Renoprotective Activity of *Citrullus lanatus* Rind Extract on Ischemia/Reperfusion-Induced Renal Damage in Rat

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Submitted By

Reg.No.26113091

Under The Guidance Of

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Certificates

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"Renoprotective Activity Of *Citrullus lanatus* Rind Extract On Ischemia/Reperfusion-Induced Renal Damage In Rat"** submitted by the student bearing [**Reg. No: 26113091]** to "**The Tamil Nadu Dr. M.G.R. Medical University**", Chennai, in partial fulfillment for the award of Degree of **Master of Pharmacy** in **Pharmacology** was evaluated by us during the examination held on……..…….

Internal Examiner **External Examiner**

CERTIFICATE

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DECLARATION

I do here by declared that the dissertation entitled **"Renoprotective Activity Of *Citrullus lanatus* Rind Extract On Ischemia/Reperfusion-Induced Renal Damage In Rat"** submitted to "**The Tamil Nadu Dr. M.G.R Medical University"**, Chennai, for the partial fulfillment of the degree of **Master of Pharmacy** in **Pharmacology,** is a bonafide research work has been carried out by me during the academic year 2012-2013, under the guidance and supervision of **Mr. V. Rajesh, M.pharm.,** Assistant professor & Head, Department of Pharmacology, J.K.K. Nattraja College of Pharmacy , Komarapalayam .

I further declare that, this work is original and this dissertation has not been submitted previously for the award of any other degree, diploma, associate ship and fellowship or any other similar title. The information furnished in this dissertation is genuine to the best of my knowledge.

Place : Komarapalayam **I. Joselin Jini,**

Date: **Reg. No.26113091.**

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Abbreviations

LIST OF ABBREVIATIONS USED

HTN	Hypertension
BP	Blood pressure
HR	Heart rate
DASH	Dietary Approaches to Stop Hypertension
ACE	Angiotensin converting enzyme
ANP	Atrial natriuretic peptide
NO	Nitric oxide
SYST-EUR	Systolic hypertension in Europe
TIA	Transient ischemic attack
BUN	Blood Urea Nitrogen
Cr	Creatinine
CKD	Chronic Kidney Disease
NPRI	Natriuretic peptide receptor-1
ESRD	End-stage renal disease
USRDS	United States Renal Data Service
GFR	Glomerular filtration rate
eGFR	Estimated glomerular filtration rate
DSHEA	Dietary Supplement Health and Education Act
FDA	Food and Drug Administration
BPH	Benign prostatic hyperplasia
DSE	*Desmodium Styraci folium*
CCE	*Clematis chinensis*
ROH	Renal artery occluded hypertensive
KPS	Kreb´s physiological solution
MDA	Melone dialdehyde
%w/w	Percent weight per weight
OECD	Organization for Economic Co-operation and Economic Development
mg/dl	milli gram per deci litre

%	percentage
kg	kilogram
ip	Intra peritoneal
MECL	Methanolic extract of *Citrullus lanatus*
LPO	Lipid peroxidation
SOD	Superoxide dismutase
CAT	Catalase
GSH	Reduced glutathione
CPCSEA	Committee for the purpose of control and supervision on experimental animals
SLE	Systemic lupus erythematosus
PSS	Progressive Systemic Sclerosis

Introduction

INTRODUCTION

Herbal medicine

Ever since the birth of mankind there has been a relationship between life, disease and plants. Primitive men started studying diseases and treatments (Lyons and Pertrucelli, 1987). There is no record that people in prehistoric times used synthetic medicines for their aliments but they tried to make use of the things they could easily procure. The most common thing they could find was their in environment i.e. the plants and animals (Singh and Abarar, 1990). They started using plants and found that majority of plants were suitable as food, where as other were either poisonous or medicinally useful. By their experience, this knowledge of herbal remedies was transferred to generation as folk medicine. So the history of herbal medicine is as old as human history. Herbal medicine is still the mainstay of about 75–80% of the world's population, mainly in developing countries, for primary health care because of better cultural acceptability, better compatibility with the human body and lesser side effects. It is estimated that approximately one quarter of prescribed drugs contain plant extracts or active ingredients obtained from or modeled on plant substances. Aspirin, atropine, artimesinin, colchicine, digoxin, ephedrine, morphine, physostigmine, pilocarpine, quinine, quinidine, reserpine, taxol, tubocurarine, vincristine and vinblastine are a few important examples of what medicinal plants have given us in the past. Most of these plant-derived drugs were originally discovered through the study of traditional cures and folk knowledge of indigenous people and some of these could not be substituted despite the enormous advancement in synthetic chemistry. Consequently, plants can be described as a major source of medicines, not only as isolated active principles to be dispensed in standardized dosage form but also as crude drugs for the population. Today in many

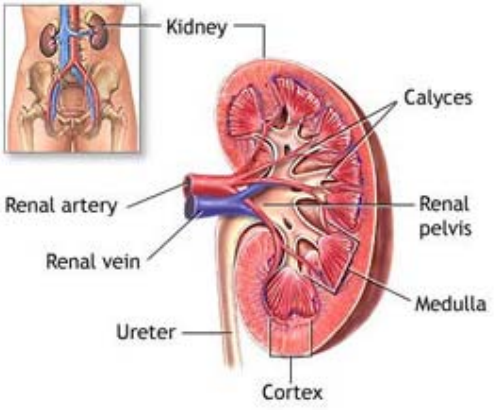
countries modern medicine has displaced plants with many synthetic products but almost 30% of pharmaceutical preparations are still obtained directly or indirectly from plants. The modern era has seen some decline in use of medicinal plants and their extracts as therapeutic agent, particularly in developed countries, many of which either been discarded by the medical profession or now given in the form of isolated compound.

The strategy of isolating the active principles from the medicinal plants and manufacturing a pharmaceutical preparation then became popular. Modern medicines and herbal medicines are complimentarily being used in areas for health care program in several developing countries including India. Of late, the interest in the plant products surfaces all over the world due to the belief that many herbal medicines are known to be free from side effects. It is the fact that the discovery of the new synthetic drug is time consuming & an expensive affair. The utility of the synthetic drug is always accompanied with its single or multiple adverse effects and in some cases the curatives are not available. Herbs had been used by all cultures throughout history but India has one of the oldest, richest and most diverse cultural living traditions associated with the use of medicinal plants. In the present scenario, the demand for herbal products is growing exponentially throughout the world and major pharmaceutical companies are currently conducting extensive research on plant materials for their potential medicinal value. In many journals, national and international, increasing number of research publications based on herbal drugs (Adithan, 1996). Plants have provided mankind a large variety of potent drugs to alleviate suffering from diseases in spite of spectacular advances in synthetic drugs in recent years, some of the drugs of plant Origin have still retained their importance. The use of plant-based drugs all over world is increasing. Inspite of the

tremendous advances made in the modern medicine there are still a large number of ailments for which suitable drugs are yet to be found. Today, there is an urgent need to develop safer drugs for the treatment of inflammatory disorders, diabetes, liver diseases, and gastrointestinal disorder. Hence, there is a growing interest in the pharmacological evaluation of various plants used in Indian traditional systems of medicine. However, the folkloric use of crude drugs is often empirical and is based on observation from clinical trials without experimental support. The need for exhaustive systemic research into indigenous drugs cannot be overemphasized.

Kidney

Figure No. 1



The kidneys play key roles in body function, not only by filtering the blood and getting rid of waste products, but also by balancing levels of electrolyte levels in the body, controlling blood pressure, and stimulating the production of red blood cells.

The kidneys are located in the abdomen toward the back, normally one on each side of the spine. They get their blood supply through the renal arteries directly

from the aorta and send blood back to the heart via the renal veins to the vena cava. (The term "renal" is derived from the Latin name for kidney.)

The kidneys have the ability to monitor the amount of body fluid, the concentrations of electrolytes like sodium and potassium, and the acid-base balance of the body. They filter waste products of body metabolism, like urea from protein metabolism and uric acid from DNA breakdown. Two waste products in the blood can be measured: blood urea nitrogen (BUN) and creatinine (Cr).

When blood flows to the kidney, sensors within the kidney decide how much water to excrete as urine, along with what concentration of electrolytes. For example, if a person is dehydrated from exercise or from an illness, the kidneys will hold onto as much water as possible and the urine becomes very concentrated. When adequate water is present in the body, the urine is much more dilute, and the urine becomes clear. This system is controlled by renin, a hormone produced in the kidney that is part of the fluid and blood pressure regulation systems of the body.

Kidneys are also the source of erythropoietin in the body, a hormone that stimulates the bone marrow to make red blood cells. Special cells in the kidney monitor the oxygen concentration in blood. If oxygen levels fall, erythropoietin levels rise and the body starts to manufacture more red blood cells.

After the kidneys filter blood, the urine is excreted through the ureter, a thin tube that connects it to the bladder. It is then stored in the bladder awaiting urination, when the bladder sends the urine out of the body through the urethra.

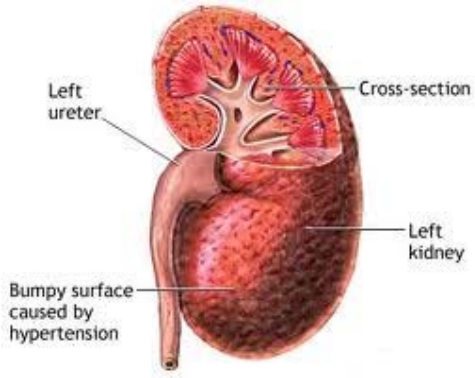
Table 1: Functions of kidney

Major Functions of the Kidneys
Non-excretory functions
Degradation of polypeptide hormones Insulin Glucagon Parahormone Prolactin Growth hormone Antidiuretic hormone Gastrin Vasoactive intestinal polypeptide
Synthesis and activation of hormones Erythropoietin (stimulates erythrocyte production by bone marrow). Prostaglandins (vasodilators that act locally to prevent renal ischemia). Renin (important in regulation of blood pressure). 1,25(OH2)D3 (final hydroxylation of vitamin D to its most potent form).
Excretory functions
Excretion of nitrogenous end products of protein metabolism (eg, creatinine, uric acid, urea). Maintenance of ECF volume and blood pressure by altering Na+ excretion. Maintenance of plasma electrolyte concentration within normal range. Maintenance of plasma osmolality by altering water excretion. Maintenance of plasma pH by eliminating excess H+ and regenerating HCO3. Provision of route of excretion for most drugs.

Hypertension and kidney damage

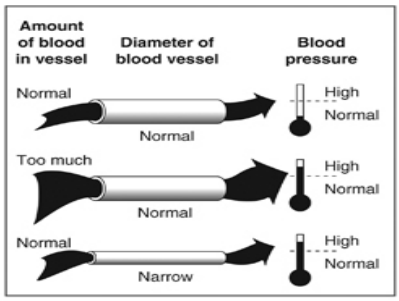
The kidneys play a key role in keeping a person's blood pressure in a healthy range, and blood pressure, in turn, can affect the health of the kidneys. High blood pressure, also called hypertension, can damage the kidneys and lead to chronic kidney disease (CKD).

Figure No. 2



Blood pressure measures the force of blood against the walls of the blood vessels. Extra fluid in the body increases the amount of fluid in blood vessels and makes blood pressure higher. Narrow, stiff, or clogged blood vessels also raise blood pressure (www.kidney.niddk.nih.gov).

Figure No.3



Medium-sized arteries, called the renal arteries, supply the kidneys with a constant flow of blood that must be filtered and returned to the body's normal circulation. Because the filtering functions of the kidney are mainly powered by the force of the blood pressure, the kidneys are very good at sensing changes in blood pressure. If the kidneys sense that blood pressure is dropping too low to power normal blood filtration, they respond by releasing hormones that act to raise blood pressure.

If the flow of blood through the renal arteries decreases for any reason, the kidneys can be tricked into thinking that blood pressure is too low. For example, a disease called renal artery stenosis can cause the renal arteries to narrow, which decreases the amount of blood that flows into the kidneys. The kidneys detect this decrease and release the hormone renin in an attempt to raise blood pressure and restore normal blood flow.

Problems arise when, as in renal artery stenosis, the decrease in blood flow is not actually caused by low blood pressure. In these cases, the kidneys end up raising blood pressure to very high levels in order to push more blood through the narrowed renal arteries.

Genetic profile

It is believed that most cases of hypertension leading to kidney failure have a genetic element (www.healthline.com). Finding a genetic link is complicated by the fact that nearly half of all people with renal failure have three or more serious disorders, such as diabetes. Animal studies have been done to find genetic linkages to hypertension and kidney failure, but genetic studies on humans are in their infancy. A recent breakthrough came in a study of African American subjects with

hypertensive end-stage renal disease. Researchers found a significant association between severe hypertension and mutations on the HSD11B2 gene. This is a gene that plays a role in sodium retention and related factors. Their data suggested that the 16q22.1 chromosome region was the location of the mutation.

In another study, researchers studied an Israeli family of Iraqi-Jewish origin whose members suffered from hypertension and renal failure. The researchers found a genetic locus at 1q21 that was autosomal dominant. They also hypothesized that the gene encoding atrial natriutetic peptide receptor-1 (NPR1) was the disease gene that led to the hypertension/renal failure.

Demographics

People of all ages, races, and both sexes may develop kidney failure due to hypertension. However, some groups are at much greater risk than others. African Americans are at particularly high risk for both hypertension and renal failure and have four times the number of ESRD cases as Caucasians. They also experience kidney failure at a younger age, with an onset at about age 56 compared to an onset at age 62 for Caucasians. African Americans also have a higher rate of diabetes than non-African Americans, another reason for their increased risk for kidney failures. Native Americans and Alaskan Natives are also at high risk for ESRD. There are about the same number of males and females with newly diagnosed ESRD.

In general, according to the National Institutes of Health, the risk for ESRD increases with age, and those who are over age 65 are at greatest risk for ESRD. The United States Renal Data Service (USRDS) of the National Institutes of Health tracks kidney failure statistics in the United States. According to the USRDS, in 1998, the rate of new cases for those under age 20 was just 13 per million, and the

rate increased to 109 for those ages 20–44. A sharp upturn of five times that rate occurred in the 45–64 age group, when the rate is 545 per million people. The rate for those over 65 is about double, at 1,296 per million people. The mean age for individuals with ESRD was 62 years in 1998.

Renal diseases

Renal failure

The classification of renal failure is based on two criteria: the onset (acute versus chronic failure) and the location that precipitates nephron destruction (prerenal, renal or instrinsic, and postrenal failure). Chronic renal failure is a slow, irreversible, and progressive process that occurs over a period of years whereas acute renal failure develops over a period of days or weeks. The distinction between acute and chronic disease is important; acute disease is usually reversible if managed appropriately whereas chronic renal failure is a progressive and irreversible process that leads to death in the absence of medical intervention. In both cases, the kidneys lose their normal ability to maintain the normal composition and volume of bodily fluids. Although the terminal functional disabilities of the acute and chronic diseases are similar, acute renal failure has some unique aspects

Acute Renal Failure

Acute renal failure (ARF) is a clinical syndrome characterized by a rapid decline in kidney function over a period of days to weeks, leading to severe azotemia (the building up of nitrogenous waste products in the blood). It is very common in hospitalized patients; ARF occurs in up to 5% of all admitted patients and in as many as 30% of patients admitted to intensive care units. Medications, surgery, pregnancy-related complications, and trauma are the most common causes

of ARF. Unlike patients who undergo chronic renal failure, patients who develop ARF usually have a normal baseline renal function; yet, mortality from ARF (even with medical intervention including dialysis) can reach 80%, demonstrating the critical illness of these patients (Thadhani *et al*., 1996). The clinical course of acute renal failure most often progresses through three stages: oliguria (urine volume < 400 mL per day), diuresis (high urine volume output > 400 mL per day), and ultimately, recovery (Racusen, 1997). The causes of ARF are often divided into three diagnostic categories: prerenal failure, postrenal failure, and acute intrinsic renal failure.

