Chapter 1

INTRODUCTION
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Chapter-1: Introduction

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Chapter 1

INTRODUCTION

1.1. Diabetes Mellitus

Diabetes mellitus is a heterogeneous metabolic disorder relating to carbohydrate, fat and protein metabolism.\(^1\) Deficiency or insensitivity of insulin causes glucose to accumulate in the blood, called as hyperglycemia. This leads to the polydipsia, polyuria, and polyphagia and weight loss.\(^2\)

1.1.1. Epidemiology

Diabetes mellitus is a verdure problem involving millions of individuals in the area. World Health Organization expected that 300 millions of people will suffer with diabetes mellitus by the year 2025.\(^3\) From this 80% would be in developing countries. It is more a fatal disorder than AIDS at present killing a great number of people.\(^4\)

1.1.2. Types of diabetes

Diabetes mellitus is of two types.

Type 1 (insulin based or juvenile onset diabetes)

Type 2 (Non insulin dependent or maturity onset diabetes)

Type 1: In this type of diabetes mellitus destruction of \(\beta\) cells leads to the lack of insulin secretion.

Patients are usually young (children or adolescents)

Causes: 1. Genetic susceptibility

2. Autoimmune factors

3. Environmental factors (infections)
Type 2: It is coupled with insulin resistance and impaired insulin secretion.

Patients are often obese and the incidence rises progressively with age as β cell function declines.

Causes: 1. Genetic factors (80%)

2. Constitutional factors (obesity, hypertension, decreased physical activity).\(^5\)

Diabetes mellitus is combined with debilitated glucose metabolism that directs to an increase in free radical production, increase in triglyceride, lipoprotein levels. Free oxygen radical should start oxidation of lipids, which is responsible for the titillation of glycation of protein, inhibition of antioxidant enzymes and take part a role in the long term complications of diabetes.\(^6\) Uncontrolled diabetes leads to several microvascular (Nephropathy, Neuropathy and Retinopathy) and macrovascular (Atheroma) complications and have an effect on many organs of the body.\(^7\)

1.2. Diabetic Nephropathy

The kidneys opera a decisive role in conserving overall health. These couple organs filter waste products and extra water from the blood and also involve in synthesis of hormones that are chief for the best maintenance of body functions. Increased blood glucose in diabetes leads to damage of many small blood vessels present in kidneys. Overtime, the kidneys are not adequate to work entirely and this edge to kidney failure.
It is a continuous and irreversible renal disease characterized by the deposition of extracellular matrix in glomerular mesangium and kidney interstitial tissue that leads to renal failure.\(^8\)

### 1.2.1. Epidemiology

DN affects approximately 30-35\% people suffering from type 1 or type 2 DM.\(^9\) Type 2 diabetes is a main cause to kidney disease in 20-40\% of population. 50\% will have microalbuminuria secondary to hypertension. 10-20\% with microalbuminuria will progress to overt Nephropathy.\(^10\)

### 1.2.2. Pathogenesis

Several mechanisms are considered to be ramified in the pathogenesis of DN and its obstacles, all of them originating from hyperglycemia and dyslipidemia.\(^8,\)\(^11\) Metabolic and haemodynamic interactions onward with glomerular proteins glycosylation are to be involved in the pathological process of DN.\(^12\)

Hemodynamic factors that are an addition to the development of DN include elevated systemic and intraglomerular pressure, proactivation of vasoactive hormone alley including the RAAS and endothelin. These alleys turn on the intracellular second messengers that are protein kinase C (PKC), mitogen activated protein kinase (MAP kinase), and nuclear transcription factors (NF), vascular endothelial growth factor (VEGF), cytokines and transforming growth factor (TGF-\(\beta\)).

Hyperglycemia stimulates PKC through denovo generation of diacylglycerol. Activation of PKC in the glomeruli has been connected
with processes elevating mesangial expansion, increasing of thickness of basement membrane, smooth muscle contraction, endothelial dysfunction.

Glucose based pathways are also activated within the diabetic kidney which augment the oxidative stress, free radicals generation and further activate renal polyol pathway causing increase in advanced glycation end products (AGES). In grouping, these routes finally direct to improved renal albumin permeability and extracellular matrix accumulation, ensuing in an increase in proteinuria, glomerulosclerosis and eventually development of tubulointerstitial fibrosis.

