1.INTRODUCTION

Everyday the kidneys filter nearly 200 litres of fluid from the blood stream allowing toxins, metabolic wastes, and excess ions to leave the body in urine while returning needed substances to the blood. Much like a water purification plant that keeps a city's water drinkable and disposes of its wastes, the kidneys are usually unappreciated until they malfunction and body fluids become contaminated. Although the lungs and skin also participate in excretion, the kidneys are the major excretory organs.As the kidneys perform these excretory functions, they also act as essential regulators of the volume and chemical makeup of the blood, maintaining the proper balance between water and salts and between acids and bases[1].

Nephrotoxicity is one of the most common kidney problems and occurs when body is exposed to a drug or toxin. A number of therapeutic agents can adversely affect the kidney resulting in acute renal failure, chronic interstial nephritis and nephritic syndrome because there is an increasing number of potent therapeutic drugs like aminiglycoside antibiotics, NSAID's, chemotherapeutic agents have been added to the therapeutic arsenal in recent years. Exposure to chemical reagents like ethylene glycol, carbon tetrachloride, sodium oxalate and heavy metals such as lead, mercury, cadmium and arsenic also induces nephrotoxicity. Prompt recognition of the disease and cessation of responsible drugs are usually the only necessary therapy. Nephroprotective agents are the substances which posess protective activity against nephrotoxicity. Medicinal plants have curative properties due to the presence of various complex chemical substances. Early literatures have prescribed various herbs for the cure of renal disorders. Coadministration of various medicinal plants possessing nephroprotective activity along with different nephrotoxic agents which may attenuate its toxicity. The term renal failure primarily denotes failure of the excretory function of kidney, leading to retention of nitrogeneous waste products of metabolism in the blood. In addition to this, there is a failure of regulation of fluid and electrolyte balance along with endrocrine dysfunction.[2]

The renal failure is fundamentally categorized into acute and chronic renal failure.[3]Acute renal failure (ARF) refers to the sudden and usually reversible loss of renal function which develops over a period of days or weeks. There are many causes for acute renal failure which

mainly includes acute tubular necrosis that commonly accounts for 85% incidence. Mostly acute tubular necrosis occurs either due to ischemia or toxins. The toxins may be exogenous or endogenous. The exogenous agents are radio contrast agents, cyclosporine, antibiotics, chemotherapeutic agents, organic solvents, acetomininophen and illegal abortifacients. Chronic renal failure (CRF) is an irrerversible deterioration in the renal function which classically develops over a period of years, leading to loss of excretory metabolic and endrocrine functions. Various causes of renal failure has been recognized like hypertension, diabetes mellitus, antineoplastic agents like cyclosphosphamide, vincristin and cisplatin.[3]

1.1 EPIDEMIOLOGY

Renal failure is one of the major complications of myeloma, found at presentation in 20% of patients and occurring in 50% of patients during the cause of disease. Only 20% of the adults with a nephritic syndrome have minimal change nephropathy and for that reason a renal biopsy is necessary to establish the type of glomerulonephritis.

Idiopathic glomerulonephritis accounts for 90% of childhood cases of nephritic syndrome and 80% in adult patients. In patients presenting with acute renal failure the proportion with acute interstitial nephritis varies from 1.5-6.5%..A recent year study (2000) from renal units and ICU in a defined geographical area of Scotland found that 131 patients per million per year required renal replacement therapy for acute renal failure.

The incidence of chronic kidney disease leading to dialysis varies worldwide: the number of patients per million population starting dialysis each year is 110 in the UK. [4]

1.2 ACUTE RENAL FAILURE

It is defined as a significant decline in renal excretory function occurring over hours or days. This is usually detected clinically by a rise in the plasma concentration of the urea or creatinine. Acute renal failure may arise as an isolated problem, but much more commonly occurs in the setting of circulatory disturbance associated with severe illness, trauma, or surgery; transient renal dysfunction.

Vascular causes of acute renal failure:

- Acute cortical necrosis
- Large vessel obstruction
- Arterial obstruction
- Venous obstruction.
- Small vessel obstruction
- Accelerated phase hypertension
- Systemic necrosis
- Glomerulonephritic and vasculitic causes of ARF
- Interstetial nephritis.
- Leptospirosis
- Hanta virus disease. [4]

1.3 CHRONIC RENAL FAILURE

It is the clinical syndrome of the metabolic and systemic consequences of a gradual, substantial and irreversible reduction in the excretory and homeostatic functions of the kidneys.

It can be difficult to recognize because the symptoms and clinical manifestations are non-specific.

1.4 CAUSES OF CHRONIC RENAL FAILURE

The most important causes of chronic kidney disease are diabetes, glomerulonephritis, hypertension and other vascular disease.

- Arteriopathic renal disease and hypertension
- Glomerulonephritis
- Diabetes
- Infective, obstructive and reflux nephropathies
- Congenital disease
- Familial or hereditary kidney disease, e.g. polycystic kidneys
- Hypercalcaemia
- Connective tissue diseases
- Neoplasms
- Myeloma
- Reflux nephropathy
- Renal bone disease is a major cause of disability in patients with terminal renal failure.[4]

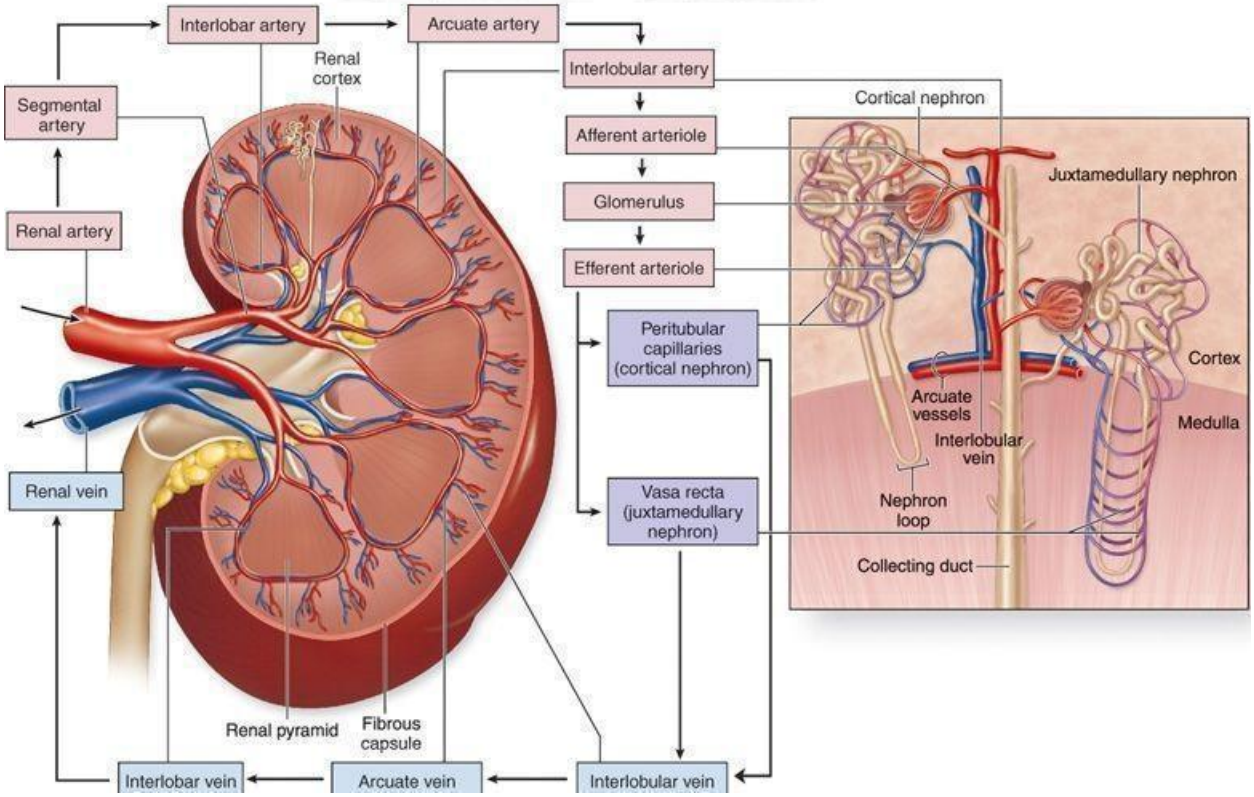


Fig I – Structure of a kidney

1.5 AGENTS WHICH CAUSES NEPHROTOXICITY

Drugs, diagnostic agents, and chemical are well known to be nephrotoxic. The following are some of the important nephrotoxic agents.

1. **Heavy metals:**
   - Mercury, arsenic, lead bismuth
2. **Antineoplastic agents**
   - Alkalating agents: Cisplastin, cyclophosphamide
   - Nitrosoureas: Streptozotocin, Carmustine, Lomustine and Semutine
   - Antimetabolites: High dose Methotrexate, Cytosine, Arabinose, high dose 6-thioguanine, flurouracil
   - Antitumor antibiotics: Mitomycin, Mithramycin, Doxorubicin
   - Biologic agents: Recombinant leukocyte and interferon.