Prerenal failure

Prerenal failure, defined as any condition that compromises renal function without permanent physical injury to the kidney, is the most common cause of hospital-acquired renal failure. This condition, often referred to as prerenal azotemia, results from reversible changes in renal blood flow and is the most common cause of acute renal failure, accounting for more than 50% of cases (Dishart *et al.,* 2000). Some etiologic factors commonly associated with prerenal failure include volume depletion, cardiovascular diseases that result in diminished cardiac output, and changes in fluid volume distribution that are associated with sepsis and burns (Wardle, 1994).

Postrenal failure

Postrenal causes of failure are less common (< 5% of patients) than prerenal causes. Postrenal failure refers to conditions that obstruct the flow of urine from the kidneys at any level of the urinary tract and that subsequently decrease the GFR. Postrenal failure can cause almost total anuria with complete obstruction or polyuria. Renal ultrasonography often shows a dilated collecting system (hydronephrosis).

Most commonly, obstruction results from prostatic enlargement (benign hypertrophy or malignant neoplasia) or cervical cancer. It is usually seen in older men as a result of the enlargement of the prostate gland. Although postrenal failure is the least common cause of acute renal failure, it remains the most treatable.

Acute intrinsic renal failure

Glomerular disease, vascular disease, and tubuleinterstitial disease comprise the three major causes of acute intrinsic renal failure and describe the sites of pathology. Glomerulonephritis is an uncommon cause of acute renal failure and usually follows a more subacute or chronic course. However, when fulminant enough to cause acute failure, it is associated with active urinary sediment. Prominent clinical and laboratory findings include hypertension, proteinuria, hematuria, and red blood cell casts. Postinfectious, membranoproliferative, and rapidly progressive glomerulonephritis, as well as glomerulonephritis associated with endocarditis and infections of the vascular access, are the most common glomerular diseases to cause a sudden renal deterioration. The pathogenesis of glomerulonephritis appears to be related to the immunocomplex and complement-mediated damage of the kidney (Kashtan, 1999). Vascular occlusive processes such as renial arterial or venous thromboses are also causes of acute intrinsic renal failure. The clinical presentation is archetypal, consisting of a triad of severe and sudden lower back pain, severe oliguria, and macroscopic hematuria. By far, the most common causes of acute intrinsic failure are tubulointerstitial disorders (> 75% of cases), including interstitial nephritis and acute tubular necrosis (ATN). Infiltrative diseases (such as lymphoma or sarcoidosis), infections (such as syphilis and toxoplasmosis), and medications are the leading causes of interstitial nephritis. With drug-induced interstitial nephritis, there are accompanying systemic signs of a

hypersensitivity reaction, and the presence of eosinophils is a common finding in the urine. Although renal function returns to normal with the discontinuation of the offending drug, recovery may be hastened with corticosteroid therapy (Meyers, 1999). ATN is a renal lesion that forms in response to prolonged ischemia or exposure to a nephrotoxin (Lieberthal and Nigam, 2000). ATN remains more of a clinical diagnosis of exclusion than a pathologic diagnosis. The period of renal failure associated with ATN can range from weeks to months, and the major complications of this transient failure are infections, imbalances in fluid and electrolytes, and uremia. Serum levels of BUN and creatinine peak, plateau, and slowly fall, accompanied by a return of renal function over 10 to 14 days in most cases (Bennett, 1999). Sudden renal failure in hospitalized patients is often very apparent from either oliguria or a rise in BUN and creatinine levels.However, renal dysfunction in the outpatient population is often more subtle. A patient can present to the dental office with vague complaints of lethargy and fatigue or entirely without symptoms. These patients can often go undiagnosed but for abnormal results on routine urinalysis, the most common test for screening for renal disease (Jungers, 1999 and Rahman *et al*., 1998).

Chronic Renal Failure

Chronic renal failure (CRF) can be caused by many diseases that devastate the nephron mass of the kidneys. Most of these conditions involve diffuse bilateral destruction of the renal parenchyma. Some renal conditions affect the glomerulus (glomerulonephritis), others involve the renal tubules (polycystic kidney disease or pyelonephritis), while others interfere with blood perfusion to the renal parenchyma (nephrosclerosis). Ultimately, nephron destruction ensues in all cases unless this process is interrupted. The prognosis of the patient with renal disease has improved

significantly during the last two decades. The improvement of antimicrobial therapy to combat increased susceptibility to infection, along with advances in dialysis and transplantation techniques, has provided patients with the opportunity for survival in the face of a complete loss of renal function.

The clinical course of CRF is divided into three progressive stages: (1) diminished renal reserve, (2) renal insufficiency, and (3) end-stage renal failure or uremia. Diminished renal reserve is characterized by normal serum creatinine and BUN levels. There are no symptoms or prominent biochemical disturbances. Renal impairment may be detected only when severe demands are being placed on the kidneys or by sophisticated testing of the GFR. The second clinical stage, renal insufficiency, occurs when the GFR drops to 25% of normal (> 75% of functional kidney tissue has then been destroyed). As nephron destruction progresses, the GFR falls, and the BUN level rises. Among the consequences are (usually) mild azotemia, nocturia, polyuria, and an impaired ability to concentrate urine. The third and final stage of chronic renal failure is end-stage renal failure or uremia.With continued destruction of nephrons (destruction of > 90% of nephron mass), frank renal disease follows, with associated polyuria. The GFR is 10% of normal, and creatinine clearance may be 5 to 10 ml/min or less. Sharp increases in serum creatinine and BUN are seen in response to small decrements in the GFR. At this point, patients experience severe symptoms as their kidneys cannot maintain fluid and electrolyte homeostasis. The complex biochemical changes, including anemia, hypocalcemia, hyperphosphatemia, and metabolic acidosis, along with vast systemic symptoms, a patient experiences, has been termed “uremic syndrome”. Without renal replacement therapy, death is a certain consequence.

The progression of the varied renal diseases, culminating in chronic renal failure, ranges from a few months to 30 to 40 years. Currently, diabetes and hypertension account for 44.4% and 26.6%, respectively, of the total cases of ESRD. Glomerulonephritis is the third most common cause of ESRD (12.2% of cases). Interstitial nephritis, pyelonephritis, and polycystic kidney disease account for 7.2% of cases. The remaining 9.6% of the causes of ESRD include systemic lupus erythematosus (SLE) and relatively uncommon conditions such as obstructive uropathy.

Glomerulonephritis

Glomerulonephritis represents a heterogeneous group of diseases of varying etiology and pathogenesis that produce irreversible impairment of renal function. This is often initiated by an attack of acute glomerulonephritis of streptococcal or nonstreptococcal origin. Glomerulonephritis also may enter the chronic stage from a nephritic syndrome. The most typical examples of this are idiopathic membranous glomerulonephritis and membranoproliferative glomerulonephritis (Levin, 1999). In most cases, the patients present with the features of CRF and hypertension or with a chance proteinuria that has progressed to chronic nephritis over a period of years. Chronic glomerulonephritis is usually insidious in onset.

The course is very slow but is steadily progressive, leading to renal failure and uremia in up to 30 years. It is thought to be a disorder of immunologic origin. The continuous nature of the immunologic injury is shown by the recurrence of disease in kidneys that have been transplanted to patients with some type of glomerulonephritis, even after their own kidneys had been removed (Couser, 1999).

Nephrotic Syndrome

Nephrotic syndrome is the clinical manifestation of any glomerular lesion that causes an excess of more than 3 g of protein excretion in the urine per day. Nephrotic syndrome is caused by multiple diseases, all of which enhance the permeability of the glomerulus to plasma proteins. Excessive protein excretion leads to a decline of plasma osmotic pressure, with consequent edema and serosal effusions. The differential diagnosis of nephrotic syndrome is vast but includes sickle cell anemia, diabetes mellitus, multiple myeloma, SLE, and membranous glomerulonephritis. Bacterial infections secondary to hypogammaglobulinemia have been described as a cause of death in children with nephrotic syndrome.

Pyelonephritis

Pyelonephritis refers to the effects of bacterial infection in the kidney, with Escherichia coli being the most frequent cause of infection (Roberts, 1991). Pyelonephritis may present in an acute form with active pyogenic infection or in a chronic form in which the principal manifestations are caused by an injury sustained during a preceding infection. The chronic form of bacterial pyelonephritis can be further subdivided into reactive and inactive forms, and one or both kidneys may be affected. Any lesion that produces an obstruction of the urinary tract can predispose to active pyelonephritis. Pyelonephritis also may occur as part of a generalized sepsis as seen in patients with bacterial endocarditis or staphylococcal septicemia.

The clinical picture of acute pyelonephritis is often characteristic, consisting of a sudden rise in body temperature (to 38.9° to 40.6°C), shaking chills, aching pain in one or both costovertebral areas or flanks, and symptoms of bladder inflammation. Microscopic evaluation of the urine reveals large numbers of bacteria

and a polymorphonuclear leukocytosis. There are no signs of impaired renal function or acute hypertension as is sometimes seen in patients with acute glomerulonephritis. Patients with chronic active pyelonephritis often suffer from recurrent episodes of acute pyelonephritis or may have persistent smoldering infections that gradually result in endstage renal failure secondary to destruction from the scarring of renal parenchyma. This process may continue for many years. The inability to conserve sodium (a feature in any patient with impaired renal function) is more pronounced in patients with pyelonephritis than in those with glomerulonephritis. This "salt-losing" defect may be pronounced and may dominate the clinical picture.

Polycystic Renal Disease

Polycystic kidney disease exhibits autosomal dominant inheritance (Avner *et al.,* 1999). Most patients present with microscopic or gross hematuria, abdominal or flank pain, and recurrent urinary tract infections. The disease causes renal insufficiency in 50% of individuals by age 70 years (Wilson and Woodford, 1999). Clinically, these patients have large palpable kidneys, and the diagnosis is confirmed via renal ultrasonography, CT, or IVP.Most patients develop hypertension during the course of their disease, and more than one-half of patients are hypertensive at the time of presentation. Although no preventive therapies have proven to be effective, treating the hypertension with angiotensin-converting enzyme inhibitors may help to slow the progression of polycystic disease. Another form of polycystic kidney disease is an acquired reactive process that is seen in over 50% of patients treated by hemodialysis or peritoneal dialysis for longer than 3 years. The development of adenocarcinomas is seen in approximately 5% of these multiple cysts throughout the remnant kidneys.

Hypertensive Nephrosclerosis

The association between the kidneys and hypertension is recognized, yet the primary disease often is not. Hypertension may be the primary disorder damaging the kidneys, but conversely, severe chronic renal failure may lead to hypertension or perpetuate it through changes in sodium and water excretion and/or in the reninangiotensin system (Townsend and Cirigliano, 1998). Hypertension remains one of the leading causes of chronic renal failure, especially in nonwhite populations. The heart, brain, eyes, and kidneys comprise the four major target organs of hypertension. Long-standing hypertension leads to fibrosis and sclerosis of the arterioles in these organs and throughout the body. Benign nephrosclerosis results from arteriosclerotic changes due to long-standing hypertension. It is the direct result of ischemia caused by narrowing of the lumina of the intrarenal vascular supply. The progressive closing of the arteries and arterioles leads to atrophy of the tubules and destruction of the glomerulus. "Malignant nephrosclerosis" refers to the structural changes that are associated with the malignant phase of essential hypertension.

Connective-Tissue Disorders.

Renal diseases are very prevalent among patients with connective-tissue disorders, commonly referred to as collagen vascular diseases. Approximately two-thirds of patients with SLE and scleroderma or progressive systemic sclerosis (PSS) have clinical evidence of renal involvement. In rheumatoid arthritis, the prevalence of renal involvement is considerably less and is often related to complications of treatment with gold salts or D-penicillamine.

Metabolic Disorders

The most common metabolic disorders that may lead to CRF include diabetes mellitus (DM), amyloidosis, gout, and primary hyperparathyroidism. By far, diabetes mellitus is one of the most important causes of CRF and accounts for nearly one-half of new ESRD patients (data from US Renal Data System, 1999). The type of diabetes the patient has affects the probability that the patient will develop ESRD. It has been estimated that about 50% of patients with type 1 DM develop ESRD within 15 to 25 years after the onset of diabetes, compared to 6% for patients with type 2 DM. The term "diabetic nephropathy" refers to the various changes that affect the structure and function of the kidneys in the presence of diabetes. Glomerulosclerosis is the most characteristic lesion of diabetic nephropathy. Other lesions include chronic tubulointerstitial nephritis, papillary necrosis, and ischemia. The natural progression of diabetic nephropathy follows five stages, beginning with early functional changes (stage 1) and progressing through early structural changes (stage 2), incipient nephropathy (stage 3), clinical diabetic nephropathy (stage 4), and finally, progressive renal insufficiency or failure (stage 5). The final stage is characterized by azotemia (elevated BUN and serum creatinine) resulting from a rapid decline in the GFR and leading to ESRD.

Toxic Nephropathy

The kidney is particularly exposed to the toxic effects of chemicals and drugs because it is an obligatory route of excretion for most drugs and because of its large vascular perfusion (Bennett, 1997). There are medications and other agents (referred to as "classic"nephrotoxins) whose use leads directly to renal failure. However, abuse of nonsteroidal anti-inflammatory drugs (NSAIDs) can also result in CRF.

The renal protective effects of prostaglandins are inhibited by NSAIDs. Currently, abuse of analgesics accounts for 1 to 2% of all ESRD cases in the United States.

Signs and Symptoms

The symptoms of kidney disease include:

- High/worsening blood pressure
- Decrease in amount of urine or difficulty urinating
- Edema (fluid retention), especially in the lower legs
- A need to urinate more often, especially at night
- A failure to eat (anorexia) and skin color changes such as a change to a yellow-brown skin color.
- Urea from perspiration may appear on the skin as whitish crystals, similar to frost.
- Pruritis (severe itching of the skin) is common.
- Patients may have muscle cramps and convulsions.
- Many have malnutrition from anorexia and vomiting.
- Gastric ulcers are common, as are cardiac symptoms stemming from the retention of sodium and water.
- Anemia (low levels of iron in the blood) is also common.

Diagnosis

- Very high blood pressure in people younger than 30
- Sudden onset of very high blood pressure in people older than 55
- Blood pressure that does not respond to drug treatment
- Blood pressure that stops responding to previously effective treatments

- Blood tests are usually done in suspected cases of renovascular hypertension, but the only sure way to diagnose the problem is to actually see a narrowing of the renal arteries. This is usually done with a non-invasive procedure such as an MRI or CT scan, but sometimes more invasive measures are required. In these cases, a small catheter is threaded through the groin into the renal artery itself, and small amounts of dye are released from the catheter tip.
- A person's glomerular filtration rate (GFR) is a measure of how well the kidneys are filtering wastes from the blood. GFR is estimated from a routine measurement of creatinine in the blood. The result is called the estimated GFR (e GFR).
- An e GFR with a value below 60 milliliters per minute (mL/min) suggests some kidney damage has occurred.
- Creatinine is a waste product formed by the normal breakdown of muscle cells. Healthy kidneys take creatinine out of the blood and put it into the urine to leave the body. When the kidneys are not working well, creatinine builds up in the blood.
- Another sign of CKD is proteinuria, or protein in the urine. Healthy kidneys take wastes out of the blood but leave protein. Impaired kidneys may fail to separate a blood protein called albumin from the wastes. At first, only small amounts of albumin may leak into the urine, a condition known as microalbuminuria, a sign of failing kidney function. As kidney function worsens, the amount of albumin and other proteins in the urine increases, and the condition is called proteinuria. CKD is present when more than 30 milligrams of albumin per gram of creatinine is excreted in urine, with or without decreased eGFR.

