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A review on therapeutic significance of some medicinal plants in chronic kidney disease management

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Abstract: Chronic kidney disease (CKD) is an incurable disease that is becoming more common globally and placing a financial and social strain on health systems. The last stage of CKD, renal failure, is potentially fatal if kidney replacement therapy is not used to treat it. Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and calcium channel blockers are examples of commercially accessible medications used in current therapy, yet they typically merely slow the course of CKD. This review article focuses on efficient plant-based or plant-extract based alternative medicines that enhance CKD prevention and therapy. Oxidative stress, fibrosis, and inflammation are three well-established mechanistic pathways in the pathophysiology of chronic kidney disease. Through their antioxidant properties, a variety of plants and their extracts are already known to improve renal dysfunction, which in turn reduces inflammation and fibrosis. There is evidence that kidney failure may significantly affect vitamin metabolism, urine excretion, *in vivo* synthesis, and food intake. Empirical data suggests that renal failure may significantly impact nutritional consumption, *in vivo* synthesis, urine excretion, or vitamin metabolism. Therefore, individuals with CKD frequently require vitamin D and B12 supplements. Here, we examined a few significant medicinal plants that may be used to cure and manage illnesses related to the kidneys. These plants include antioxidant and anti-inflammatory qualities. In future, more clinical investigations regarding usage, safety, effectiveness, side effects, and suggested dosages are recommended for various stages of CKD are recommended.

Index Terms - Chronic Kidney Disease, Medicinal Plants, Antioxidant Nature, Antiinflammatory Potential.

1.Introduction

Both in the industrialized and emerging worlds, the global pattern of disease morbidity and mortality are evolving rapidly. Infectious diseases accounted for the majority of deaths and disabilities in the 20th century. Nonetheless, noncommunicable, noninfectious diseases have emerged as the primary global cause of death and morbidity in this century. The kinds of diseases that cause chronic kidney failure, as well as how they manifest and advances, reflect this shift. Due to the global pandemic of type 2 diabetes, diabetes is currently the leading cause of end-stage renal failure (https://www.who.int/news/item/09-12-2020-who-reveals-leading-causes-of-death-and-disability-worldwide-2000-2019). One of the main causes of illness and death nowadays is chronic kidney disease (CKD). The most frequent way that end-stage renal disease (ESRD) progresses from chronic kidney disease (CKD) is through renal fibrosis. According to Boor et al. (2010), CKD is characterized by increased inflammatory cell infiltration, tubular atrophy, tubulointerstitial fibrosis (TIF), and glomerulosclerosis. Treating increasing renal fibrosis is important for chronic kidney disease (CKD) (Chen et al., 2018).

Chronic kidney disease (CKD) is brought on by a permanent alteration in the structure or function of the kidney. It progresses slowly and irreversibly. The pathology suggests an increased likelihood of consequences and mortality, especially issues related to the cardiovascular system, which is another significant factor. The clinical illness known as chronic kidney disease (CKD) is brought on by a permanent alteration in the structure or function of the kidney. It progresses slowly and irreversibly (Chen et al., 2019). The pathology suggests an increased likelihood of consequences and mortality, especially issues related to the cardiovascular system, which is another significant factor. Ten to fifteen percent of people globally suffer from chronic kidney disease (CKD), and the prevalence of this condition is rising. (Kovesdy et al., 2022).

When an adult patient has a glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m^2 for three months or more, but exhibits signs of renal structural damage, they are diagnosed with chronic kidney disease (CKD). Pathologic abnormalities indicated by imaging investigations or renal biopsies, anomalies in urine sediment, or elevated urinary albumin excretion rates are all considered forms of kidney disease. Additional health effects of CKD include low red blood cell count, or anemia, a rise in the frequency of infections, high phosphorus, high potassium, and low calcium levels in the blood, decrease in appetite or consumption, and depression or a decreased standard of living (Chen et al., 2019).

2. **Stages of chronic kidney disease (CKD)**

The five phases of chronic kidney disease relate to the functioning of kidneys. With time, kidney disease might deteriorate. However, the kidneys can still filter waste from blood during the initial stages (Stages 1-3). However, the kidneys may stop filtering blood entirely in the later stages (Stages 4-5) or they may have to work harder to do so (https://www.kidneyfund.org/all-about-kidneys/stages-kidney-disease). The following tests including eGFR tests, or blood tests, tests using urine (pee) are required to be performed to determine the stage of CKD.

3.Indicators of CKD

To either accomplish recovery or delay the deterioration of kidney function, it is imperative to identify and treat the underlying causes of both acute and chronic renal disease. Albuminuria, hematuria/leukocyturia, abnormalities in renal imaging, chronic hydroelectrolytic diseases, histological alterations in kidney biopsy, and prior kidney transplantation are a few signs of renal damage. More than 30 mg of albumin in the 24-hour urine or more than 30 mg/g of albumin in an isolated urine sample adjusted by urinary creatinine is considered albuminuria (Hull et al., 2022).

A straightforward urine test known as the urine Albumin:Creatinine ratio (ACR) is also carried out in order to search for indications of protein leakage into the urine, a condition known as proteinuria or albuminuria. This is a significant indication of renal disease. As seen in the Stages of CKD chart below, the ACR is used to determine the "A stage" of CKD. Albuminuria is known to occur in three stages. Urine protein levels (less than 3 mg/mmol) in A1 are normal to slightly elevated. In the A2 stage, slightly elevated urine protein concentrations (3–30 mg/mmol) have been reported. However, urine protein levels exceeding 30 mg/mmol indicate a significant increase in A3 stage (Wu et al., 2012). Physicians can attempt to forecast if renal disease is likely to worsen and whether complications like renal failure are more likely to occur by combining your ACR ratio with your eGFR (Hallan et al., 2009).

