Introduction

1.1 Nephrotoxicity:

Kidney is one of the vital organs of the body. Nephrotoxicity is one of the common kidney problems and occurs when kidney is exposed to a drug, its metabolite or toxin. When kidney damage occurs, body unable to rid of excess urine and wastes from the body and blood electrolytes (such as potassium and magnesium) well all become elevated. A number of the therapeutic agents can adversely affect the kidney resulting in acute renal failure, chronic interstitial nephritis and nephritic syndrome because of increasing number of potent therapeutic drugs like aminoglycoside antibiotics, chemotherapeutic agents and NSAIDS have been added to the therapeutic arsenal in recent years.

1.2 Drug induced nephrotoxicity:

Nephrotoxicity induced by aminoglycosides manifests clinically as nonoliguric renal failure, with a slow rise in serum creatinine and a hypoosmolar urinary output developing after several days of treatment. Aminoglycosides accumulated by these cells are mainly localized with endosomal and lysosomal vacuoles but are also localized with the Golgi complex. These changes are preceded and accompanied by signs of tubular dysfunctions or alterations (release of brush-border and lysosomal enzymes; decreased reabsorption of filtered proteins; wasting of K\(^{+}\), Mg\(^{2+}\), Ca\(^{2+}\), and glucose; phospholipiduria; and cast excretion. In animals, tubular alterations have clearly been associated with the development of focal necroses and apoptoses in the tubular epithelium, together with an extensive tubular and peritubular cell proliferation, without an apparent change in kidney function (Marie-Paule, et.al 1999).

1.3 Lithium induced nephrogenic diabetes insipidus.

In congenital nephrogenic diabetes insipidus (NDI), a disease in which the kidney is impaired, resulting in a severe loss of water. NDI is caused by mutations in the gene encoding V\(_2\)R, which comprises the X-linked form, or in AQP\(_2\), which results in the autosomal recessive and dominant forms of NDI (Patrik D, Walker, et.al, 2003). By this mechanism, \(~90\%\) of the water content from is reabsorbed. Water transport in collecting ducts, however, is tightly regulated by arginine vasopressin (AVP), which binds to its G-protein coupled V\(_2\) receptor (V\(_2\)R) in the
basolateral membrane of its principal cells. (Fabrizio de Mattia, 2004). This binding triggers a cyclic AMP signaling cascade which leads to protein kinase A activation and phosphorylation of aquaporin-2 (AQP2). In nephrogenic diabetes insipidus (NDI), a disease in which the kidney is unresponsive to AVP, this mechanism is impaired, resulting in a severe loss of water. NDI is caused by mutations in the gene encoding V<sub>2</sub>R (Eleanor Lederer MD, Clifford C Dacso 2009).

Lithium impairs the ADH stimulatory effect on adenylate cyclase, thereby decreasing cAMP levels. Thus, lithium most likely impairs water permeability in the principal cells by inhibiting water channel delivery and, over a prolonged period of time, by suppressing channel production.

1.4 Nephroprotection by herbal formulations: Nephroprotective agents are the substances which possess protective activity against nephrotoxicity. Medicinal plants have protective properties or curative properties due to the presence of various complex chemical substances. Ancient literature has prescribed various herbs for the cure of kidney disease. Co-administration of various medicinal plants possessing nephroprotective activity along with different nephrotoxicity agents may attenuate its toxicity. *Ficus racemosa* Linn (Moraceae) is a popular medicinal plant in India, which has long been used in ayurveda, the ancient system of Indian medicine for various diseases/disorders including diabetes, liver disorders, diarrhoea, inflammatory conditions, and hemorrhoids, respiratory and urinary diseases. As a part of this concept survey of locally available medicinal plants was undertaken. It was observed that the plant *Ficus racemosa* Linn is grown widely and abundantly. In addition, a native practitioner has claimed that this plant is very useful nephroprotective agent. The stem bark and fruits are used in India for the treatment of various diseases. Methanol extracts of *Ficus racemosa* contained relatively higher levels of total phenolics than the other extract (Baby Joseph, Justin Raj. 2010). Keeping all these facts in view the present study is aimed at giving a scientific basis for the native claims and traditional knowledge. The antidiuretic activity of *Ficus racemosa* was reported. Desmopressin is the synthetic analog of ADH, used in the treatment of nephrogenic diabetes insipidus. However there are no primary drugs for the treatment of nephrogenic diabetes insipidus. There are no reports of this plant for its possible nephroprotective activities in drug induced nephrotoxicity and in lithium induced nephrogenic diabetes insipidus. Hence this plant is selected in this study.
1.5. *Ficus racemosa*

Name: Ficus racemosa  
Botanical name: Ficus racemosa Linn.  
Family: Moraceae  
Sanskrit synonyms: Udambara, Krimiphala, Jantuphala, Sevya  
Plant names in different languages:  
English: Country fig, Cluster fig  
Hindi: Umar, Gular  
Kannada: Attimara  
Malayalam: Atti, Kattatti, Peyatti  
Distribution – Throughout India growing wild

**Ficus racemos tree**

**Distribution and descriptions of the plant:** The *Ficus racemosa* (syn. Ficus glomerata Roxb.) is a species of plant in the Moraceae family. Popularly known as the Cluster Fig Tree or Goolar. The plant grows all over India in many forests and hills.