3. **Antimicrobial agents:**
    - Tetryacycline, Acyclovir, Pentamidine, Sulphadiazine, Trimethoprin, Rifampicin, Amphotericin B
4. **Aminoglycosides:**
    - Gentamicin, Amikacin, Kanamycin, Streptomycin
5. **Miscellaneous:**
    - Radiocontrast agents: Non- steroidal anti-inflammatory agents (NSAID's), Ibuprofen, Indomethacin, Aspirin etc.[4]

1.6 NEPHROPATHIESCAUSED DUE TO DIFFERENT TOXIC MECHANISM

❖ Cisplatin Toxicity

Cisplatin is a potent antitumor drug, but its clinical use is limited due to renal toxicity. Cisplatin decreases antioxidants and anti oxidant enzymes leading to enhanced generation of reactive oxygen metabolites and lipid peroxidation. It is reported that many Indian medicinal plants show beneficial effects against renal injury. An early report indicated that nephrotoxicity might occur in as many as 50 to 75% of patients receiving this drug, and is dose limiting. It is used intensively in man, being effective in ovarian & bladder carcinoma, neuroblastoma, head and neck carcinoma, and lymphoma as well as thyroid endometrial neoplasm. However, the most significant activity is observed in testicular cancer. The clinical use of cisplatin is often complicated by nephrotoxicity, ototoxicity, gastrointestinal disturbances like nausea, vomiting and myelosuppression. Early clinical trials of cisplatin in cancer patients showed a striking incidence of persistent azotaemia and acute renal failure. Experimental studies have shown that there is an abrupt fall in the effective renal plasma flow within 3 hrs of the i.p. dose of cisplatin. It is known to be filtered by the glomeruli and concentrated in the glomerular filtrate from which it is activated in the presence of a low intra cellular chloride concentration. The low intracellular concentration of chloride facilitates the displacement of chloride by the water molecule yielding a positively charged, hydrated and hydroxylated complex. Hydration of cisplatin induces formation of mono chloromono aquodiaminoplatin or diaquodiammineplatin. These agents alkylate the purine and pyrimidine bases of nuclear material. Renal damage is seen in proximal tubular S3 portion, the distal tubule and collecting duct. Other proposed explanation of the nephrotoxicity of cisplatin include the possibility that it include generate

reactive metabolites that bind covalently to tissue macromolecules. The nephrotoxic effects might also be due to sulphydryl binding of heavy metal. A reduction in sulphydryl groups in the rat renal cortex has been demonstrated; this occurred before any significant change in renal function could be detected, suggesting that this biochemical change may be a primary event. Cell fractionations have shown that the greatest decline of sulphydryl groups occurs in the mitochondrial & cytosol

fractions; these also had the highest concentrations of platinum. A recent study found that cisplatin induced proximal tubule injury could be ameliorated by the administration of hydroxyl radical scavengers. In these studies cisplatin (5mg/kg BW) caused lipid peroxidation. The hydroxyl radical scavenger prevented acute renal failure by altering tubule damage & enhancing the regenerative response of damaged tubule cells protection from cisplatin toxicity has generally focused on providing free radical scavengers. [5]

- **Acetaminophen Toxicity**

Acetaminophen is also known as paracetamol. It is a widely used analgesic and antipyretic drug that is safely employed for a wider range of treatments. Overdose of acetaminophen in humans is

fairly common and is often associated with hepatic and renal damage. Although nephrotoxicity is less common than hepatotoxicity in acetaminophen overdose, renal tubular damage and acute renal failure can occur even in the absence of liver injury and can even lead to death in humans and experimental animals. Studies are going on throughout the world in search of protective molecules that would provide maximum protection to the liver, kidney as well as other organs and practically very little or no side effects would be exerted during their function in the body. A number of herbs are traditionally used in different countries during in response to drug or toxin induced hepatic and renal disorders. There are three pathways for acetaminophen metabolism which includes conjugation with sulfate, glucoronide and metabolism by cytochrome p450 oxidase enzyme system. 90% of ingested dose is metabolized through glucoronidation and sulfation pathway and 5% through cytochrome p450 oxidase enzyme system. Metabolism by cytochrome p450 enzyme system produces a metabolite, *N*-acetyl-*p*-benzoquinone imine (NAPQI) which is toxic to liver and kidney. In therapeutic dose, this is

rendered ineffective by reduced glutathione, an antioxidant compound in the liver and NAPQI-reduced glutathione is excreted by kidney. In acetaminophen overdose, sulfation and glucoronidation pathways become saturated. The amount and rate of formation of NAPQI is greatly increased, depleting body's reduced glutathione stores and outstripping its capability to make new glutathione. NAPQI then binds covalently with cells causing their death, resulting in liver and kidney dysfunction. Indeed

several biological compounds with antioxidant properties proved effective in protecting the kidneys against deleterious effects of acetaminophen overdose.[5]

- **Gentamicin Toxicity**

Aminoglycoside antibiotics have been widely used for gram-negative bacterial infections. However, their nephrotoxicity and ototoxicity are the major limitations in clinical use. Among several aminoglycoside antibiotics, the grade of nephrotoxicity has been reported to be in the following order as, neomycin > gentamicin > tobramycin[5]. Gentamicin is still considered to be an important aminiglycoside antibiotic against life threathening bacterial infections. Gentamicin is known to cause a number of morphological, metabolic and functional alterations in the kidney. The specificity of gentamicin nephrotoxicity is apparently related to its accumulation in the renal proximal convoluted tubules leading to tubular necrosis. The adverse interaction of the drug with critical intracellular processes leads to renal cortical phospholipidosis disrupting functions of brush border membrane (BBM) and other organelles, eg mitochondria, lysosomes and microsomes. Recently we have observed that Gentamicin administration caused marked alterations in the activities of enzymes of carbohydrate metabolism, BBM and oxidative stress and kidney. Gentamicin is known to generate reactive oxygen species (ROS) associated with an increase in lipid peroxidation (LPO) and decrease in antioxidant enzymes in the intestine and kidney. This is considered as one of the important mechanisms for Gentamicin induced nephrotoxicity and other deleterious effects.[6]

1.7 PATHOPHYSIOLOGY

- **Oxidant mechanisms in Gentamicin nephrotoxicity:**

Aminogycoside antibiotics cause acute renal failure, these are used to suppress gram negative bacteria. Reduction of oxygen sequencely leads to the generation of superoxide anion. These acts as mediators for gentamicin nephrotoxicity. Gentamicin enhance the formation superoxide anion and hydrogen peroxide. Superoxide anion and hydrogen peroxide with metal as a catalyst gives hydroxyl radical. Gentamicin release iron from renal cortical mitochondria and enhance generation of hydroxyl radical. Superoxides, oxygen metabolites and iron chelators are affective in renal failure by gentamicin. Thes results will prove as evidence for in- vitro studies. These studies are also helpful in understanding other aminoglycosides including streptomycin.[6]

- **MAPK (Mitogen activated protein kinase):**

TNF- alpha, tumor necrosis factor- alpha, PARS, poly (ADP- ribose) synthesase or poly (ADP- ribose) polymerase, NFkB, nuclear factor kappa B, TGB-b, transforming growth factor. Pathological role of reactive oxygen species in the induction of gentamicin nephrotoxicity ICAM-1, intercellular cellular adhesion molecule- 1, MCP- 1, monocyte chemo attractant protein-1, O2, suoeroxide radical, OH, hydroxyl radical, H2O2, hydrogen peroxide.[6]

1.8 GENERAL FEATURES OF AMINOGLYCOSIDE NEPHROTOXICITY

Nephrotoxicity induced by aminoglycosides manifests clinically as non oliguric renal failure, with a slow rise in erum creatinine and a hypoosmolar urinary output developing after several days of treatment. Aminoglycosides are nephrotoxic because small proportion of the administered dose (5%) is retained in the epithelial cells lining the S1 and S2 segments of the proximal tubules after glomerular filtration. Aminoglycosides accumulate by these cells are mainly localized with endosomal and lysosomal vacuoles but are also localized with the Golgi complex. They elicit an array of morphological and fuctional alterations of increasing severity.[7]

- **Clinical doses and effects:**

After administration of doses to humans or animals (typically 10 to 20 mg/kg) within few days aminogylcosides stimulate changes in lysosomes of proximal tubular cells resulting accumulation myeloid bodies. Changes brings tubular dysfunction. It is characterized by a fall in creatinine elimination. Recovery is seen upon drug withdrawing. Correlation to bring between clinical signs and rate of progression is difficult to establish. This is because of large interpatient variations. In animals, alterations in tubular connected with focal necrosis and apoptosis, peri tubular cell proliferation, phospholipiduria and cast clearance. In humans, signs are seen after overt renal failure.[7]

- **High dose in animals and its effects:**

High doses are given to animals for immediate development of cortical necrosis and renal dysfunction. Large number of structural, metabolic, and functional changes, is observed in tubular cells responsible for renal dysfunction. Changes observed in the apical membrane mediated by the drug during uptake of proximal tubular cells. Inhibition of protein synthesis and alteration of gene expression and mitochondria involve uptake and intracellular distribution of drug to the corresponding receptors.[7]