4. C**auses chronic kidney diseases**

Several risk factors are considered to increase the chance of CKD. Diabetes, hypertension, long-term glomerulonephritis, long-term pyelonephritis, long-term anti-inflammatory drug use, autoimmune disorders, polycystic kidney disease, Alport disease, congenital abnormalities, and prolonged acute renal disease are the primary causes of CKD (https://www.kidney.org/atoz/content/about-chronic-kidney-disease) (Figure 1).

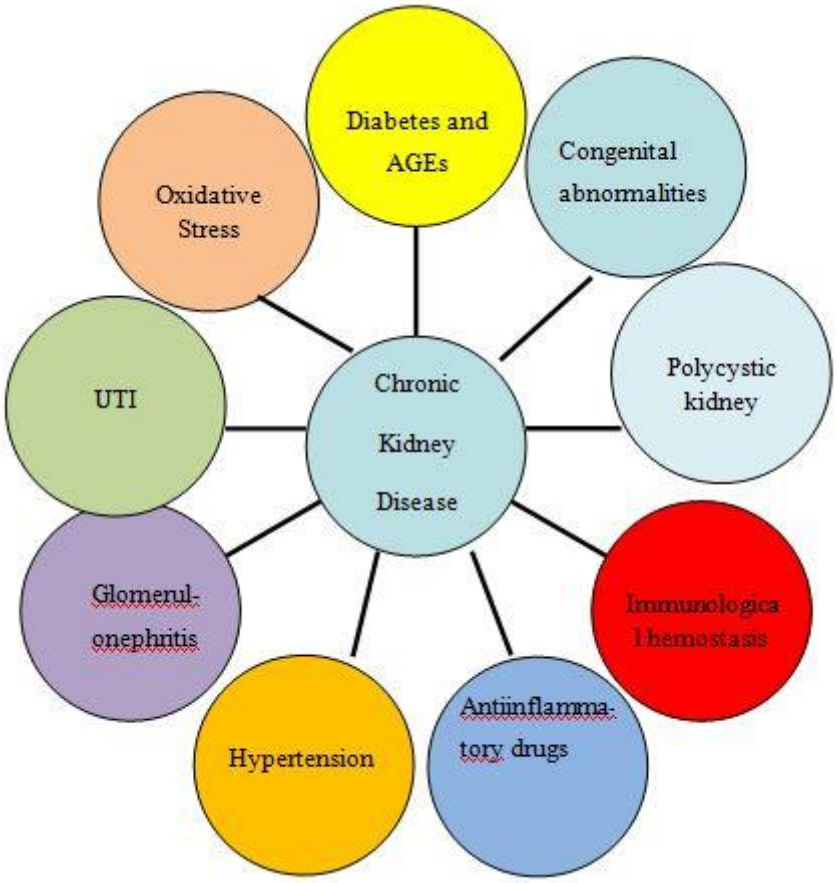

Figure 1. Risk factors of chronic kidney disease. Many causes lead to kidney disease. Prolonged untreated kidney diseases contribute to chronic kidney disease.

4.1. Diabetes

For peoples having type 2 diabetes, the cells don't react to insulin as they should. Insulin resistance is the term for this condition. The body rejects the insulin that the pancreas continues to produce. Despite the fact that type 2 diabetes can strike anyone at any age, it is typically diagnosed in those over 45 (Wilcox, 2005). A decline in kidney function that some diabetics experience is known as diabetic kidney disease. Each kidney has a trillion microscopic filters known as nephrons. Diabetes-related elevated blood sugar may eventually damage kidney blood vessels and these nephrons, impairing their ability to function as they should. High blood sugar levels have the potential to constrict and block kidney's tiny blood capillaries over time. The kidneys suffer damage when there is insufficient blood flow (Lim, 2005). In addition, diabetes may also result in harm to your body's nerves. A Person with such a condition, might not be able to tell when his bladder is full if damage has been done to the bladder's nerves. The force exerted by an overflowing bladder can harm the kidneys. Long-term retention of urine in the bladder increases the risk of urinary tract infection. Bacteria proliferate quickly in urine with a high sugar level and causes urethral infection. These infections can sometimes spread to the kidneys (Golbidi and Laher, 2010).

4.2. Oxidative stress

The imbalance between the generation and removal of reactive oxygen species is the cause of oxidative stress (Anwar et al., 2024a; Anwar and Younus, 2018). The body continuously produces reactive oxygen species, which are highly reactive chemical species containing oxygen, as a result of cell metabolism (Anwar et al., 2023a). The excessive production of highly reactive oxygen (ROS) and nitrogen (RNS) species causes oxidative stress (OS), which is characterized as disruptions in the pro-/antioxidant balance and detrimental effects on cells. Antioxidant molecules like yeast alcohol dehydrogenase are reported to fight with OS (Haque et al., 2012). OS plays a part in signal transduction and physiological responses when the equilibrium is not upset. However, biological components including lipids, proteins, and DNA oxidize when ROS and RNS levels are too high (Anwar et al., 2020). Kidney disease has been linked to oxidative stress as a result of elevated ROS generation and antioxidant depletion. Numerous functions, such as metabolism, immunological and hypoxic responses, transcriptional control, and intracellular signal transmission, depend on low ROS levels. Acute or chronic kidney injury can produce prooxidants and free

radicals, which can worsen the disease's progression and contribute to the pathophysiology of later problems. When it comes to CKD, prevention may be the key, yet individuals are sometimes reluctant to have screenings. Damage from oxidative stress to the kidneys results in inflammation and tissue damage, as well as a build-up of damaged biomolecules. Elevated membrane changes, inflammation, cell senescence, and cell death are caused by the accumulation of oxidative stress and a compromised antioxidant defense mechanism. Chronic degenerative illnesses may therefore be exacerbated by this (Vodošek et al., 2020; Podkowińska and Formanowicz, 2020).