**Description:** The tree is medium tall, growing 10-16 meters in height. The bark is reddish grey and often cracked. The leaves are dark green, 7.5-10 cm long, ovate or elliptic. *Ficus racemosa* Linn (Moraceae) is an evergreen, moderate to large sized spreading, lactiferous, deciduous tree,
without much prominent aerial roots found throughout greater part of India in moist localities and is often cultivated in villages for its edible fruit.

**Phytoconstituents:** The stem portion possesses higher percentage of phenols (8.03%) as compared to leaf (3.64%) and root (5.01%). Tannins were estimated by Folin-Denis method. Results showed stem possesses higher percentage (5.94%) of tannin as compared to leaf (2.06%) and root (4.65%). The bark was found to be a good source of dietary fiber, minerals, sugars and phenolic compounds. On dry basis, the total dietary fiber content was 20.5% of which major portion was contributed by insoluble dietary fiber (13.6%). Potassium was the most abundant mineral (11975 ppm) followed by chloride (7475 ppm) and calcium (1729 ppm). The bark was also a good source of other minerals and trace elements such as phosphorus and iron, zinc, magnesium, respectively. The qualitative phytochemical screening showed that the whole plant is a rich source of glycosides, phenols & flavonoids.

**Uses:** The roots, bark-skin, fruits, latex and leaves of *Ficus racemosa* have great medicinal value. Udumbara is used both, internally as well externally, externally; the latex is applied on chronic infected wounds to alleviate edema, pain and to promote the healing. The decoction of its bark-skin is an effective gargle in stomatitis and sore throat. Application of latex alleviates the edema in adenitis, parotitis, orchitis, traumatic swelling and toothache. Internally, *Ficus racemosa* is used in vast range of maladies. The decoction of bark skin is extremely useful in diarrhea, dysentery and ulcerative colitis. In children, the latex is given along with sugar to combat diarrhea and dysentery. The cold infusion of ripened fruits mixed with sugar, is salutary in Rakta pitta is effectively controlled with the decoction of bark-skin. In diabetes, the ripe fruits or bark-skin decoction is beneficial, as it works well as anti-diuretic. The powder of the bark-skin works well as an anorexient, hence, beneficial in hyperphagia-bhasmaka. The infusion of its bark and leaves is employed as mouth wash to spongy gums and internally in dysentery, menorrhagia, and effective remedy in glandular swelling, abscess, wound, cervical adenities and haemoptysis.

**1.6 Medicinal plants in nephrogenic diabetes insipidus nephroprotection:** As there are no primary drugs for the treatment of nephrogenic diabetes insipidus. There is need to develop a novel herbal formulation for the treatment of nephrogenic diabetes insipidus and to protect the drug induced nephrotoxicity. Herbal products are becoming popular as alternate medicine worldwide. According to 2004 update on the health risks of herbal remedies in Clinical
Pharmacology and Therapeutics, about one third of adults in the developed countries and more than 60% Asians use herbal medicines for health promotion or treatment of various chronic diseases.

1.7. **Rationale of herbal formulation**: Poly herbal formulations have plant-based pharmacological agents which may exert synergistic, potentiative, agonistic, antagonistic actions by virtue of its diverse active principles within themselves. These pharmacological principles work together in a dynamic way to produce maximum therapeutic efficiency with minimum side effects. The development procedures of herbal formulations for world-wide use has to been different form that of synthetic drugs.

1.8 **Nephroprotective herbal formulations**: Herbs are the principal form of medicine in India and they are becoming popular throughout the world. There are about 61 plant families have potential to cure renal diseases. This includes 143 species of ethnomedicinally important nephroprotective plants. Ancient literature has prescribed various herbs for the cure of kidney disease. The term “Pashanabeda” has been cited in literature to identify a group of plants, which have been extensively used in indigenous system of medicine to dissolve urinary calculi and stones. E.g. *Aerva lanata*, *Crataeva nurvala*, *Pongamia prinnata* etc. Some other plants mentioned in literature include *T.terrestris, O.sanctum, Zea mays*, etc.