- **Clinical features:**

Non oliguric acute renal failure is the common clinical representation. Urinary manifestations are increase in urine outflow and enzymuria.Enzymuria is the elimination nin the urine fragments lysosomal enzymes. The sign of renal failure is slow and the serum creatinine becomes lower than other acute renal failures. Serum creatinine, blood urea nitrogen increases from a week to 10 days after initial medication of aminiglycosides therapy. The renal function failure occurs after the therapy in more than 50% cases. Recovery is slow from aminogylcosides, usually taking 4- 6 weeks. Majority of patients recover but several risk factors alter the clinical

presentation. In chronic kidney disease patients, recovery is incomplete. Tubular dysfunction, electrolyte abnormalities occur. Nephrotoxicity is common for aminoglycoside therapy. Pre estimation of nephrotoxicity is known by urinary excretion of enzymes. Non- oliguric acute renal failure observed in patients include tubular dysfunction. Azotaemia and increased serum creatinine levels are seen in nephrotoxicity. This reflect depression of GFR (after therapy of minimum 7 days) leading to tubular cell necrosis. Pathological changes of proximal tubule can be observed in renal biopsy. Electron microscopy reveals myeloid bodies in lysosomes. Lysosomal lesions are seen in 1- 2 days of medication and increase in size with prolong medication.[7]

Nephrotoxicity and its pathogenesis is understood from rat studies. Dose of drug given to the rat relative to the body weight is larger when compared to human being whereas when compared to body surface it is same. From these studies we found that nephrotoxicity is linked to transport and aggregation of drugs by renal tubular cells. On parenteral administration, aminoglycosides are excreted in the urine without changing its form. Small fraction of drug is retain in the proximal tubular cells, transport mechanism will exhibits kinetics in which the initial step involves binding caionicaminoglycoside to membrane receptors, anionic phospholipids then follows uptake of cell results in concentration in lysosomes. Small amount of drug enters into the cell through basolateral membrane. This accumulation results nephrotoxicity.[7]

1.9 ROLE OF HERB IN NEPHROTOXICITY

In the recent years many researches have examined the effects of plants used traditionally by indigenous healers and herbalist to support kidney function and treat diseases of kidney. In most cases, research has confirmed traditional experience and wisdom by discovering the mechanism and mode of action of these plants as well as reaffirming the therapeutic effectiveness of certain plants or plant extracts in clinical studies[8]. These medicinal plants have curative properties and therapeutic values due to the presence of various complex phytochemical

compounds. This traditional medicines are assuming greater important because of its effective, safer, locally available and no side effects. *G .pedunculata*, a member of the family Clusiaceae is locally and commonly available plant in India. It is commonly called as 'sohdanei' in Khasi and 'amalvet or avetasa' in hindi. This plant has been shown hepatoprotective, antiscorbutic, antioxidant and natural antiobese agent. In this study, reported the curative properties of the medicinal plant *Garcinia pedunculata* against nephrotoxicity induced by gentamicin in rats and other related aminoglycoside antibiotics. Nephroprotective activity was confirmed by examining the biological tests for urea, uric acid, creatinine, BUN (blood urea nitrogen), sodium, potassium and protein level in blood and urine and histopathological studies.[8]

2.LITERATURE REVIEW

2.1 LITERATURE REVIEW ON NEPHROPROTECTIVE ACTIVITY:

- **Sara A et. Al (2008**) reported that Gentamicin is an effective aminoglycoside antibiotics against severe infections but nephrotoxicity and oxidative damage limits its long term clinical use. Green tea (polyphenols) have shown strong chemopreventive and chemotherapeutic effects against various pathologies. Green tea prevents gentamicin nephrotoxicity by virtue of its anti oxidative properties. Serum parameters and enzymes of oxidative stress, brush border membrane (BBM), and carbohydrate metabolism were analysed. Gentamicin increased serum creatinine, cholesterol, blood urea nitrogen (BUN), lipid peroxidation (LPO), and suppressed suoeroxidedismustase (SOD), and catalase activities in renal tissues. However, green tea given to gentamicin rats reduced nephrotoxicity parameters, enhanced antioxidant defense and energy metabolism. In conclusion, green tea ameliorates gentamicin elicited nephrotoxicity and oxidative damage by improving antioxidant defense, tissue integrity and energy metabolism.[9]

- **K. padmalochana and M. S. Dhana. Rajan (2015)** reported the potential nephroprotective active of aqueous, ethanol, and acetone extract of *Andrographispaniculata*leaves. Renal failure was induced by gentamicin which was orally administered. After oral administration for 10 days, serum levels of urea, uric acid, creatinine and total protein were assayed. The histological structure of renal was observed using light microscope. Gentamicin treated animals showed acute tubular necrosis due to the injury in kidney. In aqueous, ethanol, and acetone extract treated animals showed histopathological changes in renal revealed the nephroprotective activity of *A. paniculata* leaves. It is concluded that ethanol extract of *A. paniculata* was more sutable for nephroprotection action against gentamicin induced renal failure.[10]

- **AA Adeneye et. Al (2008)** reported the effects of pretreatments with single daily oral 100 – 500 mg/kg/day of the root aqueous extract of *Harunganamadagascariensis* in acute and repeated dose acetominiphen nephrotoxic rats for 24 hours and 14 days, respectively. It was investigated by using serum urea, uric acid and creatinine. Effects of the extract pretreatments on the hematological and renal histological profile in acetaminophen nephrotoxic rats were also evaluated. Results showed that treatment with intraperitoneal acetaminophen for 24 hours and 14 days induced elevations in serum concentration of urea, uric acid and creatinine.and alterations in the hematological parameters in acute and repeated dose acetominiphen nephrotoxic rats. However, pretreatments with graded oral doses of the extract significantly attenuated elevations in the serum concentrations of urea, uric acid and creatinine and improved necrosis in acetaminophen nephrotoxicity. Thus, the overall results showed that *Harungana* extract protects against acetaminophen nephrotoxicity.[11]

- **AA. Adeneye and AS.Benebo (2008)** reported the protective effects of the leaf and seed aqueous extract of *Phyllanthusamarus* in acetaminophen and gentamicin induced nephrotoxic rats. In the acetaminophen nephrotoxic rats there is attenuated elevations in the serum creatinine and blood urea nitrogen levels as well as, attenuation of acetaminophen induced tubolonephrosis. Similar effects were also recorded in the gentamicin model of acute renal injury. Results suggest that the nephroprotective effect of *Phyllanthusamarus* could be due to the inherent antioxidant and free radical scavenging principle contained in the extract.[12]

- **Nasim A. Begum et. Al (2006)** reported that n- hexane extract of *Nigella sativa* ameliorates gentamicin induced nephrotoxicity in rats. Gentamicin was administered and evaluated biochemically which significantly increase serum creatinine and serum urea. The n- hexane extract of *N. sativa* was administered as pre, post and concomitant treatment for 7 days in the nephrotoxic rats. Statistically significant amelioration in all biochemical parameters was observed in the n- hexane extract of *N. sativa* treated

  nephrotoxic rats, which was more evident in the post- treatment group than the pre and concomitantly treated group. It is suggested that some ingredients contained in the n-

hexane extract of *N. sativa* effected in ameliorating the signs of nephrotoxicity and that the specific active principle of the n - hexane extract of *N. sativa* is responsible for this amelioration.[13]

- **Talib Hussain et. Al (2012)** reported the nephroprotective potential of *Solanum xanthocarpum*fruit extract against gentamicin induced nephrotoxicity and renal dysfunction. In this method plasma and urine urea and creatinine, kidney weight, urine output, blood urea nitrogen, renal enzymatic and non- enzymatic antioxidants and lipid per oxidation was evaluated along with histopatological investigation in various experimental groups of rats. It was observed that gentamicin treatment induced significant elevation in plasma and urine urea and creatinine, kidney weight along with decrement in urine output and renal enzymatic and non- enzymatic antioxidants. *S. Xanthocarpum*extract treated to gentamicin treated rats recorded significant decrement in plasma and urine urea and creatinine, renal lipid peoxidation along with significant increment in renal enzymatic and non enzymatic antioxidants. Histological observations of kidney tissues too correlated with the biochemical observations. These findings supports that *S. xanthocarpum* fruit extract acts in the kidney as a potent scavenger of free radicals to prevent the toxic effects of Gentamicin both in the biochemical and histopathological parameters.[14]

- **Uzma Shaheen et. Al (2014)** reported the nephroprotective effects of different doses of aqueous extract of *Foeniculumvulgare* seed and *Solanum nigrum* fruit and their mixture on gentamicin nephrotoxicity in albino rabbits. In this study a total of 54 adult healthy male albino rabbits were divided into nine groups. Blood were taken from all the group at day 21 and concentration of serum urea, creatinine, albumin, and catalase were determined. Histopathological evaluation of kidney was also determined at day 21. Gentamicin induced oxidative stress and caused structural changes in the kidneys. The

  aqueous extract of *Foeniculumvulgare* seeds, *Solanum nigrum* fruit and their mixture significantly prevent renal damage by normalizing increased levels of renal markers. Mixture of both plants at high doses exhibited improved nephroprotective and anti oxidant activities. Hence it is suggested that ameliorative effect of aqueous extract of

F. vulgare, S. nigrum and their mixture against gentamicin induced kidney damage maybe attributed to their antioxidant properties. [15]

