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CONTROL OF PROTEINURIA IN PATIENTS WITH DIABETIC NEPHROPATHY ACCORDING TO TRADITIONAL PERSIAN MEDICINE, THE EFFECT OF PLANTAGO SEEDS: A LITERATURE REVIEW

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ABSTRACT

Diabetic Nephropathy (DN) is characterized by albuminuria and renal function loss (GFR) in diabetic patients. To prevent the progression of diabetes-related cardiovascular-kidney disease, a combined method including blood pressure control as well as glucose and lipid control is needed in addition to lifestyle changes. Despite blocking the renin-angiotensin system as the first line of treatment for diabetic nephropathy in a significant number of patients, the progression of kidney disease is not obtained. Considering that despite the treatments, diabetic nephropathy still develops, indicates that these treatments are insufficient and that other mechanisms are involved in the disease process! A large number of the world's population uses traditional medicine resources to control diabetes. The most important goal of treatment according to Traditional Persian Medicine (TPM) is to prevent the progression of diabetes related complications, so that patient does not end up with dialysis and kidney transplant, in which case the quality of life of patient is severely compromised. Considering that there are many traditional medicine compounds available in the market to prevent diabetic complications, most of which not only do not have a favorable effect, but also cause other serious complications, it is necessary to investigate the effect of simple yet effective remedy to solve this problem. The TPM herbal product that is used in this study, Plantago major, is easily available herb that has proved effective on proteinuria in couple of scientific studies and yet have no significant side effects. In order to propose a therapeutic protocol based on TPM, it is necessary to relate symptoms of chronic nephropathy and proteinuria to that of kidney diseases mentioned in TPM resources. In this study, the researcher explains DN from the viewpoint of TPM and proposes Plantain as a potential treatment for it, based on its relevant properties mentioned in TPM resources and recent in vitro studies.

Keywords: control, proteinuria, patients, diabetic nephropathy, traditional persian medicine, plantago seeds.

INTRODUCTION

Diabetes is the most common endocrine disease in the world, leading to 400 million deaths annually, according to world health organization statistics [1]. By 2025, 25% of the world's population is projected to be diabetic in developing countries, and 25-30% of them will develop type 2 diabetics [2]. The prevalence of nephropathy in diabetics is reported to be about 30-20%. Micro-albuminuria has been observed in 20-36% of diabetics and the most common cause of end-stage renal disease (ESRD) is diabetes [3],[4],[5]. Despite blocking the renin-angiotensin system as the first line of treatment for diabetic nephropathy in a significant number of patients, the progression of kidney disease is not obtained [6] ،[7] ،[8]. In IRI, the prevalence of diabetes in adults between 25 and 70 years old is reported to be 11.9% (2011), a 35% increase from 2005. It is estimated that nearly 9.2 million Iranians are most likely to have diabetes in 2030 [9] , and the current forecast suggests that this number will exceed 700 million in 2045 [10]. The prevalence of diabetic nephropathy was 37-40% in Western countries and 57.4-59.8% in Asian countries [11]. The first line of treatment for DN in modern medicine are angiotensin converting enzyme inhibitors (ACEI) such as enalapril, captopril, etc. which have several side effects that are referred to as:

1- Dry cough that the patient might be able to tolerate, and continue the medication, but there is no cure for this coughing.	6-Dizziness;
2-Angioedema, which can be from any part of the body including the intestines, but is mostly related to tongue, abdomen and laryngeal edema, that causes airway obstruction and fatal cases have been reported.	7-Hyperkalemia;
3- Renal failure in people with congestive heart failure may cause changes in kidney function using ACE inhibitors.	8- Nausea;
4- About one-fifth of patients [12] with renal artery stenosis, BUN and blood creatinine levels increase. Kidney function should be monitored during treatment for sensitive groups.	9- Diarrhea;
5-Headache;	10-Urticaria and Rash [12]

Angiotensin receptor blockers (ARB) are the second group of treatment used in the treatment of DN, which has fewer complications than the first group, but in some patients causes dizziness, headache, hyperkalemia, backache and muscle cramps [13]. However, despite the treatments, development of DN still shows that these treatments are insufficient and other mechanisms are involved in the disease process [14]. On the other hand, Yazd ZN et al. conducted a study on the effects of Plantago Major on kidney in 2019 Mar;22, that proved the efficacy of Plantago as a Reno protective agent. In this study, in a time-dependent manner, the oral administration of Plantago major extract signifcantly improved proteinuria and serum alterations in albumin and cholesterol levels, as well as the number of renal apoptotic cells in ADR treated rats [15]. Another study, conducted by Nazanin E Heravi et al. proved the effect of Plantago major hydroalcoholic extract on the oxidative stress and renal function in kidneys [16].

MATERIAL AND METHODS

All the latest studies on treatment options for DN related proteinuria were searched in extensive online database from PubMed, Cochrane library, and Web of science, gray literature searches from Google Scholar and WHO. To deeply understand the mechanism of action of how diabetes leads to long term complications and proteinuria, online database UpToDate was referred multiple times and same was looked up for probing into various treatment options for Diabetic Nephropathy according to Modern Medicine.

