REVIEW OF LITERATURE

"It is now recognised that it is the low-and -middle-income countries that face the greatest burden of diabetes. However, many governments and public health planners still remain largely unaware of the current of the current magnitude, or, more importantly, the future potential for increase in diabetes and its serious complications in their own countries"

-IDF 2010

DIABETES MELLITUS

Diabetes is characterized by group of metabolic disorders featured by hyperglycaemia resulting from defects in insulin secretion, insulin action or both (ADA, 2014). In patients with diabetes, the presence and absence of insulin causes hyperglycaemia. The two types share one common feature: elevated blood sugar (glucose) levels due to absolute or relative insufficiencies of insulin. DM can be controlled but not reversed. Diabetes with its acute and chronic complications and the myriad of disorders associated with it is a major health hazard. India has long passed the stage of a disease epidemic but the severity of the problem reached "pandemic" proportions.

Types

Type 1 diabetes mellitus

Type 1 diabetes mellitus is caused by insulin deficiency due to destruction of pancreatic β-cells principally via an autoimmune reaction that can be triggered by different factors (Chen et al., 2001). It can also develop along with various hereditary factors, such as Human Leukocyte Antigen (HLA) alleles. Typically, destruction of pancreatic β-cells progresses to major deficiency in insulin affecting around 10% cases of diabetes, covering 20 million people worldwide (American Diabetes Association, 2001).