- **Sachin Chandavarkar et.al (2016)** reported the nephroprotective activity of different extract of whole plant of *Biophytumsensitivum* in Wistar albino rats. Elevation of urea and creatinine levels in the serum was taken as the index of nephrotoxicity. Histopathological examinations of kidney was also carried out. The findings revealed that methanol and aqueous extracts of *Biophytumsensitivum* possesses nephroprotective activity. The elevations of serum urea and creatinine produced by gentamicin were considerably reduced and showed histopathological changes in the kidneys. The study concluded that *Biophytumsensitivum* possess nephroprotective activity.[16]

- **Suji arivazhagan J. J and Vimalastalin R. (2014)** reported the protective effect of *Aristolochia indica* leaf extract on gentamicin induced nephrotoxicity in rats using biochemical approaches. Nephrotoxicity was assessed by measuring the abnormal levels of serum creatinine, urea and sodium and decreased level of protein and potassium. The antioxidant defence enzymes superoxide dismutase (SOD), gluthione peroxidase (GPx) and catalase (CAT) of kidney tissue were also measured at the end of the treatment. Treatment with *Aristolochia indica* leaves extract restored the levels of serum creatinine, urea, sodium, protein and Potassium. Significantly it also increased the antioxidant defence enzymes levels of SOD, GPx, CAT ontreatment with *Aristolochia indica.* The results suggested that an *Aristolochia indica* leaf has the potential in preventing the nephrotoxicity induced by gentamicin.[17]

- **Rajneesh Kumar Singh et. Al (2014)** reported the nephroprotective activity of *Menthaarvensis* in cisplastin induced nephrotoxicity in sprague- dawley rats. The *M. arvensis* hydro alcoholic extract (MAHE) was administered orally at two dose level. The kidney function test like estimation of serum creatinine, total protein, blood urea nitrogen, oxidative stress study (estimation of superoxide dismustase) activity, glutathione content, and lipid peroxidase (LPO) and histological studies were also conducted. MAHE was found effective which was evidence by decrease in serum creatinine, total protein, BUN, urea, LPO, and increased in SOD activity. Histopathological study was also confirmed the nephroprotective action of MAHE.

Present investigation revealed that *M. arvensis* showed nephroprotective effect on cisplastin nephrotoxicity in sprague- dawley rats which may be due to the presence of flavonoids and other related compounds.[18]

- **M. Aparna Rama Laxmi Devi et. Al (2016)** reported the nephroprotective activity of ethanolic extract of *Annona reticular* in gentamicin and cisplastin induced nephrotoxicity in rats. Nephrotoxicity in gentamicin is indicated by increased in the concentration of serum urea, creatinine, Uric acid, total protein and urine urea, Uric acid and creatinine. In cisplastin treated group concentration of serum urea, creatinine, Uric acid, total protein and urine urea, Uric acid, creatinine were considerably increased which indicates severe nephrotoxicity. It is concluded that the ethanolic extract of*Annonareticulata* showed nephroprotective activity in both Gentamicin and cisplastin induced nephrotoxicity due to the presence of therapeutic phytoconstituents.[19]

3. PLANT PROFILE

3.1 LITERATURE REVIEW ON *GARCINIAPEDUNCULATA*:

- **Scientific Name:***Garcinia pedunculata*

- **Family**: Clusiaceae

Fig II: Fruits of *Garcinia pedunculata*

- **Taxonomical classification:**

Kingdom: Plantae

Division: Tracheophyta

Class: Magnoliopsida

Order: Malpigliales

Family: Clusiaceae

Genus: Garcinia

Species: *G. pedunculata*

- **Binomial name:**

Garcinia pedunculata

- **Vernacular name:**

  Hindi: Amalvet or Avetasa

  Assamese: Borthekera

  Bengali: Thaikal

  Khasi: Sohdanei

3.2 BOTANICAL DESCRIPTION

Garciniapedunculata is an evergreen tree related related to the more familiar mangostee(*Garcinia mangostana*). The tree is endemic to the south eastern regions of Asia such as parts of Myanmar and north eastern parts of India. The tree has a fluted trunk with short spreading branches. Leaves are lanceolate with prominent mid ribs. Male flowers are light green in sparsely flowered panicles, the female flowers are solitary. The fruit is round with a diameter ranging between 8cm and 12cm. It has a juicy interior with edible arils.

3.3 RESEARCH ON THE PLANT

- **Hepatoprotective activity:**

Ravi Mundugaru et. Al (2014) reported the hepatoprotective activity of fruits of *Garciniapedunculata* in paracetamol-induced liver toxicity in rats. Paracetamol-induced hepatotoxicity was evaluated by an increase in serum transaminases and alkaline phosphatase activity. Histopathological observation showed extensive disturbance in the liver cytoarchitecture in comparison to normal control liver sections. Pre-treatment with aqueous extract of fruits of *G. pedunculata*prevented the paracetamol-induced increase in serum transaminases, alkaline phosphatase and histopathological changes. Based on the above observation it can be concluded that *G. pedunculata* pretreatment exhibited significant hepatoprotective activity against paracetamol-induced hepatotoxicity**.** [20]

- **Anti - oxidant activity:**

T Mudoi et. Al (2012) reported the antioxidant properties of the dried pulp of *Garciniapedunculata*(DPGP). Antioxidant activity of the methanolic extract of DPGP with reference to standard antioxidants have been investigated employing various well-established in vitro methods i.e. 1, 1-diphenyl-2- picrylhydrazyl (DPPH) radical scavenging activity, H2O2 radical scavenging activity, reducing power and in vitro lipid peroxidation. Chemical composition analysis of DPGP revealed that it is one of the rich sources of ascorbic acid, phenolics and flavonoid compounds. FTIR analysis of DPGP revealed presence of some functional groups like carboxylic acids, amines, amides, lactone, phenols and carbohydrate which demonstrates that DPGP may be rich sources of alkaloids, polyphenolic compounds, quinines, amino acids etc. DPGP extract showed potential antioxidant activity against DPPH and H2O2 free radicals. Besides DPGP extract inhibited the lipid peroxidation induced by Fe2+-ascorbate in rat liver homogenate in a dose dependent manner. Total reducing-power assay revealed the potential reducing power of DPGP. Phenolics and ascorbic acid might contribute to its free radical scavenging potential. Trace elements like iron, copper, potassium and zinc were detected and it was found that DPGP may be a good source of iron. So DPGP might be used as an economical source of natural antioxidants. [21]

- **Anti- fungal and anti oxidant activities:**

Rahul Sarma Et. Al (2015) reported the antioxidant and antifungal activities of polyphenol-rich extracts of the dried fruit pulp of *Garciniapedunculata*(GP) and *Garciniamorella*(GM) to determine their traditional claims of therapeutic activity against certain diseases. The method is carried out by analysing the total phenolic (TP) and flavonoid (TF) contents of the extracts which were performed by Folin-Ciocalteau and Arvouet-Grand methods. The antioxidant activity of the extracts was determined by 1,1-diphenyl-2-picrylhydrazyl (DPPH), hydrogen peroxide (H2O2) free radical scavenging activity, reducing power and in vitro lipid peroxidation (LPO). Antifungal activity was evaluated by agar-well diffusion method while mineral content was evaluated by atomic absorption spectrophotometry (AAS). Significant amounts of TP (5.87 ± 0.06 and 5.46 ± 0.02 mg catechin eqivalents/g) and TF (5.61 ± 0.16 and 3.69 ± 0.04 mg quercetin equivalents/g) were found in the cold water (CW) extracts of GP and

GM, respectively, along with DPPH free radical scavenging activity (50 % inhibitory concentration (IC50) = 3.53 ± 0.04 and 1 ± 0.03µg/mL) and H2O2-radical scavenging activity (IC50 = 1.4 ± 0.02 and 1.44 ± 0.01 µg/mL). Results indicated that the CW extracts of GP and GM were potent reducing agent than the HW extracts. CW extract of both species prevented in vitro LPO (IC50= 42 ± 0.01 and 30.36 ± 0.03 µg/mL) significantly. The antifungal activity of GP and GM extracts against some human dermatophytes was high. High concentrations of K and Fe were found in the extracts. It is concluded that GP and GM extracts have great potential as a source for useful antioxidant and antifungal agents.[22]

- **Ethanopharmacological survey of *Garcinia pedunculataRoxb:***

Rahul Sharma and Rajalakshmi Devi (2015) reported the ethnomedicinal use of *GarciniapedunculataRoxb*fruit in six different districts of Assam of Northeast region of India. Gastrointestinal diseases has been a cause of concern mostly in the rural parts of developing countries worldwide. The rural Assam is predominantly inhabitated by tribal people and they are primitive indigenous community and most of them are also socio- economically backward. These people have been traditionally using natural medicine for curing of different diseases instead of allopathic medicines. So open ended and semi structured questionnaire were prepared and distributed among different sections of people. In this study, total 2,600 samples at random were collected from six districts of Assam and out of that 1,967 numbers of people (75%) use *Garciniapedunculata*fruit and they consider it as a healer of dysentery, diarrhoea and jaundice. The present study reveals some important facts like popularity of gastrointestinal diseases for treatment of gastrointestinal diseases, distribution of *Garciniapedunculata* in different districts of Assam, gradual extinction of *Garciniapedunculata*due to various threats which will create awareness among different communities of *Garciniapedunculata*for future use.[23]

- **Novel value added products prepared from fruits of *Garcinia pedunculata*Roxb**

