Figure 2.1: Conceptual model of the mourse of chronic kidney disease (CDK):
Shaded ellipses present stages of CDK. Unshaded ellipses represent potential antecedents or consequences of CDK. Thick arrows between ellipses represent risk factors associated with the initiation and progression of disease that can be affected or detected by intervention: susceptibility factors (purple), initiation factor (dark blue), progression factor (light blue), and end-stage factor (sky blue). Interventions for each stage are given beneath the stage. People who appear normal should be screened for CDK risk factor. Person known to be at increased risk for CDK should be screened for CDK. “Complications” refer to all complications of CDK and its treatment. Including complications of decreased glomerular filtration rate (GFR) (hypertension, anemia, malnutrition, bone disease, neuropathy, and decreased quality of life) and cardiovascular disease (CVD). Increasing thickness of arrows connecting later stages to complications represents the increased risk of complications as kidney disease progresses. (National kidney foundation, 2002)

Risk factors for chronic kidney disease are defined as attributes associated with increased risk of adverse outcomes of CDK. The guidelines focus primarily on identifying susceptibility factors and initiation factors (to define persons at increased risk of developing chronic kidney disease) and progression factors (to define persons at high risk for worsening kidney damage and subsequent loss of kidney function) because kidney disease usually begins late in life and progression slowly, most persons in the stage of decreased glomerular filtration rate (GFR) die to CVD before they developed kidney failure. However, decreased GFR is associated with a wide range of complications, such as hypertension, anemia, malnutrition, bone disease,
neuropathy, and decreased quality of life, which can be prevented or ameliorated by treatment at earlier stage. Treatment can also show the progression to kidney failure. Thus, measures to prevent, detect, and treat chronic kidney disease in its earlier stages could reduce the adverse outcomes of chronic kidney disease (Levey et al., 2003). The risk factors related to chronic kidney disease (CDK) are mentioned in table 2.1.

Table 2.1: Risk factors related to chronic kidney disease (CDK)

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Definition</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptibility</td>
<td>Increase susceptibility to kidney damage</td>
<td>Older age, family history of CDK, reduction in kidney mass, low birth weight, US racial or ethnic minority, low income or education.</td>
</tr>
<tr>
<td>factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiation factors</td>
<td>Directly initiate kidney damage</td>
<td>Diabetes, high blood pressure, autoimmune diseases, systemic infections, urinary tract infection, urinary stone, lower urinary tract obstructions, drug toxicity and hereditary disease.</td>
</tr>
<tr>
<td>Progression factors</td>
<td>Cause worsening kidney damage or faster decline in GFR</td>
<td>Higher level of proteinurea, higher blood pressure, poor glycemic control in diabetes and smoking.</td>
</tr>
<tr>
<td>End-stage factors</td>
<td>Increase morbidity and mortality in kidney failure</td>
<td>Lower dialysis dose, temporary vascular access, anemia, lower serum albumin level. Late referral to nephrologists.</td>
</tr>
</tbody>
</table>

As per the risk factors related to the chronic kidney disease the kidney stone higher elimination of protein urea in diabetic nephropathy and kidney toxicity potenciate the chronic kidney disease (Coresh et al., 2003). With the increasing prevalence of patients with kidney disease like urinary stone as well as patients with diabetes and hypertension, more patients at risk will be seen in primary care settings. The kidney stone and diabetic nephropathy is highly observed risk factors among all risk factors of CKD. The appropriate treatment of patients at risk and patients with already documented kidney disease should be provided through a multidisciplinary approach (Levey et al, 2005).
Identify patients at risk for kidney disease; screen patients with hypertension or diabetes slow the progression of nephropathy by

- Initiating an Angiotensine-converting enzyme inhibitor (ACE-I) or an Angiotensine receptor antagonist (ARB) if appropriate
- Controlling hypertension and hyperlipidemia
- Treating dyslipidemia
- Initiate therapies to decrease morbidity and mortality
- Promote smoking cessation

Treat sequelae of chronic kidney disease, including

- Secondary hyperparathyroidism
- Anemia
- Fluid and electrolyte disturbances
- Treat co morbid disease states
- Promote lifestyle modifications, including
  - Low-salt diet
  - Healthful eating
  - Possible protein or fluid restriction
  - Avoidance of excessive alcohol intake
  - Avoid nephrotoxic drugs
- Ensure that dosing of all medications is appropriate for the level of kidney function
- Educate patients and providers about chronic kidney disease and promote early intervention
- Treatment procedures like surgical removal, percutaneous techniques and extracorporeal shock wave lithotripsy (ESWL)