4.3. Advanced glycation end products (AGEs)

High blood glucose levels are a hallmark of diabetes mellitus, a condition that has grown to be a global health concern. Chronic hyperglycemia has been implicated in the development of diabetic complications, as well as the glycation of biomolecules. A series of non-enzymatic processes known as protein glycation, result in the irreversible development of several advanced glycation end products (AGEs). It has been discovered that a number of health-related problems are significantly influenced by glycation. Furthermore, the build-up of AGEs (ultimate products of glycation) in vivo promotes the development of diabetes by means of AGEs' interaction with their receptors (RAGEs), which in turn triggers the transcription of genes that regulate inflammation. Vascular complications are linked to hyperglycemia-induced AGE production and glycation (Anwar et al., 2020).

Increased synthesis, decreased excretion, and an imbalance between oxidizing and antioxidant capacities are the reasons behind the accumulation of AGEs in chronic kidney disease (CKD). Thus, CKD serves as an aging model. In consequence, AGEs may accelerate the course of CKD and its complications. AGEs are being researched as novel prospective indicators of disease progression and/or therapeutic targets in addition to their etiopathogenetic significance. A natural aging process called AGE accumulation is accelerated in circumstances like chronic kidney disease (CKD) that increase AGE synthesis and decrease detoxification (Dozio et al., 2023). Because AGEs can trigger reactions that accelerate the development of CKD and disorders associated to CKD, they have a pathogenetic role in these conditions. AGEs and other kinds of sRAGE can function as circulating biomarkers for the purpose of CKD risk classification. It might be helpful to target the AGE–RAGE pathways in order to stop these chemicals from negatively affecting various organs (Fotheringham et al., 2022).

4.4. Hypertension and CKD

CKD is mostly caused by high blood pressure. High blood pressure can harm blood vessels all over your body over time. This may result in less blood getting to vital organs like the kidneys. The little filtration units in your kidneys are also harmed by high blood pressure. Your kidneys may stop filtering toxins and excess fluid from your blood as a result. Blood pressure can rise further as a result of the excess fluid accumulating in your blood vessels. An additional CKD consequence is high blood pressure. A healthy blood pressure range is largely maintained by your kidneys. Kidney disease reduces the kidneys' ability to control blood pressure. Consequently, blood pressure rises.
(https://www.kidney.org/sites/default/files/docs/hbpandckd.pdf).

According to the European Society of Cardiology and the European Society of Hypertension (ESC/ESH), hypertension is defined as a blood pressure (BP) of 140/80 mmHg or higher. It affects approximately 30% of the adult population overall and up to 90% of people with CKD (https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-17/definition-of-hypertension-and-pressure-goals-during-treatment-esc-esh-guidelin). Hypertension is both a cause and an effect of CKD, and it accelerates its progression. Hypertension is more common and more severe as eGFR decreases. Furthermore, two separate risk factors for cardiovascular disease (CVD) include hypertension and chronic kidney disease (CKD). There is a significant rise in the risks of CVD morbidity and mortality when both coexist (Pugh et al., 2019). Many processes influence the management of chronic kidney disease (CKD) and lead to the development of hypertension in the disease. The development of hypertension in chronic kidney disease (CKD) is partly attributed to an increase in sympathetic tone, which is caused by afferent signals produced by functionally deteriorating kidneys (Kiuchi et al., 2020). The renin-angiotensin-aldosterone system (RAAS), which encourages salt and water retention, is upregulated when eGFR decreases. This is further worse by BP's heightened sensitivity to salt. Advanced chronic kidney disease (CKD) is characterized by endothelial dysfunction (eGFR < 30 mL/min/1.73 m2), and a strong correlation has been shown between it and hypertension. Along the whole spectrum of CKD, increased arterial stiffness is also linked to the development of hypertension, and it stands alone as a risk factor for CVD events (Banerjee et al., 2021; Pugh et al., 2019).

4.5. Glomerulonephritis

One type of kidney illness is glomerulonephritis. In kidney diseases, glomeruli, becomes damaged. Another name for glomerular disease is glomerulonephritis. It's a form of kidney disease brought on by immune system overactivity that damages your glomeruli. Because of this injury, the glomeruli are unable to perform their normal function of eliminating waste and fluid. Glomerulonephritis comes in two varieties including abrupt onset of glomerulonephritis such as that caused by a virus, and chronic glomerulonephritis. The circumstances such as high blood pressure can lead to the development of chronic glomerulonephritis (https://www.kidneyfund.org/all-about-kidneys/other-kidney-diseases/glomerulonephritis-glomerular-disease#:~:text=Glomerulonephritis%20is%20also%20called%20glomerular,and%20fluid%20like%20they%20should).

Among the numerous reasons are infections and immune system problems. Granulonephritis can occasionally be minor and resolve on its own without medical intervention. The phrase "glomerulonephritis" refers to a group of disorders of the kidneys that are defined by immune-mediated injury to the mesangium, capillary endothelium, or basement membrane, resulting in proteinuria, azotemia, and hematuria. Both a main renal cause and a secondary illness causing renal symptoms can lead to acute types of glomerulonephritis (GN) (Kazi and Hashmi, 2024). One common cause of renal dysfunction is glomerulonephritis (GN). Various forms of glomerulonephritis (GN) shares an underlying pathogenetic process that is immune-mediated and involves both humoral and cell-mediated mechanisms (Anders et al., 2023). Fibrotic events are frequently set in motion by the ensuing inflammatory response. Parietal epithelial cells multiply in extra-capillary proliferation, leading to the production of crescents, which are a feature of certain types of glomerulonephritis that advance quickly. Light microscopy reveals thicker capillary walls as a result of glomerular basement membrane thickening (Wong et al., 2021).

