Chapter 3

THEORETICAL ANALYSIS
### Chapter-3: Theoretical Analysis

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Name of the Sub Title</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>Pathophysiology of Diabetic Nephropathy</td>
<td>26</td>
</tr>
</tbody>
</table>
Chapter 3

THEORETICAL ANALYSIS

Every experiment is backed by theoretical analysis of various research frameworks. A researcher has to understand and compile the work he is intended to do with proper supporting background. The background of the study results in the elevation of newer ideas which holds the key for the successful completion of proposed research work. As every research worker goes with proper support, same is the case with the current research work.

3.1. Pathophysiology of Diabetic nephropathy

Diabetic nephropathy is kidney damage that occurs as a consequence of diabetes. DN causes ill health and occasionally death for people with diabetes. Diabetes is the foremost cause for CKD and renal failure in the nation. Diabetes people are susceptible to developing diabetic nephropathy if they

1. Have poor glycemic control

2. Have a family account of kidney disease or high B.P.

3. Had type 1 diabetes before age 20 years

All diabetic peoples does not develop the chronic kidney disease but researchers believe that those who have the poor glycemic control are at risk.
Diagnosis

It is mandatory for a doctor to check for DN in someone with diabetes as a part of a checkup.

Some laboratory tests for DN
1. Blood urea nitrogen
2. Serum creatinine
3. 24 hr urine protein
4. Blood levels of phosphorous, calcium, bicarbonate and potassium
5. Haemoglobin
6. RBC count
7. WBC count
8. Packed cell volume
9. Urinary albumin excretion rate
10. Glomerular filtration rate

3.1.1. Relationship between Diabetic Nephropathy and Oxidative Stress\textsuperscript{66, 67}

Oxidative stress may take part in the development of complications in diabetes.

1) Oxidative stress and changes in antioxidant ability, observed in both clinical and experimental diabetes mellitus, are thought to be the etiology of diabetic complications.

2) Mechanisms by which amplified oxidative stress is involved in the diabetic complications are partly known, including stimulation of
transcription factors, advanced glycated end products (AGEs) and protein kinase C.

3) The immune system may be recognizing the oxidatively modified proteins are antigens which triggers the formation of antibodies.

4) Self-oxidation of plasma glucose, stimulation of leucocytes and improved transition metal bioavailability are the numerous probable sources for enhanced free radical production in diabetes.

5) Several invivo and invitro studies have demonstrated that reactive oxygen metabolites including free radicals like superoxide radical, hydroxyl radical and hydrogen peroxide are central mediators of tissue damage.

6) Antioxidant enzymes such as glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase (CAT) and non-enzymatic scavengers like reduced glutathione (GSH) modulated the concentration of the reactive oxygen species.

7) Oxidative stress causes the peroxidation of lipids.

3.1.2. Relationship between Diabetic Nephropathy and Dyslipidaemia

Absolute or relative insulin deficiency causes the hyperglycemia. Mammalian lipid metabolism affected by insulin. Insulin stimulate the production of fatty acid in liver, adipose tissue and in the intestine. DM is commonly associated with dyslipidemia and is considered as a threat factor for the development of DN. Multiple lipoprotein abnormalities takes place in diabetic patients often such as, elevated
levels of triglycerides, augmented plasma levels of very low-density lipoprotein (VLDL), low-density lipoprotein (LDL). In addition to this the diameter of LDL particles is also reported to be smaller in patients with DN compared to diabetic patients without nephropathy. Experimental studies in animal models state that abnormality of lipids responsible for glomerulosclerosis. The participation of serum cholesterol in the development of nephropathy has also been well studied and found a direct relation between renal injuries of rats and elevated levels of blood LDL cholesterol. The study demonstrated that dyslipidaemia and hyperglycemia act jointly to provoke renal damage in LDL receptor deficient BALB mice has further indicated that lipid can worse the diabetic nephropathy.

3.1.3. Relationship between Diabetic Nephropathy and Advanced glycation end products\(^{70}\)

Tissue proteins by non enzymatic glycosylation contribute to the development of diabetic nephropathy. In chronic hyperglycemia, some of the surplus glucose combines with free amino acids of circulating or tissue proteins. This process affects the glomerular basement membrane and other matrix components of the glomerulus and primarily leads to formation of reversible premature glycosylation end products and, later, irreversible advanced glycosylation end products. These advanced products can be implicated in the mechanism of diabetic nephropathy by changing signal transduction via change in the level of soluble signals, such as cytokines, hormones and free
radicals. People with diabetes have raised circulating levels of advanced glycosylation end products particularly in renal deficiency patients since they are usually excreted in the urine. The net effect is tissue deposition of AGES (in part by cross-linking with collagen) that contributes to the related renal and microvascular complications.

3.1.4. Relationship between Diabetic nephropathy and Vascular Endothelium Dysfunction

Interior part of blood vessels covered by endothelium. The biological functions of endothelium are several and it control vascular tone and preservation of free flow of blood in vessels. VED results in reduced stimulation of endothelial NOS and amplified production of ROS, which causes reduced production and bioavailability of NO the disregulation of endothelial function up regulates the expression of procoagulant, prothrombotic and proinflammatory mediators, which are concerned for the mechanism. VED increases the accumulation of the extracellular matrix that leads to glomerulosclerosis and progressive turn down in the glomerular filtration rate to make nephropathy.

3.1.5. Relationship between diabetic nephropathy and inflammation

Inflammation has a very important role in the development of diabetic nephropathy. It is worthy of note that there is a key relationship between DN and inflammatory cytokines. In addition, the
effort to control the inflammatory pathways can slow the progression of DN. Accumulating evidences have shown that IL-6, TNF-α, TGF-B are all important inflammatory biomarkers involving in the development of DN.

Apart from the hemodynamic and metabolic abnormalities, inflammatory processes and immune cells are implicated in development of diabetic nephropathy. There are enhancing evidences, which suggest that immune cells contribute in the vascular damage in the conditions of DN, and their movement into the kidney is a vital step in the development of this disease.

The plan of work has been designed based on the following
1. Procurement of raw materials from the local market for the preparation of polyherbal formulation.
2. Standardization of the polyherbal formulation according to WHO guidelines.
3. To determine the LD_{50} value for formulation
4. To evaluate the protective effect of polyherbal formulation against diabetes induced nephropathy in rats by performing the various parameters, histopathological studies.