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Review on The Potential of Herbal Medicine in the Treatment of Diabetic Kidney Disease

Dhananjay Adhav[1], Vaibhav R Dhanlobhe[2], Nikhil B. Khandale[3], Vishal B. Mahanur[4], Akhil P Maske[5], Sharwan Hudda[6]

Students, Vardhaman College of Pharmacy, Karanja (Lad), Maharashtra, India[1,2]
Assistant Professor, Department of QA and Regulatory Affairs, L. J. Institute of Pharmacy, Ahmedabad, India[3]
Assistant Professor, Department of Pharmaceutical Analysis[4]
Associate Professor, Department of Pharmaceutics[5]
Vardhaman College of Pharmacy, Karanja (Lad), Maharashtra, India[4,5]
Research Scholar, Department of Pharmaceutical Chemistry, Lovely Professional University, Jalandhar, India[6]

Abstract: *Diabetic Kidney Disease (DKD), a leading complication of diabetes mellitus, presents a significant global health challenge due to its progression to end-stage renal disease (ESRD). Conventional therapies for DKD focus on glycemic control, blood pressure regulation, and renin-angiotensin system inhibition but often fall short in halting disease progression. This review explores the potential of herbal medicine as a complementary approach to managing DKD.*

Herbal medicines, rich in bioactive phytochemicals, exhibit antioxidant, anti-inflammatory, and renoprotective properties that may mitigate key mechanisms driving DKD progression. Notable compounds include quercetin, curcumin, berberine, and ursolic acid, which target oxidative stress, inflammation, and fibrosis. Furthermore, herbs like Curcuma longa, Zingiber officinale, and Panax ginseng have shown promising results in preclinical and clinical studies, improving renal function and reducing proteinuria.

Despite their potential, challenges remain in standardizing herbal formulations, understanding herb-drug interactions, and ensuring safety in patients with compromised renal function. Future research should prioritize large-scale clinical trials, mechanistic studies, and integrative treatment models combining herbal and conventional therapies. By leveraging the strengths of traditional and modern medicine, herbal interventions offer a promising pathway to improve outcomes for individuals with DKD..

Keywords: Diabetic Kidney Disease

I. INTRODUCTION

Diabetic Kidney Disease

Diabetic Kidney Disease (DKD), also known as **Diabetic Nephropathy,** is a chronic complication of diabetes mellitus.[1] It is characterized by progressive damage to the kidneys due to prolonged exposure to high blood glucose levels, which leads to structural and functional abnormalities.[2] DKD is the leading cause of end-stage renal disease (ESRD) worldwide and contributes significantly to morbidity and mortality among individuals with diabetes.[3][4]

Kidney

In humans, the **kidneys** are two reddish-brown bean-shaped blood filtering organs[5] that are a multilobar, multibacillary form of mammalian kidneys, usually without signs of external lobulation.[6][7] They are located on the left and right in the retroperitoneal space, and in adult humans are about 12 centimeters (4+½ inches) in length.[8] They receive blood from the paired renal arteries; blood exits into the paired renal veins. Each kidney is attached to a ureter, a tube that carries excreted urine to the bladder.

The kidney participates in the control of the volume of various body fluids, fluid osmolality, acid-base balance, various electrolyte concentrations, and removal of toxins. The nephron is the structural and functional unit of the kidney. Each adult human kidney contains around 1 million nephrons, while a mouse kidney contains only about

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12,500 nephrons. The kidneys also carry out functions independent of the nephrons. For example, they convert a precursor of vitamin D to its active form, calcitriol; and synthesize the hormones erythropoietin and renin.

II. FUNCTIONS OF THE KIDNEY

The kidneys are vital organs that perform several essential functions to maintain the body's overall health and homeostasis. Here's an overview of their key functions:

Filtration of Blood

The kidneys filter blood to remove waste products, excess water, and toxins, forming urine. They eliminate substances like urea, creatinine, and ammonia.

Regulation of Electrolytes

The kidneys maintain the balance of electrolytes, such as sodium, potassium, calcium, and phosphate, ensuring proper nerve and muscle function.

Control of Blood Pressure

By regulating the amount of fluid in the body and releasing the enzyme renin, the kidneys help control blood pressure. Renin is part of the renin-angiotensin-aldosterone system (RAAS), which manages blood vessel constriction and fluid balance.

Acid-Base Balance

The kidneys regulate the pH of the blood by excreting hydrogen ions and reabsorbing bicarbonate, preventing acidosis or alkalosis.[9]

Erythropoiesis Regulation

The kidneys produce erythropoietin, a hormone that stimulates red blood cell production in the bone marrow, especially in response to low oxygen levels in the blood.

Calcium and Phosphorus Balance

The kidneys activate vitamin D into its active form (calcitriol), which aids in calcium absorption from the gut and regulates calcium and phosphorus levels in the blood.

Water Balance

They regulate the body's water balance by adjusting the concentration and volume of urine, ensuring hydration levels are maintained.

Elimination of Drugs and Toxins

Many medications and toxins are metabolized and excreted through the kidneys, making them critical for detoxification.

Kidney Related Disease

The two main types of kidney disease are:

1. Acute Kidney Injury (AKI):

Also known as acute renal failure, AKI occurs suddenly and is typically caused by trauma, infections, or toxins that damage the kidneys. Unlike CKD, AKI is reversible if treated promptly, but it can lead to permanent damage if not addressed quickly. Common causes include dehydration, medications, infections, and conditions like sepsis or acute glomerulonephritis.[10][11][12]

2. Chronic Kidney Disease (CKD):

Chronic kidney disease (CKD) is a type of long-term kidney disease, in which either there is a gradual loss of kidney function which occurs over a period of months to years, or an abnormal kidney structure (with normal function).[13][14] Initially generally no symptoms are seen, but later symptoms may include leg swelling, feeling tired, vomiting, loss of appetite, and confusion.[15] Complications can relate to hormonal dysfunction of the kidneys and include (in chronological order) high blood pressure (often related to activation of the renin–angiotensin system), bone disease, and anemia.[16][17][18][19] Additionally, CKD patients have markedly increased cardiovascular complications with increased risks of death and hospitalization[20] CKD can lead to kidney failure requiring kidney dialysis or kidney transplantation.[21]

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Chronic kidney disease (CKD) is classified into five stages based on the severity of kidney damage, as indicated by the glomerular filtration rate (GFR) and the presence of symptoms like albuminuria (protein in urine). Here's an overview of the types of CKD, often categorized by the underlying causes:

Types of Chronic Kidney Disease (CKD) by Cause:

1. Diabetic Kidney Disease (Diabetic Nephropathy):

Diabetic Kidney Disease is the most common cause of CKD in most developed and developing countries. Approximately 40% of patients with diabetes develop CKD, so all patients with diabetes should have their GFR and UACR checked annually. Achieving good glycaemic control and early treatment of hypertension with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker are the most important interventions to slow the progression of CKD.[22]

2. Hypertensive Nephropathy:

Hypertension is an almost universal consequence of CKD but also contributes to its progression. Population-based studies have identified hypertension as an independent risk factor for ESKD, but whether or not hypertension per se causes kidney disease remains controversial. All patients with newly diagnosed hypertension should be screened for CKD as a possible cause, and treatment of hypertension is essential for slowing the rate of CKD progression.[22]

3. Glomerular Diseases:

The term 'glomerulonephritis' refers to a wide range of primary and secondary conditions that cause inflammation in and damage to the glomerulus. The pathogenesis involves the immune system in most cases but understanding of the specific mechanisms remains incomplete. The hallmark of glomerulonephritis is haematuria with proteinuria. A urine dipstick test should be therefore performed on every patient presenting with CKD or AKI. Renal biopsy is usually required to make a specific diagnosis. The treatment depends on the specific diagnosis and cause, as do the progression rate and prognosis.[22]

4. Kidney Disease (PKD):

Adult polycystic kidney disease is the most common monogenic disorder causing CKD. It is inherited in an autosomal dominant fashion and typically presents in the third and fourth decades of life. It is frequently associated with extra-renal manifestations, including cysts involving other organs (liver, spleen), cerebral aneurysms and cardiac valvular abnormalities.[23]

5. Cardiovascular diseases

Cardiovascular disease is frequently associated with CKD. Atherosclerosis can narrow the main renal arteries to cause renal artery stenosis, or affect the smaller intrarenal arteries and arterioles to cause ischaemic nephropathy. Cardiac failure results in reduced renal perfusion, and diuretics used to treat fluid retention further reduce GFR. The association between cardiac and renal failure is referred to as cardiorenal syndrome.[22]

III. OTHER CAUSES OF CHRONIC KIDNEY DISEASE

- **Vascular Disease**: Conditions like atherosclerosis, where the blood vessels to the kidneys become narrowed or blocked, leading to reduced kidney function.
- **Medications and Toxins**: Long-term use of certain medications (like nonsteroidal anti- inflammatory drugs or NSAIDs) or exposure to toxins can damage the kidneys.
- **Autoimmune Diseases**: Conditions like lupus or IgA nephropathy, where the immune system mistakenly attacks the kidneys, leading to CKD

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Diabetic kidney disease

Diabetic nephropathy, also known as diabetic kidney disease (DKD), is a chronic illness that develops when a person with diabetes gradually loses kidney function. It is the primary cause of end-stage renal disease (ESRD) and chronic kidney disease globally.