Rich, deep rooted in history and well recognized source of Traditional Medicine, that exists in the name of Traditional Persian Medicine, TPM is studied through books of Avicenna, like Canon. Finally, extensive textbooks search was done to explain Diabetes according to TPM, with the help of most recent version of Noor Software of Traditional Medicine Resources. Finally, as the most targeted aspect of this article, treatment options offered by TPM for Diabetic Nephropathy and Proteinuria associated with it was investigated, mentioning the present day, efficacy of its herbs in this regard.

RESULTS

The analysis of the factors described in the scientific literature allows the authors to draw the following: TPM physicians defined kidney disease or weakness as an inability of the kidney to perform its natural task. The natural task of the kidney is that it expels away extra water from the body towards the bladder. This extra water contains some amount of diluted blood, which is used by the bladder for its own functional nourishment. The bladder then excretes the rest of water out. Whenever kidney weakens, it does not filter the blood from waste water, rather excretes it out. Sometimes urine becomes viscous, so much so that if it is left untouched for an hour, it precipitates as a top layer on urine resembling sea foam [17]. Reasons that lead to kidney disease or weakness are either reduction in the retaining strength of the kidney tissue or its excessive loosening that reduces the retention control. This weakness of the retaining force (quwwat e masika) [18] may lead to excessive excretion of protein in the urine.
The cure for this weakness of kidney tubules according to TPM is known as Talazuz, agglutinating which means introducing agents that cause strengthening of tubules, by their thick glossy lubrication and astringent properties [18, p. 830] . The beneficial characteristics of Plantago such as wound healing, antipyretic, analgesic, disinfection, anti-bleeding, anti-inflammatory, diuretic, laxative, astringent are approved. Researchers believe that Plantago Major has existed for almost 4,000 years, especially in Europe. Plantain can inhibit the activity of angiotensin conversion enzyme and is more efficient in inhibiting the size of calcium oxalate crystals in vitro compared to allopurinol and potassium citrate and can be used to inhibit urinary stones production [19]. Modification of risk factors in diabetes has a significant impact on the incidence of disease and mortality in diabetic patients. In IRI, TPM services are provided to patients and the results indicate satisfaction with treatment. [20] . Due to the increasing interest of the society in the use of traditional and complementary medicines, the potential of TPM can be used in order to find more effective treatment strategies. [21] .

Discussion

Definition of kidney disease and treatment, according to TPM:

The use of complementary medicine today is very common and is most commonly used by those with chronic diseases [22]. In order to propose a therapeutic protocol based on TPM, it is necessary to relate symptoms of chronic nephropathy and proteinuria to that of kidney diseases mentioned in TPM resources.
In this study, the researcher explains DN from the viewpoint of TPM and proposes Plantain seeds as a potential treatment for it.Avicenna in The Canon: Avicenna, in his book The Canon mentions the causes of kidney weakness/disease (which corresponds to the definition of nephropathy: reduction of GFR or oliguria) as maltemperament of kidney, thinning and reduction in size of it, along with the widening of its ducts. This itself is caused by the excessive use of diuretics or excess sexual intercourse or from trauma to the kidneys or from long excessive walking and difficult travels [23].
Whatever be the reason of weakness of kidneys, its symptoms include reduction in size of it, oliguria and frequent urination, inability to carry out healthy intercourse, eye weakness and headache, sometimes mild pain and decreased appetite.
Symptoms of reduction of size of kidney, which is one of the causes of kidney weakness, include white colored urine, polyuria (in initial stages), slimness of body, constant mild pain in the back and lumber region, and sense of weakness in that region [24].
TPM physicians defined kidney disease or weakness as an inability of the kidney to perform its natural task. The natural task of the kidney is that it expels away extra water from the body towards the bladder. This extra water contains some amount of diluted blood, which is used by the bladder for its own functional nourishment. The bladder then excretes the rest of water out. Whenever kidney weakens, it does not filter the blood from waste water, rather excretes it out. Sometimes urine becomes viscous, so much so that if it is left untouched for an hour, it precipitates as a top layer on urine resembling sea foam [17].
Reasons that lead to kidney disease or weakness are either reduction in the retaining strength of the kidney tissue or its excessive loosening that reduces the retention control. This weakness of the retaining force (quwwat e masika) [24] may lead to excessive excretion of protein in the urine.
The cure for this weakness of kidney tubules according to TPM is known as Talazuz or agglutinating, which means introducing agents that cause strengthening of tubules, by their thick glossy lubrication and astringent properties [24, p. 830]. Plantago major seeds is one of such agents that possesses lubricating as well astringent properties, besides its anti-inflammatory and anti-oxidant and reno protective properties.