4.6. UTI (Urinary tract infections)

The underlying renal illness influences the probability of UTI development in addition to the weakened immune system linked to chronic kidney disease (CKD). Patients with analgesic nephropathy, autosomal dominant polycystic kidney disease, Randall plaques, renal stone formers, and nephrotic syndrome and hypoproteinemia are considered high-risk categories (Shankar and Narasimhappa, 2021). Besides, the people have higher chances to have UTI, are reported to have congenital metabolic errors, such as renal tubular acidosis, idiopathic hypercalciuria, nephrolithiasis, genetic defects of the calcium-sensing receptor, Fabry's disease, Dent's disease, cystinosis, oxalosis, chloride channel mutations, Bartter syndromes (e.g., Bartter type V), etc. Particularly in phases G3–G5 of CKD, UTIs can cause a more faster loss in renal function and all the associated problems. Not to mention that antibiotherapy is frequently challenging for these people since antibiotics might harm the kidneys (Scherberich et al., 2021).

4.7. Antiinflammatory drugs

For numerous reasons, it can be difficult to control discomfort in individuals with chronic kidney disease (CKD). Due to altered medication metabolism and excretion, these individuals are more vulnerable to negative drug effects, and despite a significant pain burden, there are few safety data for use in this population. Because of their potential for nephrotoxicity, nonsteroidal anti-inflammatory medications (NSAIDs) have long been considered risky for use in patients with chronic kidney disease (CKD). As a result, alternative classes of analgesics, such as opioids, are now more frequently utilized in this population to treat pain (https://www.ajkd.org/article/S0272-6386(20)30724-1/fulltext).

For many of their clinical uses, there are substitutes for non-steroidal anti-inflammatory medicines (NSAIDs), which are among the most commonly prescribed drugs. Because NSAIDs limit prostaglandin production, renal perfusion is reduced. Their widespread use is recognized to be closely linked to the emergence of acute renal injury, which is a risk factor for chronic kidney disease (CKD) (Lefebvre et al., 2020). Despite their numerous well-known side effects, including gastrointestinal (GI) bleeding and renal failure, non-steroidal anti-inflammatory medicines (NSAIDs) are one of the most often prescribed drug classes in the US. The mechanism of action of NSAIDs is to block the cyclooxygenase (COX) enzyme, which exists in two isoforms: COX-1 and COX-2. A number of population-based studies have also provided strong evidence linking the use of NSAIDs to acute kidney injury (AKI), with relative risks between 1.6 and 2.2 when compared to non-users (Sandler et al., 1991). Exposure to nonsteroidal anti-inflammatory drugs was linked to increased chances of incident eGFR drop ≥30% and <60 ml/min per 1.73 m2. The group using etoricoxib had the highest risk, whereas those using ibuprofen had the lowest risk (Wan et al., 2021).

4.8. Immunological hemostasis and CKD

A number of essential elements of innate immunity, such as the complement system, natural killer (NK) cells, dendritic cells, macrophages, toll-like receptors (TLRs), and inflammatory cytokines, have been linked to the advancement of renal disease. One essential early part of the innate immune response is complement. It is made up of serum and cell surface proteins that combine to form a cascade that kills and eliminates infections by creating a cell membrane assault complex. Complement activation occurs via three main pathways: lectin, alternative, and classical. The emergence of chronic renal illness has been linked to altered complement regulation. An important factor in the beginning, development, and resolution of renal illness is the immune system. Kidney function and the immune system are tightly related (Imig and Ryan, 2013).

The immune system mediates many acute types of renal disease and is a major factor in the evolution of chronic kidney disease. In healthy individuals, the kidneys help maintain immunological homeostasis. Renal repercussions from an immune system dysregulation can be direct or indirect. Autoantibodies against a component renal antigen—such as collagen IV in anti-glomerular basement membrane disease—usually result in direct immune-mediated kidney disorders. Indirect immune-mediated renal illness can also result from unchecked complement pathway activation. It frequently follows systemic autoimmunity with the production of immunological complexes (Tecklenborg et al., 2018).. The pathways leading to harm are comparable despite the wide spectrum of immune dysregulation causes causing kidney disease. In addition to eliminating medications, poisons, and metabolic waste products from our bodies, the kidneys also remove circulating cytokines and bacterial toxins like lipopolysaccharide (LPS) and continuously sample bloodborne proteins, all of which support the immune system's equilibrium. The elimination of cytokines from the circulation helps prevent inflammation, and the removal of bacterial components lessens the possibility that pattern recognition receptors (PRRs) will activate immune cells (Kurts et al., 2013; Betjes et al., 2013).

4.9. Polycystic kidney disease

Normal renal tubules are replaced by fluid-filled cysts in polycystic kidney disease, a common hereditary illness (Chapin and Caplan, 2010). End-stage kidney disease (ESKD), infections, heart disease, and mortality are among the unfavorable outcomes that can arise from polycystic kidney disease (PKD) and chronic kidney disease (CKD) (de Chickera et al., 2018). The illness known as polycystic kidney disease affects not only the kidneys but also other organs. Cysts, which are collections of sacs filled with fluid, form in the kidneys and obstruct the kidneys' capacity to filter waste from the blood. Polycystic kidney disease is brought on by mutations in the PKD1, PKD2, and PKHD1 genes. Autosomal dominant polycystic kidney disease (ADPKD type 1) and ADPKD type 2 are disorders resulting from mutations in the PKD1 or PKD2 genes, respectively. The instructions these genes offer for producing proteins whose roles are still unclear (Halvorson et al., 2010). They may be involved in the transfer of chemical signals from the cell's outside to its nucleus, according to research. In order to support healthy kidney growth, organization, and function, the two proteins cooperate. Renal failure may result from the enlarged kidneys brought on by cyst development. Moreover, cysts can form in other organs, especially the liver. The kidneys develop many cysts as a result of polycystic kidney disease, or PKD. These cysts have fluid inside of them. Kidney injury may result from cysts that proliferate excessively or enlarge too much. Renal failure can result from PKD cysts that gradually replace a large portion of the kidneys (Chapin and Caplan, 2010). This reduces kidney function. PKD is the fourth most common cause of kidney failure in the US, affecting around 600,000 people. The disease poses no greater risk to men than to women. It accounts for around 5% of kidney failure cases. (https://www.kidney.org/atoz/content/polycystic).