Diabetic kidney disease (DKD) is one of the major complications for diabetic patients and the most significant cause of end-stage kidney disease (ESKD).[24] Until now, chronic kidney disease (CKD) caused by diabetes mellitus is diagnosed as diabetic nephropathy, which begins with microalbuminuria, followed by macroalbuminuria and then gradual decline in kidney function, and is diagnosed pathologically by characteristic pathological findings, such as increased mesangial substrate, nodular lesions, and tubulointerstitial fibrosis.[25] However, in recent years, cases of impaired renal function without albuminuria have been reported.[26][27] In this background, a new disease concept called DKD was born. DKD is defined as CKD with diabetes being partially involved in the pathogenesis of kidney disease, encompassing the concept of classical diabetic nephropathy.[28]

Signs and symptoms

Main symptoms of diabetic nephropathy include an increase in blood pressure (hypertension) and fluid retention in the body. Other complications include arteriosclerosis of the renal artery and proteinuria. Diabetic nephropathy has no symptoms throughout its early course. They develop in late stages and may be a result of excretion of high amounts of protein in the urine or due to renal failure:

- edema: swelling, usually around the eyes in the mornings; later, general body swelling may result, such as swelling of the legs
- foamy appearance or excessive frothing of the urine (caused by the proteinuria)
- unintentional weight gain (from fluid accumulation)
- anorexia (poor appetite)
- nausea and vomiting
- malaise (general ill feeling)
- fatigue
- headache
- frequent hiccups
- generalized itching[29]

Treatment of Diabetic kidney Disease :

In the diabetic nephropathy there are specific treatment of patients can be divided into four major areas.
In practical terms, this means adequate blood glucose lowering and control of hypertension. A description of all glucose lowering agents is beyond the scope of the review but certain agents have theoretical benefits beyond glucose lowering. In addition, people with DKD are also more likely to experience retinopathy, nephropathy and foot ulcers so increased vigilance for these complications important. Treatment guidelines have been developed by several international and national organizations are summarized below-

1. Cardiovascular risk reduction (CVD):

Diabetic kidney disease (DKD) is strongly associated with CVD. DKD may be a marker of cumulative vascular damage due to diabetes or may causally promote CVD through several mechanism, such as blood pressure dysregulation, retention of uremic toxins, anemia and altered mineral metabolism. In light of high mortality of patients with diabetic nephropathy primary prevention of its development and efforts to hinder its progression once it is established are the utmost importance. Unfortunately, CKD frequently goes recognized by both patients and providers. Furthermore, patients with diagnosed CKD have been found to be less likely than the general population to receive appropriate CVD risk factor modifications. A large opportunity to improve outcome in this vulnerable patient population lies in simply raising awareness of these issues and intervening as early as possible.

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2. Glycemic control:

The effect of improved glycemic control on clinical outcomes, including progression of diabetics nephropathy, has been tested in multiple large clinical trails involving patients with T1/T2 DM. The principle evidence regarding the benefits of glycemic control in patients with T1 DM comes from the diabetes control and complications trails (DCCT). The DCCT randomized 1441 people with T1DM to intensive insulin therapy or standard therapy. After mean follow up of 6.5 years, there was a significant reduction in the development of moderate (A2) and severe (A3) albuminaria in the intensive arm, as well benefits for other microvascular complications.

3. Blood Pressure control-

The current Joint National Committee (JNC) Guidelines recommend targeting a blood pressure of <140/90mmHg for diabetic's patients, irrespective of CKD. The effect of achieved BP was analyzed in detail in IDNT and suggested the presence of a J-shaped curve such that kidney benefits reached a plateau at systolic BP < 130mmHg, and all cause mortality increased at systolic BP<120mmHg.

4. Renin Angiotensin System Inhibition:

In humans, RAS inhibition has proved to be the single most effective therapy for slowing the progression of diabetic nephropathy. These agents have been studied at each clinical stage of diabetic nephropathy. Blockade of RAS using either angiotensin converting enzyme inhibitor or angiotensin receptor blokers can attenuate progressive glomerulosclerosis in animal models, and slows disease progression in human with DKD.

5. Diuretics:

Similar to dietary sodium restriction, thiazide diuretics (eg. hydrochlorothiazide 50 mg) when combined with an ACE inhibitor (lisinopril 40 mg/day) reduced albuminuria in type 2 diabetics. However, the combination is associated with more frequent orthostatic symptoms. For advanced CKD, a loop diuretic may be more appropriate. Diuretics may increase the effectiveness of ACE inhibitors.[30]

Worldwide prevalence of DKD

DKD is highly prevalent across the globe. The odds of developing CKD in patients with diabetes was reported around 1.75 (95% CI: 1.62–1.89). A cross-sectional study from a risk assessment management program in China found 38.8% prevalence of CKD in 15856 patients with diabetes. A population-based study reported 2.9% prevalence of DKD among Chinese rural residents. A study conducted by our group found 34.4% prevalence of DKD in India. A multicentre study from India reported a composite prevalence of diabetic-CKD of around 62.3%. Similarly, a population-based study from the United Arab Emirates found 11.4% cumulative incidence of CKD after a follow-up of 9 years. The highest prevalence rates of diabetes mellitus (DM) and CKD-DM were observed among the elderly in the eastern Mediterranean region. Diabetes clinical data management study in Japan revealed 15.3% of T2DM patients had low eGFR. Findings of United Kingdom (U.K.) prospective diabetes study incorporating 4006 T2DM patients revealed that 28% patients develop renal impairment after a median follow-up of 15 years. The prevalence of DKD in United States (U.S.) population was found to be 2.2% according to the cross-sectional analysis of third national health and nutrition examination survey. It also states that prevalence of DKD in the US is increasing in proportion to the prevalence of diabetes as observed from 1988 to 2008.[31]

Risk Factors

Only 1 in 3 patients with diabetes ever developed DKD, both environmental and genetic factors have been postulated as the risk factors that determine who develops hyperglycemia-related renal injury. It has been reported that hyperglycemia, hypertension, obesity, smoking, race (Mexican American/Pima Indians) and genetic predisposition are the main risk factors for the development of DKD. However, select individuals with diabetes were at differential risk for DKD on the basis of family-based studies (9,10). It is thought that specific genetic backgrounds might influence DKD development. There is growing evidence for the role of genetic factors in the development of DKD.[32]

Pathophysiology

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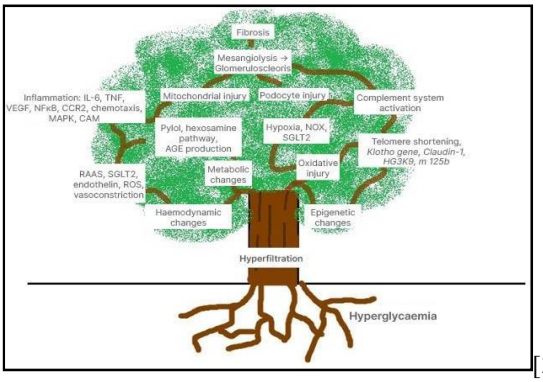
Diabetes, a name coined from passing a lot of urine and mellitus (meaning sweet) speaks itself of uncontrolled blood glucose levels. The end result of uncontrolled hyperglycaemia in the kidney is nephron death. This manifests in the form of glomerulosclerosis, interstitial fibrosis, and tubular atrophy, but there are a lot of milestones and instigators along the way. Fibrosis is the end point of years of micro- and macroscopic changes resulting from the diabetic milieu, as noted in **Figure 1**. The inception of the renal involvement in this disorder is the onset of uncontrolled levels of blood glucose. The authors will discuss the framework that stems from hyperglycemia, and concludes with renal fibrosis.