C. S. Biswas et.al (2017) reported that *Garciniapedunculata*Roxb. ex Buch.-Ham is widely known as Borthekera in Assam, an important fruit of Northeast India under the family Clusiaceae. *Garciniapedunculata* has dietary importance and widely utilized in the preparation of fish curries by the people of Assam. It has a number of medicinal properties and used as an

antiscorbutic, astringent and antidysenteric. Due to its high Hydroxycitric acid (HCA) content, it is believed to be useful as natural anti obese agent. In spite of such enormous health benefits, the fruits are underutilized due to their seasonal availability and very short shelf life. Therefore, it is necessary to prepare more value added products from these fruits to take their benefits in off season. In the present work, an attempt has been made by producing a variety of Garcinia fruit products applying modern processing techniques blending with traditional knowledge. This will help in increasing the intensity of usage of this fruit and thereby reduce lost due to rot/damage of ripen fruits. The study also evaluated the shelf life and economic qualities of the prepared products. The products prepared from *G. pedunculata* in this study were having potentiality to reproduce as good quality consumer products and may be an income source for village dwelling communities.[24]

4. AIM AND OBJECTIVE

Nephrotoxicity is one of the most common kidney problems and occurs when body is exposed to drug or toxin. A number of therapeutic agents can adversely affect the kidney resulting in acute renal failure, chronic interstitial nephritis, and nephritic syndrome because increasing number of potent therapeutic drugs like aminoglycoside antibiotics, chemotherapeutic agents and NSAIDS. Nephroprotective agents are the substances which possess protective activity against nephrotoxicity. Medicinal plants like *Garciniapedunculata*traditionally use to protect nephrotoxicity by boiling three to four pieces of dried fruit pulp of the plants and taken it after cooling it. Thus in this study i have plan to use the dried fruit pulp of *Garciniciapedunculata*which possess nephroprotective activity on Gentamicin induced nephrotoxicity.

4.1 PLAN OF WORK

I. **PHASE - I**

- Literature survey

II. **PHASE - II**

- Collection and authentication of plant
- Extraction of plant material
- Phytochemical analysis

III. **PHASE – II**

- Toxicological assessment
- Acute toxicity study

IV. **PHASE - IV**

- protective effect of ethanolic extract fruit of ***Garcinia pedunculata*** on gentamicin induced nephrotoxicity
- Estimate the serum and urine parameters
- Histopathological studies.

V. **PHASE - V**

- Compilation of data and conclusion

5.MATERIAL AND METHODS

5.1 COLLECTION OF THE PLANT

The fresh and matured fruits was collected from Ri Bhoi district Meghalaya. The plant was identified by its vernacular name and authenticated by Dr. R. Murugan scientist Botanical Survey of India Coimbatore 641003.

5.2 CHEMICAL AND REAGENTS

Matured fruits of *Garcinia pedunculata*, Ethanol, Mayers reagent, Fehling's A and B solution, ferric chloride, sodium hydroxide, sulphuric acid, hydrochloride acid, mercuric chloride, nitric acid, gentamicin, (Himedia labs Pvt. Ltd.) ethyl ether and formalin.

5.3 PREPARATION OF THE EXTRACT

The freshly fruits were collected and cut it into small pieces and was dried for two weeks under the sunlight. The dried fruit was pulverised to fine powder and 150gm was extracted with 1000ml ethanol in Soxhlet apparatus for two days. The extract was concentrated by distillation and then the solvent was evaporated to dryness on water bath.

5.4 YIELD AND COLOUR DETERMINATION

The colour of the extract was observed by naked eye. The yield of the extract was determined using the following formula

% yield = (weight of the extract / weight of powder taken)× 100

5.5 PRELIMINARY STUDIES

Small amount of the ethanolic extract of dried fruit pulp of *Garciniapedunculata*was investigated to find the presence of different phytochemicals. To determine the presence of phytochemicals standard methods are used.[25]

Table I: Preliminary studies of different phytochemicals

Sl. No	Phytoconstituents	Name of the test	Procedure	Inference
1	Alkaloids	Mayer's test	1ml of extract + add 1ml of Mayer's reagent and add far drop of iodine solution	Formation of yellow colour
2	Terpenoids	-	1ml of extract + 1ml of conc. H2SO4, water bath for 2- 4 mins	Formation of greyish colour
3	Phenol and tannins	Ferric chloride test	1ml of extract + 1ml of ferric chloride	Formation of blue green or black colour
4	Carbohydrates (sugar)	Fehling's test	1ml of extract + 1ml of Fehling's A and B solution, water bath for 2 - 4 mins	Formation of red colour
5	Saponins	Froth formation test	1ml of extract + 1ml or 2ml of distill water, shake well	Formation of 1cm foam layer
6	Flavonoids	Shinoda test	1ml of extract, add few fragment of magnesium ribbon +	Appearance of pink scarlet colour

			few drops of conc. HCL	
7	Quinines	-	1ml of extract, add 1ml of 2 % sodium hydroxide	Formation of blue green or red colour
8	Proteins	Millon's test	1ml of extract, add far drop of mercuric acid or nitric acid	Formation of yellow colour
9	Steroids	Salkowski test	1ml of extract, add 1ml of chloroform + 1ml of conc. H2SO4 siderwise	Red colour produce at the lower chloroform layer

5.6 EXPERIMENTAL ANIMALS AND THEIR CARE

Young adult Wistar rat (120- 150 gm) of either sex and Swiss albino mice of either sex (25 - 30gm) were procured from the small animals breeding station, Mannuthy, Kerala, India. The animals were housed in a polyethylene cages under standard environmental conditions (12h dark / 12H light cycles, temperature, 25^0C 35-60% humidity, air ventilation), and fed with standard rat chow and water *ad libitum.* The animals were acclimatized to the environment for two weeks prior to experiment use. The animal experiments were conducted according to the guidelines prescribed by Animal Welfare Board and with prior approval of animal ethical committee.

5.7 APPROVAL OF PROTOCOL

All the experimental procedures and protocols used in this study were reviewed and approved by the Institutional Animal Ethical Committee (IAEC) of RVS College of Pharmaceutical Sciences, Sulur, Coimbatore constituted under Committee for Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment and Forests Government of India (Reg. No. 1012/PO/c/CPCSEA). Ethical guidelines were strictly followed during all the experiments.

1.7 TOXICOLOGICAL EVALUATION

- **Acute toxicity studies**

Acute toxicity studies was performed according to Organisation for Economic Co- operation and Development (OECD) guideline 423.[26] Swiss albino mice of either sex were divided into three groups with six animals each. Dried fruit extract of *Garcinia pedunculata* was administered orally as a single dose to mice at different dose levels of 50, 200 and 2000 mg/kg body weight. Animals were observed periodically for general behavioral changes, symptoms of toxicity and death within the first four (crucial) hours and within 24hours and then daily for 14 days.

5.8 EXPERIMENTAL INDUCTION OF GENTAMICIN AND THEIR TREATMENT WITH THE EXTRACT

Thirty Wistar rats (120 - 150gm) were divided randomly into 5 groups of 6 animals each.

- **Group I** : Normal animals, orally received distill water for 10 days.
- **Group II** : gentamicin treated rats, orally received gentamicin (80 mg/kg body weight) for 10 days
- **Group III** : treated rats, orally received gentamicin (80 mg/kg body weight) and (200 mg/kg body weight) of dried fruit pulp extract of *Garciniapedunculata*for 10 days.
- **Group IV** : treated rats, orally received gentamicin (80 mg/kg body weight) and (400 mg/kg body weight) of dried fruit pulp extract of *Garciniapedunculata*for 10 days.
- **Group V** : treated rats, orally received gentamicin (80 mg/kg body weight) and (600 mg/kg body weight) of dried fruit pulp of *Garciniapedunculata*for 10 days.[2]

5.8 BIOCHEMICAL ASSAYS

Rats of each group were individually housed in metabolic cages for 24 hours and urine was collected on the 11^{th} day after the treatment. Urea and creatinine in urine were assayed andblood samples were collected from the overnight fasted animals through retro orbital under mild ethyl ether anaesthesia. Blood samples were collected for urea, creatinine, Uric acid, Blood urea nitrogen (BUN), potassium and sodium in blood and total protein and they were collected into plain sample bottles and then the animals from every group were sacrificed. Serum and urine parameters were assayed by using various biochemical laboratory analyzing methods.

5.9 HISTOPATHOLOGICAL STUDIES OF RAT KIDNEYS

After the animals were sacrificed, the rat kidneys were identified and carefully dissected out for histopathological examination. After rinsing in normal saline, sections were taken from each harvested kidney. The tissue was fixed in 10% formalin solution, dehydrated with 100% ethanol solution and embedded in paraffin. It was then processed into serial sections stained with hematoxylin - eosin and examined under light microscope with the help of a veterinary pathologist.

5.10 STATISTICAL ANALYSIS

All the results are expressed as mean SEM (standard error mean). Data obtained was analyzed by using one way ANOVAfollowed by dunnet's and $p< 0.05$ was considered as statistically significant

6.RESULTS

6.1 YIELD OF ETHANOLIC EXTRACT

150gm of powdered form of *Garcinia pedunculata* fruits was extracted with ethanol by using Soxhlet apparatus. The extraction process was continue for 48 hours. Solvent was evaporated to get the solvent free extract. Yield of the extract was found to be 5.46 % w/w. The extract was blackish and sticky in nature.