4.10. Congenital abnormalities

Congenital anomalies of the kidney and urinary tract (CAKUT) are a wide spectrum of illnesses resulting from faulty renal parenchymal development, disruption of the embryonic migration of the kidney(s), lower urinary tract developmental abnormalities, and urine collecting system abnormalities. About 50% of affected patients have abnormalities related to their lower urinary tract, such as vesicoureteral reflux (25%), ureterovesical junction obstruction (11%), and ureteropelvic junction obstruction (Stonebrook et al., 2019; Rodriguez, 2014). A variety of illnesses affecting the kidneys and/or urinary tract are together referred to as CAKUT. CAKUT has a similar genetic background and molecular signaling that influences kidney development, despite notable differences in phenotypic and clinical implications. Affected families now

have better prognoses and higher quality of life because of the breakthroughs in prenatal diagnostics, imaging, genetic testing, laboratory surveillance, and medical management—many of these congenital defects are hereditary (Stonebrook et al., 2019).

4.11. Alport syndrome

A prevalent genetic kidney condition called Alport syndrome affects about 2% of people undergoing kidney replacement therapy (KRT). The triad of familial nephritis, deafness and ocular changes was termed Alport syndrome. The clinical presentations of patients with ADAS vary widely, from kidney failure to asymptomatic states. This pattern is not strongly associated with the type of variation or causal gene. The underdiagnosis of ADAS in clinical practice is partly due to the variability of ADAS manifestations. Mutations in the CO4A3, CO4A4, and CO4A5 genes result in Alport syndrome. These genes encode the α3, α4, and α5 chains of collagen type IV, a crucial component of the kidney's glomerular basement membrane (GBM). There are currently over 500 known mutations in these genes, most of which exhibit either autosomal recessive inheritance (mutations in COL4A3 and COL4A4; 15% of patients) or X-linked inheritance (mutations in COL4A5; 85% of patients). Because heterozygous carriers of autosomal recessive Alport syndrome mutations may have distinct symptoms from intermittent microhaematuria or end-stage renal disease (ESRD), autosomal dominant inheritance may not occur (Stonebrook et al., 2019).

5.Role of natural products in CKD management

In both human and veterinary medicine, the use of herbs to treat a variety of ailments is growing in popularity. Plants and plant products have been shown to have a number of well-documented therapeutic qualities in animal models, including anti-hyperlipidemic, anti-diabetic, anti-mycotoxin, anti-pesticide, and anti-heavy metal capabilities. Moreover, a number of plant products have been determined to be safe through safety evaluation in accordance with OECD norms (Oburai et al., 2015). Due to promising complementary therapies and abundant sources for new drug discovery, natural products have attracted increasing interests throughout the world (Anwar et al., 2020b; Younus and Anwar, 2018). It has been claimed that there is a connection between chronic inflammation and CKD. This amplification of ROS and pro-inflammatory cytokines are highly connected in chronic diseases. In addition, AGEs and protein glycation-induced oxidative stress, aggregation, and structural alterations all play a major role in the development of diabetes and its sequelae (Anwar et al., 2022) like CKD. Due to strong anti-oxidant, anti-inflammatory, anti-glycation, anti-protein denaturation, and anti-aggregation properties, the natural products might be able to fight with chronic diseases. Natural products become more and more popular because they are relatively inexpensive and widely available, and have fewer adverse effects. Natural products are a unique medical system with the significant property of multicomponent drugs (Rahmani et al., 2022; Rahmani et al., 2023). Therefore, it is reasonable to assume that consuming natural products may have therapeutic benefits in terms of postponing or halting the development of chronic illnesses like CKD, cancer, diabetes, and its aftereffects like diabetic foot syndrome, neurological disorders, etc. Based on their theoretical therapeutic efficacy and long clinical applications, natural products against fibrosis have gained increasing attention for prevention and treatment of CKD in Asia, Europe and North America (Patel and Udayabanu, 2017).

5.1. *Boerhavia diffusa*

Some common names for Boerhavia diffusa (Family: Nyctaginaceae) are Varshabhu, Raktapushpa, Varshaketu, Kathillaka, Raktapunarnava, and Shothaghni. The plant is also known as "Punarnava" because of its capacity to regrow during the rainy season using perennial roots once the aerial parts of the plant have entirely dried out in the summer. (Santhosha et al., 2021; Oburai et al., 2015). It helps with digestion, keeps the BMI in check, guards against anemia, hernias, and respiratory distress. Potential stimulants for the kidneys, heart, and liver include its root extract. It shields the diabetic's failing kidneys. It is helpful in treating cough, constipation, asthma, and body detoxification because of its renoprotective, diuretic, and laxative qualities. According to reports, it can be used to treat gonorrhea, dropsy, ascites, limb edema, intestinal worm infestation, jaundice, and other liver-related issues. It strengthens the lungs, increases immunity, and soothes joint and inflammatory pain. Its root paste can be applied to swellings and ulcers like a miracle treatment. It works wonders for curing fever, appetite loss, paralysis, and nerve defects (Das et al., 2023). Numerous rotenoids can be found in *B. diffusa* roots. Punarnavoside, a phenolic glycoside, C-methyl flavone, 6.0% potassium nitrate, and ursolic acids are also present. Significant protection against urolithiasis