Urolithiasis, also called calculi or uroliths, is a condition which involves the process of stone formation in the kidney, bladder, and/or urethra. Kidney stones are a general cause of blood in the urine and pain in the abdomen and flank, with a reported incidence about 12% in the general population (Araujo et al., 1999). The majority of kidney stones are made up of calcium oxalate (CaOx) crystals in the urinary system of patients with urolithiasis. In the majority of cases, urolithiasis is a painful, but otherwise benign, condition, infrequently leading to loss of renal function, at least in common forms of calcium or uric acid stone disease. However, severe forms of
urolithiasis also exist. Although very infrequent, they should not be overlooked because they may lead to progressive loss of renal function and ultimately, end-stage renal disease (ESRD) requiring renal replacement therapy (Gambaro et al., 2001). Infection stones, especially when bilateral and growing to a staghorn development are universally considered the most frequent cause of urolithiasis-associated ESRD (Streem, 1995; Teichman et al., 1995; Worcester et al., 2003). Extensive stone development also has been observed with calcium-oxalate, uric acid, or cystine stones and in patients with anatomic abnormalities of the urinary tract (Gambaro et al., 2001).

Nephrotoxicity is a poisonous effect of some substance, both toxic chemicals and medication, on kidney. There are various forms of toxicity. Drugs cause approximately 20 percent of community and hospital acquired episodes of chronic renal failure (Kaufman et al., 1991; Nash et al., 2000; Bellomo et al., 2006). Among older adults, the incidence of drug-induced nephrotoxicity may be as high as 66 percent (Kohli et al., 2000). Compared with 30 years ago, patients today are older, have a higher incidence of diabetes and cardiovascular disease, take multiple medications, and are exposed to more diagnostic and therapeutic procedures with the potential to harm kidney function (Hoste and Kellum, 2006). Although renal impairment is often reversible if the offending drug is discontinued, the condition can be costly and may require multiple interventions, including hospitalization (Gandhi et al., 2000). Most drugs found to cause nephrotoxicity exert toxic effects by one or more common pathogenic mechanisms. These include altered intraglomerular hemodynamic, tubular cell toxicity, inflammation, crystal nephropathy and thrombotic microangiopathy (Schetz et al., 2005; Zager, 1997; Schnellmann and Kelly, 2007).

Gentamicin is an aminoglycosides antibiotic widely used for the treatment of bacterial infections. Therapeutic doses of Gentamicin and other aminoglycosides antibiotics can produce nephrotoxicity in humans and animals and use of this class of antibiotics is known as one of the most common causes of acute renal failure (Cuzzocrea et al., 2002), possibly due to increased renal uptake of the antibiotic, mainly by the proximal tubules. The effect of Gentamicin on biological membranes appears to be important in its toxicity. It has been proposed that the accumulation of aminoglycosides in
proximal tubular epithelial cells leads to membrane structural disturbance and cell death by reactive oxygen species (ROS) involvement (Kadkhodae et al., 2005). ROS produce cellular injury and necrosis via several mechanisms including peroxidation of membrane lipids, protein denaturation and DNA damage (Cuzzocrea et al., 2002).

Diabetes has become the number one cause of end stage kidney disease (ESRD) in United States (US) and incidence of diabetes mellitus continues to grow both in US and worldwide. Approximately one third of individuals with diabetes develop diabetic nephropathy with a high likelihood of progression to ESRD. However, recent studies suggest that the incidence in this group is declining (Bojesting et al., 1994). But still approximately 20% to 30% of all diabetics will develop evidence of nephropathy, although a higher percentages of type 1 progresses to ESRD. Approximately 45% of new patients entering to dialysis in US are diabetics (Augustine and Vidt, 2003). Diabetic nephropathy is the leading cause of end stage renal disease in developing country and leads to heavy burden of dialysis and transplantation. Although type 1 (insulin dependent) and type 2 (non insulin dependent) diabetes are etiologically and epidemiologically different conditions affecting different segments of population, no major difference has been identified between the nephropathies seen in these conditions, either pathophysiologically or in terms of management.