**Pathogenesis of diabetic nephropathy**

![Pathogenesis of diabetic nephropathy](image)

**Fig. 1.1. Pathogenesis of diabetic nephropathy**
Oxidative stress is significantly increased in diabetes because persistent hyperglycemia increases the production of free radicals. There is a data that diabetes mellitus increases number of pathways for the increased production of ROS. These included increased glucose oxidation, increased mitochondrial superoxide production, stimulation of NAD(P)H oxidase by angiotensin II (protein kinase c dependent), glucose and advanced glycation end products. The most known free radicals involving in the diabetic nephropathy pathogenesis are ROS such as superoxide(O$_2^-$), hydroxyl (OH) and peroxyl (RO$_2^-$) and non radical species such as hydrogen peroxide (H$_2$O$_2$) and hypochlorous acid (HOCl) and reactive nitrogen species produced from similar pathways.\textsuperscript{13}

\textbf{Fig. 1.2. Oxidative stress mechanism in diabetic nephropathy}
Modern studies have recommended diabetic nephropathy as an inflammatory process, and immune cells could be involved in the maturity of diabetic nephropathy. AGES increase inflammation and accelerate the formation of ROS during normal aging, as well as in diabetic patients. Cyclo-oxygenase-2 (COX-2), which shows anti-inflammatory properties via inhibition of its enzymatic activity, is increased in diabetic nephropathy.

**Stages of DN**

1. Hyper filtration, early renal hypertrophy.
2. Glomerular lesions without clinically evident disease.
3. Incipient nephropathy with micro-alb/cr ratio 0.03-0.3 or albumin 20-200µg/min on timed Specimen.
4. Overt diabetic nephropathy with proteinuria > 500mg/24hr, creatinine clearance <70 ml/min.
5. ESRD, Creatinine clearance <15ml/min.

**1.3. Polyherbal Formulation**

Since few years there has been an improved growth in the field of herbal medicine and these drugs are ahead demand both in developed and developing countries owing to their natural origin and less side effects. Conventional medicines resultant from medicinal plants are used by about 60% of the world population. In Indian Systems of medicine most practitioners formulate and give out their own recipes. The WHO has planned 21,000 plants, which are used for medicinal purposes around the world. India is called the “botanical garden of the world” due to principal producer of medicinal plants.
Various herbs are reported in Ayurveda for treating and preventing diabetes. In the market numerous antidiabetic regimens are available but on long term consumption some of these produce undesirable side effects. Consequently there is a biting need for new drugs that target the bottom line pathogenic mechanisms. Still diabetes is not fully correctible by the contemporary antidiabetic agents. Sulfonyl urea and metformin are admirable in the curing of NIDDM. But these agents are often unable to decrease glucose concentrations within the normal range or to reinstate a habitual pattern of glucose homeostasis. Search for an effective drug, alone or in combination for treatment of diabetic complications still remain elusive. Herbal formulations used extensively in traditional systems of medicine may provide a suitable alternative for this. In current years, there has been an increased tendency pointing to the herbal formulations due to the tenor towards the natural sources and a healthful life style. Poly herbal formulation rather than individual herbal formulation is commonly used and many herbal formulations such as D-400, Trasina, Hyponidd, cogent db, tincture of punchparna, Diasulin and Diamed have been shown for their antidiabetic, antihyperlipidemic, antioxidant or all the effects.

1.4. Standardization of polyherbal formulation

Natura is always a carriage as a palmy mark to demonstrate the outstanding phenomena for mutualism. In the Western cosmos, as the people are becoming mindful of side effects of man made drugs, there is an increasing amour in the natural remedies with a fundamental
opportunity towards the natura. WHO measures that regarding 80% of people in developing countries still realize on traditional medicine based abundant on plants and animals for their earlier healthcare.21