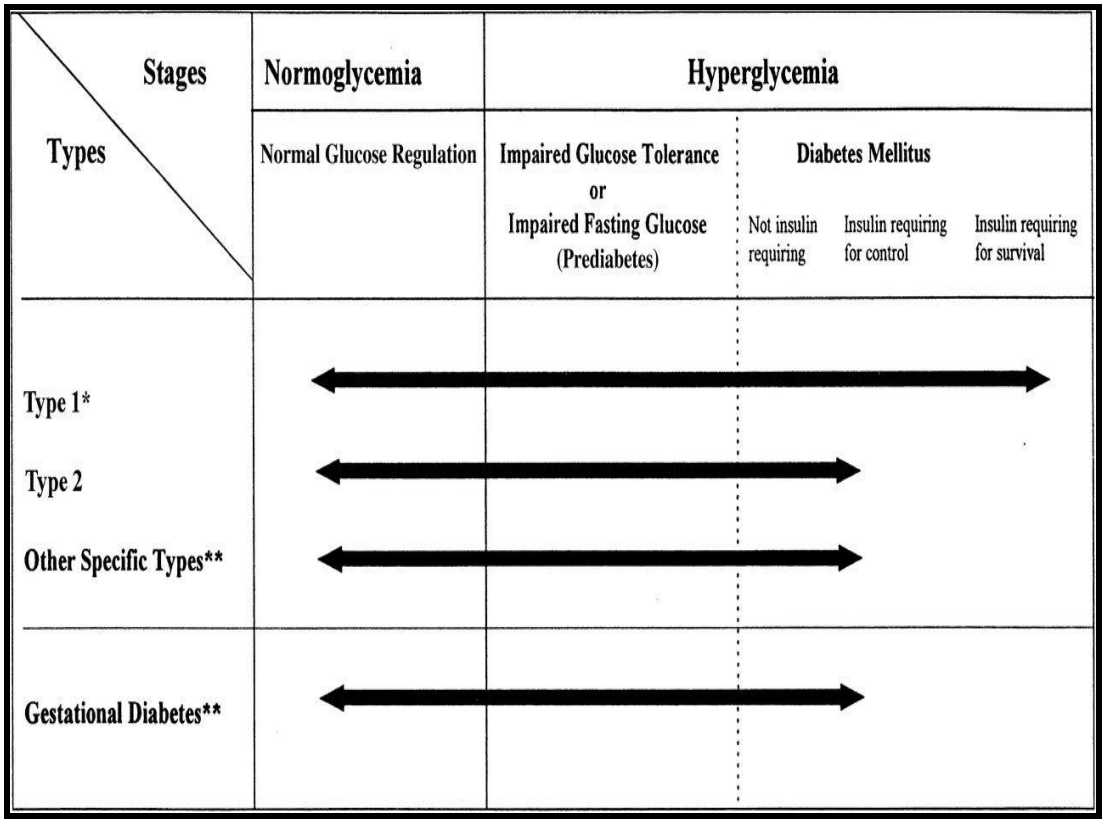
Type 2 diabetes mellitus

This form of diabetes, which accounts for 90–95% of those with diabetes, previously referred to as Non–Insulin-Dependent Diabetes, type 2 diabetes, or adult-onset diabetes, encompasses individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency (ADA, 2014). Type 2 diabetes mellitus (formerly called NIDDM, type II or adult-onset) is characterized by insulin resistance in peripheral tissue and an insulin secretory defect of the beta cell which eventually lead to impaired glucose tolerance (Defronzo et al., 2007). This type of diabetes is positively associated with various risk factors such as family history of diabetes, old age, obesity and lack of physical activity.

Gestational diabetes mellitus

Gestational diabetes is the third main form and occurs when pregnant women without a previous history of diabetes develop high blood-sugar levels. It occurs in about 4% of the pregnancies in the western countries.

FIG 2.1: DISORDERS OF GLYCAEMIA: ETIOLOGIC TYPES AND STAGES

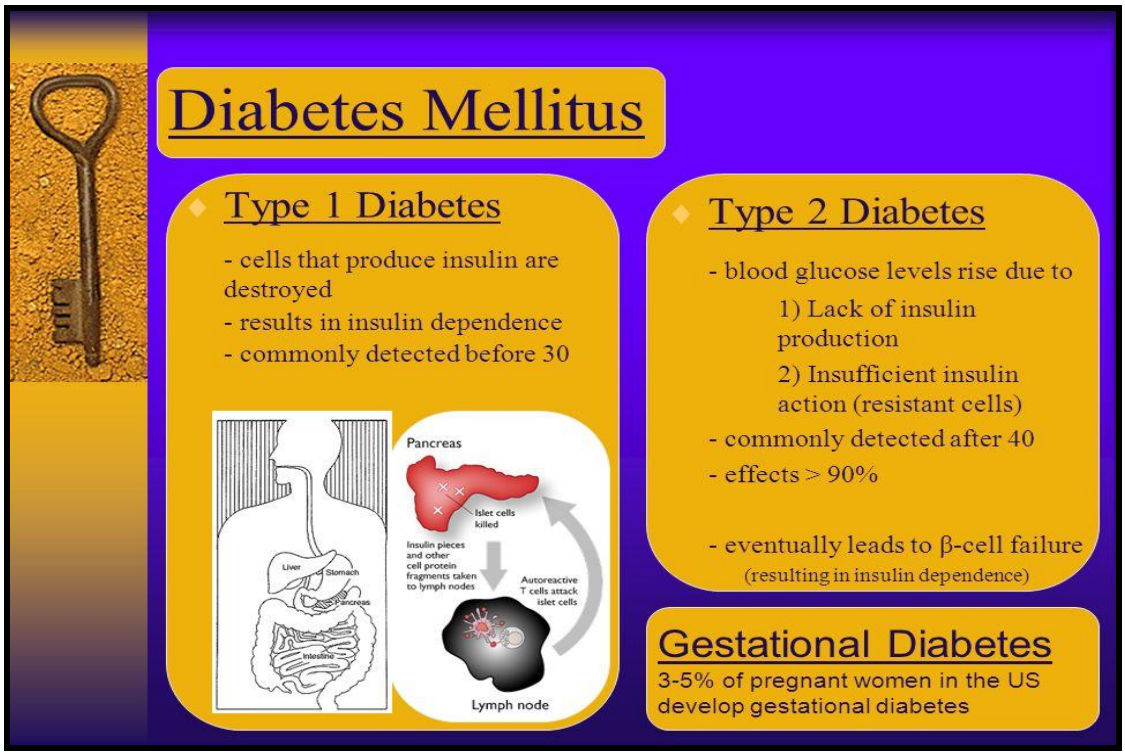


(Source: ADA, 2014)

**Even after presenting in ketoacidosis, these patients can briefly return to normoglycemia without requiring continuous therapy*

***in rare instances, patients in these categories (e.g., Vacor toxicity, type 1 diabetes presenting in pregnancy) may require insulin for survival.*

FIG 2.2: COMPARISON BETWEEN TYPE I AND TYPE II DIABETES MELLITUS



Diabetes-prevalence

Global Scenario

Diabetes mellitus is a growing public health problem in both developed and developing countries. The global prevalence of diabetes was 387 million in 2015. This number is projected to increase to 552 million by 2030, or 9.9 % of adults (IDF Diabetes Atlas, 2015). Out of this 77% people having diabetes are living in low and middle income countries. Diabetes will be the 7th leading cause of death in 2030. About half the diabetic population (46.3%) in the world are undiagnosed. In South-East Asian countries, 75 million people suffer from diabetes with the prevalence rate of 8.3% and 52.8% cases are undiagnosed.