[33]

Figure 1: Hyperglycaemia lays the roots in the pathogenesis of diabetic kidney disease.
Hyperglycaemia leads to hyperfiltration, which is followed by metabolic, hormonal, haemodynamic, inflammatory and epigenetic changes. Oxidative stress and hypoxia play a vital role. All these precipitate to podocyte injury, mitochondrial distress, tissue death, glomerulosclerosis, and interstitial fibrosis. AGE: advanced glycation end products; CAM: cell adhesion molecules; CCR2: C-C chemokine receptor 2; MAPK: mitogen activated protein kinase; NFκB: nuclear factor κ B; NOX: nicotinamide adenine dinucleotide phosphate oxidases; RAAS: renin–angiotensin–aldosterone system; ROS: reactive oxygen species; SGLT2: sodium–glucose co-transporter 2; VEGF: vascular endothelial growth factor.

Hyperfiltration

Hyperglycaemia initiates its effects on the kidney by disturbing the osmotic forces. The higher blood glucose contents cause higher osmolality in the glomerular capillaries, resulting in higher glomerular pressures. This results in more outward forces increasing the glomerular filtration. Initially, this results in a falsely low to normal eGFR calculation based on more creatinine filtration with hyperglycaemia. This hyperfiltration is proposed to be multifactorial. Chemokines and enzymes like ornithine decarboxylase, which are produced in response to hyperglycaemia (noted in the kidneys of mice with hyperglycaemia), bring about renal enlargement with increased filtration surface area per nephron. Obesity, which can be integral to most patients with diabetes, can worsen renal enlargement and hyperglycaemia, promoting this initiation of renal injury. Weight loss in patients with DKD, through surgical or non-surgical methods in animal models, showed a significant reduction in the rate of decline in the eGFR.
Intraglomerular hypertension, which can be multifactorial, also predisposes to hyperfiltration. In many patients with diabetes, coexisting systemic hypertension, increased intrabdominal pressure due to obesity, and the increased osmotic pressures in the glomeruli end up contributing to this. Hyperglycaemia and protein-rich meals result in the production of various chemicals that can impair tubule-glomerular feedback, and increase local vasoconstrictors.[33] Another mechanism for hyperfiltration is the role of sodium–glucose co-transporters 2 (SGLT2) found in the proximal convoluted tubules. With supraphysiological levels of blood glucose, there is an upregulation of SGLT2, resulting in the maximal utilisation of these transporters. Maximal reabsorption in the PCT causes decrease tubular pressures, causing more filtration from the glomerular vessel. Also, with maximal sodium and glucose reabsorption, there is decreased distal sodium delivery activating the renin–angiotensin–aldosterone system (RAAS).
This hyper-flow state also leads to protein leak, which instigates alteration in the nephron structure, with resultant mesangial hypertrophy seen in the kidneys of patients with diabetes. Measures taken to control hyperglycaemia have

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been proven to inhibit DKD progression, myocardial infarction, an mortality. Therefore, antihyperglycaemics have been the cornerstone in the management of DKD.[33]

Haemodynamic Effects and Endothelial Injury

Hyperglycaemia and SGLT2-assisted decreased distal sodium delivery leads to activation of RAAS, producing efferent arteriolar vasoconstriction and afferent vasodilation, and amplifying intraglomerular hypertension. RAAS activation worsens systemic hypertension. Renin by itself has been noted to activate the mitogen activated protein kinase (MAPK) signalling pathway, while angiotensin II directly assists fibrosis by boosting transforming growth factor (TGF) production, vascular endothelial growth factor (VEGF), cell adhesion molecules, nuclear factor κ B (NFκB) pathway, and toll-like receptors activation. TGF-β keeps a check between fibrosis and inflammation, and any imbalance in the concentration of TGF-β leads to abnormalities amongst them. TGF-β acts via *SMAD3* and *SMAD7*. The former positively regulates non- coding RNA for inflammatory and fibrotic mediators, while the latter negatively affects it. Angiotensin II also stimulates production of reactive oxygen species (ROS) and inflammatory cellular attraction through activation of monocyte chemoattractant protein 1 (MCP-1), C-C chemokine receptor 2 (CCR2; in rat models), and co-stimulation of NK and T cells (in human subjects). In animal models and cultured kidney tissue, aldosterone was noted to facilitate fibroblast production by triggering TGF-β/*SMAD2*, fibronectin, stimulating platelet derived growth factor receptor plus EGFR via phosphoinositide 3-kinases/MAPK signalling, c-Jun N terminal kinase phosphorylation, and epithelial-mesenchymal transition. It also increases expression of plasminogen activator inhibitor-1, promoting hypercoagulable milieu. Angiotensin and hyperglycaemia prompt endothelin production, worsening vasoconstriction, inflammation, podocyte injury, nephrin shedding, and interstitial fibrosis.

Metabolic Changes

Diabetes is associated with dysregulation of multiple metabolic pathways. Hyperglycaemia brings about activation of pathways including RHO/ROCK, hexosamine, pylol, advanced glycation end products (AGE), and protein kinase C (PKC), producing higher ROS, generating higher levels of MAPK, JAK signal transducers and activators of transcription, and NFκB, which are building blocks to inflammation and fibrosis. MAPK is linked to extracellular matrix production and podocyte injury. NFκB signals production of adhesion molecules and cytokines like macrophage chemoattractant protein MCP-1, IL-6, and tissue necrosis factor α. ROS also directly causes damage to cellular structures by oxidising various lipids, nucleic acids, and proteins. This lipid oxidation is aggravated with coexisting obesity and Type 2 diabetes, due to higher load of lipids.[33]

Hypoxia and Oxidative Stress

Renal hypoxia is the inability of the oxygen supply to meet renal demands. This correlates directly with the blood supply, while the majority of demand depends on the metabolic activity in the tubules.

Hyperglycaemia can lead to oxidative stress and hypoxia in multiple ways. RAAS-mediated vasoconstriction causes ischaemic injury, hyperglycaemia causes hyperfiltration and tubular hypertrophy and overactivates SGLT2 channels, which depletes higher amounts of adenosine triphosphate and oxygen, leaving the nephron in a hypoxic state. An imbalance between antioxidants and ROS is a strong determinant for expediting tissue damage. Chronic hyperglycaemia also mediates overexpression and hyperactivity of nicotinamide adenine dinucleotide phosphate oxidases (NOX) 1, NOX2, NOX4, and NOX5 These produce higher ROS levels, causing Ras-related C3 botulinum toxin substrate 1 and VEGF-mediated foot process effacement, p53-driven apoptosis, protein kinase C, and A disintegrin and metalloprotease 17-mediated mesangial expansion, and uncoupling of nitric oxide synthase, causing vasocontraction. This hypoxia also produces hypoxia inducible factor which, under hyperglycaemic state, becomes unstable, and when chronically stimulated sparks a profibrotic effect. Ultimately, this becomes a vicious cycle of inflammation, vascular injury, and further hypoxia.[33]

Role of Inflammation and the Complement System

DKD has multiple intersecting pathways propagating its disease process. Inflammation plays a vital role in the pathogenesis of DKD. Diabetes sets in motion various inflammatory cascades via oxidative stress, AGE, obesity,

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ischaemia, and damaged cells, producing inflammatory molecules like NFκB, NLR family pyrin domain containing 3 (NLRP3)-linked caspases, IL- 1B, IL-6, and IL-18. This increase in AGE has been shown to be linked directly with increased expression of NLRP3-related proteins, which have been postulated to be mediators of chronic kidney disease, with a role in activation of mesangial cells. NLRP3-related proteins are found in macrophages and inflammasomes and have been linked to multiple inflammatory disorders. In various mice models, attenuation of NLPR3 helped reduce chronic kidney disease (CKD) progression in a dose-dependent manner. Neutrophil and macrophage infiltration, lipoprotein oxidisation, and immune complex deposition can also occur. With this ongoing inflammation there is increased production and deposition of amyloid A protein, which can also be used as a marker of disease progression. CCR2 signalling distorts actin cytoskeleton and nephrin stability, damaging podocytes. Hyperglycaemia-mediated promotion of elective cell simulated adhesion molecules cause tight junction abnormalities, resulting in proteinuria.[33] Furthermore, the complement system activation has a huge impact on DKD progression. DKD progression has been linked to complement activation through mannose-binding lectins and ficolin-associated activation of the lectin pathway in the complement cascade. Hyperglycaemia leads to higher levels of glycan and galactosamine-bound substances that are recognised by these receptors.

