . Because of increasing use of contrasts for computed tomography and angiography studies and coronary interventions, the incidence of CIN is on rise(4, 5) . One of the main risk factors developing CIN in the paitients is exposure to contrast agents(6). Contrast agents lead to activation of inflammation system, decreased circulation, and ischemic damage to kidney tubules, and in over 15% of cases, acute renal failure(7). Diagnosing contrast-induced nephrotic syndrome is based on three important principles consisting of increase in serum creatinine levels by 0.5-1.5 mg/dl or by 25% compared to the baseline level and/or decrease in glomerular filtration rate by 25% within 24-72 hours after administering contrast agents(8, 9) .

Despite taking preventative measures in hospitals including use of contrast agents with low osmolarity, liquid therapy (0.5-1.5 mg/kg body weight before and after angiography according to left ventricular function), and taking aspirin, n-acetylcysteine, angiotensin-inhibitors, and beta-blockers, CIN remains the third leading cause of acute renal failure in inpatients(8, 10) that leads to certain complications such as elongated hospital stay, increased hospitalization costs, increased risk of developing chronic kidney disease and even end-stage renal disease, increased possibility of death, and increased risks related to percutaneous coronary intervention(3, 11-14) . The incidence rate of nephropathy is approximately 3% in thegeneral population butmay reach 50-70% in people at high risk of CIN including those over 75 years, taking contrast agents at high doses, suffering from diabetes mellitus, hypertension, heart failure, and dehydration, taking diuretics, suffering from myeloma, having low blood levels of albumin, suffering from anemia, taking nonsteroidal anti-inflammatory drugs, taking nephrotoxins, having high levels of creatine kinase-MB and uric acid, and women(1, 8, 9, 12, 15, 16). This

rate is three times higher in patients with acute coronary syndrome(17).

Because of increased serum levels of creatinine in CIN that lead to adverse conditions and increased use of contrast agents compared to the recent years(18), and with emphasis on the use of various medicinal plants with high safety and efficiency to treat and decrease different diseases, this review was conducted to collect evidence on the plants that are effective in decreasing serum creatinine levels and potentially on CIN through antioxidant and anti-inflammatory properties that possibly cause a decrease in the incidence rate of CIN. These plants can be used to achieve this purpose if their effects in preventing contrast-induced nephrotic syndrome are sufficiently documented.

MATERIALS AND METHODS

This study was conducted to collect evidence on the plants that are effective in decreasing serum creatinine levels. For this purpose, the key words *contrast media, herbal, acute kidney injury*, and *nephropathy* were used to retrieve relevant articles indexed in *Google Scholar*, *Magiran*, *Elsevier*, and *PubMed*. Then, the eligible articles were included in the review.

RESULTS

Recently, many plants and herbal combinations have been investigated for their effects in preventing and treating numerous diseases including CIN. The results of studies are reported in this section. The data on the plants and the obtained results are summarized in Table 1.

NettleStudies on malerabbitshave demonstrated that the dry ethanolic extract of nettleat concentration of 200 mg/mL can lead to decrease in serum levels of creatinine and potentially restoration of glomerular function by producing antioxidant properties(20).In addition, nettle seed extractscausea decrease in serum creatinine levels and blood urea nitrogen (BUN) because of their potent antioxidant property(19).

Table 1: Medicinal plants effective on serum creatinine, main findings, mechanisms, and pathways