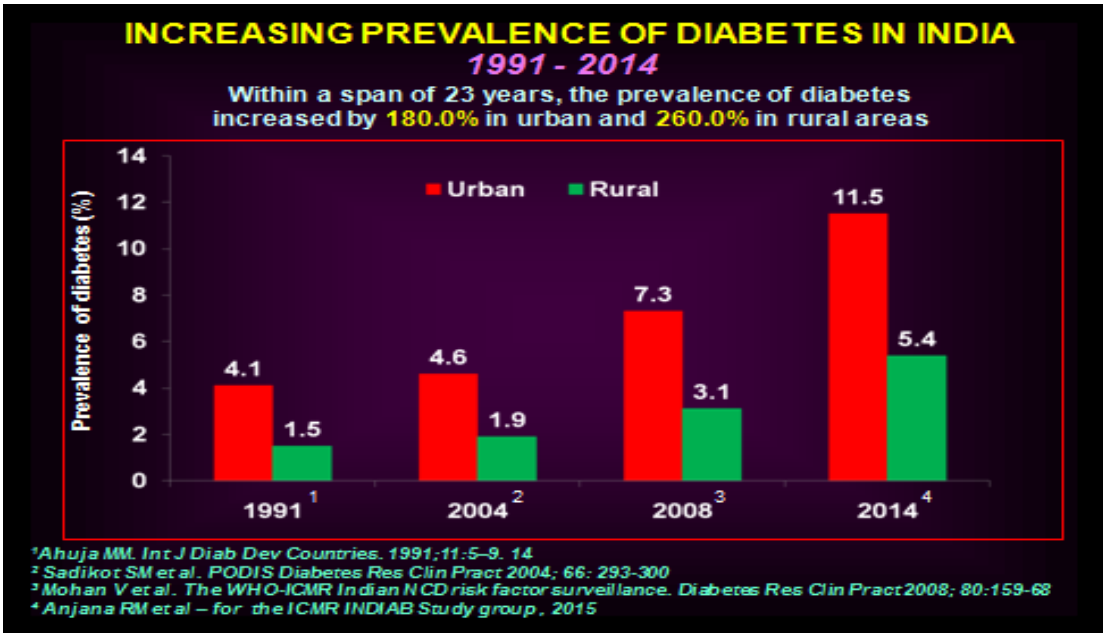
Diabetes is causing health related economic burden as the cost per person with diabetes is around 95 USD leading to total expenditure of U.S. Ş 612 billion globally

(IDF Diabetes Atlas 6th Edition revised, 2014). Out of total pandemic of diabetes in the world, China, India and USA ranks at the top three positions respectively.

Indian scenario

According to the Diabetes Atlas 2015 published by the International Diabetes Federation, the number of people with diabetes in India currently around 69.1 million is expected to rise to 102 million by 2030 unless urgent preventive steps are taken (IDF, 2015).

