Chapter 1

Introduction
INTRODUCTION:

The prevalence of diabetes is rapidly rising all over the globe at an alarming rate (Huizinga MM, et al., 2006). Over the past 30 years, the status of diabetes has changed from being considered as a mild disorder of the elderly to one of the major causes of morbidity and mortality affecting the youth and middle aged people. It is important to note that the rise in prevalence is seen in all six inhabited continents of the globe (Wild S et.al, 2004). Although there is an increase in the prevalence of type 1 diabetes also, the major driver of the epidemic is the more common form of diabetes, namely type 2 diabetes, which accounts for more than 90% of all diabetes cases. Nowhere is the diabetes epidemic more pronounced than in India as the World Health Organization (WHO) reports show that 32 million people had diabetes in the year 2002. The International Diabetes Federation (IDF) estimates the total number of diabetic subjects to be around 40.9 million in India and this is further set to rise to 79.4 million by the year 2030 (Fig. 1.1) (V. Mohan et al., 2007).

![2030 People with Diabetes (millions)](image)

**Fig. 1.1** Estimated number of people suffering from diabetes in 2030.

Diabetes mellitus (DM) is one of the most growing public health problems and causes major morbidity all over the world. DM is the commonest endocrine disorder, affecting 173 million adults or about 6% of the world population in the year 2002. Around two thirds of these
people live in developing countries and 97% of these had (non-insulin dependent diabetes mellitus). Diabetes has emerged as a major healthcare problem in India. According to Diabetes Atlas published by the International Diabetes Federation (IDF), there were an estimated 40 million persons with diabetes in India in 2007 and this number is predicted to rise to almost 70 million people by 2025 (Holman, Ruby R.1991).

The past 2 decades have seen an explosive global increase in the number of people diagnosed as NIDDM. In India, it is estimated that 19.4 million individuals are affected by NIDDM, which is likely to go up to 57.2 million by the year 2025. India leads the world today with the largest number of diabetics in any given country (Engelgau MM, Narayan, 2000).

The countries with the largest number of diabetic people will be India, China and USA by 2030. It is estimated that every fifth person with diabetes will be an Indian. Due to these numbers, the economic burden due to diabetes in India is amongst the highest in the world. The real burden of the disease is however due to its associated complications which lead to increased morbidity and mortality. WHO estimates that mortality from diabetes, heart disease and stroke costs about $210 billion in India in the year 2005. Much of the heart disease and stroke in these estimates was linked to diabetes. WHO estimates that diabetes, heart disease and stroke together will cost about $333.6 billion over the next 10 years in India. The global rise in diabetes will occur because of population ageing and growth, and because of increasing trends towards obesity, an unhealthy diet and sedentary lifestyles alone (Gupta Rajiv, 2008).

Diabetes is a chronic condition characterized by raised blood glucose levels. It develops when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. There are two main forms of diabetes: The first one is characterized by insulin dependence and onset in early age, with weight loss and ketonuria. This is generally termed as type I or Insulin Dependent Diabetes Mellitus (IDDM). The second is characterized by late onset, insensitivity to insulin and partial insulin deficiency. It is generally called Non-Insulin Dependent Diabetes Mellitus (NIDDM), or type II. The prevalence of diabetes, especially NIDDM, is spiraling upwards, both in developed and developing countries. Fueled by rapid economic growth, the prevalence of diabetes has now reached upto 8% of the world population. Poorly controlled diabetes aggravates the risk of diabetes complications and particularly cardiovascular diseases (Mayes, 1993).
People with type II diabetes do have insulin production but the body is not able to use insulin effectively. Type II diabetes constitutes 90% of the diabetes population. The resulting hyperglycemia can cause serious damage in the nerves and blood vessels, which leads to macro- and microvascular complications. The heart, kidneys, eyes, and lower extremities are at especially elevated risk in diabetes. These complications can be reduced by a near normalization of the glucose level, this normalization being the ultimate focus of all diabetes treatment.