Prevention of kidney damage from hypertension

To prevent kidney damage from high blood pressure:

- Try to keep blood pressure controlled.
- Blood pressure checked on a regular basis.
- Eat a proper diet.
- Get moderate exercise, such as walking, 30 minutes daily.
- Take the medication - doctor prescribes.

Treatment and Management

- Anemia is treated and transfusions are given if anemia is severe.
- ACE inhibitor drugs may be prescribed at low doses to treat cardiac symptoms.
- Diuretics may be prescribed to reduce fluid retention.
- Multivitamins may be recommended because of food restrictions.
- Patients with kidney failure, despite the cause of the failure, must receive kidney dialysis or kidney transplantation. Eventually, those on dialysis will require transplantation of a kidney, either from a recently deceased person or a live donor. (Each person has two kidneys and can live normally with only one kidney.) About 13,000 kidney transplants are performed in the United States each year and about 47,000 people wait for a donated kidney per year.
- There are two types of dialysis. The most common type of treatment is "hemodialysis," a procedure that uses a machine called a dialyzer to clean and filter the blood, since the kidneys can no longer perform that function. A connection from the machine is made to the patient's bloodstream and the blood travels through the dialyzer where it is cleaned for 2–4 hours. This

procedure is generally performed three times a week. Patients must also change their diets to carefully limit the amount of salt, potassium, and fluids that are consumed, among other dietary restrictions that are given.

- "Peritoneal dialysis" is another option for patients with kidney failure. In this procedure, the patient's own abdominal lining (the peritoneal membrane) is used to help clean the blood. Rather than the patient's own blood traveling to a machine, as with a dialyzer, a cleansing solution is transferred through a special tube (catheter) directly into the body. The catheter remains in the body. The number of treatments and time to perform the cleansing procedures vary.

Herbal medicines for kidney failure

Herbs	Parts Used	Chemical Constituents
Aerva javanica	Fresh Roots	Isoquercetin, 5 methylmellein and Kaempferol (Movaliyaa *et al*., 2011).
Aerva lanata	Whole plant	Botulin, β-sitosterol, Amyrin, Hentriacontane, Campesterol (Shirwaikar *et al*., 2004).
Bauhinia variegatea linn	Stems	stigmasterol, flavone glycosides, lupeol, β-setosterol (Saumya *et al*., 2011).
Cassia auriculata	Roots	Tannins, Di-(2-ethyl) hexyl phthalate, Alkaloids, Resins (Saumya *et al*., 2005).

Carica papaya	Seeds	Flavonoids, Phenols, Alkaloids, Protein, Sterols, Terpenoids, Terpenes and Saponins (Movaliyaa *et al*., 2011).
Ceratonia silique	Pods and Leaves	Flavonoids (Ahmed, 2010).
Cucurbita pepo	Seeds	Flavonoids, Phenols, Alkaloids, Protein, Sterols, Terpenoids, Carbohydrates, Terpenes and Saponins
Dichrostachys cinera	Roots	Fixed oils, Steroids, Flavonoids, Friedlen and α amyrin (Adikay *et al*., 2009).
Ficus religiosa	Latex	Amino acids and Tannins (Yadav *et al*., 2011).
Kigelia Africana	Matured fruits	Iridoids, Naphthoquinones, Flavonoids, Terpenes, Saponins and Caffeic acid (Azu *et al*., 2010).
Lepidium sativum	Seeds	Vitamin B-carotene, Riboflavine, Niacin, Flavonoids , Glycosides and Isothiocynates (Chandyadav *et al*., 2010).
Panax ginseng	Roots	Ginsenosides (Dammarol), Panaxosides (Oleanolic acid) and Chikusetsu saponin (http://farmacists.blogspot.com).
Picrorhiza kurroa Royle	Rhizome	Tannins (Yamgar *et al*., 2010).
Pongamia pinnata	Flowers	Alkaloids, Tannins, Sugar (http://farmacists.blogspot.com).
Salviae radix	Whole plant	Salvianolic acid A-G, Rosmarinic acid, Lithospermic acid, Isoferulic acid
Vernonia cinerea	Aerial parts	Triterpenoids like α-amyrin, β-amyrin and lupeol (Sreedevi *et al*.,

		2011).
Aegle marmelos	Leaves	Mamesinine, Lupeol, Tannins, Phlobatannins, Flavonoids, Umbelliferone, Quercetin and Volatile oils (Kore *et al*., 2011).
Crataeva nurvula	Fruits	Kaemferol-3-O-a-D-glucoside, Quercitin-3-O-a-D-glucoside, Flavonoids, Glucosinolates, Steroids, Lupeol and Tannins.
Emblica officinalis	Fruits	Darabinosyl, D-xylosyl, L-rhamnosyl, G-glycosyl, D-manosyl, D-galactosyl, Embicol, Mucic and Phyllambic acid.
Glycyrrhiza glabra	Rhizomes	Glycyrrhizin, Glyciyrrhizic acid, Glycosides, Steroids, Glucose, Sucrose, Resin, Starch and Essential oil
Hygrophilaspinosa	Whole plants	B-sitosterol, Lupeol, Minerals like Anders6 Plant Na, K, Ca, P and Poluphenols (Bibu *et al*., 2010)
Kalanchoe pinnata Pars	Leaves	Tricontane, Alpha & Beta Amyrin, Beta-Sitosterol, Fumaric acid, Mallic acid and Calcium Oxalate (Harlalka *et al*., 2007).
Morinda citrifolia L	Fruit	Americanoic acid A, Morindolin and Isoprincepin (Shenoy *et al*., 2011).
Nigella sativa	Whole plant	Alanine, L-Spinasterol, Arabic acid, Arginine, Amino acid, Aspargine, Aspartic acid, Carvone, Cystine
Ocimum sanctum	Leaves	Apigenin, Luteolin, Ascorbic acid, Carotene, Alkaloids, Glycosides, Saponins and Tannins (Kannappan *et al*., 2010).
Orthosiphon stamineus	Whole plant	Steroids, Tannins, Glycosides, Terpins and Saponins (Kannappan *et al*., 2010)

Rhazya stricta	Leaves	1-carbomethoxy-β-carboline, Condyloacarpine and Vincanicine
Solanum nigrum	Whole plant	Glucose, Fructose, Caffeicsolasodine, Tamatidenol, Solamargine, Solasomine, Trigogenine, Pottasium, Sulphur, Calcium and Phosphorous.
Strychnos potatorum	Seeds	Flavanoids, Phenols, Saponins, Alkaloids, Steroids, Tannins, Glycosides, and Lignins (Varghese *et al*., 2011)
Tribulus sativus	Fruits	Flavanoids, Kaemferol, Tribuloside, Fixed oil, Resin, Essential oil and Nitrates
Withania somnifera	Roots	Amino acids, Essential Oils, Withaniol, Hexatriacontane, Phyto sterol and oils.
Pedalium murex Linn	Dried fruits	Flavanoids, Flavones, Alkaloids, Triterpenoids, Carbohydrates, Glycosides, and Saponins (Shelke *et al*., 2009)
Acorus calamus	Aerial Parts	Monoterpene, Sesquiterpene, Phenyl propanoid, Flavonoid, Quinone and basarone (Palani *et al*., 2010).
Boerhaaviadiffusa	Root	Flavonoids, Alkaloids, Steroids, Triterpenoids, Lipids, Lignins, Carbohydrates, Proteins and Glycoproteins (Surendra *et al*., 2011).
Caranarium schweinfurthii	Stem Bark	Octylacetate, Nerolidol, Protein,Starch, Cellulose, K, Ca, Oleic acid and Stearic acid (Okwuosa *et al*., 2009).

ClitoriaternateaLin	Aerial parts	Varidiflorene, Pterocarpin, 6HBenzofuro[3,2-c][1] benzopyran, Isoparvifuran, Hexadecanoic acid, 1, 2, 3 , 5-Cyclohexanetetrol and Propane (Sarumathy *et al*., 2011).
DioscoreaalataL	Whole Plant	Dioscorine, Starch, Vitamin-B, Calcium Oxalate, Protien and Iron (Shih-Chang *et al*., 2002).
Harunganamadaga scariensis(L)	Fresh Root	Feruginin, Harunganin, Harunganelol A, B, Friebelan 3-one and Betlinic acid (Adeneye *et al*., 2008).
IndigoferabarberiL	Whole plant	Flavonoids, Phenolic acid and sterols (Palani *et al*., 2008).
Monochoria vaginalis	Aerial Parts	3- trifluoroacetoxy pentadecane and 4- ethyl-5-octyl-2,2-bis (trifluoromethyl) - cis-1,3-dioxalone (Palani *et al*., 2011).
Pimpinella tirupatiensis	Whole plant	Volatile oils, β-Bisaboline, Δ-3-Carene, Cis-Carveol, Enemol, Δ-Carveol and Methylgeranate (Palani *et al*., 2010)
ZingiberzerumbelSmith	Rhizome	Zerumbone, Afzelin, Diacetylafzelin, derivatives of kaemferol and 3- flavonol (Hamid *et al*., 2011).
ZingiberOfficinaleroscoe	Rhizome	Volatile oil, Gingerol, Shogaol, Resins, Starch, Fibres, Capsaicin and Paradol (Ajith *et al*., 2008).
RubiacordifoliaLinn.	Root	Purpurin, Manjistin, Garancin, Purpuroxanthin, Resin, Fattyacids and Gum (Divakar *et al*., 2010).
Vitisvenefera L.	Seed	Gallocatechin, Abscisic acid, Acetic acid, A-Hemicellulose, Alanine, α-Viniferin, α- tocoferol.

Curcuma longa	Rhizome	Curcumin, Termeric oil, Terpenoids, Curcumen(Terpene), Starch and Albumnoids (Jijon *et al*., 2011).
BrideliaretusaSpreng	Bark	Arpodomapuic acid, 5 Allyl 1,2,3 trimethoxy benzene (or) Elemicin and +Sesamin (Cordeirom and Kaliwalb, 2011).
Drynaria fortune	Whole plant	Arsenic, Ca2+, Cu2+, Glucose, Iron, Mg, Mn, Hg, Naringin, K+, Na+, Starch and Zinc
Eruca sativa	Seeds	Flavanoids (Alam *et al*., 2007).
Moringa oleifera	Seeds	Sucrose, Citric acid, Malic acid, Succinic acid, Fumaric acid and Oxalic acid (Ranjan *et al*., 2009).
Tamirindus indica	Fruit Pulp	Ethanollamine, Serine, Inositol, Alkaloid, Citric acid, Tartaric acid and Pottasiumbitartrate (Ranjan *et al*., 2009).
PunicagranatumL	Fruit peel	Ellagic acid, Ellagitannins and gallic acid (Mohammed *et al*., 2010).
Euphorbia neriifolia	Leaves	Saponins, Flavonoids and Tannins (Pracheta *et al*., 2011).
Tectona grandis	Bark	Lapachol, Dehydro-α-lapachone, Methyl quinizarin and Squalene (Ghaisas *et al*., 2010).
Ginkgo biloba	Whole plant	Flavonoids, Bilobalide, Gingkolide A, Gingkolide B and Gingkolide CandBiflanoide (Welta *et al*., 2007).

Herbs	Uses
Cordyceps sinensis	Improving the regeneration of renal tubular epithelial cells
Salvia miltiorrhiza	Increase the blood flow on the kidney
Rheum Officinale	Used to reduce elevated serum creatinine level and high blood urea nitrogen level
Astragalus Mmngholicus	Correcting patients' immune sysdtem and giving a good internal environment to kidney
Punarnava (Boerhavia diffusa)	It helps in removing excess water from the body due to kidney failure. (www.planetayurveda.com).
Varun (Crataeva nurvala)	It is very effective for obstruction in urinary tract and helps in removing the renal stones.
Gokshur (Tribulus terrestris)	It clears away the obstruction in the urinary tract and is also act as anti-infective. It also helps to avoid dialysis.
Rakt Chandan (P. santalinus- Red Sandalwood)	It acts like a cooling agent in the urinary tract and is a urinary alkaliser.
Palaash (Butea monosperma)	It is a urinary alkaliser and also relieves painful micturition.
Kaasni (Cichorium intybus)	It is useful in Nephrotic syndrome, nephritis and other conditions leading to kidney failure.

Literature Review

PLANT PROFILE

Citrullus lanatus

Kingdom	:	Plantae - Plants
Subkingdom	:	Tracheobionta – Vascular plants
Superdivision	:	Spermatophyta – Seed plants
Division	:	Magnoliophyta – Flowering plants
Class	:	Magnoliopsida – Dicotyledons
Subclass	:	Dilleniidae
Order	:	Cucurbitales
Family	:	Cucurbitaceae –Cucumber family
Genus	:	*Citrullus* Schrad. – watermelon
Species	:	*Citrullus lanatus* (Thunb.) Matsum. & Nakai – watermelon

Variety	:	*Citrullus lanatus* (Thunb.) Matsum. & Nakai var.*lanatus* – watermelon
Scientific name	:	*Citrullus lanatus*
Synonym	:	*Citrullus vulgaris*
English	:	Watermelon

Crop categories

Fruits

Food crops

Tropical crops

Basic information and facts

Origin:

Southern Africa

Distribution:

Now grown in most tropical and sub-tropical regions of the world.

Flowers:

Flowers are five-petaled with a light yellow color. Plants produce both male and female flowers. Flowers are usually 2 to 3 cm in diameter.

Leaves:

The leaves are deeply lobed and have a dark grayish green color. They are covered with soft downy hairs.

Figure No. 4 Fruits:

The big round or oval fruits have a thick rind and a fleshy center, usually with many dark brown to black seeds. The fruits has a green and yellow color on the outside. The flesh inside is usually red, but color variations include type with yellow or orange flesh. Fruits can weigh from 2 to 20 kilos, depending on the variety.

Climate and weather:

Tropical and sub-tropical climates. Watermelon prefers a hot, dry climate (daily temperatures between 22 to 30°C). It can survive desert conditions when groundwater is available.

Fruit development:

Watermelon fruits that are grown under hot and dry conditions have a higher sugar content than fruits that grew up under cool and humid conditions.

Harvesting:

Harvest by hand when the fruits have fully ripened.

Nutrition:

A watermelon contains about 6% sugar and 92% water by weight. As with many other fruits, it is a source of vitamin C.

Table 2:

Watermelon, raw (edible parts)			
Nutritional value per 100 g (3.5 oz)			
Energy	**127 kJ (30 kcal)**	**Niacin (vit. B_3)**	**0.178 mg (1%)**
Carbohydrates	**7.55 g**	**Pantothenic acid (B_5)**	**0.221 mg (4%)**
Sugars	**6.2 g**	**Vitamin B_6**	**0.045 mg (3%)**
Dietary fiber	**0.4 g**	**Folate (vit. B_9)**	**3 µg (1%)**
Fat	**0.15 g**	**Vitamin C**	**8.1 mg (10%)**
Protein	**0.61 g**	**Calcium**	**7 mg (1%)**
Water	**91.45 g**	**Iron**	**0.24 mg (2%)**
Vitamin A equiv.	**28 µg (4%)**	**Magnesium**	**10 mg (3%)**
Thiamine (vit. B_1)	**0.033 mg (3%)**	**Phosphorus**	**11 mg (2%)**
Riboflavin (vit. B_2)	**0.021 mg (2%)**	**Potassium**	**112 mg (2%)**

Nutritional Values of water melon:

- Water melon sugar consist of sucrose, glucose and fructose**.**
- It also contains vitamins like A, B6, C, PP, folacin and carotene.
- 100 gms of water melon contains 38 calories
- Watermelon contains the highest amount of lycopene.