Table 1. Characteristics of Plantago major

"Plantango major"	
Nomenclature	Scientific Name: Plantago major L General Name: Greater plantain Arabic name: Lesan al-Hamel, Plantaginaceae family In TPM: "Lesan al-Hamal" or "Barhang" It is capable of growing in all parts of Iran. Researchers believe that Plantago Major has existed for almost 4,000 years, especially in Europe.
Pharmocolgy	Its important compounds include iridoid glycosides including aucubin, 6.5% mucilage containing at least four polysaccharides. Tannins, coumarin, flavonoids, silicin acid are 1% and zinc and potassium. [25].
Forms of applications in Modern medicine	The beneficial part of the plant are leaves and seeds. Boiled with honey, it is used to relieve sore throat and topically in the elimination of inflammation. Planting leaves are used to treat swelling of the upper respiratory tract. Aqueous extract while cold is used as liquid extract. Its leaf extract has the effect of stopping bacterial growth and killing it, while brewing and decoction of leaves prevents the activation of subsequent pathogens due to the breakdown of d-glucosidase. Plantago seeds are used in the treatment of constipation and are an anti-inflammatory for gastrointestinal tract. There are drops and syrup products from its leaf which are used as expectorant and anti-cough. Plantain can inhibit the activity of angiotensin conversion enzyme and is more efficient in inhibiting the size of calcium oxalate crystals in vitro compared to allopurinol and potassium citrate and can be used to inhibit urinary stones production [19] .
Forms of applications in Traditional Persian Medicine	In different sources, daily consumption of 2-4 grams of leaves and 5-15 grams of seeds have been recommended. Seeds and leaves do not have any side effects [26] It has traditional characteristics such as wound healing, antipyretic, analgesic, disinfection, anti-bleeding, anti-inflammatory, diuretic, laxative, astringent are approved. Plantago is a safe herb, but some adverse reactions such as nausea, vomiting, diarrhea, anorexia, bloating, hypersensitivity and dermatitis may develop after treatment [27].
Major characteristics of different forms of Plantago major according to TPM resources	The temperament of the plantain is cold and dry in second degree and is an astringent. Cools down stomach and liver which are hot and strengthens them. Opens up the obstruction of the liver and is a subtle resolvant (tehleel), and has little element of earth (ariziyaat), and because of its tenderness and high fluid nature, the delay in its influence is not enough to reduce its power and thus removes obstruction of the liver. Drinking the extract of the plant or its seeds relieves kidney and bladder pain, which strengthens the kidney muscle by its cooling effect and refrains it from releasing its waste towards other vulnerable organs. [28]. The leaves and seeds of the plantain are tender and cleansing(Jaali), divertive (radeh), astringent (qaabiz), strengthening or calorific(muqawwi) for liver, opener (mufatteh) for obstructions of liver and spleen and kidneys, and beneficial for burning micturition. Harmful to the lungs which is neutralized by honey and its extract is harmful for spleen which is neutralized by Mastic. Dosage from its leaf extract is ten mithqāl (unit of mass each equals to 4.25 grams) to half ratl (1 ratl equals 470.4 g). The properties of plantain seeds are like its extract and its roasted seeds acts as astringent and lubricant. The Dosage of the seeds is up to 3 dirhams (1 dirham equals to 3.088 g) [29]. In this study, plantain seeds are proposed as being effective in controlling proteinuria DN.

Definition of kidney disease and treatment, according to Modern medicine:

CKD is divided into five stages (1 to 5) according to glomerular filtration rate (GFR) and albuminuria degree. The global prevalence of CKD increases with increasing age. The prevalence of end-stage kidney disease (ESRD) is increasing everyday [30].

Classical diabetic nephropathy begins with microalbuminuria, the urinary excretion rate of 30-300 mg albumin, which after 5 to 15 years leads to macro albuminuria (protein excretion of more than 300 mg in 24 hours). This leads to decrease in GFR glomerular purification rate and subsequently may lead to ESRD if without treatment in 5 to 7 years [31]. Screening for diabetic kidney disease is necessary to identify patients at risk. Intervention aimed at reducing glucose, fats and blood pressure improves renal and cardiovascular prognosis and reduces mortality rates by 50%. Therefore, despite treatment, the progression of the disease continues, and does not stop with blood pressure control. Reduction in glomerular filtration rate, increase in arterial blood pressure and increase in cardiovascular mortality are complications of diabetic nephropathy. [31], [32]. Risk factors for diabetic nephropathy include male gender, hyperglycemia, long-term diabetes, cigarettes, genetics, insulin resistance, high blood cholesterol, familial history (hypertension, cardiovascular disease, nephropathy), and certain race (Asian, Native American, Mexican American) [33]. In nephropathy, with the loss of negative charge of capillary glomerular membrane, protein with lower molecular weight is filtered, especially albumin, and appears in urine [34].

CONCLUSION

- The most important goal of treatment according to Traditional Persian Medicine (TPM) is to prevent the progression of diabetes related complications, so that patient does not end up with dialysis and kidney transplant, in which case the quality of life of patient is severely compromised [16]. In renal disease, the final stage of kidney transplantation is associated with better survival compared to dialysis. However, surgery is severely limited due to shortage of available organs for transplantation. While the number of ESRD patients continues to increase, researchers are determined to produce functional kidneys with new methods [17], and in such circumstances, TPM may prove to be a useful option!
- In this review, authors suggest Plantago major seeds might be a useful and promising treatment for control of proteinuria in DN. Although, couple of recent studies have proved its clinical efficacy, yet another focused RCT based study is being looked forward for, by the same authors to prove this literature review.

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