6.2 PRELIMINARY PHYTOCHEMICAL ANALYSIS

Qualitative phytochemical analysis test was carried out using several test and results shows that ethanolic extract of *Garcinia pedunculata* fruits contain alkaloids, terpenoids, carbohydrates, saponins, quinines, proteins and steroids and do not contain phenol and tannins (glycosides) and flavonoids.

6.3 ACUTE TOXICITY STUDIES

Acute toxicity studies on albino rats shows no mortality at a dose of 2000mg/kg during a time period of 14 days. This acute study helps to predict that it does not contain any type of toxicity and it it full safe. Therefore, one tenth of the maximum non mortality dose were selected as therapeutic lower dose 200 mg/kg b.w, then 400 mg/kg b.w and 600 mg/kg b.w respectively, in this study.

6.4 EFFECT OF *GARCINICINIA PEDUNCULATA* EXTRACT ON PLASMA UREA, CREATININE AND URIC ACID

The effect of various doses of *Garciniapedunculata*were studied in urea, creatinine and Uric acid in gentamicin intoxicated animals. Renal injury induced by gentamicin caused significant changed in renal marker in plasma as urea by 86.39%, creatinine by 160.24% and Uric acid by 57.5% respectively compared to control group. The percentage protection in renal marker in treated groups at 200 mg/kg as urea is 34.26% (P< 0.05), creatinine 27.77% (P<0.05) and Uric acid 13.83% (P<0.01) then at a dose of 400 mg/kg the percentage protection for urea is 38.21% (P<0.01), creatinine 71.75% (p<0.05) and Uric acid 31.29% (P<0.01)respectively when compared to toxic group while maximum percentage protection in renal markers is at a dose of 600 mg/kg as urea by 51.96% (P<0.01), creatinine by 83.79%(P<0.01) and Uric acid by 51.02% (P<0.01) respectively.(Table II).

Table II: Effect of GPon serum urea, creatinine and uric acid level against GM induced nephrotoxicity in rats (n= 6)

GROUPS	UREA (mg/dL)	CREATININE (mg/dL)	URIC ACID (mg/dL)
CONTROL(CON)	31.83 ±1.92	0.838± 0.05	2.8 ±0.14
GENTAMICIN (GM)	59.33± 1.05*	2.16± 0.06*	4.41± 0.09*
GM + GP 200	39± 0.57**	1.56 ±0.11**	3.8± 0.09***
GM + GP 400	36.33± 0.66***	0.61 ±0.06**	3.03± 0.07***
GM + GP 600	28.5± 1.56***	O.35± 0.03***	2.16± 0.06***

Values are expressed as mean ± SEM. * P<0.001 when compared with respective control group CON. **P<0.05, *** P<0.01 were considered significant when compared with gentamicin group (GM)

6.5 EFFECT OF *GARCINIA PEDUNCULTA* EXTRACT ON TOTAL PROTEIN, SODIUM AND POTASSIUM IN SERUM

The effect of various doses of *Garcinia pedunculata* were studied in total protein, sodium and potassium in gentamicin intoxicated animals. Renal injury induced by gentamicin caused significant changed in serum total protein by 47.49%, sodium 21.43% and potassium by 82.8% respectively compared to control group. The percentage protection in renal marker in treated groups at 200 mg/kg as total protein 7.01% ($P<0.05$), sodium 6.31% ($P<0.05$) and potassium by 7.99% ($P<0.05$) then at a dose of 400 mg/kg the percentage protection for total protein is 18.38% ($P<0.01$), sodium by 14.23% ($P<0.01$) and potassium by 7.25% ($P<0.05$) respectively when compared to toxic group while maximum percentage protection in total protein, sodium and potassium is at a dose of 600 mg/kg as total protein 34% ($P<0.01$), sodium by 19.33% ($P<0.01$) and potassium by 53.71% ($P<0.01$) respectively. (Table III).

Table III: Effect of GP on total protein, sodium and potassium level in serum against GM induced nephrotoxicity in rats (n=6)

GROUPS	TOTAL PROTEIN (gm/dL)	SODIUM (mEq/L)	POTASSIUM (mEq/L)
CONTROL (CON)	6.38 ±0.11	136.83± 1.95	3.9 ±0.13
GENTAMICIN (GM)	9.41± 0.15*	166.16 ±1.01*	7.13± 0.10*
GM + GP 200	8.75 ±0.07**	155.66 ±1.14**	6.56± 0.11**
GM + GP 400	7.68 ±0.14***	142.5± 0.76***	5.9± 0.13**
GM + GP 600	6.21± 0.08***	134.03± 1.70***	3.3± 0.17***

Values are expressed as mean. ± SEM. *$P<0.001$ when compared with respective control group CON. **$P<0.05$, ***$P<0.01$ were considered significant when compared with gentamicin group(GM)

6.6 EFFECT OF *GARCINIA PEDUNCULATA* EXTRACT ON SERUM BLOOD UREA NITROGEN

The effect of various doses of *Garcinia pedunculta* were studied on serum blood urea nitrogen in gentamicin intoxicated animals. Renal injury induced by gentamicin caused significant changed in BUN plasma by 97.42% compared to control group. The percentage protection in blood urea nitrogen of treated groups at 200 mg/kg as 12.51% ($P>0.05$) and then at a dose of 400 mg/kg as 21.71% ($P<0.01$) respectively when compared to toxic group while maximum percentage protection in blood urea nitrogen is at a dose of 600 mg/kg by 41.45% ($P<0.01$) respectively.(Table IV).

Table IV: Effect of GP on serum BUN, urine urea and urine creatinine level against GM induced nephrotoxicity in rats (n=6)

GROUPS	SERUM BUN (mg/dl)	URINE UREA (mg/dl)	URINE CREATININE (mg/dl)
CONTROL (CON)	12.83± 0.94	62.5 ±0.76	11.58± 0.26
GENTAMICIN (GM)	25.33± 1.22*	106.83± 3.14*	31.58± 0.47*
GM + GP 200	22.16 ±0.94**	85.16 ±0.94***	27.5± 0.76**
GM + GP 400	19.83± 0.47***	79.5 ±0.76***	18.33± 0.88 ***
GM + GP 600	14.83± 0.94***	60.66± 1.66***	10.5± 0.76***

Values are expressed as mean ±SEM.*$P<0.001$ when compared with respective control group CON. **$P<0.05$, ***$P<0.01$ were considered significant when compared with gentamicin group (GM)

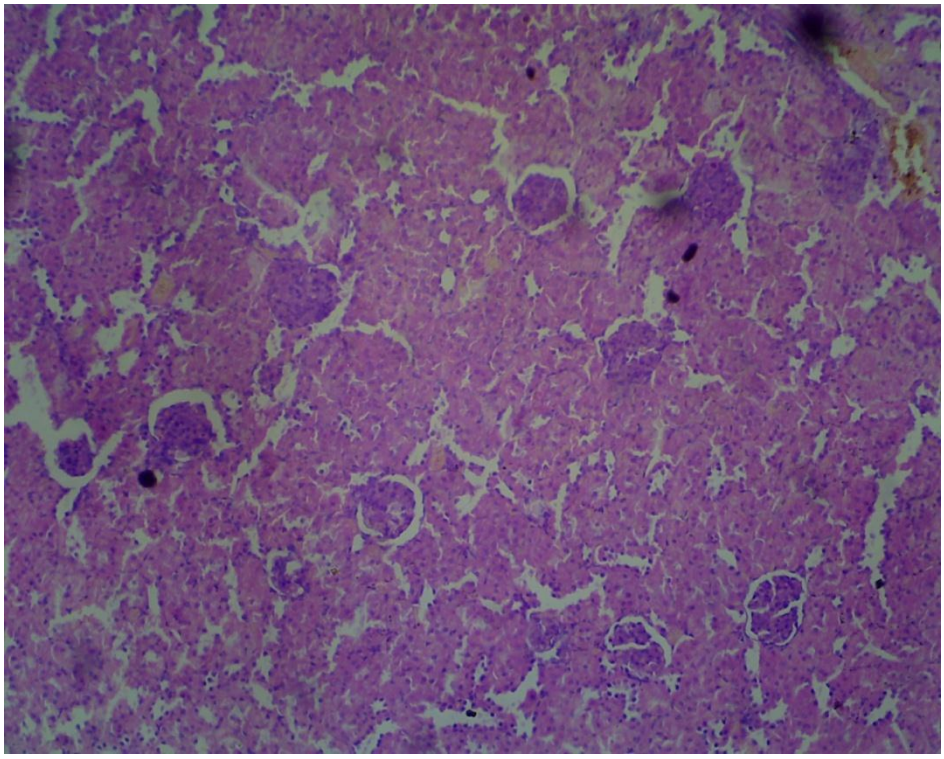
6.7 EFFECT OF *GARCINIA PEDUNCULTA* EXTRACT ON URINE UREA AND CREATININE

The effect of various doses of *Garciniapedunculata*were studied on urine urea and creatinine n gentamicin intoxicated animals. Renal injury induced by gentamicin caused significant changed in urine urea by 70.92% and creatinine by 172.71% compared to control group. The percentage protection of treated groups at 200 mg/kg as urea 20.28% ($P<0.01$) and creatinine 12.91% ($P<0.05$) and then at a dose of 400 mg/kg the percentage protection for urea 25.58% ($P<0.01$) and creatinine 41.95% ($P<0.01$)respectively when compared to toxic group while maximum protection in urine urea and creatinine is at a dose of 600 mg/kg as urea 43.21% ($P<0.01$) and creatinine as 66.75% ($P<0.01$) respectively. (Table III).