- It contains Argenine an amino acid.

Health benefits of watermelon

- The Rich in electrolytes and water content, melons are nature's gift to beat tropical summer thirst.

- Watermelons are very low in calories (just 30 calories per 100 g) and fats yet very rich source of numerous health promoting phyto-nutrients and anti-oxidants that are essential for optimum health.

- Watermelon is an excellent source of Vitamin-A, which is a powerful natural anti-oxidant. 100 g fresh fruit provides 569 mg or 19% of daily-required levels of this vitamin. It is essential for vision and immunity. Vitamin-A is also required for maintaining healthy mucus membranes and skin. Consumption of natural fruits rich in vitamin-A is known to protect from lung and oral cavity cancers.

- It is also rich in anti-oxidant flavonoids like lycopene, beta-carotene, lutein, zeaxanthin and cryptoxanthin. These antioxidants are found to offer protection against colon, prostate, breast, endometrial, lung, and pancreatic cancers. Phyto-chemicals present in watermelon like lycopene and carotenoids have the ability to help protect cells and other structures in the body from oxygen-free radicals.

- Watermelon is an excellent source of carotenoid pigment, lycopene and indeed, superior to raw red tomato. 100 g of fresh melon provides 4532 µg lycopene, whereas only 2573 µg in tomatoes. Studies suggest that lycopene offer certain protection to skin from harmful UV rays.

- Watermelon fruit is a good source of potassium; Potassium is an important component of cell and body fluids that helps controlling heart rate and blood pressure; It thus offers protection against stroke and coronary heart diseases.
- Furthermore, it contains a good amount of vitamin-B6 (pyridoxine), thiamine (vitamin B-1), vitamin-C, and manganese. Consumption of foods rich in vitamin-C helps the body develop resistance against infectious agents and scavenge harmful oxygen-free radicals. Manganese is used by the body as a co-factor for the antioxidant enzyme, superoxide dismutase.
- Total measured antioxidant strength (ORAC value) of watermelon is 142 μmol TE/100 g.
- Watermelon is a less fat fruit, having low calories, and it is an ideal diet food.
- Argenine relaxes blood vessels. It also improves muscle growth, stimulating a good immune system.
- Arginine also helps the urea cycle, by removing ammonia and other toxic compounds from our body.
- Watermelon contains lycopene an anti-oxidant that may help to prevent diseases like cancer.
- It does not have cholestral.
- In liver diseases, it's good to drink watermelon juice because it will take the liquid from organism.
- Watermelon can also be used to treat anemia, calculi formation.

- Watermelon contains lot of potassium, which is helpful in cleaning the toxic depositions in the kidney.
- The potassium and magnesium in the watermelon helps in reducing the high blood pressure to normal ones.
- Watermelon's cleansing and nourishing face packs.
- Take watermelon's pulp and have a paste and apply it on face for 15minutes, and wash it off, it leaves skin beautiful and soft.
- And can also add curd to melon pulp paste for a soft skin, it will nourish skin.
- Take the watermelon seeds, grind them add to boiled hot water and mix it as a thick paste and apply as face masks. These melon seed's oil act as a good moisturizer for dry skin.
- For sun burns, take watermelon, and cucumber in equal half, mix it and apply.
- Watermelon has thirst quenching properties. Plus, it has anti-inflammatory, antioxidant, demulcent, vermifuge, febrifuge, purgative and mildly diuretic qualities.
- Apart from the pink flesh, juicy watermelon rind also has several health benefits. For instance, it can heal acne breakouts and improve blood circulation.

- Regular consumption of fresh juice extracted from this fruit, which is loaded with lycopene, protects against heart disease.
- Moreover, studies have shown that higher levels of lycopene avoid damage caused by exposure to sunlight. Furthermore, watermelon works as a good hormone regulator. Plus, it strengthens immunity and helps reduce the severity of asthma.
- Watermelon aids in weight loss as well as it helps the metabolism work efficiently. It can prevent the formation of kidney stones, too. Intake of this amazing fruit benefits in soothing burning sensation caused by mouth sores and ulcers.
- This fruit is also useful for healing mild erectile dysfunction as it contains citrulline that helps relax blood vessels. Consuming this fruit can serve as a natural cure for increasing libido, too.
- In addition, watermelon protects the eyes from age related macular degeneration**,** glaucoma and other similar ailments associated with the eyes.
- It is good for brain and relieves symptoms of depression and nervous anxiety. Besides, it works as an efficient home remedy for bedwetting.
- It is good for individuals suffering from osteoarthritis and rheumatism.
- Eating this fruit on a daily basis during the summer season helps avoid heat stroke. Being rich in electrolytes, it prevents dehydration.

- Consuming watermelon rind relieves heartburn and morning sickness during pregnancy. It also reduces muscle cramps.
- Boil a handful of watermelon seeds in water until the solution becomes thick. Drink this decoction on an empty stomach, first thing in the morning to get rid of intestinal worms. Follow this therapy for a few days.
- Dry watermelon seeds under the sun for a day or two and boil two teaspoons of these seeds in a cup of water for about an hour. Cool and strain the solution. Drink this home medicine to reduce blood pressure.
- Drinking watermelon seed tea can prove to be useful in dealing with urinary tract infection.
- Having a glass of watermelon juice in the morning, on an empty stomach provides relief from headache.
- Watermelon seed oil benefits in the natural treatment of rickets.
- Consuming watermelon seed tea cleanses the kidney and bladder. To prepare this tea, pour two cups of hot water over a tablespoon of ground watermelon seeds.
- Leave the solution for 15 minutes and then strain it. Drink this tea daily for about three days. This therapeutic tea also helps dissolve kidney stones.
- Eating slices of watermelon mixed with a little black salt cures dry cough.
- Simply eating this fruit for a few days relieves constipation.
- Rubbing a piece of cold watermelon can heal skin sores.

- Applying watermelon juice on skin for about 15 minutes helps avoid wrinkles as it tightens the skin.

- Regularly using a combination of watermelon pulp and yogurt on skin serves as a natural remedy to exfoliate the skin and fade blemishes. And can also blend a mixture of watermelon, yogurt and banana, and apply it as a face mask for 15-20 minutes to get glowing skin.

- To get rid of blackheads and avoid sunburn, apply a combination of grated cucumber, watermelon juice, tomato juice and sufficient rice flour to form a paste. Wash it off after 10-15 minutes.

- Roasted watermelon seeds can be eaten as snacks or sprinkled on salads. And can also make watermelon seed tea or include the seeds (ground) in soups to reduce the risk of developing cardiovascular disease or type 2 diabetes.

- These seeds are high in protein and low in carbohydrates. Moreover, pickle or marinate the rind of this fruit after removing green part.

Benefits of watermelon rinds

Nutritional Benefits

A 1-inch cube of watermelon rind contains 1.8 calories. The majority of the calories come from carbohydrates, with 0.32 g per serving. While we will not derive a tremendous amount of macronutrients from eating watermelon rind, this food does contain some vitamins. One serving provides 2 percent of the daily recommended intake of vitamin C and 1 percent of the vitamin B-6 our body requires every day. This makes watermelon rind good for skin and immunity, as well as the health of nervous system.

Economic Benefits

Considered primarily a Southern food, pickles made from watermelon rind offer a tart taste and stretch food dollars. Homemade pickles made from watermelon rind offer an inexpensive alternative to purchased pickles. Because watermelon rind is often thrown out and not used, finding ways to use it for food, such as pickles, relishes or jam, extends the functionality of this fruit. And cut the rind into spears and chunks, as well as shred it for recipes.

Citrulline Content

Watermelon rind contains a compound known as citrulline, according to a study published in the June 2005 issue of the "Journal of Chromatography." Citrulline might serve up a range of medicinal benefits. Evidence in the March 2011 edition of the "Journal of the Science of Food and Agriculture" suggests that the citrulline in watermelon rinds gives it antioxidant effects that protect from free-radical damage. Additionally, citrulline converts to arginine, an amino acid vital to the heart, circulatory system and immune system, say researchers from Texas A &

M's Fruit and Vegetable Improvement Center. These researchers speculate that watermelon rind might relax blood vessels and have a role in treating erectile dysfunction.

Acne Treatment

Acne, especially when it occurs on face, can be a humiliating medical condition, but using watermelon rind might help prevent breakouts. An article at the Complete Mother website notes that eating watermelon is key for treating acne, but can also rub watermelon rind on acne as a method of naturally clearing up face or other areas affected.

Watermelon May Have Viagra-Effect

“Arginine boosts nitric oxide, which relaxes blood vessels, the same basic effect that Viagra has, to treat erectile dysfunction and maybe even prevent it.”Citrulline, the precursor to arginine, is found in higher concentrations in the rind of watermelons than the flesh.

Watermelon & the kidney

Watermelon contains 92 percent water to hydrate body. One cup of raw watermelon contains 170 mg of potassium and only 2 mg of sodium. Potassium and sodium are minerals that help regulate blood pressure and fluid balance. Whereas sodium increases blood pressure, potassium can play a role in lowering blood pressure, according to an American Heart Association Nutrition Committee report published in "Circulation" in August 1998. Reducing blood pressure lowers risk of kidney disease.

Nitric Oxide

Eating watermelon increases levels of nitric oxide and lowers risk of kidney disease (Traister, 2011). Watermelon, particularly the rind, is a rich source of citrulline, according to research from the United States Department of Agriculture in University, Missouri, and published in the "Journal of Chromatography A" in June 2005. Citrulline is an amino acid that body converts to arginine, which is converted to nitric oxide. This gas increases blood flow and reduces blood pressure. A deficiency of nitric oxide is associated with an increased risk of chronic kidney disease, according to research from the University of Florida College of Medicine in Gainesville and published in the "American Journal of Physiology and Renal Physiology" in January 2008. The scientists report that nitric oxide deficiency occurs due to limitations in arginine availability.

Lycopene

Watermelon is a rich source of lycopene, an antioxidant that reduces oxidative stress in the kidneys. One cup of watermelon contains 6,889 mcg of lycopene. There have not been specific studies on lycopene from watermelon and the kidneys, but there has been research on the association between lycopene from tomatoes and kidney disease. Scientists at Firat University in Elazig, Turkey, found that lycopene has protective effects against kidney toxicity, according to research published in "Nutrition and Cancer" in April 2011.

Eliminating Kidney Stones

Watermelon is one of the best natural remedies for kidney stones available. It has the highest level of water among all types of fruit, and water is essential to being able to pass kidney stones. Watermelon is used as a diuretic, increasing the urine.

What's more important, though, is watermelon's high level of potassium. This substance is a form of salt that actually helps to dissolve the kidney stones, therefore easing the pain and helping to eliminate them. This whole process can take up to 15 days but the difference, of course, can be felt much sooner than that.

Preventing Kidney Stones

Watermelon can also be used in preventative measures against kidney stones, especially for those who already have a history of kidney stones. If have a family history but haven't experienced stones yet, incorporate watermelon diet on a regular basis.

Because there are no side effects with using this as a remedy or preventative measure, it can be consumed at any time unless have an allergy.

Literature survey

- **Swapnil Sharma *et al*., 2011** evaluated the laxative activity of Citrullus lanatus fruit pulp extract. It was observed, the fruit pulp aqueous extract of Citrullus lanatus produced significant and dose dependent increase in faeces output of rats and the stimulation of gastrointestinal motility.

- **Adesanya A *et al*., 2011** evaluated the effect of methanolic extract of Citrullus lanatus seed on experimentally induced prostatic hyperplasia. It was observed, treatment with extracts caused a significant decrease in the enlarged prostate, seminal vesicle and testes sizes in a dose related manner.

- **Munglue P *et al*., 2012** evaluated the effects of Citrullus lanatus flesh and rind extract and L-citrulline on rat uterine contractility. It was observed watermelon and citrulline are potent tocolytics, decreasing the force produced by calcium entry and SR release and arising by different pathways, including oxytocin stimulation. Their major mechanism is to stimulated the NO – cyclic guanosine monophosphate (cGMP) relaxant pathway.

- **Asghar MN *et al*., 2012** evaluated the effect of phytochemical and *in vitro* total antioxidant capacity analyses of peel extracts of different cultivars of Cucumis melo and Citrullus lanatus pulp and seeds. It was observed the potency of C.melo and C.lanatus extracts as antioxidant and radical scavenger plants which may be used as good sources of natural antioxidants. The peels of both the plants can be added to the diet at various stages to compensate

- **Fernandez – Bayon JM *et al*., 1993** evaluated the physiological effects of ozone on cultivars watermelon (Citrullus lanatus) and muskmelon (Cucumis melo) widely grown in spain. It was observed, the exposure to ozone reduced flower production in both muskmelon and watermelon, which indicated effects on yield.

- **Olarewaju M.Oluba *et al*., 2008** evaluated the fatty acid composition of Citrullus lanatus (Egusi Melon) oil and its effect on serum lipids and some serum enzymes. It was observed, a corresponding significant reduction in serum activities of the enzyme in the egusi melon oil – fed rats. In addition, feeding egusi melon oil (5% in the diet) to rats reduced severe atherosclerosis in the aorta. Histopathological examination showed that egusi melon oil reduced foam cell formation and inhibited smooth cell migration in the blood vessels of rats.

- **Okunrobo O.Lucky *et al*., 2012** evaluated the quantitative determination, metal analysis and antiulcer evaluation of methanol seeds extract of Citrullus lanatus Thunb (Cucurbitaceae) in rats. Proximate and metal content analysis of the seeds provided information that the consumption of the seeds of Citrullus lanatus was safe. This study also confirmed the exact mechanism underlying the ulcer healing and protecting property of the extract and to identify the chemical constituents responsible for it.

- **Naresh Singh Gill *et al*., 2011** evaluated the antioxidant and anti-ulcerative potential of Citrullus lanatus seed extract in rats. It was showed significant decrease in the gastric volume, free acidity and total acidity in case of pyloric ligated model and showed significant percentage inhibition of ulcer as indicated by decrease in ulcerative index.

- **Deng Jia-gang *et al*., 2010** evaluated the anti-inflammatory and analgesic effects of extract from roots and leaves of Citrullus lanatus. It was observed, the extract significantly inhibited the ear edema, granuloma hyperplasia and paw edema. The extracts could protect mice/rats from inflammation and

analgesia and may be safe as an orally administered natural product for human.

- **Hassan L E A *et al*., 2011** evaluated the *In vitro* antigiardial activity of Citrullus lanatus Var. citroides extracts and cucurbitacins isolated compounds. The results suggested that all the crude extracts and isolated compounds were against Giardia lamblia, hence C.lanatus var. citroides may be recommended as new source for the treatment of giardiasis.

- **Madhavi P *et al*., 2012** evaluated the Anti-Inflammatory Activity of *Citrullus lanatus* Seed Oil by *In-vivo* and *In-vitro* Models. The results showed significant reduction of edema in carrageenan induced rat paw edema model maximum at 3 hr.

- **Poduri A *et al*., 2013** evaluated the *Citrullus lanatus* 'sentinel' (watermelon) extract reduces atherosclerosis in LDL receptor-deficient mice. It was observed, the extract led to reduced body weight gain, decreased plasma cholesterol concentrations, improved homeostasis of pro- and anti-inflammatory cytokines, and attenuated development of atherosclerosis without affecting systolic blood pressure in hypercholesterolemic mice.

- **Oyewo O. O *et al*., 2012** evaluated the effects of aqueous extract of Citrullus lanatus on the Histology of the Kidney of adult wistar rats. The results revealed that aqueous extract of Citrullus lanatus on the histology of the kidney in all the groups were normal when compared with the control groups.