The contribution of modification of lifestyle and role of insulin sensitizing drugs in prevention of non-insulin dependent diabetes is still obscure. Until date, treatment aimed at decreasing release or oxidation of non esterified fatty acids has produce inconsistent results and the toxicity of drugs has also been a problem. Fibril acid derivatives designed primarily to reduce dyslipidemia have also been tried in patients with diabetes but they bring about only a modest improvement in correcting hyperglycemia. Other strategies employed recently include experimental therapies with these agents, the problems with these experimental therapies are either that they are too toxic or have limited efficacy, which restrict their therapeutic use. The use of appetite suppressants in obese patients, which are likely to develop non-insulin dependent diabetes, is questionable. An association between pulmonary hypertension and fenfluramine derivatives has recently focused attention on the risks and benefits for appetite suppressants. At present, it is postulated that any agent that modulates insulin resistance is likely to have significant effect in the prevention of long term complications of diabetes mellitus and also in the day to day measures. In humans, fructose induced insulin resistance has been found in obese (and normal subjects) but not in well controlled diabetic subjects. (The exact mechanism of fructose induced hyperinsulinaemia and hypertriglyceridemia are not known but various mechanisms have been proposed, i.e. Suppress activation of hepatic glucose - 6 - phosphatase and fructose-1, 6 – di phosphates activity).

Though insulin is widely accepted as an ideal choice for treatment of diabetes mellitus, it shows various drawbacks and exists with some unmet needs. Treatment with insulin is essential for type I patients apart from insulin resistance; insulin therapy may lead to other complications like blurred vision and hypoglycemia. However insulin has been found very valuable in the treatment of type I diabetes. In an attempt to meet with the unmet needs in
diabetic therapy drug development research has now focused on traditional herbal remedies as a potential source for new and more effective medical therapies. Despite considerable progress in the management of DM by synthetic drugs, the search for indigenous natural anti-diabetic agents is still going on.

Exercise and having a controlled diet are recommended for the treatment of both types of diabetes. In addition, insulin is used to treat cases of type 1 diabetes. Oral hypoglycemic agents (OHA) such as sulfonylureas, biguanidines, thiazolidinediones and α-glucosidase inhibitors are often used to treat cases of type 2 diabetes. When therapy with oral hypoglycemic agents is ineffective, insulin also can be used to treat type 2 diabetes (Liu R.Y, 1996).

Despite understanding the etiopathogenesis of NIDDM, there is an alarming rise in the insulin-resistant cases and failure of OHA. The mainstay for the current management of diabetes mellitus is dietary restrictions, oral hypoglycaemics and insulin. In established diabetic cases, oral hypoglycaemic agents and insulin have considerably improved the course and complication of the entire disease process, but prolonged use of these agents has shown many untoward side-effects. Profound hypoglycaemia may occur as a result of accumulation of these drugs with a long half-life, particularly if their elimination is impaired (Goldbeck-Wood S, 1996).

As the knowledge of heterogeneity of this disorder increases, there is a need to look for more efficacious agents with lesser side effects. In recent years popularity of complementary medicine has increased. Dietary measures and traditional plant therapies as prescribed by ayurvedic and indigenous systems of medicine are used commonly in India.

In 600-800 B.C. Ayurveda described the complete pathophysiology of diabetes mellitus. The role of diet, physical activity and obesity in the aetiopathogenesis and management of diabetes was described by Sushruta as early as in 600 B.C (Upadhyay et al., 1984). Ayurveda has been the first to give an elaborate description of this disease, its clinical features, patterns and its management by diet, exercise and herbal or herbomineral drugs (Jai Deo et al., 1960). More emphasis was laid on the prophylactic and curative measures and not merely symptomatic treatment as has been described in Charak Samhita (300 B.C.) followed by Sushruta Samhita.
and Wagbhat (Shanmugasundaram KR et al., 1963). The Ayurvedic concept of management of Madhumeha (diabetes) is still recognised specially in view of the potential, ready availability and lack of toxicity and side-effects of indigenous drugs.

Number of plants have been claimed in Ayurveda for the cure of diabetes. In fact some of them have been experimentally evaluated with isolation of active principles as well. Yet not a single plant has been accepted globally as a herbal medicine that can cure diabetes.