Diabetic nephropathy is a progressive rise in renal protein excretion, coupled with increasing blood pressure, leading to declining glomerular filtration and eventually end stage renal failure. The natural history of diabetic nephropathy is a process that progress gradually over year. Diabetic nephropathy is an important cause of morbidity and mortality in type 1 (Krolewski et al., 1985) and type 2 diabetes mellitus (Shett, 1999). Early diabetes is heralded by glomerular hyperfiltration and increase glomerular filtration rate. This is though to be related to increase cell growth and expansion in the kidney, possibly mediated by hyperglycemia itself (Augustine and Vidt, 2003). The common progression form microalbuminuria to overt nephropathy has led many to consider microalbuminuria to define early or incipient nephropathy. Clinically diabetic nephropathy is characterized by a progressive increase in urine protein and decline GFR, decline renal function and high risk of cardiovascular morbidity and mortality in patient with diabetes mellitus (Augustine and Vidt, 2003).
Obesity is associated with insulin resistance and compensatory hyperinsulinemia, metabolic derangements that may lead to the formation of calcium containing kidney stones. A recent metabolic trial demonstrate that insulin resistance was associated with defects in renal ammonium production (Abate et al., 2004), and an examination of more than 4500 patients with a history of kidney stones showed that urinary pH was inversely related to body weight (Maalouf et al., 2004). A defect in renal acid excretion could lead to hypocitraturia, an important risk factor for calcium nephrolithiasis (Coe et al., 1992; Hamm, 1990). Hyperinsulinemia may contribute to development of calcium stones by increasing the urinary excretion of calcium (Kerstetter et al., 1991; Shimamoto et al., 1995; Nowicki et al., 1998). Larger body size may also result in increased urinary excretion of uric acid and oxalate, risk factors for calcium oxalate kidney stones (Coe et al., 1984; Pak et al., 1975; Coe et al., 1980). Urinary oxalate excretion increases with increasing lean body mass, presumably reflecting changes in endogenous oxalate synthesis (Lemann et al., 1969).

Extracorporeal shock wave lithotripsy (ESWL), Intravenous Pyelogram and drug treatment revolutionized urological practice almost became the standard procedure for eliminating kidney stones. But shock waves had traumatic effects, residual stone fragments persisted and infection could occur. Moreover, ESWL may cause acute renal injury, a decrease in renal function, hemorrhage and hypertension. Therefore, it is worthwhile to look for alternative means such as medicinal plants or phytotherapy (Bouanani et al., 2010). There is growing interest in the health benefits of herbs and botanicals. Medicinal plants have played a significance role in various ancient traditional systems of medicine. Even today, plants provide a cheap source of drug for majority of world's population (Kraisintu, 2003). A large majority of this research has determined the degree of clinical support for the traditional use of common or folklore medicines. Many remedies have been employed during the ages to treat urinary diseases. In the traditional systems of medicine, most of the remedies were taken from plants and they were proved to be useful though the rationale behind their use is not well established through systematic pharmacological and clinical studies except for some composite herbal drugs and plants. A large number of Indian medicinal plants have been used in the treatment of urolithiasis and they are reported to be effective with no side effects (Nadkarni, 1976).
Hordeum vulgare Linn. (Family: Gramineae; Poaceae) locally known as ‘Barley’ or ‘jav’ is distributed throughout India. It is an annual climber with reported to be highly medicinal (Nadkarni, 1976; Khare, 2007). Locally in India, the Hordeum vulgare seeds are being used for the different medicinal purpose. As per the indigenous system of Ayurveda medicine and the Ayurveda literature survey indicated the use of Hordeum vulgare Linn. seeds reported to be useful in the treatment of a wide range of ailments, including urinary stones, diabetes, hyperlipidemic, carminative, expectorant as well as other complications of kidney (Ross, 2005). The literature review shows absence of any documentation on Hordeum vulgare seeds as therapeutic effectiveness in kidney disease and metabolic disease like diabetic mellitus and hyperlipidemia. Hence, we have selected aforementioned medicinal plant to evaluate its activity in kidney disease viz. urolithiasis, drug induced nephrotoxicity, diabetic nephropathy and hyperlipidemia.

In the light of above facts, the précised objectives of the present investigation were:-

1. Pharmacognostical and phytochemical standardization of Extract of Hordeum vulgare seeds.
2. To study the effect Ethanolic extract of Hordeum vulgare seeds against kidney stone by different models of urolithiasis.
3. To study the effect of Ethanolic extract of Hordeum vulgare seeds on Gentamicin induced nephrotoxicity.
4. To study the effect of Ethanolic extract of Hordeum vulgare seeds in STZ-diabetic rats with special reference to diabetic nephropathy.
5. To study the effect of Ethanolic extract of Hordeum vulgare seeds on fructose induced hyperlipidemia in rats.
6. To study in-vitro antioxidant activity of Ethanolic extract of Hordeum vulgare seeds.
Introduction

Reference


Introduction


Introduction


Introduction