- **Chidan Kumar CS *et al*., 2012** evaluated, Sugars extracted from watermelon (Citrullus lanatus) rind. The extracted sugars were put through some chemical characterization procedures for purposes of separation and identifying its components. The various standard sugars were spotted using the solvent system n-butanol - acetone - diethyl amine - water (10:10:2:6, v/v/v/v) in the cellulose layer for TLC analysis which indicated the presence of Rhamnose, sucrose, mannose and glucose.

- **Adi Kristanto T *et al*., 2013** evaluated the enhancement of fibroblast cell number due to oral administration of Watermelon (Citrullus lanatus) seeds extract in wound healing. The consumption of watermelon seed extract with 100 % consentration can increase the amount of fibroblas in wound healing.

- **Hassan L E A *et al*., 2011** evaluated the *In vitro* antimicrobial activities of chloroformic, hexane and ethanolic extracts of citrullus lanatus var. citroides. The ethanolic extract of the fruit pulp and stem showed the highest antifungal activity on Candida albican. Aspergillus nigar was very sensitive to the chloroform extract of the seed and the ethanolic extract of the leaves . Based on the current findings, it can be concluded that this plant has antimicrobial activity, which is as potent as standard antimicrobial drugs against certain microorganisms.

- **Alok B *et al*., 2012** evaluated the anti-ulcer activity of Citrullus lanatus seed extract in wister albino rats. It was observed , Citrullus lanatus has significantly decreased the gastric volume (53.55%), free acidity (57.02%) and total acidity (36.53%) in case of pyloric ligation model. Conclusively the

ulcer protective effect of Citrullus lanatus may be due to its anti-secretory along with cytoprotective mechanism.

- **Raziq S *et al*., 2012** evaluated the characterization of seed oils from different varieties of watermelon [Citrullus lanatus (Thunb)] from Pakistan. The results indicated that the seeds of the tested watermelon varieties from Pakistan are a potential source of high-linoleic oil and thus can be explored for commercial use and value addition.

- **Asghar *et al*., 2013** evaluated the phytochemical and *in vitro* total antioxidant capacity analyses of peel extracts of different cultivars of *Cucumis melo* and *Citrullus lanatus. Employing* GC-MS analyses and standard *in vitro* antioxidative assays, the data presented that the potency of *C. melo* and *C. lanatus* extracts as antioxidant and radical scavenger plants which may be used as good sources of natural antioxidants. The peels of both the plants can be added to the diet at various stages to compensate food shortage and dietary deficiency problems of living beings.

- **Johnson J.T. *et al*., 2012** evaluated the anti-nutrient contents of watermelon *Citrullus lanatus* pulp, seeds and rinds. The study was carried out on both fresh and dried samples. Results of the investigation revealed that the anti-nutritional components such assaponin, alkaloid, hydrocyanic acid, phenols, oxalate, tannins, phytates were detected in all the samples but at a varying tolerable concentration.

- **Besler M *et al*., 2001** presented Allergen Data Collection of Watermelon *(Citrullus lanatus).* The data informed the symptoms of allergy to

watermelon as well as diagnostic features, and the occurrence of cross-reacting allergens.

Aim and Objectives

AIM AND OBJECTIVE

Acute renal failure (ARF) is a clinical syndrome characterized by rapid deterioration of renal function, which is faced in many clinical situations. ARF is classically divided into pre-renal, renal (intrinsic) and post-renal failure. Pre-renal AFR is a consequence of decrease in renal perfusion (due to hypovolemia/shock or ischemia), which leads to reduction in GFR. Intrinsic renal failure occurs when there is damage to the structures of nephron such as glomeruli, tubules, vessels or interstitium. The major cause of intrinsic ARF is acute tubular necrosis (ATN) that results from ischemia or neprotoxic injury. Pre-renal ARF and ischemic ATN may occur as continuation of the same pathophysiological process, and together account for 75 % of the causes of ARF. Post-renal ARF follows obstruction of the urinary collection system with an increase in pressure within the renal collecting systems resulting in reduced GFR and renal failure.

ARF following ischemia/reperfusion (I/R) is major complication after renal transplantation, renal surgery including partial nephrectomy, renal artery angioplasty, aneurysm surgery, elective urological operations and clinical conditions associated with renal perfusion. The mortality rate of patients with ARF has remained 25-70 % despite the use of various pharmacological agents. Therefore, it continues to be a frequent threatening complication following trauma, complex surgical procedures, and in patients hospitalized in intensive care units. In the

absence of reliable and effective modern therapy for ARF, concerted efforts are currently challenged towards exploring alternative therapy in the disease treatment and/or prevention. Recently, plant products have been of great interest for their potential uses as alternative remedies for the treatment of many diseases. Ancient literature has prescribed various herbs for treatment of kidney diseases and certain Indian medicinal plants have been reported to exhibit protective effect on renal tissues against injuries.

Citrullus lanatus (Watermelon) belongs to family Cucurbitaceae originally from South Africa, is widely distributed in Africa and Asia. The growth is favoured in dry climate and is mainly a dry season crop in monsoon areas, requiring only limited rainfall. It is an annual herb with long stems lying or creeping on the ground, with curly tendrils. Fruits vary considerably in size range from about 7 cm in diameter to over 20 cm. The flesh amounts to about 65 % of the whole fruit, and of this 95 % is water. Fruit is good source of vitamin A, vitamin B, vitamin C and potassium which are essential for maintenance of human health. The seeds are used as vermifuge and possess antimicrobial property. It is also used in treatment of prostatic hyperplasia and possesses anti-oxidant, anti-inflammatory and analgesic properties. The juice squeezed from pulp is used as anthelmintic and diuretic. The other ethno-medicinal uses of fruit include purgative, remedy for urinary stones, gonorrhoea and leucorrhoea in women, anti-ulcerative. The fruit is rich in lycopene, an antioxidant carotenoid effective against certain types of cancer and cardiovascular diseases.

The rind of fruit is rich source of aminoacid citrulline, a precursor of L-arginine, the substrate for nitric oxide synthase in the production of nitric oxide

(NO). NO activates soluble guanylate cyclase leading to an increased conversion of GTP to cGMP, which provides the signal for smooth muscle relaxation, including corpus cavernosum of penis and myocardium. Recent work has shown that watermelon consumption increased plasma arginine levels which improved aortic haemodynamics. Citrulline in watermelon rind also possessed anti-oxidant property against free radical damage. Based on the reports of several studies on vascular smooth muscle relaxant effect of watermelon rind, a study was planned to evaluate the renoprotective effect of watermelon rind on ischemia/reperfusion induced acute renal damage in albino wistar rats.

Plan of work

PLAN OF WORK

Plan of work is

- To collect watermelon (*Citrullus lanatus*) rinds, to shade dry and powder dried rind.
- To extract dried rind powder using methanol in soxhlet apparatus for 72 hours.
- To analyse the phytoconstituents present in *Citrullus lanatus* rind extract.
- To evaluate the acute oral toxicity study of *Citrullus lanatus* extract.

Pharmacological Screening

- To evaluate relaxant effect of *Citrullus lanatus* rind extract on rat thoracic aorta rings (*Invitro*).
- To evaluate renoprotective activity of *Citrullus lanatus* rind extract on Ischemia/Reperfusion – Induced Renal Damage in rat by assessing renal function
    1) By biochemical investigation of renal parameters.
    2) By measuring lipid peroxidation and anti-oxidant enzyme activities in kidney.
    3) By histopathological examination of kidney tissue.

Statistical analysis

- Evaluation of results obtained by One way ANOVA followed by standard Dunnet's test.

Materials and methods

MATERIALS AND METHODS

Plant material

The fresh rind of *Citrullus lanatus* fruits were collected from local market at komarapalayam, Tamilnadu. The collected rind of *Citrullus lanatus* fruits were shade dried and the dried materials were crushed to coarse powder with mechanical grinder. The powder was stored in air tight container for extraction.

Extraction

About 57.26 gm of dried powder were subjected to extraction with methanol using soxhlet apparatus for 72 hours. After completion of extraction, methanol was removed by distillation. The residue obtained was air dried. The dried methanol extract was stored in air tight glass container for further investigation.

Phytochemical screening

The extract obtained was subjected to preliminary phytochemical screening (Tiwari *et al*., 2011).

Qualitative tests:

1. Detection of alkaloids:

Extracts were dissolved individually in dilute Hydrochloric acid and filtered.

a) Mayer's Test:

Filtrates were treated with Mayer's reagent (Potassium Mercuric Iodide). Formation of a yellow coloured precipitate indicates the presence of alkaloids.

b) Wagner's Test:

Filtrates were treated with Wagner's reagent (Iodine in Potassium Iodide). Formation of brown/reddish precipitate indicates the presence of alkaloids.

c) Dragendroff's Test:

Filtrates were treated with Dragendroff's reagent (solution of Potassium Bismuth Iodide). Formation of red precipitate indicates the presence of alkaloids.

d) Hager's Test:

Filtrates were treated with Hager's reagent (saturated picric acid solution). Presence of alkaloids confirmed by the formation of yellow coloured precipitate.

2. Detection of carbohydrates:

Extracts were dissolved individually in 5 ml distilled water and filtered. The filtrates were used to test for the presence of carbohydrates.

a) Molisch's Test:

Filtrates were treated with 2 drops of alcoholic α-naphthol solution in a test tube. Formation of the violet ring at the junction indicates the presence of Carbohydrates.

b) Benedict's Test:

Filtrates were treated with Benedict's reagent and heated gently. Orange red precipitate indicates the presence of reducing sugars.

c) Fehling's Test:

Filtrates were hydrolysed with dil. HCl, neutralized with alkali and heated with Fehling's A & B solutions. Formation of red precipitate indicates the presence of reducing sugars.

3. Detection of glycosides:

Extracts were hydrolysed with dil. HCl, and then subjected to test for glycosides.

a) Modified Borntrager's Test:

Extracts were treated with Ferric Chloride solution and immersed in boiling water for about 5 minutes. The mixture was cooled and extracted with equal volumes of benzene. The benzene layer was separated and treated with ammonia solution. Formation of rose-pink colour in the ammonical layer indicates the presence of anthranol glycosides.

4. Legal's Test:

Extracts were treated with sodium nitropruside in pyridine and sodium hydroxide. Formation of pink to blood red colour indicates the presence of cardiac glycosides.

5. Detection of saponins

a) Froth Test:

Extracts were diluted with distilled water to 20ml and this was shaken in a graduated cylinder for 15 minutes. Formation of 1 cm layer of foam indicates the presence of saponins.

b) Foam Test:

0.5 gm of extract was shaken with 2 ml of water. If foam produced persists for ten minutes it indicates the presence of saponins.

6. Detection of phytosterols

a) Salkowski's Test:

Extracts were treated with chloroform and filtered. The filtrates were treated with few drops of Conc. Sulphuric acid, shaken and allowed to stand. Appearance of golden yellow colour indicates the presence of triterpenes.

b) Libermann Burchard's test:

Extracts were treated with chloroform and filtered. The filtrates were treated with few drops of acetic anhydride, boiled and cooled. Conc. Sulphuric acid was added. Formation of brown ring at the junction indicates the presence of phytosterols.

7. Detection of phenols

Ferric Chloride Test:

Extracts were treated with 3-4 drops of ferric chloride solution. Formation of bluish black colour indicates the presence of phenols.

8. Detection of tannins

Gelatin Test:

To the extract, 1% gelatin solution containing sodium chloride was added. Formation of white precipitate indicates the presence of tannins.

9. Detection of flavonoids

a) Alkaline Reagent Test:

Extracts were treated with few drops of sodium hydroxide solution. Formation of intense yellow colour, which becomes colourless on addition of dilute acid, indicates the presence of flavonoids.

b) Lead acetate Test:

Extracts were treated with few drops of lead acetate solution. Formation of yellow colour precipitate indicates the presence of flavonoids.

10. Detection of proteins and aminoacids

a) Xanthoproteic Test:

The extracts were treated with few drops of conc. Nitric acid. Formation of yellow colour indicates the presence of proteins.

b) Ninhydrin Test:

To the extract, 0.25% w/v ninhydrin reagent was added and boiled for few minutes. Formation of blue colour indicates the presence of amino acid.

11. Detection of diterpenes

Copper acetate Test:

Extracts were dissolved in water and treated with 3-4 drops of copper acetate solution. Formation of emerald green colour indicates the presence of diterpenes.

Acute oral toxicity study of methanol extract of *Citrullus lanatus*. rinds

Animals:

Swiss albino mice of female sex weighing 20-25 gms were used for the study. The animals were housed in polypropylene cages. The animals were maintained under standard laboratory conditions (25º ± 2ºC; 12hr light and dark cycle). The animals were fed with standard diet and water *ad libitum*. Ethical clearance (for handling of animals and the procedures used in study) was obtained from the Institutional Animal Ethical Committee before performing the study on animals.

Acute Toxicity Test:

Acute oral toxicity study for methanol extract of Citrullus lanatus rinds was carried out as per OECD guideline 425 (Up and Down procedure). The test procedure minimizes the number of animals required to estimate the acute oral toxicity. The test allows the observation of signs of toxicity and can also be used to identify chemicals that are likely to have low toxicity.

Animals were fasted (food but not water was with held overnight) prior to dosing. The fasted body weight of each animal was determined and the dose was calculated according to the body weight.

Limit Test at 2000 mg/kg

The drug was administered in the dose of 2000 mg/kg body weight orally to one animal. If the test animal survived, then four animals were dosed sequentially; therefore, a total of five animals were tested. Animals were observed individually at least once during the first 30 minutes after dosing., periodically during the first 24 hours (with special attention given during the first 4 hour), and daily thereafter, for a total of 14 days. After the experimental period, the animals were weighed and humanely killed and their vital organs including heart, lungs, liver, kidneys, spleen, adrenals, sex organs and brain were grossly examined.

Evaluation of *Citrullus lanatus* rind extract on vascular response in pre-contracted rat thoracic aortic rings

Preparation of rat thoracic aortic rings and experimental protocol

Rats were anesthetized with pentobarbitone sodium (60 mg/kg body weight, *ip*) and subsequently bled and exsanguinated. A midline incision was made through the sternum to expose the thoracic aorta. The aorta was carefully isolated, freed from surrounding fat and adherent connective tissue and cut into 3-5 mm long rings. The rings were suspended horizontally in tissue chambers containing kreb's physiological solution. Special care was taken to avoid damage to the endothelium. The tissue bath solution was constantly bubbled with a mixture of 95% O_2 and 5% CO_2 (carbogen) at 37°C. All aortic rings were allowed to equilibrate under a resting tension of 500 mg for 30 min. During this period, kreb's physiological solution was replaced every 15 min to protect against interfering metabolites (Altura, *et al.,* 1970 and Guedes, *et al.,* 2004).

After stabilization, the effect of *Citrullus lanatus* rind extract on response of phenyeprine in rat thoracic aortic rings was recorded.

Evaluation of renoprotective activity of *Citrullus lanatus* rind extract on Ischemia/Reperfusion – Induced Renal Damage in rat by assessing renal function

Healthy, young adult albino wistar rats (150 – 200 gms) were used for the study. The animals were obtained from Agricultural University, Mannuthy, Thrissur, Kerala (328/99/CPCSEA) and were housed in polypropylene cages. The animals

were maintained under standard laboratory conditions (25˚ ± 2˚C; 12 hours light and dark cycle). The animals were fed with standard diet and water *ad libitum.* Ethical clearance (for handling of animals and the procedures used in study) was obtained from the Institutional Animal Ethical Committee (887/ac/05/CPCSEA) before performing the study on animals.