Glomerular Changes

The earliest changes in DKD are due to hyperfiltration in the glomerulus, causing thickening and stiffness of the glomerular basement membrane from sheer pressure and deposition of extracellular matrix. Secondly, mesangial expansion occurs due to leakage of protein, inflammation, and ongoing damaged tissue collection. This further disturbs the precision of glomerular filtration. Mesangiolysis leads to accumulation of matrix and cellular debris, which forms nodular structures named Kimmelstiel and Wilson nodules. Additional mesangial destruction ends up in widespread glomerulosclerosis. Vascular changes with thickening of vessel walls and hyalinosis are also classic for DKD.[33]

Podocyte Injury

Podocytes are the building blocks of the renal system. They are the prime managers of the filtration system. Podocyte injury has been shown to mimic diabetic changes even in absence of hyperglycaemia, which indicates that podocyte injury is the key in development of DKD. Hyperglycaemia, oxidative stress, and inflammation leads to podocyte effacement, actin rearrangement, increased tight junction, slit diaphragm abnormalities, and apoptosis. In mice models, activation of mammalian target of rapamycin complex 1, dynamin-related protein in mitochondria, nicotinamide adenine dinucleotide phosphate oxidase, and AMP-activated protein kinases are responsible for these changes.[33]

Cellular and Mitochondrial Injury

The renal tubules, given their high metabolic demand, are rich in mitochondria. Patients with diabetes have been noted to have mitochondrial abnormalities, including mitochondrial fragmentation, decreased adenosine triphosphate, increased mitochondrial permeability, and mitochondrial uncoupling as early as 4 weeks after hyperglycaemia. Peroxisome proliferator- activated receptor-gamma coactivator-1α is amongst the prime regulators of mitochondrial synthesis, and its expression is altered in DKD. The electron transport chain subunits in the mitochondria are also directly damaged by the oxidative stress that occurs with hyperglycaemia, leading to worsening mitochondrial metabolic functions via DNA damage and decreased activity of glyceraldehyde 3-phosphate dehydrogenase. This leads to shifts in the glycolytic pathway to pylol and hexosamine pathways. Resultant oxidative stress causes decrease in AMP-activated protein kinase activity, leading to NFκB-mediated inflammation.[33]

Fibrosis

Unfortunately, all of the above mechanisms merge together and result ultimately in fibrosis and atrophic kidney tissue. The degree of tubulointerstitial fibrosis can even supersede glomerular lesions in determining renal function. Local myofibroblasts, bone marrow-derived fibrocytes, and epithelial to mesenchymal transition as a response to the chemokines have been noted to produce this effect. [33]

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Herbal medicine

Herbal medicines are naturally occurring, plant-derived substances that are used to treat illnesses within local or regional healing practices. These products are complex mixtures of organic chemicals that may come from any raw or processed part of a plant.[34]

Herbal medicine is the use of plants or plant parts to treat disease, improve health, or prevent illness. Herbal medicines can be used in many forms, including tablets, capsules, powders, teas, extracts, and fresh or dried plants.

Herbal medicines have gained significant importance in the last few decades and the demand to use natural products in the treatment of diabetes is increasing worldwide. Available literature shows that there are more than 400 plant species showing antidiabetic activity. In the indigenous Indian system of medicine, many plant species remain to be scientifically established especially those with renoprotective effects.[35]

Importance Of Herbal Medicine

Herbal medicine has its roots in every culture around the world. There are many different systems of traditional medicine, and the philosophy and practices of each are influenced by social conditions, environment and geographic location, but these systems all agree on a holistic approach to life. Well-known systems of herbal medicine like Traditional Chinese Medicine and Ayurvedic Medicine believe in the central idea that there should be an emphasis on health rather than on disease. By using healing herbs, people can thrive and focus on their overall conditions, rather than on a particular ailment that typically arises from a lack of equilibrium of the mind, body and environment. Herbal medicine has its origins in ancient cultures. It involves the medicinal use of plants to treat disease and enhance general health and wellbeing. Herbal medicine, also known as herbalism or botanical medicine, is a medical system based on the use of plants or plant extracts that may be eaten or applied to the skin. Since ancient times, herbal medicine has been used by many different cultures throughout the world for many treatments like malaria, warts, bowel disorders, heart conditions and chronic pain, come from pharmacists and doctors learning about folk knowledge.[36]

History of traditional medicine

The history of herbalism is closely tied with the history of medicine from prehistoric times up until the development of the germ theory of disease in the 19th century. Modern medicine from the 19th century to today has been based on evidence gathered using the scientific method. Evidencebased use of pharmaceutical drugs, often derived from medicinal plants, has largely replaced herbal treatments in modern health care. However, many people continue to employ various forms of traditional or alternative medicine. These systems often have a significant herbal component. The history of herbalism also overlaps with food history, as many of the herbs and spices historically used by humans to season food yield useful medicinal compounds [37][38] and use of spices with antimicrobial activity in cooking is part of an ancient response to the threat of food-borne pathogens.[39]

Key Phytochemicals with Renoprotective Properties in Herbal Medicine for Diabetic Kidney Disease

Diabetic kidney disease (DKD) has historically been treated with a variety of herbal remedies.[40] Numerous phytochemicals found in these herbs support their renoprotective properties.[41]

The following are important phytochemicals and the herbs that go with them:

1. Flavonoids:

Quercetin:

Quercetin, which is present in tea, berries, apples, and onions, has anti-inflammatory and antioxidant qualities that can shield the kidneys from inflammation and oxidative stress.[42]

Rutin:

Similar to quercetin, rutin is found in berries, citrus fruits, and buckwheat. It may help lower proteinuria and enhance kidney function.[43]

Resveratrol:

Resveratrol, which is present in peanuts, berries, and grapes, has anti-inflammatory and antioxidant qualities that can shield the kidneys from harm.[44]

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2. Polyphenols:

Curcumin:

Curcumin, the active ingredient in turmeric, possesses potent anti-inflammatory and antioxidant qualities. It can shield the kidneys from harm by lowering inflammation and oxidative stress.[45]

Gallic acid:

Gallic acid, which is present in tea, grapes, and oak bark, has anti-inflammatory and antioxidant qualities that may help shield the kidneys from harm.[46]

3. Alkaloids:

Berberine:

Berberine, which is present in plants like barberry and goldenseal, has antioxidant and anti- inflammatory qualities.[47] It can shield the kidneys from harm by lowering inflammation and oxidative stress.[48]

4. Terpenoids:

Ursolic acid:

Ursolic acid, which has anti-inflammatory and antioxidant qualities, is present in a variety of plants, such as apple peel and rosemary.[49] It can shield the kidneys from harm by lowering inflammation and oxidative stress.[50]

5. Other Phytochemicals:

Vitamin C:

Vitamin C, a potent antioxidant that can shield the kidneys from oxidative stress, is present in citrus fruits, berries, and other fruits and vegetables.[51]

Vitamin E:

Vitamin E, another potent antioxidant that can shield the kidneys from oxidative stress, is present in nuts, seeds, and vegetable oils.[52]

Potential Herbal Interventions for DKD

1. Anti-Inflammatory Herbs

Turmeric (Curcuma longa):

Curcuma longa (common name is Turmeric in English, हल्दी in Hindi) is an Indian indigenous plant.[53] The most important secondary metabolite of *C. longa* is curcumin, which is responsible for anti-inflammatory effect of this plant.[54]

Many clinical trials have been done for proving the anti-inflammatory effect of curcumin.

