INTRODUCTION

> *"Today, globalization has led to an unprecedented level of interdependence among countries and interwoven interests. Health factors and social determinants for NCDs exists in every country. Therefore the prevention and treatment of NCDs is an inevitable option for our common interests and the healthy road for the common development of all mankind"*
> - WHO, 2005

Non-communicable diseases (NCDs), also known as chronic diseases, are not passed from person to person. They are of long duration and generally progress slowly. The four main types of non-communicable diseases are cardiovascular diseases, cancers, chronic respiratory diseases (such as chronic obstructed pulmonary disease and asthma) and diabetes. These four groups of diseases account for 82% of deaths caused due to NCD. Non Communicable Diseases affect low- and middle-income countries accounting nearly three quarters, around 28 million of NCD deaths (World Health Organization, 2015).

As far as India is concerned, every year approximately 5.8 million die from cancer, heart and lung diseases, stroke and diabetes. In other words, one out of four Indians have risk of dying from an NCD before they reach the age of 70 (World Health Organization, 2015).

The prevalence of diabetes in the world

The prevalence of diabetes is rapidly rising all over the world at an alarming rate (Huizing and Rothman, 2006). According to the World Health Organization (WHO), diabetes is currently causing biggest health concerns in the world. There are 415 million people diabetics worldwide and 78 million diabetics in the SEA Region; by 2040 this will reach 140 million (IDF, 2015).

The global prevalence of diabetes was 387 million, 9.9% adults in 2015. This number is projected to increase to 552 million by 2030 (IDF Diabetes Atlas, 2015). It is

predicted that by 2030, there will be 79.4 million diabetics in India, 42.3 million in China and 30.3 million in the United States of America (IDF Diabetes Atlas, 2015).

TABLE 1.1: WORLD DEMOGRAPHICS ON DIABETES

DIABETES IN THE WORLD (20-79 YEARS)	**2014**	**2035**
Adult population (billions)	4.6	5.9
Diabetes cases (millions)	386.7	591.9
Global Diabetes prevalence (%)	8.3	10.1
Comparative prevalence (%)	8.2	8.8
Undiagnosed cases (millions)	179.2	-
Total diabetes-related deaths (millions)	4.9	-
Deaths under the age of 60 (%)	48.2	-
Total Health Expenditure (USD billions)	612.2	627.3

(Source : IDF Diabetes Atlas 6th edition revised, 2014)

Table 1.1 show the global scenario of diabetes and Table 1.2 gives the top ten diabetes afflicted countries in the world wherein India leads the world with highest number of diabetics and projections for year 2030.

TABLE 1.2: LIST OF COUNTRIES WITH THE HIGHEST NUMBERS OF ESTIMATED CASES OF DIABETES FOR 2000 AND 2030

RANKING				
Sr. No.	**2000**		**2030**	
	Country	**People with diabetes (millions)**	**Country**	**People with diabetes (millions)**
1	India	31.7	India	79.4
2	China	20.8	China	42.3
3	U.S.	17.7	U.S.	30.3
4	Indonesia	8.4	Indonesia	21.3
5	Japan	6.8	Pakistan	13.9
6	Pakistan	5.2	Brazil	11.3
7	Russian Federation	4.6	Bangladesh	11.1
8	Brazil	4.6	Japan	8.9
9	Italy	4.3	Philippines	7.8
10	Bangladesh	3.2	Egypt	6.7

(Source: IDF Diabetes Atlas 6th edition revised, 2014)

Prevalence in India (Urban/Rural)