Twenty four albino rats were divided into four groups of six animals each. First group served as normal received 0.5% carboxy methyl cellulose 2 ml/kg for 6 days. Second group served as (Ischemia/Reperfusion induced Renal damage) untreated group received 0.5% carboxy methyl cellulose 2ml/kg for 6 days. Third group served as treatment group received, methanolic rind extract of *Citrullus lanatus* 200 mg/kg for 6 days. Fourth group served as treatment group received methanolic rind extract of *Citrullus lanatus* 400 mg/kg for 6 days. On seventh day, the rats in all groups were anesthetized by intraperitoneal injection of ketamine 100 mg/kg and xylazine 10 mg/kg. Both renal pedicles were identified through a midline incision and occluded with a renal pedicle occlusion clamp for 60minutes. The clamps were then removed and reperfusion of the kidneys was allowed. Afterwards, the abdomen was closed with continuous sutures in 2 layers. All of the rats were sacrificed after 6 hours of reperfusion period and both kidneys were harvested for antioxidant and histological analyses.

Kidney Function Study

Blood was collected from the rats by retro-orbital puncture at the time of sacrify and was allowed to clot for 10 minutes at room temperature. Clots were centrifuged at 2500 rpm for 10 minutes to separate the serum. Serum creatinine, urea, and uric acid levels were analysed.

Preparation of Tissue Homogenates

After sacrificing the animals, their kidneys were quickly removed, perfused immediately with ice cold hypertonic saline solution, and homogenized in chilled potassium chloride (1.17 %) using a Potter Elvehjem homogenizer (Remi, Mumbai, India). The homogenate was centrifuged at 10500 g for 20 minutes at 4°C to get the postmitochondrial supernatant, which was used to assay superoxide dismutage, catalase, reduced glutathione, and lipid peroxidation activity.

Estimation of Antioxidant Enzymes

Estimation of Lipid peroxidation (LPO)

By the method described by Ohkawa et al, the levels of thiobarbituric acid reactive substances in the kidney was measured (Ohkawa and Ohishi *et al*., 1979). The portion of kidney homogenates was mixed with 0.2 ml of 8.1% Sodium dodecyl sulphate, 1.5 ml of 20% acetic acid and 1.5 mL of 0.8% thiobarbituric acid, then the volume was adjusted to 4.0 ml with distilled water. With 1.0 ml of distilled water and 5.0 ml of n- butanol and pyridine (15:1 v/v) the reaction mixture was extracted and the absorbance was measured in organic layer at 532 nm after centrifugation.

Estimation of superoxide dismutase (SOD) activity

After diluting the 0.5 ml of tissue homogenate with water, 2.5 ml of ethanol and 1.5 ml of chloroform were added and mixed for 1 min at 4 °C and centrifuged. The supernatant was separated and determined for enzyme activity. Appropriately diluted enzyme preparation is mixed with 1.2 ml of sodium pyrophosphate buffer (0.025 M, pH 8.3), 0.1 ml of 186 μM PMS, 0.3ml of 30 μM Nitroblue tetrazolium (NBT), 0.2 ml of 780 μM NADH, and water in a total volume of 3 ml. By addition

addition of NADH, the reaction was started. After the reaction, by the addition of 1 ml glacial acetic acid and incubation at 30°C for 90 seconds, the reaction was stopped. With 4 ml of n-butanol, the reaction mixture was stirred vigorously and shaken. At 560 nm, the intensity of the chromogen was measured in the butanol layer against butanol blank. A system devoid of enzyme served as control (Kakkar *et al.*, 1984)

Estimation of catalase activity

0.1 ml of tissue homogenate is mixed with 1.0 ml of 0.01M phosphate buffer (pH 7.0), and 0.4 ml of 2M H_2O_2. By the addition of 2.0 ml of dichromate-acetic acid reagent the reaction was stopped (5% potassium dichromate and glacial acetic acid were mixed in 1:3 ratio). The absorbance was measured at 620 nm. Catalase activity was expressed as nM of H_2O_2 consumed/min/mg protein (Sinha, 1972).

Reduced Glutathione (GSH) activity

Reduced glutathione was estimated by the method of Ellman (1959). 0.5 ml of tissue homogenate was precipitated with 2 ml of 5 % TCA. After centrifugation, 1 ml of supernatant was taken and added 0.5 ml of Ellman's reagent (19.8 mg of 5,5' dithio (bis) nitrobenzoic acid in 100 ml of 1% sodium citrate) and 3 ml of phosphate buffer. Standards were treated in a similar way and the colour developed was read at 412nm.

Histological Analysis

The kidneys fixed in a 10% neutral-buffered formalin solution were embedded in paraffin and were used for histopathological examination. Five micrometer- thick sections were cut, deparaffinized, hydrated, and stained with hematoxylin-eosin. The renal sections were examined blindly for tubular cell swelling, interstitial edema, tubular dilatation, and moderate to severe necrosis in all groups.

Statistical Analyses

Results were expressed as mean ± standard error of mean (S.E.M). The results were analysed for statistical significance by one way ANOVA followed by dunnett's test (Graphpad software Inc, La Jolla, CA. Trial version). The criterior for statistical significance was set at $P<0.05$.

Results and Discussion

RESULTS AND DISCUSSION

Extraction yield

Watermelon rind powder used for extraction - 57.26 gm

Solvent used for extraction- 1000 ml

Extraction yield obtained using methanol as solvent – 30.70 % w/w

Table. 3 Phytoconstituents detected in methanol extract of *Citrullus lanatus* rind

Phytochemicals	Test	Methanoll extract
Alkaloids	a. Mayer's test b. Dragendroff's c. Hager's test d. Wagner's test	+ + + +
Phytosterols	a. Leiberman Burchard b. Salkowaski test	+ +
Flavonoids	a. Alkaline reagent test b .Lead acetate test	+ +
Saponins	a. Froth test b. Foam test	+ +
Proteins and Aminoacids	a. Xanthoproteic test b. Ninhydrin test	+ +
Diterpenes	a. Copper acetate test	+
Phenolics and Tannins	a. Ferric chloride test b. Gelatin test	- -
Carbohydrate	a. Molisch's test b. Fehling's test c. Benedict's test	- + +
Gylcosides	a. Modified Borntrager's test b. Legal's test	- -

(+ Present ; - Absent)

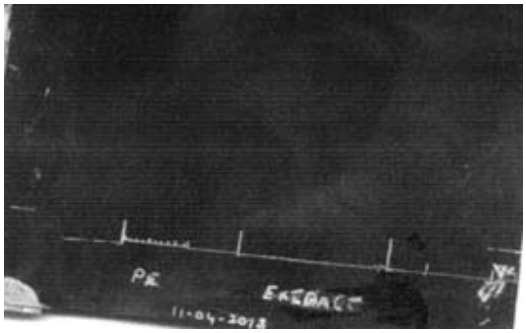
Table. 4 : Acute oral Toxicity study of methanolic extract of *Citrullus lanatus* rind. (Guideline 425)

RESPIRATORY BLOCKAGE IN NOSTRIL	
Dyspnoea	Nil
Apnoea	Nil
Tachypnea	Nil
Nostril discharge	Nil
MOTOR ACTIVITIES	
Locomotion	Normal
Somnolence	Nil
Loss of righting reflex	Nil
Anaesthesia	Nil
Catalepsy	Nil
Ataxia	Nil
Toe walking	Nil
Prostration	Nil
Fasciculation	Nil
Tremor	Nil
CONVULSION (INVOLUNTRAY CONTRACTION)	
Clonic/tonic/tonic-clonic convulsion	Nil
Asphyxial convulsion	Nil
Opistotones (titanic spasm)	Nil
REFLEXES	
Corneal	Normal

Eyelid closure	Normal
Righting	Normal
Light	Normal
Auditory and sensory	Normal
OCULAR SIGNS	
Lacrimation	Nil
Miosis	Nil
Mydriasis	Nil
Ptosis	Nil
Chromodacryorrhea	Nil
Iritis	Nil
Conjunctivitis	Nil
SALIVATION	
Saliva secretion	Nil
PILOERECTION	
Contraction of erectile tissue	Nil
ANALGESIA	
Decrease in reaction to induced pain	Nil
MUSCLE TONE	
Hypo or hypertonia	Nil
GIT SIGN	
Solid dried / watery stool	Nil
Emesis	Nil
Red urine	Nil
SKIN	

Oedema	Nil

Figure No. 5 : Evaluation of *Citrullus lanatus* rind extract on vascular response in pre-contracted rat thoracic aortic rings



The effect of *Citrullus lanatus* rind extract on aortic rings on response of phenylephrine was studied. Phenylephrine by acting on α_1 receptor produced contraction of aortic rings. A contraction of 40 µg was used to contract aortic rings. Methanol extract of *Citrullus lanatus* rind extract at concentration of 100 µg blocked the effect of phenylephrine. This might be due to vasorelaxant effect of *Citrullus lanatus* rind extract through α_1 receptor blockade activity, mediated through endothelium – derived relaxant factors.

Figure No. 6 Renal pedicle occlusion

Normal **I/R injury**

untreated

I/R injury + Extract 200 mg/kg **I/R injury + Extract 400 mg/kg**

Table. 5 : Effect of *Citrullus lanatus* rind extract on serum urea, uric acid and creatinine in rats exposed to renal ischemia reperfusion(I/R) injury

Group	Treatment	Urea (mg/dl)	Uric acid (mg/dl)	Creatinine (mg/dl)
Group I normal	0.5% CMC (2 ml/kg)	80.59 ± 5.91	1.75 ± 0.05	1.41 ± 0.03
Group II I/R injury untreated	0.5% CMC (2 ml/kg)	$139.1 \pm 2.55^{***}$	$2.71 \pm 0.07^{***a}$	$2.77 \pm 0.09^{***a}$
Group III Treated	MECL (200mg/kg)	$129.7 \pm 1.37^{ns b}$	$2.15 \pm 0.08^{** b}$	$2.70 \pm 0.04^{ns b}$
Group IV Treated	MECL (400mg/kg)	$110.4 \pm 2.31^{*** b}$	$1.73 \pm 0.10^{*** b}$	$2.08 \pm 0.02^{*** b}$

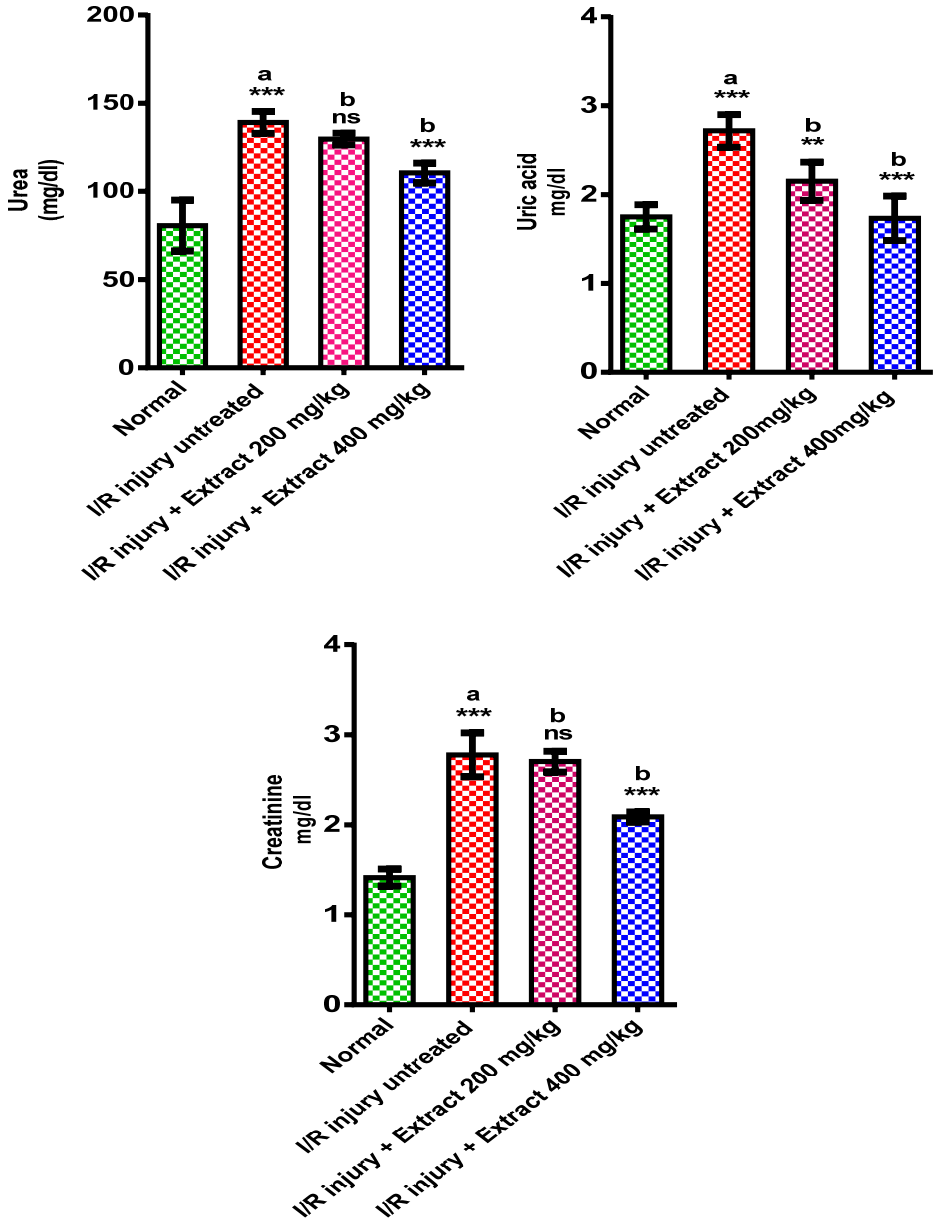
All values are expressed as mean ± S.E.M, n=6 in each group. One way ANOVA followed by Dunnett's test was used to compare experimental groups.

[a] Values are significantly different from control group; ns-non significant; $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$.

[b] Values are significantly different from I/R injury untreated group; ns-non significant; $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$.

Effect of *Citrullus lanatus* rind extract on serum urea, uric acid and creatinine in rats exposed to renal ischemia reperfusion(I/R) injury

Figure No. 7



Effect of *Citrullus lanatus* rind extract on serum urea, uric acid and creatinine in control and experimental rats exposed to Ischemia/Reperfusion induced kidney damage. Results are expressed as mean ± S.E.M, n=6 in each group. One way ANOVA followed by Dunnett's test was used to compare experimental groups. [a]Values are significantly different from control group; ns-non significant; $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$. [b]Values are significantly different from I/R injury untreated group; ns-non significant; $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$. Significant increase in activites of urea ($^{***}P<0.001$), uricacid ($^{***}P<0.001$), creatinine ($^{***}P<0.001$) were noted in Ischemia/Reperfusion induced untreated animals compared to normal animals. Ischemia/Reperfusion induced animals treated with extract (I/R injury + Extract 200 mg/kg and I/R injury + Extract 400 mg/kg) showed a significant decrease in activities of urea (200 mg/kg- ^{ns}non significant, 400 mg/kg- $^{***}P<0.001$), uricacid (200 mg/kg- $^{**}P<0.01$, 400 mg/kg- $^{***}P<0.001$) and creatinine (200 mg/kg- ^{ns}non significant , 400 mg/kg- $^{***}P<0.001$) compared to I/R injury untreated animals.