Their results suggest that curcumin can be effective in improving inflammation of rheumatoid arthritis (RA) and reducing clinical manifestation of RA, such as joint swelling

and morning stiffness in comparison with phenylbutazone which is used as a positive control. Also, curcumin was tested in patients with anterior uveitis; after 2 weeks, exhaustive remission occurred. The effectiveness of curcumin in patients with dyspepsia and/or gastric ulcer was proved by another clinical trial. In this study, subjects experienced remission after 12 weeks (maximum). Curcumin is beneficial in irritable bowel syndrome (IBS) treatment and also works as a reducing agent to delayed graft rejection (DGR) after kidney transplant surgery. Curcumin likewise has a beneficial effect in inhibition of inflammatory bowel disease (IBD) and reduction in sedimentation rate in patients who suffered from IBD. It is also proven to be beneficial in maintaining amelioration of ulcerative colitis and psoriasis (by the selective prohibition of phosphorylase kinase).[55]

Ginger (Zingiber officinale):

Zingiber officinale (common name is ginger in English, अदरक in Hindi is a native plant from south-east Asia.[56] Oral administration of *Z. officinale* extract has shown different and inconsistent effects, depending on the quantity of consumption. Although administration of squeezed ginger extract to mice one time or twice has elevated the tumor

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necrosis factor-α (TNF-α) in peritoneal cells, long-term consumption of the extract has increased the serum corticosterone level and has reduced proinflammatory markers. *Z. officinale* was also tested in type 2 diabetic patients with low-grade inflammation; after 2 months of treatment, serum level of TNF-α and high-sensitivity C-reactive protein (hs- CRP) were decreased definitely. In patients with osteoarthritis, ginger had not only efficacy in pain improvement identical to Diclofenac 100 mg but also no side effects. Ginger extract has been compared to Ibuprofen and Indomethacin in OA patients; the results have exerted improving function of Ibuprofen, Indomethacin, and ginger extract equally in pain score. Ginger powder has had ameliorative effect in musculoskeletal and rheumatism patients through inhibiting cyclooxygenase and lipoxygenase pathway in synovial fluid.[55]

2. Antioxidant Herbs

Ginseng (Panax ginseng):

Panax ginseng (common name is Asian Ginseng in English, अश्वगंधा in Hindi. ***Panax ginseng***, ginseng, also known as Asian ginseng, Chinese ginseng or Korean ginseng, is a species of plant whose root is the original source of ginseng. It is a perennial plant that grows in the mountains of East Asia. The root of *Panax ginseng* has been widely used for the management of many diseases, including cancer, DM, and CVD for thousands of years.[57][58] Ginsenosides, main pharmacologically active constituents of ginseng and the secondary metabolites of the *Panax* species, have antioxidants and free radicals scavenging properties. It reduced the cisplatin-induced nephrotoxicity in cultured renal proximal tubular epithelial cells in a dose-dependent manner. North American ginseng has preventive effects on DN and it works through its antihyperglycemic and antioxidant activities.

In type 1 insulin-dependent DN animal models induced by STZ, it was found that sun ginseng, heat-processed American ginseng, and 20(S)-ginsenoside Rg3 ameliorated hyperglycemia and renal damage. In type 2 insulin-independent DN animal models, ginsenoside Rg3 decreased hyperglycemia and proteinuria and augmented creatinine clearance.

Panaxytriol, an active component of red ginseng extracts, is a potent ARE inducer. The upregulation of aldo–keto reductase enzymes, induced by chemically homogeneous panaxytriol, was partially dependent on PKC and PI3K kinases. Aldo–keto reductase enzymes play an important role in the transformation and detoxification of aldehydes and ketones generated during drug detoxification and xenobiotic metabolism. This cellular mechanism may account for panaxytriol's neurotrophic, neuroprotective, and anticancer properties. It has been shown that ginseng induces NQO1, a phase 2 detoxification enzyme protect against carcinogenesis and OS, and the most potent inducing red ginseng extract has the highest panaxytriol content.

Ginkgo biloba

Ginkgo biloba, commonly known as ginkgo or gingko also known as the maidenhair tree, is a species of gymnosperm tree native to East Asia. *Ginkgo biloba* has a number of benefits including scavenging ROS. Extract of *Ginkgo biloba* could inhibit AGEs production and downregulate RAGE expressions by reducing OS, and improve the renal tissue structure and renal functions of DN rats.[60] Furthermore, *Ginkgo biloba* extract has a protective property against glomerulosclerosis of mesangial cells in DN. Data showed that *Ginkgo biloba* decreased BGL, SCr, BUN, urine protein, and the intensity of the OS in DN rats. It reduced AGE, collagen IV, laminin, TGF-β1 mRNA, CTGF, mesangium hyperplasia, and thickness of GBM. A systemic review of randomized controlled trials conducted on adults with early DN showed that *Ginkgo biloba* extract decreased the urinary albumin excretion, BGL, SCr, and BUN.[61]

Endothelial progenitor cells are precursor cells that can differentiate into vascular endothelial to form new blood vessels. These cells could be damaged by OS in DM. It was found that *Ginkgo biloba* can improve SOD activity and reduce the rate of apoptosis of endothelial progenitor cells within the peripheral blood of diabetic patients.

In mouse C2C12 myoblasts, *Ginkgo biloba* extract shows that cytoprotective effects from OS induced by alcohol depend on the transcriptional upregulation of HO-1 via the major mitogen-activated protein kinases/Nrf2 pathway. Furthermore, *Ginkgo biloba* extract produced an increase in Nrf2 and upregulation of HO-1. It could inhibit cytokine-induced endothelial adhesiveness by inducing HO-1 expression via the activation of p38 and Nrf-2 pathways. *Ginkgo biloba* extract might exert its anti-atherogenesis and vascular protective effects by inducing vascular HO-1 expression.

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It could reduce leukocyte adherence to injured arteries, and enhance HO-1 expression in circulating monocytes and in blood vessels.[62]

3. Diuretic Herbs

Dandelion (Taraxacum officinale):

Taraxacum officinale has traditional uses in Germany, North America, Turkey and China.[63] Briefly, in Germany it has been used in the treatment of gout, diarrhoea, blisters, and spleen and liver complaints. In North America, it has been used in kidney disease, dyspepsia and heartburn. In Mexico is suggested to aid the control of Diabetes. In Turkey the herb is applied as a laxative, diuretic and used as an anti-diabetic medicine. Other uses include the treatment of arthritis and rheumatoid arthritis, certain skin conditions (e.g., eczema), weight control[64][65] and as a diuretic.

The effect of Taraxacum folium (herb) and Taraxacum radix (root) on diuresis and weight loss, in conscious rats, have been compared and investigated previously.[66] The concentration of the extracts ranged between 0.5 and 6% and effects were assessed on 2 days—days 1 and 30. UV and UNa were assessed using indices of diuretic and sodium excretion (i.e., the ratio of responses to placebo). This comparison showed that the herb had more marked effects that the root both acutely (diuretic index, 1.9 versus 1.4; and, sodium Sali uretic index, 6.3 versus 2.6) and chronically (diuretic index, 2.1 versus 1.7; and, sodium Sali uretic index, 4.0 versus 1.3). Numbers on days 1 and 30 seem to be similar, although this was not equivocal as no statistics were provided. The authors did provide a comparison by looking at responses to 80 mg kg−1 of furosemide (the diuretic index was 1.9 and the sodium Sali uretic index was 7.9), again suggesting responses with the herb were similar to those achieved with the furosemide. In the second part of this study, diuretic effects were coupled with the measurement of changes in body weight and led the authors to conclude that diuresis may be one mechanism explaining decreases in body weight.

The diuretic activity of crude and partially purified fractions from Taraxacum radix (chloroform, ether and methanol) has been assessed. The ether fraction is believed to contain Beta-amyrin and Beta-sitosterol, whilst the methanol contains compounds of medium polarity. The Fractions were administered orally and urine was then collected for 5 h. Extracts had no effect on UV, but ether and chloroform extracts did evoke a small, significant increase in UNa (~6.5 mEq kg−1 versus 3.8 mEq kg−1 after 5 h [extracts versus placebo]). However, this effect was much smaller that than that of furosemide which led to a three-fold increase in UV and an increase in UNa to 13.8 mEq kg−1 after 5 h. This lack of efficacy was taken as evidence that Taraxacum radix contained no organic secondary metabolites with diuretic capabilities.[67]

Horsetail (Equisetum):

The common names for the horsetail plant include horsetail, marestail, and scouring rush. In Chile and Mexico, Equisetum has traditional uses as a diuretic and a means of treating kidney stones. It has also been used for polishing copper utensils, cleansing teeth[68][69] and to have anti-diabetic[70] and platelet sedating effects.[71]

Two studies[72][73] have tested the effects of[74] tested four species of Equisetum— Equisetum fluviatile, Equisetum hiemale var. affine, Equisetum giganteum and Equisetum myriochaetum. Extracts were prepared in distilled water and administered orally. Urine was then collected every 2 h over a 6 h period. All species increased UV after 6 h with the largest change being observed with Equisetum hiemale var. affine (9.0 ml versus 2.9 ml [versus placebo]) and the smallest with Equisetum giganteum (5.0 ml versus 2.9 ml [versus placebo]). For comparison, hydrochlorothiazide (25 mg kg−1) was administered and was not so different (7.1 ml). Analysis of urinary electrolytes showed a similar trend. Indeed, with Equisetum hiemale var. affine and Equisetum giganteum, UNa was 161.7 and 147.0 mEq l−1 (versus 110.0 mEq l−1 achieved with placebo). In the group receiving hydrochlorothiazide, UNa was 160.0 mEq l−1. The data also showed that Equisetum had similar effects on urinary potassium and chloride excretion, and it was suggested to act in a fashion to hydrochlorothiazide. The second study also reported positive effects with Equisetum. This was a clinical trial in humans in which a 10% solution of Equisetum bogotense (equivalent to 0.75 g day−1) was given for 2 days. Urine was collected for 24 h on the second day and water balance was assessed.