The Indian System of medicine, mainly comprising of Ayurveda, Siddha and Unani, is one of the oldest holistic management system with thoroughly documented remedies. Of all these, Ayurveda is being practiced by a large population in India and abroad.22 In the present epoch, merchandise of all foodstuffs has become worldwide. Wellness has been of furthermost splendor since initial times for the mankind. Market of wellness-related goods has been active and these products are manufactured at different parts of the world and sold all over. Homogeny is obligatory to make confident the availability of a uniform output in all parts of the earth. Standardization assures a constantly stronger product with guaranteed intersections.23 The main prerequisite for polyherbal formulation is the existence of each constituent has to be naturalised. The microscopic characters of each component are very sure to distinguish and also sometime these are overlapping with the quality of other ingredient. Standardized ayurvedic formulations of uniformity are essential for beneficial therapeutic use. Due to lack of regulations and quality control methods, there are batch to batch variations in the same formulation procured from different sources.24 Standardization is a prerequisite factor for polyherbal formulation in order to evaluate the quality of the drugs based on the compactness of their active principle.25
1.5. Aminoguanidine

1.5.1. Chemistry of Aminoguanidine

Aminoguanidine is a nucleophilic hydrazine derivative and small molecular size compound (MW around 74.1 Da)\textsuperscript{26}. Aminoguanidine is an agent structurally similar to laevo-arginine.

\[
\text{NH} \\
\text{H}_2\text{N} \mid \text{NH} \mid \text{C} \mid \text{NH}_2
\]

Two main varieties of aminoguanidine are there, the bicarbonate and hydrochloride variety. Even though the bicarbonate compound is more normally presented, the hydrochloride report is supposed to be the most active (bioavailable) as it is more soluble.

1.5.2. Mechanism of Action of Aminoguanidine

Aminoguanidine contains a terminal amino group, which has higher chemical reactivity than terminal amino groups of proteins. Based on this characteristic feature aminoguanidine has been selected as an inhibitor of glucose binding to proteins. Aminoguanidine has been found to reduce the development of AGE products, principally by reacting with Amadori products, i.e. by blocking the carbonyl groups on ketoamines and their derivatives\textsuperscript{27}. Aminoguanidine is active mainly against certain aldehyde, which contributes to cross-linking as malondialdehyde and alpha-o xoaldehyde. However, its primary
mechanism of action is now believed to be trapping of bicarbonyl intermediates\textsuperscript{28}.

**1.5.3. Pharmacokinetics of Aminoguanidine**

Aminoguanidine is absorbed after intraperitoneal (i.p) administration, peaked in plasma (9μg/ml) at 0.5 hours and had a half life of 1.88 hours. Steady-state values for the area under the curve for therapeutic regimens were 20.5 and 16.35 μg/ hr/ ml\textsuperscript{29}

**1.5.4. Pharmacological Actions of Aminoguanidine**

Aminoguanidine has aroused an enormous deal of curiosity from the last few years, due to its established ability to obstruct the formation of AGEs and AGEs–produced cross linkages in both preclinical and clinical trial studies. Though it inhibits AGEs formation and AGE-induced cross linkage in collagen and other tissues, it could not impede the development of normal collagen cross-links, which are essential for structural integrity\textsuperscript{30}. In experimental diabetic animals, it averts the annoyed-linking in tendons and skin which shows its probable action for prevention of muscle and joint age-related stiffness, and skin aging (wrinkles)\textsuperscript{30}. It also prevents cardiac enlargement by plummeting the risk of glycation-induced injury to cardiac collagen. Also, it inhibits the cross-linking between lipoproteins, and therefore reduces the threat of obstruction of the arteries\textsuperscript{31}. It reduces the development of lipofuscin (age pigment) and prevents diabetic neuropathy and cataract\textsuperscript{32}. Moreover, aminoguanidine was able to protect against diabetes-accelerated erectile dysfunction and atherosclerosis\textsuperscript{33, 34}. 
Aminoguanidine is a pathetic copper chelator. Grand levels of free copper are more liable to augment AGE-induced damage. In addition to inhibiting AGE formation, aminoguanidine has other pharmacological activities. It is a selective inhibitor of inducible nitric oxide synthase (iNOS)\textsuperscript{35}. Furthermore, antioxidant activity of aminoguanidine has been described by some studies. In diabetic subject aminoguanidine has been reported to lower total cholesterol, LDL cholesterol and triglycerides independent of glucose control\textsuperscript{36}. It has shown positive actions in civilizing DN in double blind human trials.

1.5.5. Uses of Aminoguanidine

Aminoguanidine is still under clinical investigation (phase III trial) for the prevention of diabetic complications including neuropathy, nephropathy, and retinopathy. The recommended dose is 300 mg twice a day\textsuperscript{37}. 