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An Appraisal of Nephroprotection and the Scope of Natural Products in Combating Renal Disorders

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Abstract

Although the concept of nephroprotection is relatively new but evidences are accumulating to demonstrate that the drugs described to be useful in various renal disorders because of their nephroprotective and nephrotonic effect as described in Unani or other traditional medicines, have diverse therapeutic uses and can be used to manage many renal diseases and their complications or at least to arrest their progression. The traditional systems of medicines would offer some novel drugs, which may be effective in different pathological conditions of the kidney. The drugs of traditional systems of medicines are frequently used to protect the renal function and to delay the progression of renal diseases to CKD and ESRD. In recent past it has been shown that a number of drugs from herbal medicine possess promising nephroprotective effect. The researchers are keen to develop an effective, safe and low cost drug from alternative medicine. However, the drugs identified to be effective in renal diseases on the basis of age-old practices of traditional medicines and few scientific studies need to be evaluated for their pharmacological profile and wide therapeutic potential. This paper gives a detailed account of the traditional drugs useful in renal diseases and the scientific studies conducted so far to validate them.

Keywords: Nephroprotection; Traditional medicine; Ayurveda; Unani; Nephroprotective herbs

Introduction

Nephroprotection has known ample development lately and consists in the measures which protect the kidney against many aggressive factors. The concept of nephroprotection in modern medicine is relatively new and can hardly be traced before eighties. The complex nature of renal diseases and their progression to renal failure (both acute and chronic) and end stage renal disease (ESRD) makes its management quite difficult. The majority of cases of renal disease remain unnoticed unless they progress to advance stages when the conventional therapeutic interventions are usually not sufficient to cure them completely. But the major problem with kidney disease is its progression to a stage when virtually no option works at all except the renal replacement therapy (RRT).

Two major components of RRT viz. dialysis and kidney transplantation are highly sophisticated and thereby too costly to be affordable for an average income group. Only small chunk of the elite class can take the luxury of such a regimen subject to the availability of this facility in reach. That is why most of the patients of kidney disease are left to die mainly in developing and poor countries because of non-availability of RRT facilities in their region or their inability to pay for it. Globally, it has been estimated that by 2010 over 2 million individuals has been treated by RRT at a cost of $1 trillion [1]. More than 100 countries worldwide do not have any provision for RRT [2] and consequently, more than a million individuals can be assumed to die every year from ESRD. About 100 countries have been identified that possess no such facility at all [3]. Availability of kidneys for transplantation is another important problem consistent with RRT. Although, expenditure on RRT is costing about 1 trillion dollar but the substantial percentage of patients in need of it, still remains untreated and consequently has out-numbered those receiving the treatment. In 1990 it was 3.78 million and is expected to become 7.63 million in 2020 [4]. The alarming increase in the prevalence of CKD that progresses to end stage renal disease requiring renal replacement therapy, demands huge fund allocation [5], In addition, individuals with kidney diseases are at an increasing risk of other systemic diseases which frequently proves to be fatal [6]. At the end of 2004, 1783000 patients worldwide were receiving treatment for ESRD, of which 77% were on dialysis and 23% had functioning renal transplant, and this number is increasing at the rate of 7% every year.

In nut shell therefore it can be said that it is almost next to impossible to provide replacement therapy to all patients requiring it. The next option left with the physicians is to think of alternatives and the best way to come out of such a situation or at least scale down the prevalence and consequently the financial burden to a significant level, is to protect the kidney function, slow the progression of disease and delay the need of RRT. This second option actually paved the way for envisaging a concept that is broadly termed as nephroprotection [7,8].

The skyrocketing cost of CKD and ESRD management in developed countries due to the relentlessly increasing number of patients who have outnumbered the patients maintained at RRT, and availability of very limited facilities in poor countries almost ensured that RRT cannot be provided to all in need of it. This forced the physicians to think to adopt some alternate measures to preserve the renal function as long as possible and slow the renal disease progression with an aim

to protect the kidney and delay the need of RRT to the maximum possible extent.