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4. Herbs with Hypoglycemic Effects

Fenugreek (Trigonella foenum-graecum):

Fenugreek, also known as its scientific name of *trigonella foenum-graecum L., leguminosae*, belongs to the plant family *fabaceae* (or *leguminosae*). It grows in most of the countries around world with major production in Asia, Europe and American including United States. The health-promoting property of fenugreek has been long documented when it is taken as vegetables, food supplements or medicinal remedies. Four recent patents or patent applications described usages and applications of fenugreek in managing metabolic diseases including hyperglycemia and diabetes. One patent application described making dietary supplements with fenugreek fibers to control blood glucose. Another patent application claimed making food products with fenugreek seed powder for prevention of obesity and diabetes.[76] The third patent application disclosed an anti-diabetic composition of food supplement with fenugreek seed extract.[77] Clinical studies with human volunteers showed a dosage form of 500 mg given once or twice daily either alone or in combination with standard, synthetic anti-diabetic drugs such as metformin and glipizide provided beneficial effects on controlling plasma glucose levels. One recently issued patent illustrated a composition with fenugreek seeds to lower glucose and cholesterol.[78]

Bitter Melon (Momordica charantia)

Momordica charantia, known as bitter melon or gourd, is widely consumed as a vegetable and bitter flavoring in cookery, especially in Asian countries such as China and India. Consumption of momordica charantia has been linked to a variety of health-promoting benefits, including lowering blood glucose in hyperglycemic subjects. Five recent patent applications described momordica charantia-containing compositions for managing hyperglycemia.[79][80][81] A large number of preclinical studies support the claim that momordica charantia is able to lower plasma glucose levels. However, the results from human clinical trials are not conclusive.

The results from three early clinical trials support the hypoglycaemic activity of momordica charantia. The first study recruited 14 diabetic patients and 5 healthy volunteers.[82] Insulin-like substance, called vegetable insulin (v-insulin), was extracted from momordica charantia. Injection of mormordica charantia extract containing 10, 20 or 30 units of v-insulin dependent on the severity of the diabetes in 9 diabetic patients resulted in significant reduction in FBS by 21.5% to 49.2% within the period of 12 hours post-treatment. The control group including 5 diabetic and 5 healthy subjects received a placebo and exhibited a 5% decrease in FBS. The second trial with 9 diabetic patients showed that daily consumption of 230 g fried momordica charantia fruit for 8 to 11 weeks significantly improved glucose tolerance.[83] Drinking of 50 ml of fresh momordica charantia fruit juice also significantly reduced plasma glucose levels and the area under curve within the period of 1.5 hours post-drinking. The third trial is a case study with 100 moderate non-insulin dependent diabetic patients.[84] Drinking of the aqueous homogenized suspension of the vegetable pulp resulted in a significant reduction in FBS and postprandial sugar levels in 86 subjects with a mean reduction of 18%.[85]

Safety Considerations and Potential Side Effects

Adverse Effects:

Nephrotoxicity:

Certain herbs may be detrimental to the kidneys, particularly in those who already have kidney disease. Aristolochic acid, which is present in some Chinese herbs, and specific heavy metals that can contaminate herbal products are two examples.[86]

Herb-Drug Interactions:

Prescription drugs and herbal remedies may interact, decreasing the effectiveness of the former or raising the possibility of adverse effects. Those with DKD who frequently take several medications should be especially concerned about this.[87]

Allergic Reactions:

Certain herbs can cause allergic reactions in some people, which can include breathing difficulties, hives, and skin rashes.[88]

Digestive Issues:

Digestion issues like diarrhea, vomiting, and nausea can be brought on by herbal medications.[89]

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Other Adverse Effects:
Other possible negative effects could include hormonal imbalances, liver damage, and nervous system disorders, depending on the particular herb.

Contraindications:
Pregnancy and Breastfeeding:
Using a lot of herbal remedies while pregnant or nursing is not safe.
Kidney Disease:
Individuals with kidney disease should exercise caution when using herbal medicines, as some herbs can worsen kidney function.
Liver Disease:
Herbal medications that can damage the liver should be avoided by those who have liver disease.
Autoimmune Diseases:
Some herbal medicines can suppress the immune system, which may be harmful for individuals with autoimmune diseases.[91]
Important Considerations for DKD Patients:
Consult with a Healthcare Provider:
Always talk to your doctor about using herbal supplements, especially if you are taking prescription drugs or have underlying medical conditions.
Start Low, Go Slow:
Start with a low dosage when starting a new herbal supplement and increase it gradually as necessary.
Monitor for Side Effects:
Keep a close eye out for any negative side effects or reactions. If necessary, stop using.
Avoid Combining Multiple Herbs:
Interactions may become more likely when taking several herbal supplements at once.

IV. CONCLUSION

Finally, the potential of herbal medicine in managing DKD, a serious diabetes complication, represents a promising avenue for complementary and integrative care. Numerous studies have shown that herbal formulations can reduce proteinuria, improve renal function, and lower oxidative stress. The combination of herbal and conventional therapies provides a more comprehensive approach, addressing both the physiological and psychological aspects of DKD. However, it is critical to recognize the importance of rigorous scientific research in developing standardized dosages, safety profiles, and precise mechanisms of action for herbal interventions. Future research should include large-scale randomized controlled trials, pharmacokinetic and pharmacodynamic studies, and the identification of bioactive compounds that cause therapeutic effects.
Furthermore, collaboration among herbal medicine practitioners, conventional healthcare providers, and researchers is essential for improving patient care. By combining the strengths of traditional and modern medicine, we can create effective and personalized treatment plans for people with DKD. By doing so, we can improve patient outcomes, reduce disease burden, and improve the overall quality of life for those living with this chronic condition

REFERENCES

[1]. American Diabetes Association. (2023). Standards of Medical Care in Diabetes. Diabetes Care, 46(Suppl 1), S125–S138.
[2]. Alicic, R. Z., Rooney, M. T., & Tuttle, K. R. (2017). Diabetic Kidney Disease: Challenges, Progress, and Possibilities. Clinical Journal of the American Society of Nephrology, 12(12), 2032–2045.
[3]. Tuttle, K. R., Bakris, G. L., Bilous, R. W., et al. (2014). Diabetic Kidney Disease: A Report from the ADA Consensus Conference. Diabetes Care, 37(10), 2864–2883.
[4]. Gross, J. L., de Azevedo, M. J., Silveiro, S. P., et al. (2005). Diabetic Nephropathy: Diagnosis, Prevention, and Treatment. Diabetes Care, 28(1), 164–176.

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 2, December 2024

[5]. "Kidneys: Anatomy, Function, Health & Conditions". Cleveland Clinic. Archived from the original on 2023-06-29. Retrieved 2023-07-13.

[6]. Zhou, Xin J.; Laszik, Zoltan G.; Nadasdy, Tibor; D'Agati, Vivette D. (2017-03-02). Silva's Diagnostic Renal Pathology. Cambridge University Press. p. 19. ISBN 978-1-316-61398-

[7]. Archived from the original on 2023-04-04. Retrieved 2023-08-16.

[8]. Haschek, Wanda M.; Rousseaux, Colin G.; Wallig, Matthew A.; Bolon, Brad; Ochoa, Ricardo (2013-05-01). Haschek and Rousseaux's Handbook of Toxicologic Pathology. Academic Press. p. 1678. ISBN 978-0-12-415765-1.

[9]. (Lote CJ (2012). Principles of Renal Physiology, 5th edition. Springer. p. 21.) (Mescher AL (2016). Junqueira's Basic Histology, 14th edition. Lange. p. 393.)