Scientific name	English name	Main findings	Pathways &mechanisms	References
Urtica dioica	Nettle	Reducing serum creatinine	Maintaining intracellular levels of biological pathways by increasing the glutathione level and reducing malondialdehyde level	(19, 20)
Plantago psyllium	fleawort	Reducing proteinuria, edema, serum creatinine and blood urea nitrogen, treating glomerular morphological changes	Reducing inflammation markers such as ICM-1, MCP-1, TNF-α, $HMGB_1$ and decreasing the phosphorylation levels of MAPKs such as ERK, JNK and p38	(21, 22)
Punica granatum	Punice apple	Reducing serumcreatinine,blood urea nitrogen, lipids and glucose as well as tissue damage and atherosclerosis	Reducing oxidative stress by exhibiting potent antioxidant activity	(23-26)
Allium sativum	Garlic	Reducing the levels of glucose, uric acid, and urea	Antioxidant and anti-inflammatory properties (reducing TNF-α)	(27-31)
Astragalus lentiginosis	Monogolian milkvetch	therapeutic effect including renal protective effect (Decreasing BUN, SCr, CCr and urine protein) and systemic state improvement (serum albumin level)	Rebalancing TGFβ-SMADsignaling	(32-37)
Boerhavia diffusa	Spreading hogweed	Reducing serum creatininelevel and blood urea nitrogen,	Exhibiting antioxidant properties and reducing inflammatory and pro-inflammatory factors (elevating glutathione and superoxide dismutase levels, reducing TNF-α level)	(38-40)
Tribulus terrestris	bhindi	Reducing serum creatinine, blood urea nitrogen, serum urea	Increasing antioxidants' activities and reducing lipid peroxidation	(39)
Curcuma zedoaria	zedoary	Reduced serum creatinine, blood urea nitrogen, serum urea and tubular necrosis	Exerting antioxidant and hepatoprotective properties, scavenging various free radicals, and stimulating antioxidant enzymes	(12, 39, 41)
Hydrangea paniculate	Panicled hydrangea	Decreasing serum creatinine, blood urea nitrogen, renal oxidative stress, tubular pathological injury and apoptosis	Exerting antioxidant properties and suppressing renal inflammation and tubular cell apoptosis	(42, 43)
Dilichorsla florusl	Horse grem	Reducing serum creatinine, serum urea, and uric acid	Exerting antioxidant properties and scavenging various free radicals	(39, 44)

Ligusticum striatum	*ligusticum striatum*	Reducing blood urea nitrogen, serum creatinine, 24-hour urine protein, and urine microalbumin, improving renal function, and reducing necrosis and apoptosis in the tubules	Reducing malondialdehyde level and ameliorating the downregulation of superoxide dismutase activity	(45-48)
Beragenia ligulata	*Saxifiaga ligulata*	Reducing levels of creatinine, uric acid, and urea of both urine and serum	By exerting antioxidant properties and scavenging various free radicals	(39, 49)
Asparagus racemosus	Satavari	Reducing serum creatinine, serum urea, and uric acid	Exerting antioxidant properties and scavenging various free radicals	(39)
Paeonia lactiflora	*Paeonia lactiflora*	Reducing levels of serum creatinine, blood urea nitrogen, 24-hour urine protein, mean glomerular area, and mean glomerular volume	Inhibiting the Wnt/beta-catenin signaling	(34, 48, 50-52)
Heracleum persicum	Persian hogweed	Lowering serum creatinine level and improving renal function	Decreasing endothelin and inhibiting binding to its receptors	(33-35, 47, 53, 54)
Perilla frutescence	Korean perilla	Decreasing serum creatinine	Anti-nephritic mechanism and lowering proliferation of glomerular cells, IgAdeposition	(47)
Saliva miltiorrhiza	Red sage	Decreasing serum creatinine, glomerular hypertrophy, and microalbuminuria and suppressing the progression of renal injury and hyperglycemia	Inhibiting TGF/β1 through preserving tubular function and structure	(47)
Panax notoginseng	notoginseng	Decreasing the concentrations of blood urea nitrogen, serum creatinine, and urinary NAG	Inhibiting the apoptosis of renal cells	(34, 55, 56)
Lingusticum chuanxiong	Sichuan lovage rhizome	Reducing blood urea nitrogen, serum creatinine, 24-hour urine protein, urine mAlb, and urinary albumin excretion rate (UAER)	By reducing oxidative stress, inhibiting cell apoptosis, abrogating neutrophils recruitment, and suppressing the overexpression of TNF-α and ICAM-1	(34, 57, 58)
Curcumin	Curcuma longa l Turmeric	Reducing serum creatinine, blood urea nitrogen, and albuminuria and attenuating glomerular sclerosis	By reducing aging-induced oxidative stress	(34, 59, 60)