Effect of *Citrullus lanatus* rind extract on lipid peroxidation and antioxidants in rats exposed to renal ischemia reperfusion (I/R) injury

Table. 6

Group	Treatment	LPO (MDA nmole/ hr/ gm of tissue)	SOD (U/mg of protein)	CAT (Nmole of H_2O_2 consumed/ min/ of protein)	GSH (µmole of NADPH oxidized/ min mg protein)
Group I normal	0.5% CMC (2 ml/kg)	0.68 ± 0.04	1.71 ± 0.04	1.38 ± 0.07	1.28 ± 0.04
Group II I/R injury untreated	0.5% CMC (2 ml/kg)	$^{s\,a}$ 1.6 ± 0.12***	^{a} 0.88 ± 0.07***	^{a} 0.70 ± 0.06***	^{a} 0.76 ± 0.05***
Group III Treated	MECL (200mg/kg)	^{b} 0.86 ± 0.07***	^{b} 1.23 ± 0.09^{ns}	^{b} 1.33 ± 0.09***	^{b} 1.01 ± 0.04*
Group IV Treated	MECL (400mg/kg)	^{b} 0.71 ± 0.06***	^{b} 1.40 ± 0.09**	^{b} 1.46 ± 0.06***	^{b} 1.15 ± 0.05***

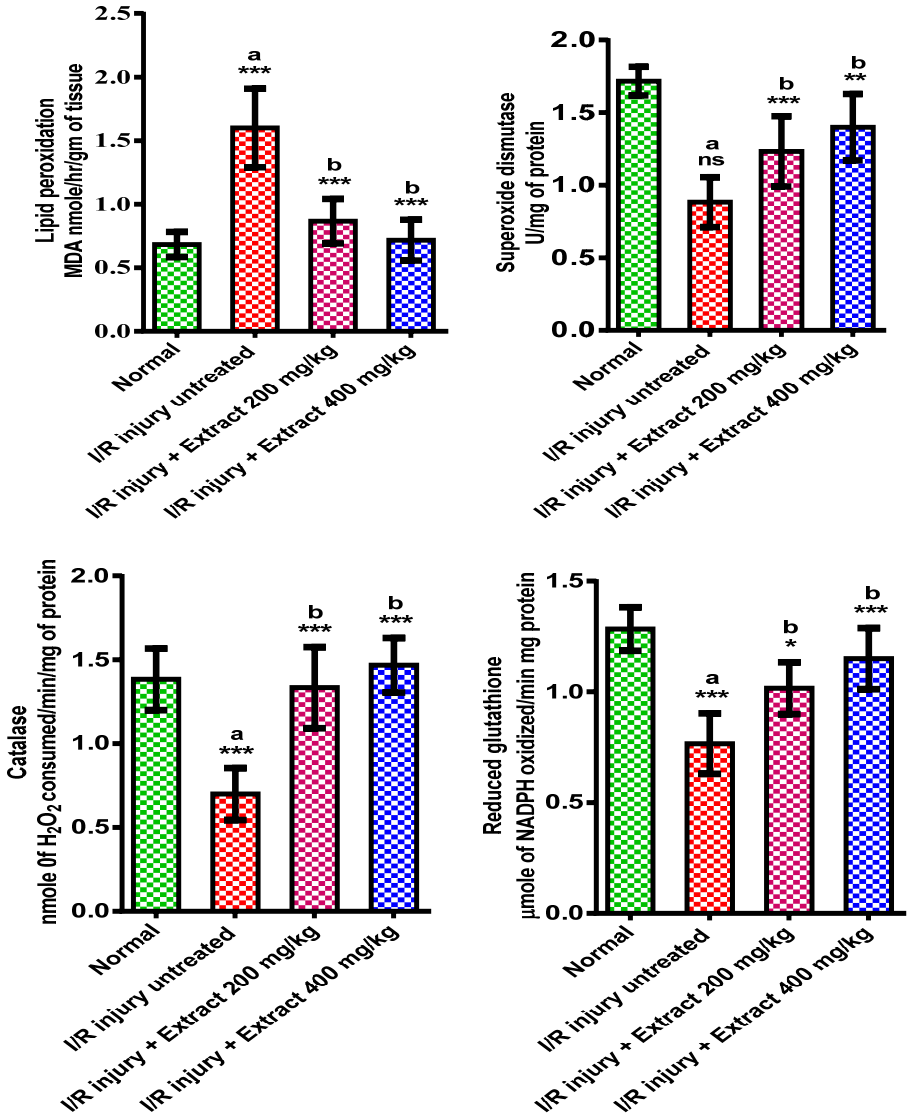
All values are expressed as mean ± S.E.M, n=6 in each group. One way ANOVA followed by Dunnett's test was used to compare experimental groups.

[a] Values are significantly different from control group; ns-non significant; $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$.

[b] Values are significantly different from I/R injury untreated group; ns-non significant; $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$.

Effect of *Citrullus lanatus* rind extract on lipid peroxidation and antioxidants in rats exposed to renal ischemia reperfusion (I/R) injury

Figure No. 8



Effect of *Citrullus lanatus* rind extract on lipid peroxidation in kidney homogenate of control and experimental animals during Ischemia/Reperfusion induced kidney damage. Results are expressed as mean ± S.E.M, n=6 in each group.

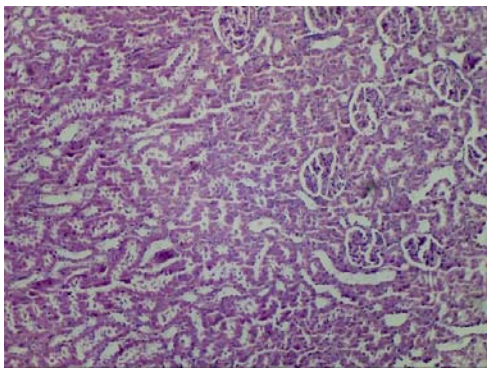
One way ANOVA followed by Dunnett's test was used to compare experimental groups. [a] Values are significantly different from control group; ns-non significant; *P<0.05; **P<0.01; ***P<0.001. [b] Values are significantly different from I/R injury untreated group; ns-non significant; *P<0.05; **P<0.01; ***P<0.001. Significant increase ($^{***}P$ <0.001) in lipid peroxidation were noted in Ischemia/Reperfusion induced untreated animals compared to normal animals. Ischemia/Reperfusion induced animals treated with extract (I/R injury + Extract 200 mg/kg and I/R injury + Extract 400 mg/kg) showed a significant decrease in lipid peroxidation levels (200 mg/kg- $^{***}P$<0.001, 400 mg/kg- $^{***}P$ <0.001) compared to Ischemia Reperfusion injury untreated animals.

Effect of *Citrullus lanatus* rind extract on the status of antioxidants in kidney homogenate of control and experimental animals during Ischemia/Reperfusion induced kidney damage. Results are expressed as mean ± S.E.M, n=6 in each group. One way ANOVA followed by Dunnett's test was used to compare experimental groups. [a] Values are significantly different from control group; ns-non significant; *P<0.05; **P<0.01; ***P<0.001. [b] Values are significantly different from I/R injury untreated group; ns-non significant; *P<0.05; **P<0.01; ***P<0.001. Significant decrease in activites of SOD ($^{***}P$<0.001), catalase ($^{***}P$<0.001), GSH ($^{***}P$<0.001) were noted in Ischemia/Reperfusion induced untreated animals compared to normal animals. Ischemia/Reperfusion induced animals treated with extract (I/R injury + Extract 200 mg/kg and I/R injury + Extract 400 mg/kg) showed a significant increase in activities of SOD (200 mg/kg- ^{ns}non significant, 400 mg/kg- $^{**}P$<0.01), catalase (200 mg/kg- $^{***}P$<0.001, 400 mg/kg- $^{***}P$<0.001) and GSH (200 mg/kg- $^{*}P$<0.05, 400 mg/kg- $^{***}P$<0.001) compared to I/R injury untreated animals.

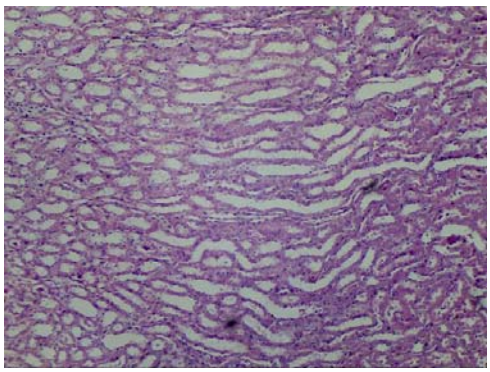
HISTOPATHOLICAL IMAGE OF KIDNEY

NORMAL

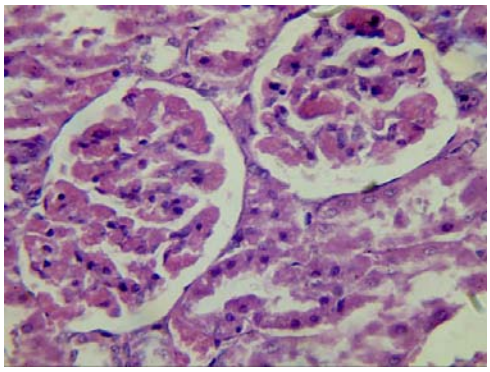
Figure No. 9



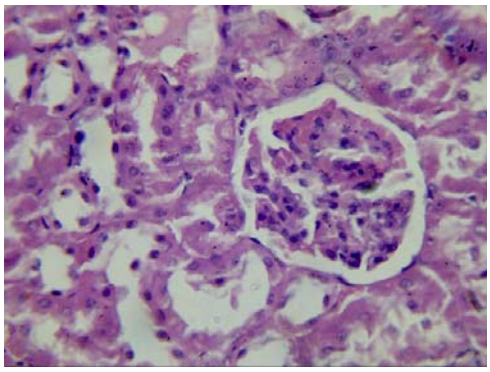
Normal cortex and medulla (10 X)



Normal interstitium (10 X)



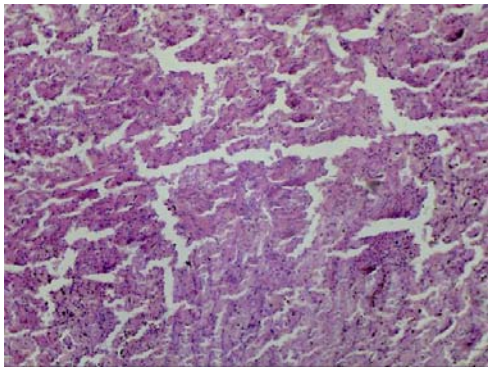
Normal glomeruli (40 X)



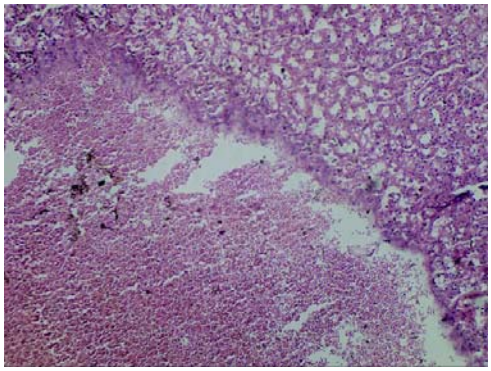
Normal glomeruli (40 X)

I/R INJURY UNTREATED

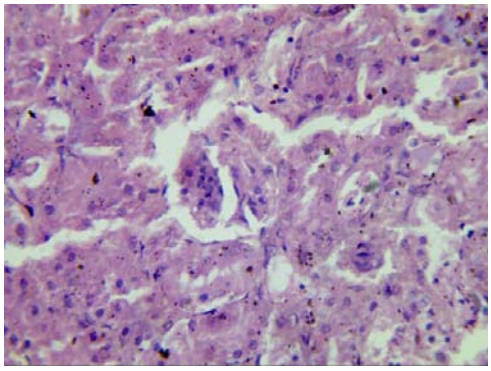
Figure No. 10



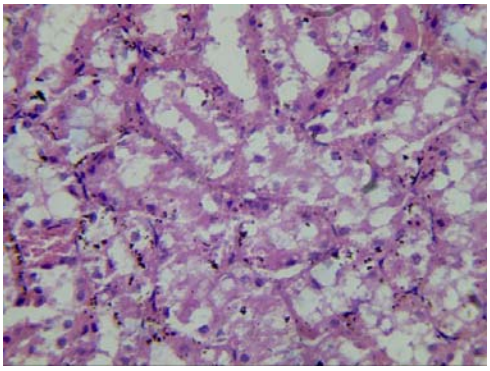
Nerosis with edema (10 X)



Large areas of hemorrhage (10 X)

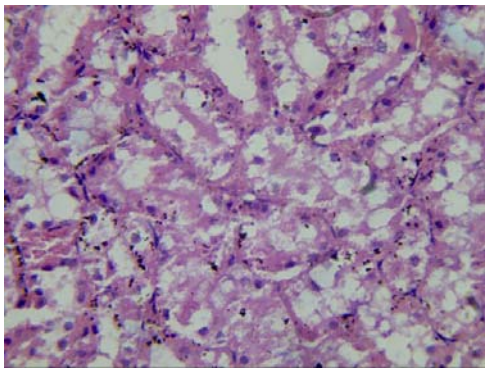


Glomeruli shows loss of shape (40 X)

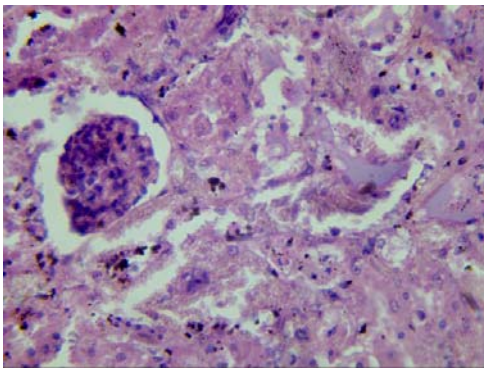


Glomeruli shows loss of shape (40 X)

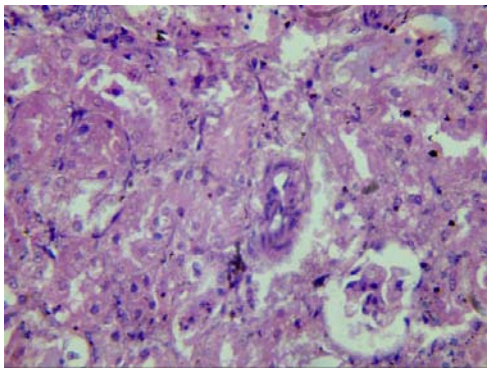
I/R INJURY UNTREATED



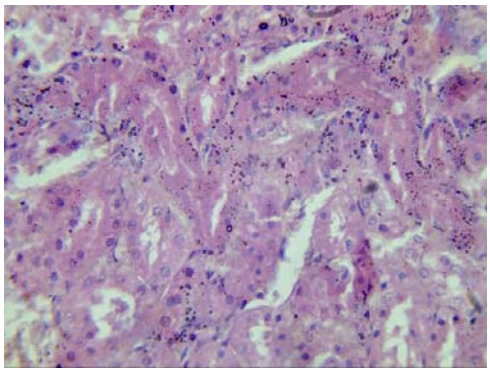
Shows dilated tubules (40 X)



Glomeruli damage, congested tubules with eosinophilic material (40 X)



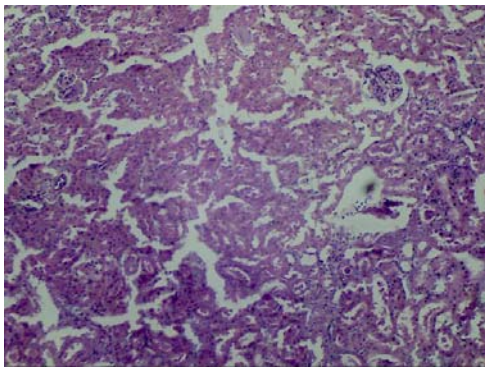
Damaged glomeruli with congested tubules (40 X)