and kidney disease has been reported to be provided by *B. diffusa*. There have also been reports of B. diffusa's ability to regenerate kidneys. Treatment with B. diffusa root extract produced results similar to those of enalapril. The benefits of *B. diffusa* included a higher rise in serum potassium in CRF dogs and a quicker improvement in major end variables, such as Hb, potassium, phosphorus, and urine protein between day 30 and 90 (Oburai et al., 2005). Combining different herbs or phytochemicals together can have amazing biological effects that can help with both acute and chronic illnesses (Santhosha et al., 2021). Boerhaavia diffusa (BD) and Tinospora cordifolia (TC) are well-known medicinal herbs utilized as the folk medicinal regimen for treating various diseases. The combination of herbs demonstrated a noteworthy ($p < 0.05$) nephroprotective impact by diminishing oxidative and inflammatory stress in the kidneys. Network pharmacological research revealed that polyphenols regulate several genes involved in oxidative stress, inflammation, the renin-angiotensin system (RAS), and other physiological processes that contribute to kidney malfunction (Khan et al., 2022). Wistar rats' kidneys were used to measure the levels of SOD, CAT, LPO, Vitamin C, TRG, GPx, GR, and GST in order to evaluate the nephroprotective efficacy of Boerhavia diffusa against Cisplatin-induced nephrotoxicity. The plant extract was able to improve cell damage when different extracts were treated, as well as change metrics like normalized ion concentration in the kidney and raised levels of urea, creatinine, uric acid, BUN in blood, and LPO in the kidney. All of these studies demonstrated that Boerhavia diffusa protects the kidneys and their disorders. There are a number of research that have been conducted on laboratory animals and a limited number of human studies that demonstrate the possible protective effects on the kidney and its toxicity (Santhosha et al., 2022).

5.2. *Tinospora cardif*olia

Indian Ayurvedic medicine makes extensive use of the powerful plant material Tinospora cordifolia (TC) as a tonic, vitalizer, immunomodulator, and treatment for metabolic problems (Chopra et al., 2018). This huge, glabrous, climbing succulent shrub is deciduous and a member of the Menispermaceae family, which is why hedges often contain it. With anti-diabetic (Gupta et al., 1967), immunomodulatory (Atal et al., 1986), hepatoprotective (Peer and Sharma, 1989), and anti-pyretic (Vedavathy and Rao, 1991) properties, plant stems have been regarded as an indigenous source of medicine. The documented literature indicates that during diabetes, diets containing TC had a positive impact on blood sugar and urine sugar. A review of several indicators, including kidney index, GFR, microalbuminuria, and glomerular area, demonstrated that it also had positive effects on the kidneys. Reduced production of sulphated GAG and CS/DS in the kidney was also observed after TC-feeding (Joladarashi et al., 2012). On rats with diabetic nephropathy brought on by streptozotocin (STZ), the renoprotective impact of TC-loaded PLA Nanoparticles (TC-PLA NPs) was examined. The findings demonstrated that TC-PLA NPs' nephroprotective action lowers blood glucose levels, controls renal parameters, lowers cytokine levels, and lowers the levels of many genes associated with diabetic nephropathy's mRNA expression (Ambalavanan et al., 2021). The groups that were pre-treated with *Tinospora cordifolia* showed a noteworthy ($p<0.001$) restriction in the increase of BUN and serum creatinine levels in a dose-dependent fashion. Additional histopathological observations supported the biochemical results (Sharma et al., 2019).

9.3. *Tribulus Terrestris*

Gokshura, also called Tribulus Terrestris, is a small, leafy herb used in Ayurveda medicine that is a member of the Caltrop family. In Ayurvedic medicine, gokshura is used in India to treat a variety of conditions including hair loss, rheumatic pain, piles, obesity, weak nervous system, headaches and tension, coughing, asthma, edema, and kidney issues (https://pharmeasy.in/blog/ayurveda-uses-side-effects-precautions-of-gokshura/. Researchers have found that this herb contains anti-cancer, aphrodisiac, hypotensive, and diuretic properties. The Gokshura churna may help with peeing-related ailments include burning during peeing, painful urination, and urinary incontinence. Gokshura is a mild diuretic that can aid with dysuria and induce normal urination. It can also ease discomfort and burning micturition. Urinary tract infections may be prevented by gokshura's antimicrobial and antibacterial properties (Khare et al., 2005). In rats with reperfusion injury, oral administration of Tribulus terrestris extract for two weeks can reduce oxidative stress, cellular damages, and disturbances in kidney function (Najafi et al., 2014). Because miR-155-5p suppresses the production of H2AC6, TrT has a reno-protective impact on AngII-induced hypertensive renal damage (Pei et al., 2021).

In rats with reperfusion injury, oral administration of *Tribulus terrestris* extract for two weeks can reduce oxidative stress, cellular damages, and disturbances in kidney function. T. terrestris dramatically lowered blood urea nitrogen, uric acid, creatinine, and oxalate excretion as well as calcium and phosphate levels in serum. Additionally, *T. terrestris* decreased the oxidative stress brought on by hyperoxaluria and restored the expression profile and antioxidant enzyme activity in kidney tissue. According to histological investigation, the administration of T. terrestris reduced inflammation and damage to the renal epithelium while restoring the normal morphology of the glomeruli (Kamboj et al., 2011). As a conventional administration, govkshura helps the kidneys excrete extra uric acid and keeps the level of uric acid in the kidneys stable, which helps prevent or treat gout. Because the bark has anti-lithiasis properties, it prevents kidney stones from forming, breaks them up, or lessens their size. This helps to prevent kidney stones, polycystic kidney disease, and cystitis, among other underlying health concerns https://www.netmeds.com/health-library/post/world-kidney-day-2021-7-astonishing-ayurvedic-herbs-to-uplift-renal-functions.

In the kidney tissues of rats, ET and TT alone or in combination decreased oxidative stress and apoptotic markers. For TT, a dose-dependent impact was noted (Farokhi et al., 2023).