Plantago ovate

Studies in mice with nephrotic syndrome have shown thatthe dried raw seed of *P. ovate*(200 mg/kg/day),by exerting anti-inflammatory and anti-apoptotic properties, exhibitsprotective effects in addition to decreasing lipidemia and ascites(22) while theplant displayed no hepatotoxic and neurotoxic effects(21).

Pomegranate

Studies in the mice treated with pomegranate flower extract demonstrated that this extract at low doses(e.g., 25 mg/kg) led to decreased serum creatinine levels, BUN and kidney injury(23-26).

Garlic

Studies in Wistar rats have shown that garlic extractexerts antioxidant and anti-inflammatory properties and leads to decreased serum levels of creatinine and structural kidney damage(at20 mg/kg)(27, 29-31, 61).

Astragalus*membranaceus*

*In vitro*findings and *in vivo* datain rats have shown that extracts of ***A.*** *membranaceus* leads to a significant decrease in serum creatinine levels, BUN, and urea. In addition, this plant causes a decrease in serum creatinine levels and improves glomerular function in humans(40 g/day for 3 weeks in patients with different types of chronic glomerulonephritis)(32, 34, 36, 37). In patients with glomerulonephritis, the plant has been reported to decrease proteinuria(47).

Punarnava

*In vitro*and *in vivo* datahave shown that punarnavain ratscauses a decrease in serum creatinine levels and BUN, and prevents kidney damage(at 25 mg/kg/day) (38-40).

Gokshura

In vitro and *in vivo* datahave indicatedthat cystone, a herbal compoundthat contains gokshura, leads to decreased serum creatinine levels and kidney damage in rats(5ml/kg,p.ofor seven days) (39). Evidence has indicated that the plant causes no specific side effect on heart, kidney, and liver in the patients(62), but a young man was reported to develop acute kidney damage following oral use of the drug(63).

Karchura

In vitro and *in vivo* datahave shown that karchura has protective effects on kidneys and causes a significant decrease in serum creatinine levels, BUN, and serum urea levels, and prevents nephrotoxicity in adult male mice due to its antioxidant properties(at 100–200 mg/kg body weight p.o)(39, 41).

Hydrangea paniculata

Due to its antioxidant property,aqueous extract of*H. paniculata* can improve acute kidney injury in female rats(42), suppress diabetic nephropathy in these animals, prevent development of glomerular lesions, and lead to improvement of renal functionat 30 mg/kg(43).

Kulattha

Studies have indicated that this kulattha causes a decrease in serum creatinine levels in humans(at 1-2mg/daily)(44), urea, BUN, and serum creatinine levels as well as a decline in renal dysfunction in rats(at 21mg)(39).

Ligusticum wallichii

Investigations have shown that *L. wallichii* causes a significant decrease in serum creatinine levels and adecrease in proteinuria and hematuria in the patients(at 80 mg twice a day for three weeks)(47), as well as a decrease in BUN, serum creatinine levels, and tubular necrosis in murine kidney(at 80 mg/kg)(64).

Pashanabheda

Research findings have indicated that the herbal combination containing pashanabheda causes decrease in serum creatinine levels, urea, and BUN in rats(at 185mg/kg administered for 28 days)(39, 49).

Satavari

Clinical trials have shown that the herbal combination containing satavari causes a decrease in serum creatinine levels, urea, and BUN and exert protective effects on the kidney(39).

Paeony

Studies in rats have shown that paeony causes a decrease in serum creatinine levels and BUN(34). The

clinical investigations on laboratory animals have indicated that paeony decreases serum creatinine levels, BUN, and kidney damage(50). In patients treated with this plant, the levels of albuminuria and inflammatory markers in the blood decreased(at 1800 mg/day for 6 months)(51, 52), with protective effects on the kidney and preventive effects against diabetic nephropathy(48).