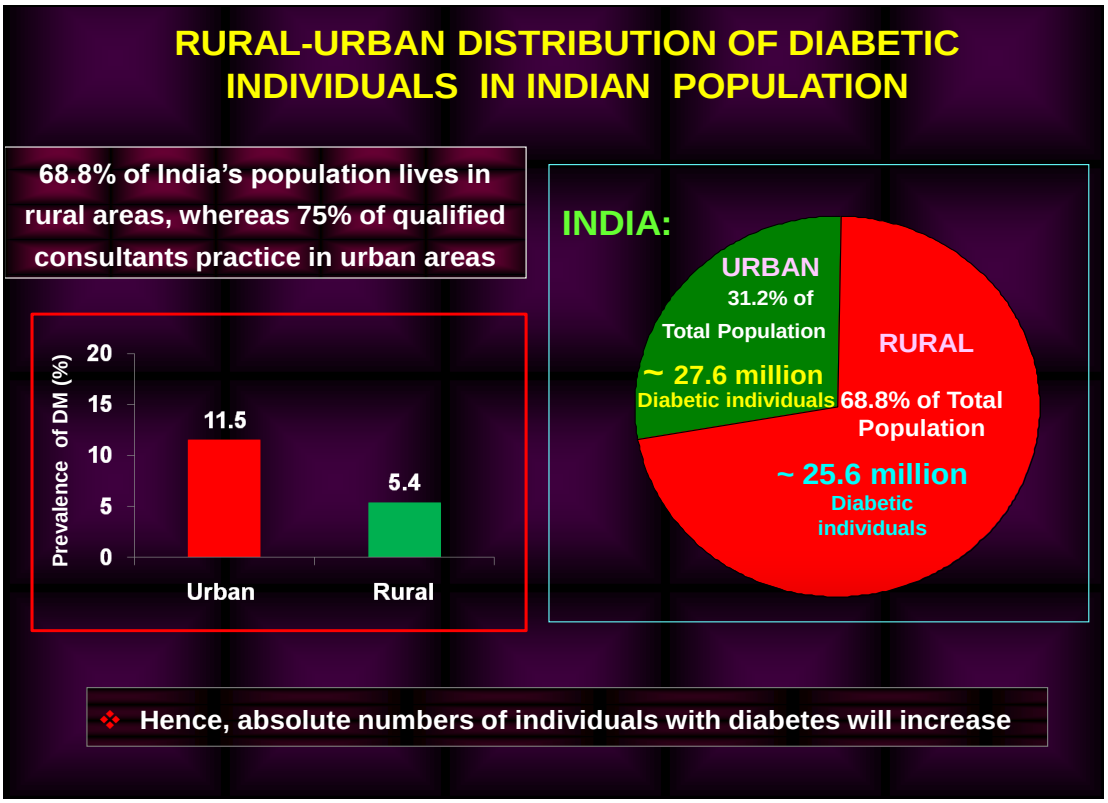
FIG 2.3: INCREASING PREVALENCE OF DIABETES IN INDIA (1991 - 2014)



Within a span of 23 years, the prevalence of diabetes increased by 180.0% in urban India and 260.0% in rural areas (Fig 2.3) (Anjana et al., 2015). So though the prevalence for rural areas is less, the prevlence rate of rising epidemic is more than the urban areas which will have devastating effect on emerging problem. About 68.8% of India's population lives in rural areas, whereas 75% of qualified consultants practice in urban areas hence absolute number of diabetic individuals will increase. In urban population, there are 31.3% self-reported subjects having good control on diabetes (HbA1c), 36.9% having fair control and 31.8% having poor control on diabetes (HbA1c) in India whereas among the rural population 30.8% having good control, 31.9% having fair control and 37.3% having poor control on diabetes (HbA1c). Thus overall, 19 million urban diabetic population and 17,7% rural diabetic

population have an HbA1c ≥ 7% (ICMR INDIAB, 2015). ICMR-INDIAB in 2015 conducted study from various parts of India showed further increases in prevalence of diabetes and pre-diabetes in urban and rural areas (ICMR-INDIAB, 2015) (Fig 2.4).

FIG 2.4: RURAL - URBAN DISTRIBUTION OF INDIAN POPULATION



There is a large heterogeneity of diabetes prevalence within urban and rural populations. Earlier studies conducted from various parts of urban India show that the prevalence of diabetes varied from prevalence of 12.1% in T2DM (a population based study- NUDS) (Ramachandran et al., 2001), age-standardized prevalence of 8.6 per cent in urban population (Gupta et al., 2003), 8% from The Indian Industrial Population Surveillance Study (Reddy et al., 2006), urban prevalence rate of 8-20% and 5-15% in rural areas (Mohan et al., 2007), 5.9 % to 19.5 %. (Ramachandran and Snehalatha, 2009). Various multisite studies such as DESI (Ebrahim et al., 2010), PODIS (Sadikot et al., 2004) and INDIAB (ICMR-INDIAB, 2011) reported prevalence around 7% urban and 5% rural population, INDIAB (ICMR-INDIAB, 2011) reported prevalence around 7% urban and 5% rural population. and The Indian Women's Health Study reported diabetes in 2.2% rural and 9.3% urban women (Pandey et al., 2013). More recent reports from various parts of India showed further

increases in prevalence of diabetes and pre-diabetes in urban and rural areas (ICMR-INDIAB, 2015) (Fig 2.4).