Various herbs have been found beneficial in the management of NIDDM and are gaining considerable recognition in the management of NIDDM worldwide (Nadkarni KM, 2000). The analysis of available data indicates that the use of herbs is increasing during the last several years (Eisenberg DM et al., 1998, Margolin A et al., 1998). Recently, guidelines for investigation of herbs have been developed and herbal extracts have been clinically studied in detail for their pharmacodynamic and pharmacotherapeutic properties (Wild S et al, 2004).

Several plants have been identified as the potential source of drugs in Indian system of medicine for the treatment of diabetes. The extracts of various plants known to have antidiabetic effects like Eugenia jambolana, Pterocarpus marsupium, Gymnema sylvestre, Momordica charantia and Ocimum sanctum, Annona squamosa, Emblica officinalis, Musa sapientum, Gmelina Arborea, Allium sativum etc. Market survey of India, Srilanka, China revealed that there are several herbal products available in the market for the treatment of diabetes in various formulations like powders, decoctions, extracts, tablets/capsules of dry extracts etc. Various herbal formulations like D-400 (Mitra, S.K, 1995), Trasina are well known for their antidiabetic effects (Bhattacharya S.K., 1997). While going through the previous works of different investigators, some variations in their experimental results have been observed.

After detailed review of literatures, current market need and future commercialization opportunities, Momordica charantia (MC Fruit), Eugenia Jambolana (seeds) and Gmelina arborea (GA bark) were considered for present study. Since the EJ and MC know to have different mechanism of action it was assumed that they may produce some additive effect in terms of hypoglycaemic activity.
**Momordica charantia**, (MC fruit) is known to have a polypeptide considered to be similar to bovine insulin, which has been shown to have a hypoglycemic effect in all types of diabetes. It also promotes peripheral utilization of glucose and potentiates the action of oral hypoglycemic agents like tolbutamide.

**Eugenia jambolana** L. (EJ seeds) seeds are more used part as compared to its other parts like leaves, fruit, bark and pulp. (Nadakarni, 1954). The aq. Extracts have been known to lower the level of blood sugar. It also decrease the urine sugar and allays Polydipsia, a common manifestation of diabetes.

**Gmelina arborea** (GA Bark) is a plant of wild origin and mainly used in inflammatory disorders like arthritis, stomachic, as galactagogue, laxative and anthelmintic, improve appetite, piles etc. There are very few literatures reports the antidiabetic activity of GA bark and so GA bark was selected as third options of combination with MC and EJ.

In the traditional system of Indian medicine plant formulation and in several cases, combined extracts of plants are used as the drug of choice rather than individual. Literature search revealed that there is no reported data available about activity of combined extracts of **Momordica charantia** (MC), **Eugenia jambolana** (EJ) and **Gmelina arborea** (GA).

The antidiabetic activity of EJ and MC has been documented in ayurvedic books and also published in the literature. Antidiabetic activity of GA bark is also documented in ayurvedic books but very few literatures are available to confirm the potency and dose. Also there is no formulation available in market which contains GA and indication for its use in diabetes. However there are formulations available in market which contains aqueous extract of EJ or MC and indicated to be used as supplement to antidiabetic medicines. However none of the products available in market has data to support the claim and the dose mentioned on it. Also none of the product available in India, China and Srilanka have support of clinical trial data behind the claimed indication and has received regulatory permission to market it for its use in Diabetes Mellitus. Also there is no literature published yet to justify the additive effect of combined aqueous extract of EJ+MC+GA or EJ+MC.
Taking this into consideration in present study, it was planned to perform preclinical and clinical study of combination of herbal extracts containing *Momordica charantia, Eugenia jambolana* and *Gmelina arborea*.

So the broad objectives of the present research work are:

- To evaluate safety and antidiabetic activity of combined aqueous extracts of *Momordica charantia, Eugenia jambolana* and *Gmelina arborea* in animal model
- To evaluate safety and antidiabetic activity of aqueous extracts of *Momordica charantia* and *Eugenia jambolana* in patients with NIDDM