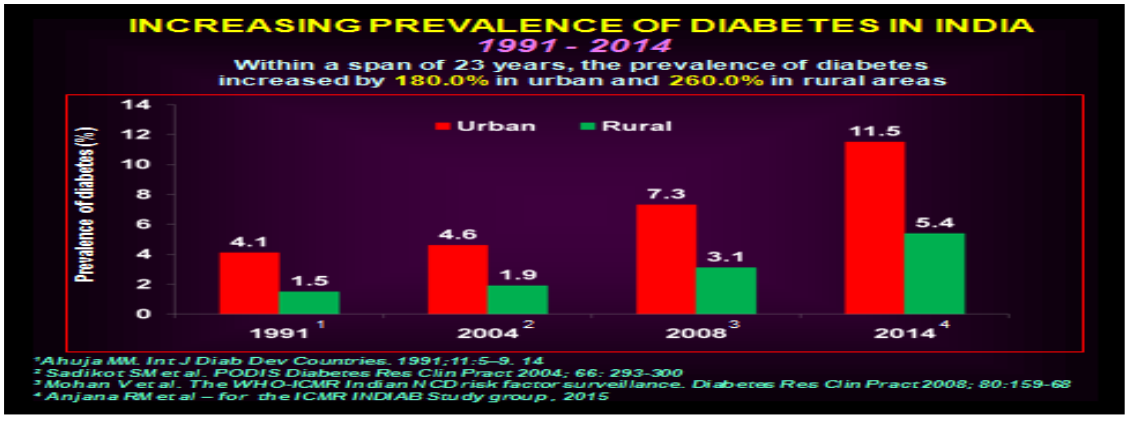
In India diabetes is fast becoming a potential epidemic (Joshi and Parikh, 2007; Kumar et al., 2013). There were 69.1 million cases of diabetes in India in 2015 (IDF, 2015). This figure is projected to rise from 69 million to 101.2 million by 2030 (IDF Diabetes Atlas, 2015).

Estimated prevalence rates in for urban and rural India are based on national surveys and individual studies. Estimates vary depending on geographical location and year of study. The occurrence rates of diabetes for urban, semi urban and rural population vary from 5-15%, 4-6% and 3-5%, respectively, showing wide regional disparities depending on different local settings (Gupta and Misra, 2007). There was 3 times shift in the rural population (2.4% to 6.4% during last 14 years) in the prevalence rate similar to urban population and the number is increasing rapidly**.** Fig 1.1 shows increase in the prevalence of diabetes for urban and rural population from 1991 to 2014 reported by various studies conducted (Ahuja, 1979, Sadikot et al., 2004; Mohan et al., 2008; Pradeepa et al., 2015).

TABLE 1.3 : PREVALENCE OF DIABETES IN INDIA FROM 1991-2014

	Prevalence (%) of diabetes in these years in India			
Region	1991	2004	2008	2014
Urban (%)	4.1	4.6	7.3	11.5
Rural (%)	1.5	1.9	3.1	5.4

FIG 1.1: INCREASING PREVALENCE OF DIABETES IN INDIA



Prevalence (Regional)

Gujarat has the highest number of diabetes in the country. As per the recent health profile report, there are 1,61,578 out of the total 7,87,435 persons screened (20.5%). Gujarat tops all other states with the highest number of diabetes and hypertension cases as reported in the recent National Health Profile 2015 by Central Bureau of Health Intelligence under Ministry of Health and Family Welfare (NHP, 2015).

The people of Gujarat are prone to develop diabetes because of genetic susceptibility, sedentary lifestyle and dietary preference for sweet and oily foods. A multicentric study conducted phase wise by ICMR INDIAB in Gujarat reported 7.1% prevalence of diabetes and 10.7% pre-diabetes (Anjana et al., 2015).

National Programme for Prevention and Control of Cancer, Diabetes, cardio-vascular Diseases and stroke (NPCDCS, 2014) has revealed that region wise **Gujarat had the second highest prevalence of diabetes (more than 50 lakhs)** after Tamilnadu . It is diabetic capital of India. Also the study conducted by SITE in 8 states (Screening India's Twin Epidemic) on prevalence of diabetes and hypertension indicated high prevalence and poor control of diabetes and HT and also stressed on the need for early diagnosis and management to reduce the complications (SITE, 2015) (Table 1.4).