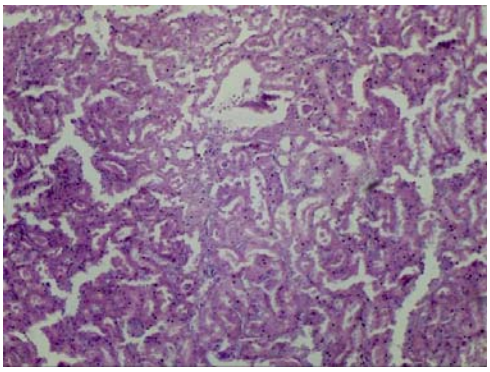
Shedding of epithelium (40 X)

I/R INJURY + EXTRACT 200 mg/kg

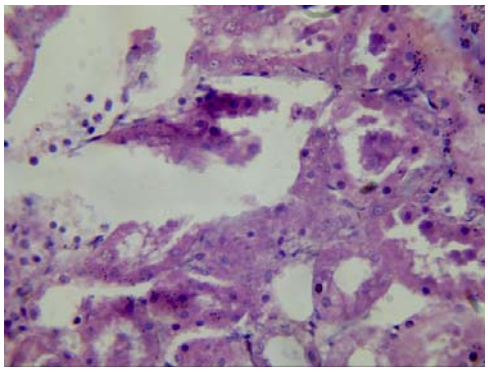
Figure No. 11



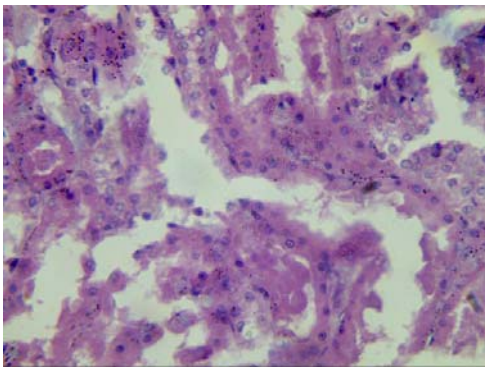
Edema with necrosis (10 X)



Glomeruli with loss of shape, necrosis (10 X)



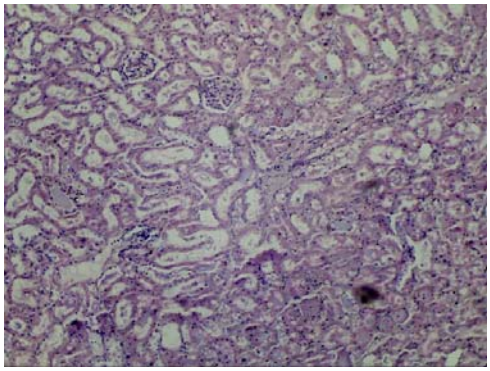
Glomeruli with loss of shape and architecture (40 X)



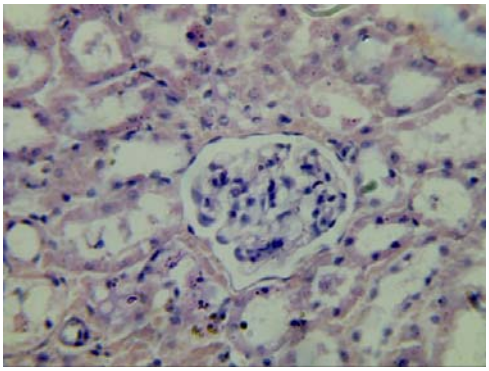
Edema with necrosis (40 X)

I/R INJURY + EXTRACT 400 mg/kg

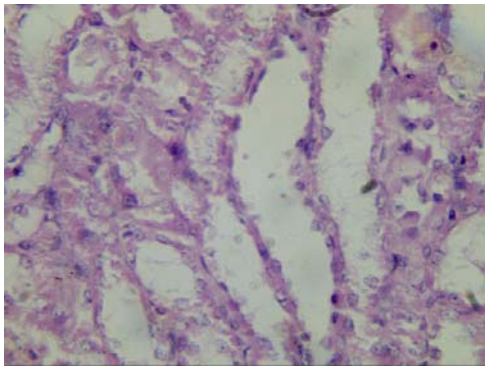
Figure No. 12



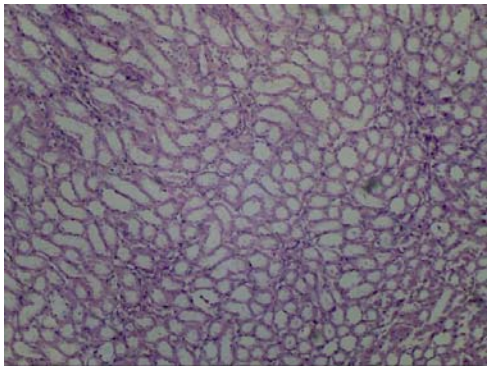
Normal glomeruli and eosinophilic material in the tubules (10 X)



Normal glomeruli (40 X)



Interstitium appear normal (40 X)



Normal PCT and DCT

Percentage yield

The percentage yield of extract obtained from extraction of powdered rind material of *Citrullus lanatus* using methanol as solvent was found to be 30.70 % w/w.

Phytochemical study

The phytochemical examination of methanol extract of *Citrullus lanatus* rind revealed the presence of carbohydrates, alkaloids, phytosterols, flavonoids, saponins, aminoacids, diterpenes, phenolics and tannins (Table 3).

Acute oral toxicity study of methanol extract of *Citrullus lanatus* rind

Acute oral toxicity study was carried out as per OECD guideline 425. From the limit test results, it was observed that the methanol extract of *Citrullus lanatus* rind was safe upto a dose level of 2000 mg/kg. There was no mortality and the experimental animals did not show any toxic effect throughout the observation period of 14 days (Table 4).

Effect of methanol extract of *Citrullus lanatus* rind on serum urea, uric acid and creatinine levels in rats exposed to renal ischemia reperfusion (I/R) injury

Rats in group II disease control exposed to renal ischemia reperfusion (I/R) injury for 60 minutes showed a significant increase ($p<0.001$) in serum urea (139.1 ± 2.55), uric acid (2.71 ± 0.07) and creatinine (2.77 ± 0.09) levels compared to group I control animals with serum urea (80.59 ± 5.91), uric acid (1.75 ± 0.05) and creatinine levels (1.41 ± 0.003). Animals in group III treated with methanol extract of *Citrullus lanatus* rind 200 mg/kg for 6 days prior to renal ischemia reperfusion (I/R) injury

showed a significant decrease ($p<0.01$) in uric acid levels (2.15 ± 0.08) compared to disease control animals. Whereas serum urea and serum creatinine levels in animals treated with methanol extract of *Citrullus lanatus* rind 200 mg/kg were statistically non-significant (ns) compared to untreated animals. Group IV animals treated with methanol extract of *Citrullus lanatus* rind 400 mg/kg for 6 days prior to renal ischemia reperfusion (I/R) injury showed a significant decrease ($p<0.001$) in serum urea (110.4 ± 2.31), uric acid (1.73 ± 0.10) and creatinine levels (2.08 ± 0.02) compared to disease control animals (Table 5).

Effect of methanol extract of *Citrullus lanatus* rind on lipid peroxidation in rats exposed to renal ischemia reperfusion (I/R) injury

The levels of lipid peroxidation in kidney of control and experimental animals are illustrated in table 6. A significant increase ($p<0.001$) in production of malondialdehyde (MDA) (1.6 ± 0.12) was observed in group II disease control animals exposed to renal ischemia reperfusion (I/R) injury for 60 minutes compared to MDA levels in kidney of group I control animals. Administration of methanol extract of *Citrullus lanatus* rind to group III and group IV animals at dose levels of 200 mg/kg and 400 mg/kg respectively for 6 days prior to renal ischemia reperfusion (I/R) injury significantly decreased the MDA levels. The MDA levels were 0.86 ± 0.07 nmole/hr/gm of tissue in animals treated with 200 mg/kg extract and 0.71 ± 0.06 nmole/hr/gm of tissue in animals treated with 400 mg/kg.

Effect of methanol extract of *Citrullus lanatus* rind on antioxidant status in rats exposed to renal ischemia reperfusion (I/R) injury

Table 6 illustrates the effect of methanol extract of *Citrullus lanatus* rind on antioxidant status in kidney of control and experimental animals. A significant decrease ($p<0.001$) in superoxide dismutase (SOD) (0.88 ± 0.07), catalase (CAT) (0.70 ± 0.06) and reduced glutathione (GSH) (0.76 ± 0.05) were observed in group II disease control animals exposed to renal ischemia reperfusion (I/R) injury for 60 minutes compared to group I normal animals with SOD (1.71 ± 0.04), CAT (1.38 ± 0.07) and GSH levels (1.28 ± 0.04). Administration of methanol extract of *Citrullus lanatus* rind to group III and group IV animals at dose levels of 200 mg/kg and 400 mg/kg for 6 days prior to renal ischemia reperfusion (I/R) injury significantly increased the SOD levels to 1.23±0.09 and 1.40 ± 0.09 ($p<0.05$ to $p<0.001$), catalase levels to 1.33 ± 0.09 and 1.46 ± 0.06 ($p<0..001$ to $p<0.001$) and GSH levels to 1.01 ± 0.04 and 1.15 ± 0.05 ($p<0.05$ to $p<0.001$) respectively compared to group II disease control animals.

Histopathology

Section of kidney from group I control animals showed normal cortex and medulla. The glomeruli, proximal and distal convoluted tubules, interstitium and vessels are unremarkable (Figure 9).

Section of kidney from group II disease control animals exposed to renal ischemia reperfusion (I/R) injury showed glomeruli with loss of shape, shrinking and increase in interstitium. Large areas of haemorrhage and edema also noted. The proximal convoluted tubules showed dilatation and shedding of epithelium indicating tubular necrosis. The distal convoluted tubules are markedly dilated and filled with eosinophilic material. Interstitium shows Congested (Figure 10).

Section from the kidney from group III animals treated with methanol extract of *Citrullus lanatus* rind 200 mg/kg for 6 days prior to renal ischemia reperfusion (I/R) injury showed some of the glomeruli with loss of shape, Shrinking and increase in interstitium (fibrosis). The proximal convoluted tubules showed dilatation and shedding of epithelium indicating tubular necrosis. The distal convoluted tubules are markedly dilated at places filled with eosinophilic material. Interstitium shows Congested (Figure 11).

Section from kidney from group IV animals treated with methanol extract of *Citrullus lanatus* rind 400 mg/kg for 6 days prior to renal ischemia reperfusion (I/R) injury showed normal cortex and medulla. The glomeruli, proximal and distal convoluted tubules, interstitium and vessels are unmarkable. Focal lymphomononuclear infiltration noted (Figure 12).

DISCUSSION

The present study demonstrates the renoprotective effect of *Citrullus lanatus* rind extract against ischemia-reperfusion induced acute renal failure. Renal ischemia is a major cause of acute renal failure and results in high rates of morbidity and mortality. Several mechanisms has been postulated to be involved in the mechanism of acute renal failure in ischemia/reperfusion injury. Ischemia reduces vasodialatory eNOS, thus compounding ischemia mediated renal injury through adversely altering the internal endothelin-1/NO balance. In the present study, *Citrullus lanatus* rind extract showed a significant renoprotective activity against ischemia/reperfusion acute renal injury. The renoprotective activity of *Citrullus lanatus* rind extract might be due to presence of citrulline, which has an important role in nitric oxide system to produce vasodialatory effect.

Generation of ROS has been postulated as one of the major factors contributing to reperfusion injury. After reperfusion and reoxgenation, the imbalance between restoration of oxygen supply and mitochondrial respiratory function results in massive generation of superoxide anion in mitochondria. Under these conditions, the defensive system, which is known as antioxidant or antioxidant enzymes, cannot prevent the escape of ROS, especially in mitochondria, and their effects on other intracellular sites. This cascade of events is known as reperfusion injury.

As a free radical generating system, lipid peroxidation has been closely related with I/R induced tissue damage. ROS attach to the polyunsaturated fatty acids in the membrane lipids and results in lipid peroxidation, which In turns impacts enzymatic

processes ,such as ion-pump activity, inhibiting transcription and repair of DNA which will ultimately result in cell death. Since MDA is a good indicator of the degree of lipid peroxidation, in present study renal MDA was measured. A significant increase in MDA content was observed during I/R induced renal injury and our results show pretreatment with *Citrullus lanatus* rind extract significantly decreased the MDA levels, implying a reduction in lipid peroxidation and cellular injury that protected the kidney against I/R induced oxidative damage .

The enhanced formation of lipid peroxides is further evidenced by decrease in activities of antioxidant enzymes in I/R induced renal tissue damage. Antioxidants constitute the foremost defense that limit the toxicity associated with free radicals SOD is said to act as the first line defense against superoxide radical generated as a byproduct of oxidative phosphorylation. SOD mediated dismutation of superoxide radical generates H_2O_2. Accumulation of excess of H_2O_2 causes toxic effects on cellular system .In this regard, catalase detoxifics H_2O_2 in to water and oxygen. Thus SOD and catalase act mutually and constitute enzymatic defense against ROS.

In the present study decrease in activities of SOD and catalase in kidney of I/R induced could be attributed to excessive utilization of enzymes in detoxification of peroxides and hydroperoxides generated during oxidative stress. Restoration in the levels of lipid peroxidation upon treatment with *Citrullus lanatus* rind extract might have resulted in the recoupment in the activities of SOD and catalase to normally. Glutathione is known to be a major low molecular weight scavenger of free radicals in the cytoplasm. GSH is found to be present in high concentration in cells, protects cells against free radical attack.GSH acts directly as free radical scavenger by donating a hydrogen atom and there by neutralizing hydroxyl radical. It reduces

peroxides and maintain protein thiols in the reduced state. Glutathione peroxidase uses GSH as a substrate to catalyze the reduction of hydroperoxide and H_2O_2. Reduced glutathione in tissues maintains the cellular levels of vitamin C and vitamin E in active form. In the present study, the decrease level of non-enzymatic antioxidant GSH observed in kidney of I/R perfusion might be due to excessive utilization of antioxidant for quenching enormous free radical produced. Treatment with *Citrullus lanatus* rind extract effectively restored the depleted levels of GSH.

Citrullus lanatus is a rich source of lycopene, a carotenoid that has been reported to reduce oxidative stress in the kidneys might be responsible for cytoprotection against oxidative stress induced by I/R injury.

Renal I/R- induced damage was associated with impaired kidney function, leading to marked increase in serum creatinine, urea and uric acid levels. Pretreatment with extract significantly decreased the creatinine, urea and uric acid level which indicates the protective effect of *Citrullus lanatus* rind extract.

In *invitro* evaluation of *Citrullus lanatus* rind extract on isolated rat thoracic aortic rings a possible involvement of the endothelium derived factors in the vasorelaxant activity of *Citrullus lanatus* rind extract can be inferred, since it is well known that the vasoconstrictor effect of α_1- adrenergic receptor agonists can be modulated by endothelium – derived relaxant factors such as endothelium derived nitric oxide and prostacyclin.

The histopathological examination of kidney provided a supporting evidence for the results obtained from *Invivo* evaluation of renoprotective activity in experimental analysis.

Conclusion

CONCLUSION

In conclusion, the findings of the current study illustrate that *Citrullus lanatus* rind extract, with its potent vasodilatory and free radical scavenging properties, seems to be a highly promising agent in protecting renal tissue against oxidative damage and in preventing renal dysfunction due to ischemia/reperfusion. The study has confirmed the presence of phytoconstituents such as aminoacids, proteins, alkaloids, phytosterols, flavonoids, saponins, diterpenes, phenolics, tannins, carbohydrate and glycosides. However, further studies should be performed to isolate the active principles responsible for nephroprotection and to elucidate the mechanism of nephroprotection.

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