4. *Rosa roxburghii*

Rosa roxburghii Tratt (RRT) is a type of fruit that is wonderful and has numerous health benefits. The potential for preventing type 2 diabetic mellitus (T2DM) has been impressively established by RRT fruit dietary treatments (Wei et al., 2023). *R. roxburghii* is an important resource of medicinal and edible origin, which is mainly distributed in southwestern China, especially in Guizhou Province. Antioxidant, immunomodulatory activity, hypoglycemic effects, hypolipidimic effect, antiatherosclerosis activity, antitumor activity, gastro-protective, hepatoprotective, renal protective effects, detoxification and antiradiation effect (Wang et al., 2023). *Rosa roxburghii*, or *R. roxburghii* is prized for having remarkably high levels of vitamin C, SOD, and flavonoids. A diet high in protective antioxidants such vitamin C, polysaccharides, superoxide dismutase (SOD), and phenolics is linked to a lower risk of developing chronic illnesses. Fruit extracts from *R. roxburghii* exhibited antioxidant properties and a growth-inhibiting effect on cancer cells in culture. R. roxburghii fruit thus demonstrated its potential for use in the development of medicines, dietary supplements, and functional foods (Xu et al., 2019). An investigation was carried out to look into the impact and potential mechanism of Rosa roxburghii fruit polyphenols (RRP) on mice's hypertension brought on by NG-nitro-L-arginine methyl ester (L-NAME). It is possible that RRP increases NO bioavailability, improves endothelial cell dysfunction, inhibits the over-activation of the renin-angiotensin-aldosterone pathway, and reduces inflammation and oxidative stress, all of which contribute to its clear hypotensive impact (Qing et al., 2023). A study aimed to identify the structure, antioxidant activity, and protective effects of crude polysaccharides (RRP) and crude selenium polysaccharides (SeRRP) from Rosa roxburghii Tratt fruit in mice exposed to cadmium (PONY-2020-FL-62). The findings indicated that SeRRP exhibited increased superoxide dismutase (SOD) activity. SeRRP reduces kidney damage by raising the renal index. Additionally, alterations in the gut microbiome might be connected to SeRRP or RRP. Beneficial bacteria (such as Lachnospiraceae, Muribaculaceae, and Ruminococcaceae) were more prevalent and the Firmicutes/Bacteroidetes ratio was lowered by SeRRP and RRP. These results suggest the potential functionality of SeRRP and RRP against kidney damage (Lu et al., 2023). Two fermentation broths (FBA and FBB) made up of Rosa roxburghii and edible fungi in varying amounts were investigated in a rat model of type 2 diabetes induced by streptozotocin and fed a high-fat diet. According to the findings, administering FBA and FBB to diabetic mice could improve the morphology of liver and kidney, their levels of oxidative stress, blood lipids, insulin, blood glucose, and body weight reduction (Hu et al., 2023).

Because of its distinct bioactivities, *Rosa roxburghii* Tratt fruit is widely utilized in China as a food and medicine. In a recent study, a rat model of hyperlipidemia was used to examine the plant's possible hypolipidemic effects and analyze the composition of its phenolic acid content. The phenolic acid-rich *Rosa roxburghii* Tratt fruit was shown to reduce lipid levels in hyperlipidemic mice (Wu et al., 2020). It is unknown what mechanisms underlie the antifibrosis properties of the osa roxburghii fruit (Cili) in chronic renal disease. The UUO rats' kidneys showed reduced BUN, Scr, and proteinuria (all $P<0.05$) and reduced pathological alterations and oxidative stress due to the use of chili powder. In obstructive kidneys, the downregulation of SMAD7 (mRNA and protein) was reversed and the elevation of TGFB1, TGFBR1, TGFBR2, SMAD2, and SMAD3 was suppressed (all $P<0.05$) by turmeric powder. Based on the results, it can be concluded that Cili freeze-dried powder successfully protects renal impairment and fibrosis in UUO rats. This is linked to the suppression of TGF-β1/Smads signaling and oxidative stress (Zhan et al., 2019).

6.Vitamin D and CKD

A prehormone, vitamin D is produced by the skin or through nutrition. It then undergoes a two-step sequential activation process, wherein the active product 1,25 vitamin D, also known as calcitriol, is produced by first 25-hydroxylation in the liver to form 25-(OH)vitamin D and then 1-hydroxylation, which was previously believed to occur largely in the kidney (Jones, 2007; Heany, 2008). With a particular cytosolic receptor, vitamin D is a fat-soluble secosteroid. Approximately three percent of the human genome is regulated by this hormone system. Vitamin D deficiency was first identified as being crucial for the metabolism of calcium and phosphate, but more recently, it has been linked to a host of conditions and events in the general population, including depression, cancer, falls, fractures, diabetes, autoimmune diseases, cardiovascular and renal diseases, tuberculosis, and neurodegenerative diseases (Jean et al., 2017).

Many peripheral (non-renal) tissues produce calcitriol as a result of a peripheral autocrine mechanism that converts 25-(OH)vitamin D to 1,25-(OH)2vitamin D. Actually, it seems that the peripheral autocrine pathway accounts for the majority of the daily metabolic consumption of 25-(OH)-vitamin D; but, because of its rapid local degradation, it contributes very little to the circulating 1,25-(OH)2vitamin D.2 The synthesis of calcitriol in these pathways-containing cells and tissues is an essential part of the signaling cascades that connect environmental stimuli to transcription of genes.1, 2 Calcitriol regulates cellular proliferation and differentiation, inflammation, the immunological system, and the endocrine system, which includes RAS, insulin resistance, and lipid metabolism, via binding with its intracellular vitamin D receptor (VDR) in these organs (Williams et al., 2009). Hemodialysis patients' vitamin D status might be safely and successfully improved by a weekly cholecalciferol regimen, however not all patients were able to attain the NKF-KDOQI target due to the dose. In the clinical management of patients undergoing hemodialysis, establishing an efficient vitamin D dose regimen that reliably raises serum 25(OH)D levels to the NKF-KDOQI target (0.30 ng/mL) is crucial (Jean et al., 2017).