TABLE 1.4: DIABETIC PREVALENCE IN MAJOR CITIES OF GUJARAT

Cities	Diabetes Prevalence (%)	Hypertension (%)
Ahmadabad	13.37	11.54
Gandhinagar	9.72	7.91
Surendranagar	5.49	6.70
Rajkot	7.23	5.84
Jamnagar	9.71	3.58
Porbandar	11.30	11.20
Junagadh	12.1	6.73

Source: (Npcdcs, 2014)

Several studies were done in Food and Nutrition department to study the prevalence of Type II Diabetes Mellitus in Gujarat (Vadodara, Ahmadabad and Godhra). It was

found that prevalence of diabetes was higher in Godhra (19%) as compared to Vadodara (12%) and more pronounced in males (Iyer et al., 2011).

Types of Diabetes mellitus

Diabetes mellitus has been classified into following categories:

Type 1 DM previously known as Insulin dependent Diabetes Mellitus, (IDDM) or Juvenile diabetes

This type of diabetes account for less than 2 % percent in our country and onset of Type 1 DM is usually very acute and in childhood. These patients depend upon insulin for their survival and withdrawal of insulin leads to ketoacidosis. It occurs either due to auto-immune or idiopathic destruction of insulin producing beta cells in Islets of Langerhans in pancreas resulting in inability to produce endogenous insulin which is vital for control of blood sugar and other metabolic functions.

Type 2 DM previously known as Non-insulin Dependent Diabetes Mellitus (NIDDM), or Maturity onset Diabetes Mellitus

This type of diabetes is the commonest type of diabetes all over the world, especially in India affecting more than 96% of diabetics in the country. It is usually diagnosed in the middle age. Environmental and genetic factors are the chief causes of type II diabetes. Most of the patients are found to be suffering from both, beta cell dysfunction and insulin resistance. Genetic and acquired factors are responsible for this pathology.

Etiology of Diabetes Mellitus

Diabetes mellitus is a chronic disease characterized by relative or absolute deficiency of insulin, resulting in glucose intolerance. Diabetes mellitus develops from abnormal glucose metabolism. The lack of insulin activity results in failure of transfer of glucose from the plasma into the cells. The body responds as if it were in the fasting state. There is stimulation of glucogenolysis, gluconeogenesis and lipolysis producing ketone bodies.

There is abnormal glucose absorption and it accumulates in the blood (hyperglycaemia) to be excreted in the urine (glycosuria). Glucose in the urine causes osmotic diuresis, leading to increase urine production (polyuria). Due to stimulation of protein breakdown to provide amino acids for gluconeogenesis, there is muscle wasting and weight loss. These classic symptoms occur only in patients with severe insulin deficiency, most commonly in type I diabetes. Many patients with type II diabetes do not have these symptoms but present with one of the complications of diabetes.

The etiology of diabetes in India is multifactorial and includes genetic factors coupled with environmental influences such as obesity associated with high living standards, continued urban migration, and lifestyle disorders. So Sedentary habits coupled with unhealthy diet pattern are the major contributing factors for the higher prevalence of diabetes and hypertension in urban poor population (Vigneshwari et al., 2015).

Diabetes has been cited to be a growing epidemic over India, particularly in urban areas. In the urban Indian middle class, more than a 25% of patients with diabetes are undiagnosed and having poor glycemic control (Gupta et al., 2015). Many cardiovascular risk factors like hypertension, hypercholesterolemia, low HDL cholesterol, hypertriglyceridemia, and smoking/smokeless tobacco use are highly prevalent. There is low awareness, treatment, and control of hypertension and hypercholesterolemia in patients with diabetes (Gupta et al., 2015).

Treatment for Diabetes

Pharmacological

Treatment of type II diabetes involves diet, exercise, often combined with one or more oral hypoglycaemic agents. Optimal treatment, however, may require the use of insulin with or without oral agents. Among adults with diagnosed diabetes, 12% use both insulin and oral drugs, 16% use insulin only, 57% use oral agents only, and 15% do not use pharmacotherapy (Norris et al., 2004).