6.8HISTOPATHOLOGICAL OBSERVATIONS

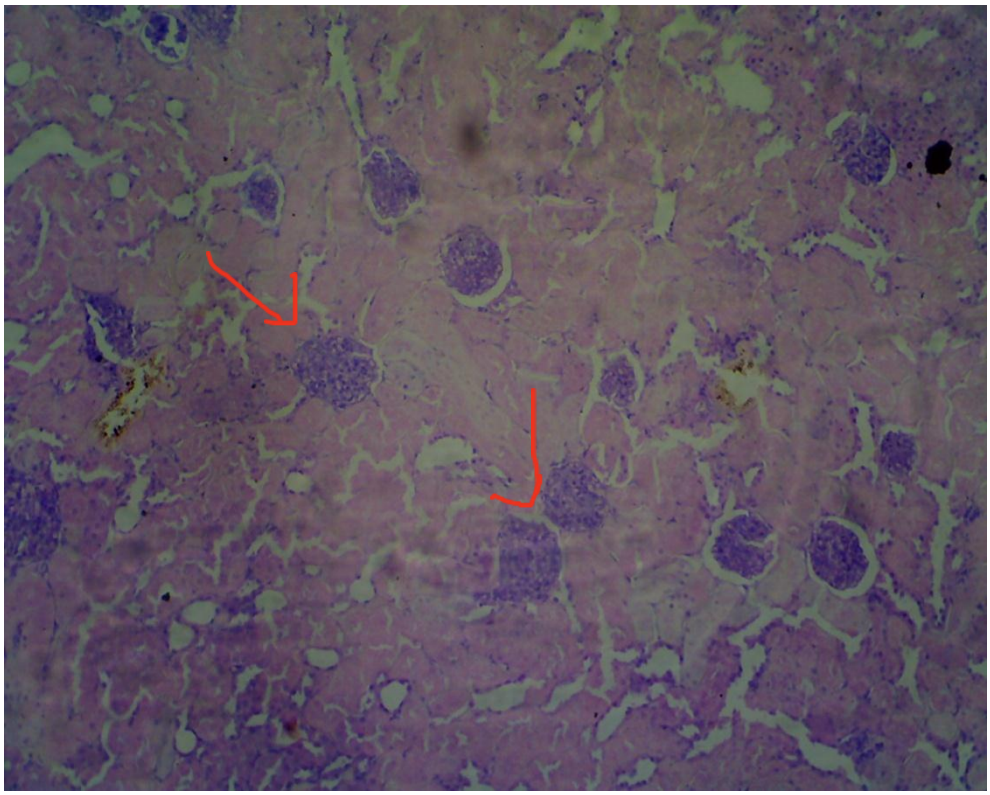
The nephrotoxicitywere confirmed by evaluating the pathological symptoms such as degeneration, desquamation, necrosis in tubules, blood vessel congestion and swelling in glomerulus. Treatment with GP extract 200, 400 and 600 mg/kg b.w ameliorated the toxic manifestations in the kidney. The histopathological observations supported this conclusion

Fig III: Histological study of kidney tissue in control group of rats



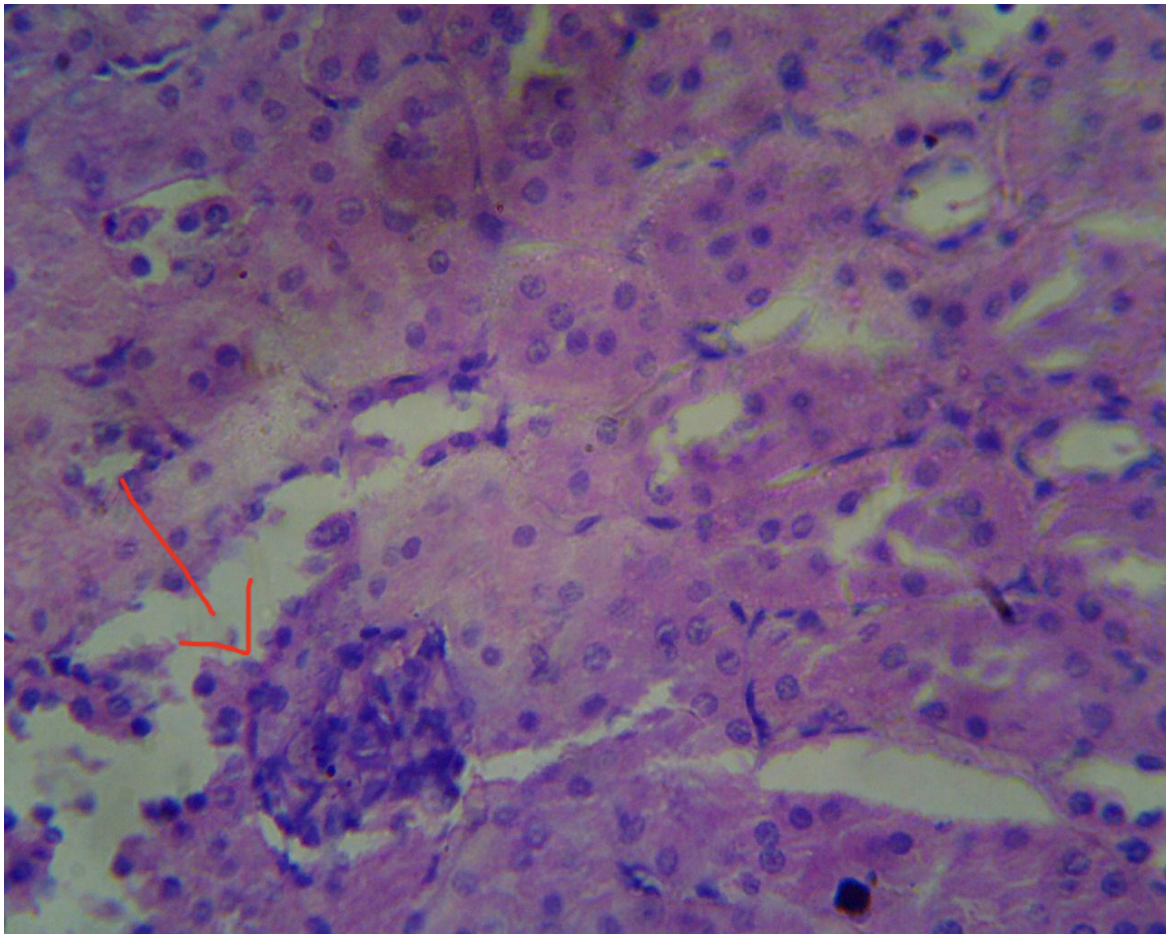
- No degeneration, necrosis, desquamation or any inflammation
- Blood vessels shows unremarkable
- Glomeruli show normal morphology

Fig IV: Histopathological study of kidney tissue in gentamicin treated groups



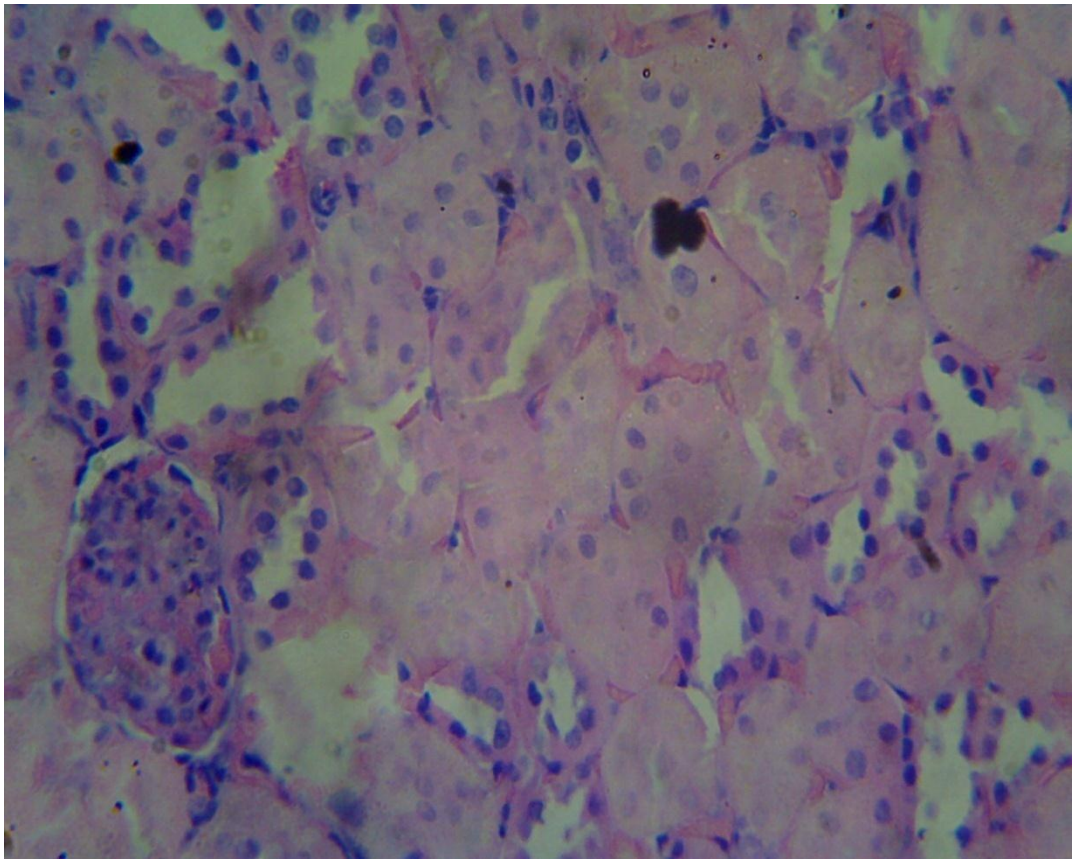
- Gentamicin treated groups showed degeneration, desquamation
- Necrosis in tubules, blood vessel show congestion
- Swelling in glomerulus (indicated by arrows)