After the experimental demonstration that ACE inhibitors slow the progression of loss of renal function in a number of models of renal diseases [7,8]. It was for the first time conceived that a treatment strategy can be devised aiming at preserving renal function instead of providing some supportive and passive therapy to the patients of kidney diseases. The concept of renoprotection/nephroprotection thus emerged and strongly stimulated the clinicians to apply this concept into practice aiming at early detection and subsequent prevention of progression of kidney disease, mainly through lifestyle adjustment and the use of new pharmacological agents [3]. The nephroprotection thus includes:

Preservation of renal function as long as possible.

Treating the kidney disease at the onset/primary stage.

Slowing the progression of kidney disease.

Delaying the need of RRT to maximum possible extent.

The pathology of renal disease that compromises its functional ability and the structural integrity has been described to arise mainly through following mechanisms:

Impairment of lysosomal function which in turn causes decrease in the density and height of the brush border microvilli, dilation of the cisternae of rough endoplasmic reticulum and cytoplasmic vacuolization of the tubular epithelium. As injury progresses, mitochondrial swelling, tubular necrosis and desquamation occur.

Oxidative stress in which chemicals may produce membrane damage and cell death.

Disturbance in intracellular Ca2+ homeostasis and sustained increase in cytosolic Ca2+ which causes cell death by the disruption of the plasma membrane, cytoskeleton, endoplasmic reticulum and mitochondria.

Chemical may also induce cell death through an initial DNA damage or by apoptosis.

Several chemicals (both therapeutic and non-therapeutic) have toxic effects on one or more anatomical elements of the kidney. Toxic effects may be acute or chronic, and they may be direct or mediate indirectly through immunological mechanisms. The health impact of nephrotoxic chemicals is related to risk factors, which include the intergrade of the renal functional reserve and factors such as pre-existing renal damage, disease, age, sex, and diet. Irrespective of the mechanism however, the toxicant set into motion a number of physio-chemical processes that initiate a series of degenerative changes and alter the morphology and the functions of the kidney [9-11]. A drug that can ameliorate one of the mechanisms or processes mentioned above can be used as an important nephroprotective agent because such an agent will help in the restoration of kidney function and improvement in the structural impairment of the kidney and thereby slowing its progression. The mechanisms discussed above cannot be said however to be exclusively responsible for nephrotoxicity, because several other intricacies and complex processes have been described to be associated with the normalization of kidney functions which directly or indirectly influence the hemodynamics of kidney. Similarly, some related pharmacological effects such as diuretic and anti-inflammatory etc. have also been shown to complement the nephroprotection [12]. Few drugs in recent years have been found to possess significant nephroprotective effect not withstanding that their mechanism was not fully elucidated [13]. Still, they satisfied the criteria of nephroprotection owing to their overall efficacy on renal function [7].

In modern medicine ACE inhibitors and ARBs are mainly used to induce renoprotection, however these agents are neither the drugs of choice for this purpose nor can be used exclusively to produce renoprotective effects, rather they are mainly effective in nephropathies associated with blood pressure and diabetes etc [13]. Thus, by treating a patient with the above mentioned drugs it is obligatory to induce a pharmacological effect that may not be necessarily needed by him. The associated toxicities of these agents also limit their use to a great extent. Although, ARBs are comparatively safer than ACE inhibitors but some of the side effects are common to both such as neutropenia, proteinuria, angioneurotic edema, hyperkalemia especially in patients with renal impairment etc. [13], which undermine the therapeutic utility of these agents. A drug categorized to be effective specifically as a nephroprotective agent without having liability to produce some serious side effects will be the obvious choice for the patients suffering from renal dysfunction or failure.

Medicinal plants are a source for a wide variety of natural antioxidants and are used for the treatment of diseases throughout the world [14]. Some of these properties are antimicrobial [15], anti-cancer [16], anti-diabetic [17], anti-atherosclerosis [18], immunomodulatory [19], and even reno-protection or hepato-protective effects [20].

It is being appreciated that traditional systems of medicine can offer some effective drugs from their treatise to be useful in diverse pathological conditions of kidney and thus can be used to protect the renal function and prevent/slow the progression of renal diseases to CKD or ESRD. A number of drugs from herbal sources have been shown to possess promising nephroprotective and related effects in some recent studies and researchers are making it a point to concentrate seriously on the development of nephroprotective agents from traditional sources [21,22].