Non-pharmacological

Healthy eating habits and good nutrition can be very effective in preventing and managing diabetes. Healthy food items such as whole grains are rich in components like dietary fibre, starch, fat, antioxidant nutrients, minerals, vitamin, lignans, and phenolic compounds that have been linked to the reduced risk of obesity, insulin resistance, dyslipidemia, T2DM and heart diseases (Chandalia, 1999). Several prospective studies have shown that adoption of lifestyle modification help in preventing the onset of diabetes (Knowler et al., 2002). Early identification of the high risk patients would help in preventing or delaying the onset of diabetes by taking appropriate intervention in the form of dietary changes and increasing physical activity.

Economic burden of disease

Diabetes is emerging as a serious health challenge in India because it is also associated with an increased risk for cardiovascular disease. Despite diabetes being a life-long disorder and expensive to manage and treat for the masses in developing societies, there is lack of data on its economic burden in India. In the Indian context the financial burden is often shared by relatives of the patients.

The total amount needed for India to treat Type II diabetes mellitus is estimated to be around 2.2 billion USD. (Ramachandran, 2007). In India the direct medical cost of treatment to identify one subject with insulin glucose tolerance is INR 5,278. The cost of insulin amounts to 350.00 USD (16,000 Indian Rupees) per year, while medication for non-insulin-requiring patients costs about 70.00 USD per year (Ramachandaran, 2007). In the Indian context these costs are prohibitive: 75.5% of the Indian population is earning less than $2 per day and 41.6% less than $1.25 per day (Prabhakaran and Ajay, 2009).

At present the treatment of diabetes mainly the use of biguanides, thiazolidinediones, sulfonylurea, D-phenylalanine and α glycosidase inhibitors in addition to insulin. However, due to unwanted side effects and their high cost, the efficacies of these compounds are questionable and there is a demand for new compounds for the treatment of diabetes (UK Prospective Diabetes Study Group, 1995; Moller, 2001).

Alternative Treatments for T2DM

The National Centre for Complementary and Alternative Medicine, part of the National Institutes of Health, defines complementary and alternative medicine as a "group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine." Complementary medicine is used with conventional therapy, whereas alternative medicine is used instead of conventional medicine.

There are a number of alternative systems of medicine for the treatment of diabetes, who used the essence of herbs; some of them are Ayurveda, Siddha, Yunani, Homeopathy etc. Among these 'The science of life' - Indian Ayurvedic system of medicine is very ancient and existed even before the birth of modern medicine, making use of plants, herbs and minerals for treatment of diabetes. Siddha system is one of the oldest systems of medicine which is indigenous to India prevalent mostly in South India especially in Tamilnadu. In this system of medicine a number of herbs, minerals and their admixtures have been used for treatment of diabetes mellitus (Neerazhivu). In India the admixture of Graeco-Roman and Arabian medicine is known as 'Yunani' medicine and uses herbs and minerals for treatment of diabetes. Homeopathy founded and developed by Samuel Hahnemann (1755-1843) was the earliest important alternative system of medicine in West. Homeopathy uses different herbal decoctions for treatment of diabetes (Saxena et al., 2002; Majumdar, 2005).

In recent years the popularity of complementary medicine has increased. The commonly used therapies available for diabetic patients include herbal medicine, nutritional supplements, diet modifications, spiritual healing and relaxation technique.

Traditional medicinal plants with various active principles and properties have been used by physicians since ancient times to treat a great variety of human diseases. It has been suggested that compounds present in medicinal plants (alkaloids, glycosides, terpenes, flavonoids, etc) isolated from plants, either alone or in combination, impart therapeutic effect holistically in disorders like diabetes and its complications (Iyer et al., 2009; Rai et al., 1997; Sharma et al., 1990). In Indian system of medicine several herbal remedies had been tried for the treatment of diabetes mellitus since the time of 'Charaka' & 'Sushruta'.