Fig V: Histopathological study of kidney tissue in animals treated with 200mg/kg GP



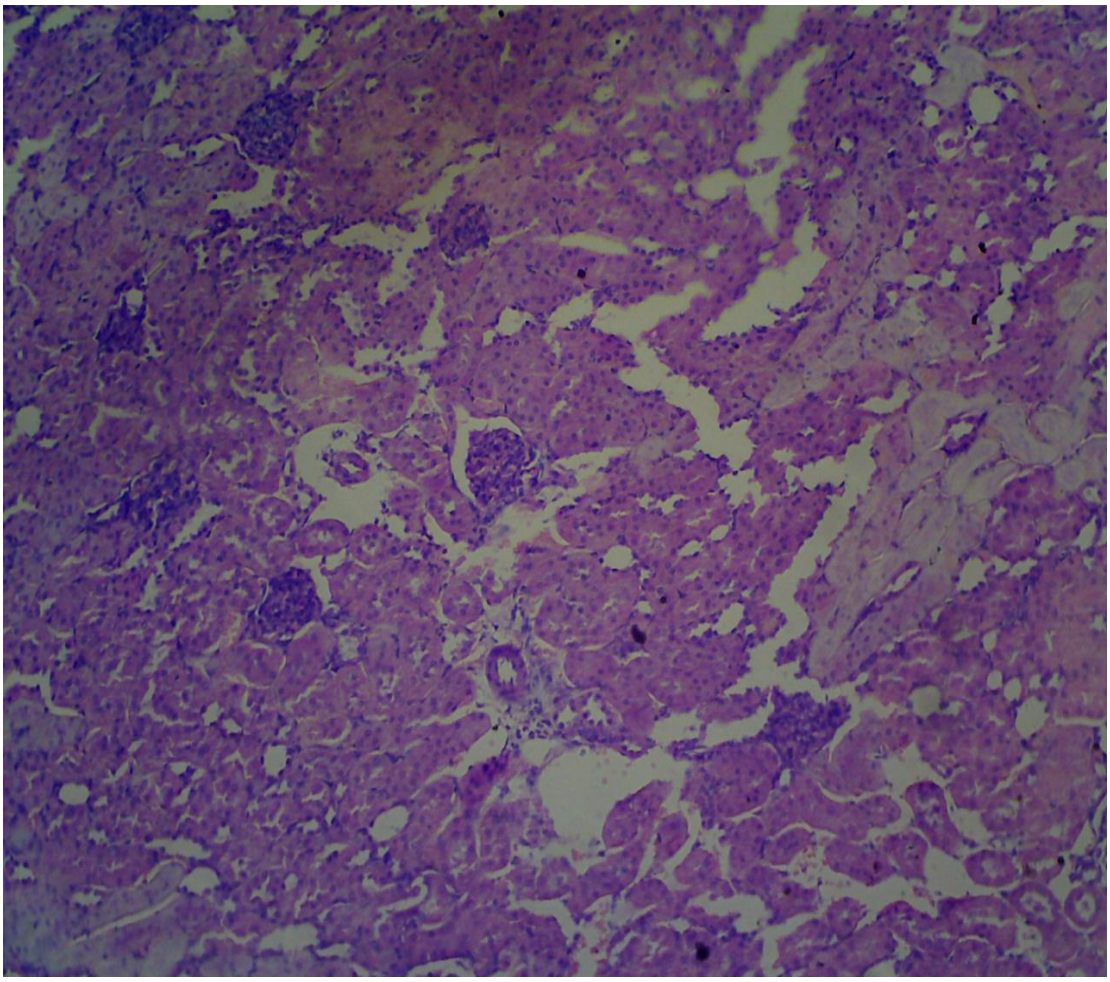
- Shows tubular degenerative and necrotic changes
- Shows karyopicnosis (indicated by arrow)
- Glomeruli shows mesangeal matrix expansion.

FigVI: Histopathological study of kidney tissue treated with 400 mg/kg GP



- Glomeruli show mild mesangeal matrix expansion
- Blood vessel show no congestion.
- Mild tubular epithelial changes.

Fig VII: Histopathological study of kidney tissue treated with 600 mg/kg GP



- Showed regeneration in tubular epithelial cells

7.DISCUSSION

7.1 Acute toxicity study:

Herbal products prepared from various medicinical plants have become famous in health care and obtained from natural sources.[6] It is well known known that the herbal medicines contain more than one plant or active constituents and their therapeutic efficacy is not provided by a single group of compounds. Some of these impound act synergistically to modify the bioavailability and efficacy of active constituent [3]. The bioactive compound from the medicinal are concluded to be safe without knowing the possible health care benefits and thus commonly used as self medication. However, there is a defect on toxicological data of these compounds. So, acute toxicity study is required to identify the range of doses and probable clinical signs evoked by the test impound in animal under investigation. Moreover, it is a tool for calculating therapeutic index of a lead compound.

The present study reveals the acute toxicity of *Garcinia pedunculata* fruit extract. No morbidity and mortality were observed at a higher dose of2000 mg/kg throughout the 14 days observation period. This acute study helps to predict that it does not contain any type of toxicity and it it full safe.

7.2 Experimental induction of gentamicin and their treatment with the extract.

Nephrotoxicity is an undesired side effect of chemotherapy in general. Most chemotherapy drugs target pathways that are essential to dividing cells[27]. Several studies have now documented the importance of reactive oxygen metabolites in gentamicin induced renal damage[28]. Nephrotoxicity of the drugs is usually associated with their accumulation in renal cortex, dependent upon their affinity to kidneys and on kinetics of drug trapping process[27]. The nephrotoxicity of aminoglycosideantibiotics, and specially that of the most commonly used compound, gentamicin is well documented[30,31]. Several studies have reported that oxygen free radical are considered to be important mediators of gentamicin induced renal failure.

Gentamicin induced nephroxicity is characterized by elevated levels of urea, creatinine, uric acid, total protein sodium and potassium in serum as well as urine urea and creatinine, severe proximal tubularnecrosis, renal failure were found to be significantly increased in rats

treated with only gentamicin. Similar pattern of changes were also observed in this study following gentamicin treatment. GP supplemation to GM treated rats recorded decrement in levels of urea, creatinine, uric acid, total protein, sodium and potassium in serum and also in urine urea and creatinine. These observations indicate an improved in renal function. GM administration to control rats produced a typical pattern of nephrotoxicity which was manifestated by marked increase in serum BUN. GP supplementations to GM treated rats recorded decrement in levels of blood urea nitrogen in plasma.

Histopathological results demonstrating structural changes n renal tissue of aminoglycoside antibiotics such as GM were reported by some researches[31]. Histopathological view of renal sections in GM treated groups showed the degeneration, desquamation and necrosis in tubules, blood vessel congestion and swelling in glomerulus, as compared to control groups. Groups treated with GM + GP 200 mg/ kg showed tubular necrosis, necrotic changes, karyopicnosis, glomeruli showed mesangeal matrix expansion. Glomerular and tubular epithelial changes were considerably mild in groups treated with GM + 400 mg/kg and GM + 600 mg/kg i.e animal treated with GP 400 mg/kg showed mild glomerular mesangeal matrix expansion, mild tubular epithelial changes and no congestion in blood vessels while in case of animal treated with GP 600 mg/kg showed regeneration in tubular epithelial cells. Thus, morphological changes in kidneys were because of GM administration, but these changes tended to be mild in GM + GP treatment.

8. CONCLUSION

In conclusion, gentamicin treatment resulted in impairments of renal function markers, and histopathological changes in the kidneys of rats.Co-administration of GM with GP lessened the negative effects of GM- induced nephrotoxicity and significant decrease of all the parameters in gentamicin treated rats.

The beneficial effects of *Garciniapedunculata*may be attributed to the amelioration of renal function.Thus the result showed that the ethanolic fruit extract of *Garciniapedunculata*offer protection against the damaging renal side effects of gentamicin. Further investigation of these promising protective effects of *Garciniapedunculata*fruit extract against gentamicin- induced renal injury may have a considerable impact on developing clinically feasible strategies to treat patients with renal failure.

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