Recently, attentions are mostly on protection or prevention as well as accelerating the regeneration of tubular cells against injurious insults to the kidney [23,24] .

Keeping in view of above, Scientists are focusing to develop herbal nepheoprotective agents from the plants source which possess antioxidant properties for the prevention and cure of renal disorders as in most of the cases it was found that the oxidative stress are the common factor with other associated cause resulting renal tubular necrosis [23]. So it can be assumed that plants which have antioxidant activities due to phytochemicals including phenolic and carotenoid compounds can reduce the risk of several chronic and degenerative complications [25,26].

Traditional System of Indian Medicine including Ayureveda, Unani etc. are also not wanting in offering drugs for numerous kidney diseases. It claims to possess a number of drugs that can be used successfully in the treatment of renal diseases [21,22]. Some of the drugs mentioned in Ayurveda and Unani literature and being practiced by physicians, have been demonstrated to produce some important effects such as diuretic, anti-inflammatory, antioxidant & nephroprotective effect against known toxicants. Recently some important drugs of Unani Medicine such as Bisehri Booti (Aerva lanata, Juss) [27], Revand Chini (Rheum officinalis) [28,29], Haleela

(Terminalia chebula) [30], Zanjabeel (Zingiber officinale) [31], Asgand (Withania somnifera) [32], Khare khasak (Tribulus terrestris) [33], Banadequl Buzoor (a poly herbal formulation) [34], and Jawarish Zarooni Sada (a poly herbal formulation) [21] have been investigated for their diuretic, nephroprotective and associated effects they have shown promising nephroprotective effect. Quercetin isolated from vegetable sources has been shown to produce nephroprotective effect against cisplatin induced nephrotoxicity [35]. Cordyceps sinenses has been shown to produce protective effect against gentamicin and kanamycin induced nephrotoxicity [36]. Leaf extract of Clerodendron trichotomum, has been reported to possess diuretic, natriuretic and kaliuretic activity [37]. Similarly, curcumin isolated from turmeric has been reported to produce protective effect against adriamycin induced nephrotoxicity [38].

Plant as Nephroprotective Agents

Ginger which was studied for its nephroprotective effect significantly protected the renal cells and reduced the severity of tubular damage caused by gentamicin and also showed the tubular regeneration potential in animal models [39]. Another study in which pomegranate seed oil is evaluated for its nephroprotective activity the findings clearly showed attenuation of Diazinon -induced nephrotoxicity via; a) improving kidney function by reducing urinary glucose; b) reducing serum urea and creatinine; and c) decreasing MDA concentration[40]. The co-administration or post administration of garlic juice found to be effective in gentamicin induced acute kidney failure [41].

A polyherbal formulation was studied for its protective effect on mice administered with 3 mg/kg of Cisplatin. Among the ingredients of the formulation Angelica radix was more effective and it showed strongest protective effect against the toxicity, the effectiveness of Angelica radix was found to be due to its constituent L-malate which was isolated and tested for nephroprotective activity [42].

The simultaneous administration of the plant Cordyceps sinesis with gentamicin protects the proximal tubular cells from gentamicin toxicity [36]. Results are reported on the clinical, experimental and immunological studies on Biskhapra (Boerhavia diffusa) the observations reveal equivalent diuretic effect of frusemide, Biskhapra (Boerhavia diffusa) increases serum protein level and decreases urinary protein excretion in patients of nephritic syndrome. Clinically Biskhapra was proved to be useful and safe drug in patients of nephritic syndrome [43]. Simultaneous administration of Gokhroo (Tribulus terresteris) 200 mg/kg/day/orally and gentamicin to female rats decreased the gentamicin induced nephrotoxicity in both structural and functional terms. The effects were comparable to that of Verapamil [33]. Methanolic extract of Icacina tricantha tuber was found to be effective in carbon tetra chloride induced nephrotoxicity. The rats treated only with carbon tetra chloride lost weight, but those with carbon tetra chloride and extract gained weight. Histopathological examination of the kidney revealed complete protection against carbon tetra chloride induced nephrotoxicity [44].