TABLE 1.5: DEPARTMENTAL STUDIES ON INDIGENOUS FOOD FOR THEIR FUNCTIONAL ROLE

Indigenous Foods	Year	Author	Conclusion
Flaxseeds	2007	Mani et al	Low GI, hypoglycaemic & hypolipidemic functions
Cinnamon	2003	Khan et al (human study)	Decreases fasting glucose levels
Cinnamon	2003	Qin et al (Animal study)	Improves metabolic action of insulin, prevents insulin resistance, increase glucose uptake into cells, enhances insulin signalling pathways in muscles
Spirulina	1998	Mani et al	Reduces FBS, PPBS and HbA1c
Bitter melon	1993	Srivastava et al	Improves PPBS, Blood and urine sugar, decreases HbA1c levels
Curry leaves	1989	Iyer & Mani	Decreases fasting and PPBS

Many of the botanical products and food components are not identified as nutrients but they are effective as hypoglycaemic agent showing improvement in lipid metabolism, antioxidant status and capillary function in their clinical trials. These include fenugreek seeds (powder 25-50g twice a day), bitter melon (57g of juice/day or 15g aqueous extract), spirulina (2g/day), Soybean (69g/day), flaxseeds (40g ground/day) curry leaves, cinnamon (1,3 or 6g/day)/, Tulsi (2g powder/day), Amla (35g/day) etc. which have been clinically proved (Raghuram and Sharma, 1990, Srivastava et al., 1993, Shah and Iyer, 2003, Mani et al., 1990, Kochhar et al., 2009) and Panchratna juice (Desai and Iyer, 2008). Various studies done in the department on indigenous food used in the treatment of diabetes is shown in Table 1.8.

Aegle Marmelos (L.) Correa

Aegle Marmelos (L.) Correa is a promising treatment for diabetes and has a long history of use in traditional Indian medicine. *Aegle Marmelos* (*L.) Correa* also known as Bael in Hindi or Billipatra in Gujarati has been used in India from Vedic or

prehistoric times. It has been described in ancient medical treatise *Charak Samhita* as *Rasayana,* besides its other uses and cures (*Charaka-samhita*, 1983). *Aegle Marmelos* (*L.) Correa* has been known for its antihyperglycemic effect (Saxena and Vikram, 2004). The leaves and the shoot of the plant are used as green vegetable in Indonesia (Sharma et al., 2007; Rathore, 2009).

Animal Studies on *Aegle Marmelos (L.) Correa*

Several studies conducted on experimental animals have indicated a positive role of *Aegle Marmelos (L.) Correa* leaf extract, 250-500mg/kg BW given orally to the glucose fed hyperglycaemic rats for a period of one to two months improved their blood sugar levels (Ponnachan et al., 1993, Paulose et al., 1993, Das et al., 1996, Sharma et al., 1996, Sachdeva et al., 2001, Upadhya et al., 2004). Miyazaki (2007) reported hypoglycaemic activity after administration of the extracts of the leaves of *Aegle Marmelos (L.) Correa* at doses of 50, 70, 90 and 100-mg/kg body wt for 14 consecutive days to male and female Wistar rats. He also concluded that *Aegle Marmelos (L.) Correa* have a high margin of drug safety and there was no short term toxicity (Miyazaki, 2007).