[10]. Loder, Elizabeth. "Time's up for he and him as the default pronouns for doctors." BMJ (Clinical research ed.) vol. 367 l6565. 16 Dec. 2019, doi:10.1136/bmj.l6565

[11]. Muroya, Yoshikazu et al. "Enhanced renal ischemia-reperfusion injury in aging and diabetes." American journal of physiology. Renal physiology vol. 315,6 (2018): F1843- F1854. doi:10.1152/ajprenal.00184.2018

[12]. Palevsky, Paul M. "Endpoints for Clinical Trials of Acute Kidney Injury." Nephron vol. 140,2 (2018): 111-115. doi:10.1159/000493203

[13]. Zuber, Kim, and Jane Davis. "The ABCs of chronic kidney disease." JAAPA : official journal of the American Academy of Physician Assistants vol. 31,10 (2018): 17-25. doi:10.1097/01.JAA.0000545065.71225.f5

[14]. "What Is Chronic Kidney Disease?". National Institute of Diabetes and Digestive and Kidney Diseases. June 2017. Retrieved 19 December 2017.

[15]. "What is renal failure?". Johns Hopkins Medicine. Retrieved 18 December 2017.

[16]. "What Is Chronic Kidney Disease?". National Institute of Diabetes and Digestive and Kidney Diseases. June 2017. Retrieved 19 December 2017.

[17]. Liao, Min-Tser et al. "Insulin resistance in patients with chronic kidney disease." Journal of biomedicine & biotechnology vol. 2012 (2012): 691369. doi:10.1155/2012/691369

[18]. "Kidney Failure". MedlinePlus. Retrieved 11 November 2017.

[19]. (KDIGO: Kidney Disease Improving Global Outcomes (August 2009). "KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)" (PDF).

[20]. Kidney Int. 76 (Suppl 113). Archived from the original (PDF) on 2016-12-13.

[21]. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY (September 2004). "Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization". The New England Journal of Medicine. 351 (13): 1296–1305.

[22]. "Kidney Failure". National Institute of Diabetes and Digestive and Kidney Diseases. Retrieved 11 November 2017.

[23]. Noble, Rebecca, and Maarten W. Taal. "Epidemiology and causes of chronic kidney disease." Medicine 47.9 (2019): 562-566.

[24]. Groopman EE, Marasa M, Cameron-Christie S, et al. Diagnostic utility of exome sequencing for kidney disease. N Engl J Med 2019; 380: 142e51.

[25]. Tuttle KR, Bakris GL, Bilous RW, Chiang JL, de Boer IH, Goldstein-Fuchs J, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Diabetes Care. 2014; 37:2864–83.

[26]. Tervaert TW, Mooyaart AL, Amann K, Cohen AH, Cook HT, Drachenberg CB, et al. Pathologic classification of diabetic nephropathy. J Am Soc Nephrol. 2010; 21:556–63.

[27]. Yokoyama H, Sone H, Oishi M, Kawai K, Fukumoto Y, Kobayashi M, et al. Prevalence of albuminuria and renal insufficiency and associated clinical factors in type 2 diabetes: the Japan Diabetes Clinical Data Management study (JDDM15). Nephrol Dial Transplant. 2009; 24:1212–9.

[28]. Afkarian M, Zelnick LR, Hall YN, Heagerty PJ, Tuttle K, Weiss NS, et al. Clinical manifestations of kidney disease among us adults with diabetes, 1988-2014. JAMA. 2016; 316:602–10.

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 2, December 2024

[29]. Hirakawa Y, Tanaka T, Nangaku M. Mechanisms of metabolic memory and renal hypoxia as a therapeutic target in diabetic kidney disease. J Diabetes Investig. 2017; 8:261–71.

[30]. Shafi, Sabeeha, Nahida Tabassum, and Feroz Ahmad. "Diabetic nephropathy and herbal medicines." International Journal of Phytopharmacology 3.1 (2012): 10-17.

[31]. Savant, Priti B., et al. "Herbal Drugs used in the Management of Diabetic Nephropathy." Asian Journal of Pharmaceutical Research 12.1 (2022): 54-60.

[32]. Hussain, Salman, et al. "Diabetic kidney disease: An overview of prevalence, risk factors, and biomarkers." Clinical Epidemiology and Global Health 9 (2021): 2-6.

[33]. Satirapoj, Bancha. "Review on pathophysiology and treatment of diabetic kidney disease." J Med Assoc Thai 93. Suppl 6 (2010): S228-41.

[34]. Qazi, Moarij, et al. "Pathophysiology of Diabetic Kidney Disease." Nephrology 10.1 (2022): 102-113.

[35]. Sam, Susan. "Importance and effectiveness of herbal medicines." Journal of pharmacognosy and phytochemistry 8.2 (2019): 354-357.

[36]. Grover, J. K., et al. "Traditional Indian anti-diabetic plants attenuate progression of renal damage in streptozotocin induced diabetic mice." Journal of Ethnopharmacology 76.3 (2001): 233-238.

[37]. Sam, Susan. "Importance and effectiveness of herbal medicines." Journal of pharmacognosy and phytochemistry 8.2 (2019): 354-357.

[38]. Tapsell LC, Hemphill I, Cobiac L et al. "Health benefits of herbs and spices: the past, the present, the future". Med. J. Aust. 2006; 185(4):S4-24. PMID 17022438.

[39]. Lai PK, Roy J. "Antimicrobial and chemopreventive properties of herbs and spices". Curr. Med. Chem. 2004; 11(11):1451-60. doi:10.2174/0929867043365107. PMID 15180577.

[40]. Billing Jennifer, Sherman PW. "Antimicrobial functions of spices: why some like it hot". Q Rev Biol. 1998; 73(1):3-49. doi:10.1086/420058. PMID 9586227.

[41]. Chen, Dan-Qian, Jun Wu, and Ping Li. "Therapeutic mechanism and clinical application of Chinese herbal medicine against diabetic kidney disease." Frontiers in Pharmacology 13 (2022): 1055296.

[42]. Mardani, Saeed, et al. "Herbal medicine and diabetic kidney disease." Journal of Nephropharmacology 2.1 (2013): 1.

[43]. https://www.mountsinai.org/health-library/supplement/quercetin#:~:text=Fruits%20and%20vegetables%20are%20the%20primary%20dietary%20sources%20of%20quercetin%2C%20particularly%20citrus%20fruits%2C%20apples%2C%20onions%2C%20parsley%2C%20sage%2C%20tea%2C%20and%20red%20wine.

[44]. Han, Yu, et al. "Rutin ameliorates renal fibrosis and proteinuria in 5/6-nephrectomized rats by anti-oxidation and inhibiting activation of TGFβ1-smad signaling." International Journal of Clinical and Experimental Pathology 8.5 (2015): 4725.

[45]. Kitada, Munehiro, and Daisuke Koya. "Renal protective effects of resveratrol." Oxidative medicine and cellular longevity 2013.1 (2013): 568093.

[46]. D'andurain, Javiera, et al. "Effect of curcumin consumption on inflammation and oxidative stress in patients on hemodialysis: a literature review." Nutrients 15.10 (2023): 2239.

[47]. Alhazmi, Areej I., Mohamed F. El-Refaei, and Eman AA Abdallah. "Protective effects of gallic acid against nickel-induced kidney injury: impact of antioxidants and transcription factor on the incidence of nephrotoxicity." Renal Failure 46.1 (2024): 2344656.

[48]. Xu, Xiaofan, et al. "Anti-inflammatory mechanism of berberine on lipopolysaccharide-induced IEC-18 models based on comparative transcriptomics." Molecular Medicine Reports 22.6 (2020): 5163-5180.

[49]. Liu, Ya-Fei, et al. "Advances of berberine against metabolic syndrome-associated kidney disease: Regarding effect and mechanism." Frontiers in Pharmacology 14 (2023): 1112088.

[50]. Zahran, Eman Maher, et al. "Ursolic acid inhibits NF-κB signaling and attenuates MMP- 9/TIMP-1 in progressive osteoarthritis: a network pharmacology-based analysis." RSC advances 14.26 (2024): 18296-18310.

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 2, December 2024

[51]. Jia, Zhaohui, et al. "Ursolic acid treats renal tubular epithelial cell damage induced by calcium oxalate monohydrate via inhibiting oxidative stress and inflammation." Bioengineered 12.1 (2021): 5450-5461.