Mineral bone disease (CKD–MBD) is a result of vitamin D deficiency, which affects a significant percentage of people with chronic kidney disease (CKD) (plasma 25-hydroxyvitamin D; 25(OH)D) < 25 or 30 nmol/L according to US and UK population standards) (Christodoulou et al., 2021). For both patients with end-stage renal disease (ESRD) who need dialysis and patients with chronic kidney disease (CKD) who do not, vitamin D medication was linked to a lower risk of cardiovascular and all-cause mortality. The sort of vitamin D analogue used had a small impact on the survival rate (Zheng et al., 2013). Serum uric acid levels can be raised with the typical dosage of vitamin D, however there was no discernible change in serum uric acid levels with large dosages of vitamin D supplementation. Elevated levels of vitamin D supplementation can also raise the level of alkaline phosphatase (Feng et al., 2022).

Patients with chronic kidney disease also frequently have low enough quantities of vitamin D substrate. In a recent multisite study involving 1814 individuals with chronic kidney disease (CKD) in the United States, over 20% of patients had overt vitamin D insufficiency (25-hydroxy vitamin D levels < 15 ng/mL) if their estimated glomerular filtration rate was less than 30 mL/minute.37]. In this context, activated vitamin D drugs are recommended in clinical practice to patients receiving chronic dialysis and those with late-stage CKD. Numerous observational studies indicate that vitamin D may play a significant impact in the general population as well as in patients with CKD and ESRD.
(https://www.medscape.org/viewarticle/571558_2#:~:text=In%20a%20recent%20multisite%20study,rate%20%3C%2030%20mL%2Fminute).

Vitamin D molecules that are active and those that are nutritious may have distinct functions. Vitamin D from nutrition may be more important in infections, while vitamin D from active substances may be more important in albuminuria and mortality. At some point, both nutritional and active vitamin D have an impact on the same vitamin D receptor; however, nutritional vitamin D needs more activation within the body, maybe at locations other than the kidney. In patients with diabetic kidney disease, active vitamin D has been demonstrated to lower eGFR, blood pressure, and albuminuria (Christodoulou et al., 2021; Melamed et al., 2012). FMD measurements show improvements in endothelial function following a brief vitamin D intervention. The vascular disease in CKD appears to benefit from vitamin D (Lundwall et al., 2018).

7.Vitamin B12 in CKD

B12 that is also referred to as "cobalamin" is not produced by an individual's metabolism. It is the most vast and intricate water-soluble substance that has ever been discovered by humans; it contains cobalt and can only be made by particular bacteria (Anwar et al., 2023; Anwar et al, 2024b). Chronic Kidney Disease (CKD) is a rapidly increasing global public health concern. The scientific community is more interested than ever in learning more about the role and influence of vitamin B12 in chronic kidney disease (CKD), as impairment in vitamin B12 metabolism is thought to be a nontraditional risk factor of poor outcomes associated with the disease (Wu et al., 2022). 47 CKD individuals were found to have a vitamin B12 deficiency. In addition to finding a larger prevalence of vitamin B12 insufficiency in CKD patients, the mean duration of CKD is longer in the B12deficient group than in the Normal Group (Dandge and Variya, 2020). End-stage renal disease (ESRD) patients are more likely to experience nutritional deficiencies, which can lead to a vitamin B12 shortage and its detrimental effects on the hematological factors. Vitamin B12 administration raises blood B12 levels in HD patients, which has been linked to higher WBC, RBC, Hb, and PLT levels as well as lower MCV levels. Renal anemia in HD patients can be improved with vitamin B12 treatment (Nahas et al., 2022).

One of the main contributing factors to the development of left ventricular hypertrophy, diastolic and later systolic dysfunction, and cardiovascular illness—which is the single biggest cause of mortality in CKD—is anemia, a multifactorial aspect of the disease. Haematopoiesis is adversely affected by severe chronic kidney disease. Anaemia in CRF is mostly caused by a lack of erythropoietin, iron deficiency anemia, decreased red cell life span, nutritional deficiencies, or abnormal vitamin metabolism (Dandge and Variya, 2020). Elevated plasma B12 was linked to a significant prevalence of RKF in persons with elevated homocysteine levels (McMahon et al., 2015). Gavriilaki and colleagues have proposed that early recognition of B12 deficiency is very necessary in chronic kidney disease (Gavriilaki et al., 2015). Because there is less cobalamin being taken up by peripheral tissues from the circulation, transcobalamin II synthesis will be lower in CKD/DKD patients with chronic inflammation. Plasma cobalamin levels would rise as a result of enhanced transcobalamin I and III production. Moreover, the impact of a deficiency in cobalamin on the accumulation of oxidative stress outside of the hyperhomocysteinemia pathway has been examined in diabetic and CKD/DKD states. However, the relationship between cobalamin deficiency and elevated pro-oxidant and decreased antioxidant status has been found to be controversial (Wu et al., 2023). Cardiovascular events are the primary cause of death for patients with end-stage renal disease (ESRD) and chronic kidney disease (CKD). These patients are at high risk for cardiovascular complications. The increased risk of cardiovascular disease cannot be entirely explained by traditional risk factors, which is why non-traditional risk factors like hyperhomocysteinemia and impaired folic acid and vitamin B12 metabolism are becoming more and more popular. It is yet unknown if hyperhomocysteinemia serves as a valid cardiovascular and mortality risk measure or a therapeutic target in this population, despite the fact that patients with CKD and ESRD frequently have increased homocysteine blood levels (Capelli et al., 2019).

8.Conclusion

There are several types of plants with anti-inflammatory and antioxidative qualities in the natural world. According to research thus far, different phytoconstituents that give plant-based remedies their unique qualities are present in them. By reducing oxidative stress and scavenging the free radicals that cause damage to the liver and kidneys, the antioxidant protection mechanisms of various medicinal plants might be helpful extract prevent lipid peroxidation, damage to cells, oxidation of proteins, and damage to DNA within the nucleus. This study could help to find out complementary and alternative medicine to investigate the use of plant-based therapies for the treatment of kidney illnesses, such as chronic kidney disease (CKD). To verify these possible advantages and the safety of these plants, additional research with sizable sample numbers and in various stages of CKD is required through *in vivo* and clinical studies.

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