Angelicasinensis

Clinical trials have demonstrated that treatment with *A. sinensis* causes a significant decrease in proteinuria and treats nephrotic syndrome(at 2 mg/kg/day for 4 weeks). In addition, the rejection rate of kidney transplants in such patients decreased significantly(47). This treatment also leads to a decrease in urea levels and improves renal function(65), and in laboratory animals,a decline in kidney damage(53) and tubular fibrosis(35). In patients with glomerulonephritis, treatment with *A. sinensis*leads to a significant decrease in proteinuria with minimal side effects(54).

Perilla

In vitro data and findings on ratmodel have shown thatperillaoil treatment leads to a decrease in proteinuria and improves renal function, and in clinical trials, this treatment led to improvement of renal function and a decrease in proteinuria and hematuria in children. Orally administered perilladecoction lowered serum IgA levels and proteinuria and improved renal histology(47).

Zingiber *officinale*

Study in rats shown that ginger Freezedried or extract concentration can help improve renal function(at 0.5-2%)(66). This plant at high doses(e.g., 1000mg/daily) causes a decrease in C-reactive proteinin human(67).

Saliva

In laboratory animals treated with saliva, renal circulation improved and renal filtration increased, and in renal failure patients treated with this plant, serum creatinine levels decreased and the remaining renal function persisted(47).

Notoginseng

Clinical trials have reported that notoginseng causes a decrease in serum creatinine levels and BUN(34, 55).

Chuangxiong

The clinical investigations on laboratory animals have shown that chuangxiong causes a decrease in serum creatinine concentrations, BUN, and kidney damage in cisplatin-exposed mice. In fact, this plant exhibits protective effects on the kidney against toxins(55, 56).

Lingusticum chuanxiong

Clinical trials have reported that *L.chuanxiong*Hort causes a decrease in serum creatinine levels and improvesrenal function(34, 57, 58).

Although most studies have reported the positive effects of medicinal plants on renal function and in decreasing creatinine and uric acid levels and BUN, inconsistent findings of some studies present some challenges for researchers and physicians as follows:

Rhubarb

A number of studies have shown that rhubarbproduces protective effects in the kidney cells in patients with diabetic nephropathy and in the animals with glomerulonephritis, decreasesproteinuria andimprovesrenal function significantly(47, 68, 69), Clinical findings on laboratory animals, however, have reported using this plant leads to increased blood urea levels and weakening of nephropathy(47), studies on DNA microarrays have determined that this plant leads to nephrotoxic complications resulting in swellingof renal tubules(70).

Aristolochia

Although some studies on theanimalmodels have shown that aristolochia causes a decrease in serum creatinine levels and BUN(65), Balkan endemic nephropathy is currently considered to be a type of nephropathy due to consumption of this plant(71, 72).

Carambola

Although some clinical investigations have shown that carambolacauses a decrease in serum

creatinine levels and BUN(34), acute nephropathy even in people with normal renal function has recently been reported, probably due to high levels of oxalate in the plant (73, 74).

Discussion

CIN is a serious and common side effect ofthe use of contrasts. Nephrotoxicity is a concern among patients elderly, hypovolemic, suffering from diabetes or cardiovascular diseases, etc. This study was conducted to collect evidence on the medicinal plants that are effective in decreasing serum creatinine levels and CIN development . findings This study show that most plants could help decrease serum creatinine levels and improve renal function.

CONCLUSION

Although some studies have suggested that some herbs have a toxic effect on kidney function, in the present review, most plants could help decrease serum creatinine levels and improve renal function.Although positive effects of herbal compounds in improving renal function and decreasing serum creatinine levels can contribute to a novel approach to treat contrast-induced nephrotic syndrome, inconsistent findings and lack of large clinical trials in human populations to study certain plants necessitate additional studies.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper.

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