[52]. Darenskaya, Marina, et al. "Diabetic nephropathy: significance of determining oxidative stress and opportunities for antioxidant therapies." International Journal of Molecular Sciences 24.15 (2023): 12378.

[53]. Traber, Maret G. "Vitamin E regulatory mechanisms." Annual review of nutrition vol. 27 (2007): 347-62. doi:10.1146/annurev.nutr.27.061406.093819

[54]. Nishiyama, Tozo, et al. "Curcuminoids and sesquiterpenoids in turmeric (Curcuma longa L.) suppress an increase in blood glucose level in type 2 diabetic KK-Ay mice." Journal of Agricultural and food Chemistry 53.4 (2005): 959-963.).

[55]. Jurenka, Julie S. "Anti-inflammatory properties of curcumin, a major constituent of Curcuma longa: a review of preclinical and clinical research." Alternative medicine review 14.2 (2009).

[56]. Ghasemian, Mona, Sina Owlia, and Mohammad Bagher Owlia. "Review of anti‐inflammatory herbal medicines." Advances in Pharmacological and Pharmaceutical Sciences 2016.1 (2016): 9130979.

[57]. Mahluji, Sepide, et al. "Anti-inflammatory effects of Zingiber officinale in type 2 diabetic patients." Advanced pharmaceutical bulletin 3.2 (2013): 273.

[58]. Bolton, W. Kline, et al. "Randomized trial of an inhibitor of formation of advanced glycation end products in diabetic nephropathy." American journal of nephrology 24.1 (2004): 32-40.

[59]. Tilton, Ronald G., et al. "Prevention of diabetic vascular dysfunction by guanidines: inhibition of nitric oxide synthase versus advanced glycation end-product formation." Diabetes 42.2 (1993): 221-232.

[60]. Al-Waili, Noori, et al. "Natural antioxidants in the treatment and prevention of diabetic nephropathy; a potential approach that warrants clinical trials." Redox Report 22.3 (2017): 99-118.

[61]. Li, X. Z., H. D. Yan, and Jun Wang. "Extract of Ginkgo biloba and alpha-lipoic acid attenuate advanced glycation end products accumulation and RAGE expression in diabetic

[62]. nephropathy rats." Zhongguo Zhong xi yi jie he za zhi Zhongguo Zhongxiyi Jiehe Zazhi= Chinese Journal of Integrated Traditional and Western Medicine 31.4 (2011): 525-531.

[63]. Zhang, Lei, et al. "Ginkgo biloba extract for patients with early diabetic nephropathy: a systematic review." Evidence‐Based Complementary and Alternative Medicine 2013.1 (2013): 689142.

[64]. Al-Waili, Noori, et al. "Natural antioxidants in the treatment and prevention of diabetic nephropathy; a potential approach that warrants clinical trials." Redox Report 22.3 (2017): 99-118.

[65]. Schütz, Katrin, Reinhold Carle, and Andreas Schieber. "Taraxacum—a review on its phytochemical and pharmacological profile." Journal of ethnopharmacology 107.3 (2006): 313-323.

[66]. Râcz–Kotilla, Elisabeth, G. Racz, and Ana Solomon. "The action of Taraxacum officinale extracts on the body weight and diuresis of laboratory animals." Planta medica 26.07 (1974): 212-217.

[67]. Hook, I., A. McGee, and M. Henman. "Evaluation of dandelion for diuretic activity and variation in potassium content." International Journal of Pharmacognosy 31.1 (1993): 29- 34.

[68]. Râcz–Kotilla, Elisabeth, G. Racz, and Ana Solomon. "The action of Taraxacum officinale extracts on the body weight and diuresis of laboratory animals." Planta medica 26.07 (1974): 212-217.

[69]. Wright, C. I., et al. "Herbal medicines as diuretics: a review of the scientific evidence." Journal of ethnopharmacology 114.1 (2007): 1-31.

[70]. Gutiérrez, RM Férez, G. Yescas Laguna, and Aleksander Walkowski. "Diuretic activity of Mexican equisetum." Journal of Ethnopharmacology 14.2-3 (1985): 269-272

[71]. Lemus, I., et al. "Diuretic activity of an Equisetum bogotense tea (Platero herb): evaluation in healthy volunteers." (1996): 55-58.

[72]. Andrade-Cetto, Adolfo, and Michael Heinrich. "Mexican plants with hypoglycaemic effect used in the treatment of diabetes." Journal of ethnopharmacology 99.3 (2005): 325-348.

[73]. Mekhfi, Hassane, et al. "Platelet anti-aggregant property of some Moroccan medicinal plants." Journal of ethnopharmacology 94.2-3 (2004): 317-322.

[74]. Gutiérrez, RM Férez, G. Yescas Laguna, and Aleksander Walkowski. "Diuretic activity of Mexican equisetum." Journal of Ethnopharmacology 14.2-3 (1985): 269-272.

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[75]. Lemus, I., et al. "Diuretic activity of an Equisetum bogotense tea (Platero herb): evaluation in healthy volunteers." (1996): 55-58.

[76]. Gutiérrez, RM Férez, G. Yescas Laguna, and Aleksander Walkowski. "Diuretic activity of Mexican equisetum." Journal of Ethnopharmacology 14.2-3 (1985): 269-272.

[77]. Wright, C. I., et al. "Herbal medicines as diuretics: a review of the scientific evidence." Journal of ethnopharmacology 114.1 (2007): 1-31.

[78]. Losso, Jack N., et al. "Fenugreek flour for incorporating into food products." No. 2700918A.

[79]. Goel, Pawan Kumar. "Novel antidiabetic furostanolic saponin rich (fsr) fraction from fenugreek seeds." U.S. Patent Application No. 13/322,460.

[80]. Murthy, Pothapragada Suryanarayana, et al. "Anti-diabetic and cholesterol lowering preparation from fenugreek seeds." U.S. Patent No. 7,815,946. 19 Oct. 2010.

[81]. Djang, Arthur. "Dietary supplement for promoting control of blood-sugar levels and associated pathology in type 2 diabeties." U.S. Patent Application No. 10/563,713

[82]. Ye, Yang, et al. "Use of compounds extracted from Momordica charantia L. in the manufacture of medicaments for prevention and treatment of diabetes and obesity." U.S. Patent No. 8,722,634. 13 May 2014

[83]. Lee, Sung Young. "Composition comprising an extract of herbal combination thereof for preventing and treating diabetes mellitus." U.S. Patent Application No. 12/848,568.

[84]. Baldwa, V. S., et al. "Clinical trial in patients with diabetes mellitus of an insulin-like compound obtained from plant source." Upsala journal of medical sciences 82.1 (1977): 39-41.

[85]. Leatherdale, B. A., et al. "Improvement in glucose tolerance due to Momordica charantia (karela)." Br Med J (Clin Res Ed) 282.6279 (1981): 1823-1824.

[86]. Ahmad, N., et al. "Effect of Momordica charantia (Karolla) extracts on fasting and postprandial serum glucose levels in NIDDM patients." Bangladesh Medical Research Council Bulletin 25.1 (1999): 11-13

[87]. Deng, Ruitang. "A review of the hypoglycemic effects of five commonly used herbal food supplements." Recent patents on food, nutrition & agriculture vol. 4,1 (2012): 50-60. doi:10.2174/2212798411204010050

[88]. Cheung, Thomas P et al. "Aristolochic acids detected in some raw Chinese medicinal herbs and manufactured herbal products--a consequence of inappropriate nomenclature and imprecise labelling?." Clinical toxicology (Philadelphia, Pa.) vol. 44,4 (2006): 371-8. doi:10.1080/15563650600671712

[89]. https://www.nccih.nih.gov/health/tips/tips-how-herbs-can-interact-with-medicines#:~:text=Some%20supplements%20can%20decrease%20the,unwanted%20side%20effects%2C%20of%20medicines.

[90]. https://www.aaaai.org/tools-for-the-public/conditions-library/allergies/https%3A%2F%2Fwww.aaaai.org%2Ftools-for-the-public%2Fconditions-library%2Fallergies%2Falternative-meds

[91]. Sleisenger, Marvin H., et al. "Sleisenger & Fordtran's gastrointestinal and liver disease: pathophysiology, diagnosis, management." (No Title) (2010)

[92]. https://www.webmd.com/hepatitis/toxic-liver-disease

[93]. Amirghofran, Zahra. "Herbal medicines for immunosuppression." Iranian journal of allergy, asthma, and immunology vol. 11,2 (2012): 111-9.