The hydro alcohol standardized extract of Echinacea pallida given to mice in association with the intraperitoneal administration of cisplatin exhibited protective effect expressed by a diminished loss and fast recovery of the animals' body weight, pretreatment with Echinacea pallida also decreased cisplatin nephrotoxicity estimated from the level of kidney homogenate oxygen consumption [45]. The protective effect of Asgand (Withania somnifera) on Cadmium induced toxicity in mice kidney has been studied. Aqueous extract of 40 mg/0.1ml concentration was prepared from the dried roots of Asgand, Mice were fed with Cadmium chloride along with Asgand extract and Asgand extract alone (1.14 gm/kg body weight) for 20 days. Results based on lipid peroxidation indicate that Asgand is capable of reducing toxicity caused by cadmium [46].

A Unani formulation "Banadequl Buzoor" was tested for nephroprotective activity. The formulation was found to decrease the serum urea and serum creatinine levels significantly [23]. Effects of Geranin tannin extracted from the herb Geranium humbergii on Puromycin Amino nucleoside nephrosis were studied in rats. The urine protein excretion in female rats (140-160 gm) receiving puromycin amino nucleoside on 7th day, reached its maximum after injection of puromycin amino nucleoside injection on 14th day, but in animals treated intramuscularly with geranin 10 mg/kg body weight the urinary protein was reduced approximately 35%. The increase in serum cholesterol and lipid peroxide produced by puromycin amino nucleoside were also suppressed by geranin, observation by electron microscopy revealed that the degree of abnormality in glomerular epithelial cells was lower in rats treated with geranin after the puromycin amino nucleoside injection than in the rats treated with the puromycin amino nucleoside alone [47]. A Unani formulation "Jawarish Zarooni Sada" has been reported to possess nephroprotective activity [21]. A Unani drug Kabab chini (Piper cubeba) was investigated for nephroprotective activity in chemically induced nephrotoxicity showed significant nephroprotective effect against gentamicin and cisplatin nephrotoxicity [48,49]. . Another study demonstrated that Khurfa (Portulaca oleracea Linn.) possesses significant nephroprotective effect against gentamicin and doxorubicin induced nephrotoxicity [50].

Milk thistle (Silybum marianum) seeds containing several potent antioxidant flavonolignans collectively called silymarin have both hepatic and renal protective effects in rodent models [51]. The main constituents composing silymarin are silibinin, silicristin, isosilibinin, and silidianin. Silibinin and silicristin, aside from their antioxidant effects against damaging free radicals, also stimulate RNA and protein synthesis which is important for renal and hepatic repair mechanisms. In addition these same flavonolignans protect kidney cells in culture from the renal toxic effects of the drugs paracetamol, cisplatin, and vincristine [52]. Another study in rats demonstrated that silibinin protected renal tubular cells from the oxidative damage from cisplatin [53]. Silibinin also protects against experimental cyclosporine nephrotoxicity [54].

Another potentially useful nephro-protective medicinal herb popular in Ayurvedic medicine is picroliv (Picrorhiza kurrooa). Extracts from the roots and rhizomes offer protection against various hepatic and renal toxins. Picroliv protects the kidney in a renal ischemia-reperfusion induced injury (IRI) model in rats [55]. Pretreatment of rats orally with picroliv for 7 days before initiation of experimental IRI lowered renal lipid peroxidation, reduced apoptosis, and generally increased the viability of renal cells. Another study in rats found that oral administration of picroliv to rats exposed to the carcinogen 1,2-dimethylhydrazine decreased the extent of renal necrosis [56]. As with milk thistle animal studies using picroliv support their potential clinical benefit as nephro-protectants. However, human clinical studies are needed to confirm these Results in cell culture and animal models.