Possible Mechanism of Action

This medium deciduous plant has been shown in many animal studies to improve blood glucose control by regenerating insulin-producing cells in the pancreas, improving insulin sensitivity, decreasing glucose absorption from the gut, and improving glucose storage in the body. It has also been shown to decrease glucose binding to proteins, which contributes to the complications of diabetes. It produces hypoglycaemic effect enhancing the peripheral utilization of glucose, correcting the impaired hepatic glycolysis and limiting its gluconeogenic formation similar to insulin (Banerji and Nigam, 1984 ; Das et al., 1996). *Aegle Marmelos (L.) Correa* leaf extract reduce oxidative stress by scavenging lipid peroxidation and enhancing certain antioxidant levels which causes lowering of elevated blood glucose level on Alloxan induced diabetes (Kuttan and Sabu, 2004). Hema and Lalithakumari (1999) documented its hypoglycaemic action along with other pharmacological actions on molecular level (Hema and Lalithakumari, 1999). Still, more research is required with

the *Aegle Marmelos (L.) Correa* to investigate the mechanism of actions with diabetes along with other therapeutic activities (Sharma et al., 2011).

Aegle Marmelos (*L.) Correa* plant has been included in the World Health Organization list of herbal drugs wherein HPTLC fingerprint is available for standardization of the herb (Ayurvedic Pharmacopoeia, 2000). The Ayurvedic Pharmacopoeia of India includes the monographs on "stem" and "root" of the plant. However reports on physico-chemical constituents and trace elements present in the leaves are few though this plant has been regarded as good dietary supplement. (Shankar and Garg, 1967; Rathore, 2009).

Aegle Marmelos (*L.) Correa* has been used as a herbal medicine for the management of diabetes mellitus in Ayurvedic, Unani and Siddha systems of medicine in India (Choudhry and Bandhopadhyay, 2003), Bangladesh (Lampronti et al., 2003) and Sri Lanka (Karunanayake et al., 1984).

Ayurveda practitioners commonly use the roots of *Aegle Marmelos* (*L.) Correa* as an ingredient of *dasamula* (ten roots), which is useful in recovering from the loss of appetite and use fruits in the preparation of *Chyavanprash*. The leaves of this plant are used as salad greens in Indonesia and other parts of Asia (Farooq, 2005).

Ethanobotanically also this medicinal plant is used by traditional healers in different tribal belts of India for cure of various diseases in addition to diabetes but the requisite level of activity as well as toxicity should be considered to further scrutinize this plant as the potential medicine (Chakravorty and Kalita, 2012 ; Tripathy et al., 2000).

All these studies exhibit the dependence and usage of *Aegle Marmelos* (*L.) Correa* as a herbal remedy for different diseases. However, the review reveals that the standardization of the dosage and formulations are not documented. Despite these unique properties, a good safety profile, and the low cost of this treatment, there have been no well-designed clinical trials that have tested the safety and effectiveness of *Aegle Marmelos* (*L.) Correa* for diabetes in humans. In light of the substantial and increasing burden of diabetes on the health system, economy, and increasing concerns about the cost, safety and compliance of current oral hypoglycaemic therapy, there is a clear and urgent need for this research. Thus an in-depth clinical trial on this would

enable us to combine the scientific knowledge along with traditional knowledge for improvement of the health of the people in rural and tribal belts of India who do not have an access to costly western system of medicine.

Therefore the present study entitled "**In-depth Study of the Antioxidant Profile of *Aegle Marmelos* (*L.) Correa* and Its Impact on Type II Diabetes Mellitus Subjects"** was undertaken in the following three phases:

BROAD OBJECTIVE

To study the impact of *Aegle Marmelos* (*L.) Correa* leaf juice supplementation in Type II diabetes subjects

SPECIFIC OBJECTIVES

i. To study in-depth antioxidant profile, proximate composition, trace elements and heavy metals in the cultivated ('*Gomayasi*') and wild variety of *Aegle Marmelos* (*L.) Correa* leaves

ii. To conduct knowledge, practice and use (KPU) of *Aegle Marmelos* (*L.) Correa* leaves with practitioners of Ayurveda and Naturopathy.

iii. To assess the impact of *Aegle Marmelos* (*L.) Correa* leaf juice supplementation on blood sugar levels, lipid profile, liver and kidney functions of Type II diabetes subjects.