Astragalus (Astragalus membranaceus), a popular herb used in Chinese traditional medicine, is effective against experimentally

induced glomerulonephritis in rats, especially in reducing proteinuria [57]. Several clinical studies also showed a reduction in proteinuria in patients with chronic glomerulonephritis by Astragalus [58]. Cordyceps (Cordyceps sinensis), a fungus found growing in caterpillar larvae of certain moths, has long been valued as a kidney tonic in China [59]. One study in 61 patients with lupus nephritis showed that a combination of 2 g to 4 g of cordyceps powder together with 0.6 grams of artemisinin from the plant Artemisia annua for 3 years improved kidney function as measured by creatinine clearance [60]. Another study found that cordyceps lessened the nephrotoxicity of cyclosporine in kidney transplant patients [61].

The Japanese traditional remedy Sairei-to, a 12 herb mixture, has shown in human and animal studies to protect the kidney in gentamicin renal toxicity, IgA nephropathy, and lupus nephritis [62]. Another study in rats showed that extracts from the root of the plant Salvia miltiorriza (Danshen) along with fructose 1,6-diphosphate prevented the decline of renal cortical Na-K-ATPase activity induced by ischemia and gentamicin [63]. Further, extracts of the plant Herniaria hirsute inhibit calcium oxalate crystal aggregation and thus could be useful in preventing kidney stone formation [64] (Table 1).

Herbs	Protective effect
Jawarish Zarooni Sada	The formulation was found to decrease the serum urea and serum creatinine levels significantly [21].
Withania somnifera	Significantly reduced toxicity caused by cadmium [32].
Tribulus terresteris	Possess protective effect against the gentamicin induced nephrotoxicity in both structural and functional terms [33].
Banadequl Buzoor	The formulation was found to decrease the serum urea and serum creatinine levels significantly [34].
Quercetin	Produced nephroprotective effect against cisplatin inducednephrotoxicity [35].
Cordyceps sinesis	Protects the proximal tubular cells from gentamicin toxicity [36].
Clerodendron trichotomum	Reported to possess diuretic, natriuretic and kaliuretic activity [37]..
Curcumin	reportedto produce protective effect against adriamycin induced nephrotoxicity [38].
Ginger	Showed the tubular regeneration potential in animal models [39].
Pomegranate seed oil	Showed attenuation of Diazinon -induced nephrotoxicity [40].
Garlic	Found to be effective in gentamicin induced acute kidney failure [41].
Angelica radix	Demonstrated protective effect against the toxicity [42].
Boerhavia diffusa	Clinically proved to be useful and safe drug in patients of nephritic syndrome [43].
Icacina tricantha	Offered protection against CCL4 induced nephrotoxicity [44].
Echinacea pallida	Showed protective effect against cisplatin nephrotoxicity [45].
Geranium humbergii	Protected abnormality in glomerular epithelial cells [47]
Piper cubeba	Showed significant protective effect against cisplatin and gentamicin induced nephrotoxicity [48,49].
Silybum marianum	Has both hepatic and renal protective effects in rodent models [51].
Picrorhiza kurrooa	Offered protection against various hepatic and renal toxins [55].
Astragalus membranaceus	Effective against experimentally induced glomerulonephritis in rats, especially in reducing proteinuria [57].
Artemisia annua	Improved kidney function as measured by creatinine clearance [58].
Sairei-to, a 12 herb mixture	Shown in human and animal studies to protect the kidney in gentamicin renal toxicity, IgA nephropathy, and lupus nephritis [62].
Salvia miltiorriza	Prevented the decline of renal cortical Na-K-ATPase activity induced by ischemia and gentamicin [63].
Herniaria hirsute	Inhibit calcium oxalate crystal aggregation and thus could be useful in preventing kidney stone formation [64].

Table: 1: Herbs which are scientifically evaluated for nephroprotective effect

Conclusion

These reports mentioned above are although of preliminary nature and most of them have been carried out on animals models but showing great potential of Traditional Medicine viz Unani, Ayurveda to deliver some promising agents that can be used to treat the kidney diseases or at least, preserve its function and slow its progression. Therefore, the comprehensive clinical trial of Unani diuretics, tonics and nephroprotective drugs gain importance as one of the means of characterizing and identifying a better group of drugs that can be used as actual nephroprotective agent after scientific validation.

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