TABLE 2.1: DEMOGRAPHY OF DIABETES IN INDIA

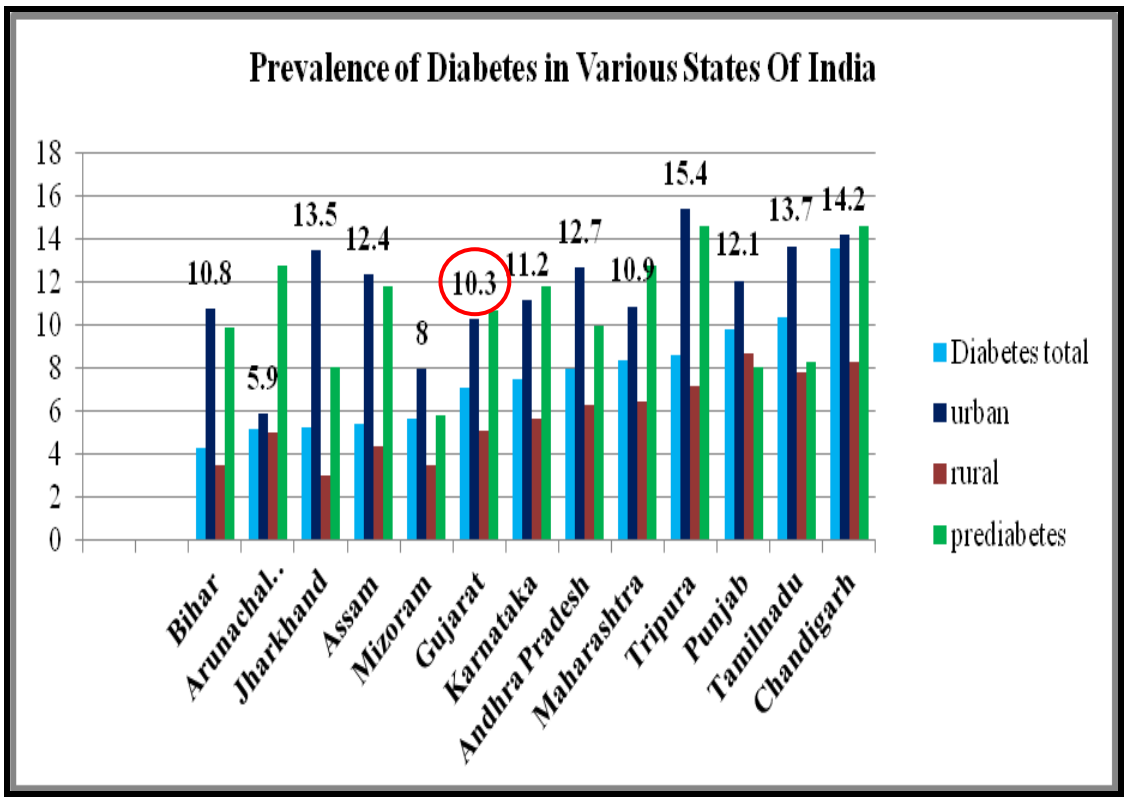
Variables	**Figures**
Total Adult Population (1000s) (20-79 years)	798,988
Prevalence of diabetes in adults (20-79 years)	8.7
Total cases of adults (20-79 years) with diabetes (1000s)	69,188.6
Number of death in adults due to diabetes	1,027,911
Cost per person with diabetes (USD)	94.9
No. of cases of diabetes in adults that are undiagnosed (1000s)	36,061.1

(Source: IDF, 2015)

TABLE 2.2: PREVALENCE OF DIABETES IN URBAN INDIA

Region	**Year**	**Age (subjects in (yrs)**	**Prevalence (%)**		
			Diabetes	**IGT**	**IFG**
National Ramachandran et al 2000	2000	> 20	12.1	14.0	-
Ramachandran et al	2000	>20	11.6	8.6	-
Ramachandran et al	2000	>20	13.5	16.8	-
Reddy et al	2003	20-69	8.4	-	6.4
Gupta et al	2003	>20	8.6	-	5.3
Sadikot et al (Northern India)	2004	>20	5.9	6.3	4.8
Mohan et al	2004	>20	14.3	10.2	-
Prabhakaran et al (Southern India) (men only)	2005	20-59	15	37	
Menon et al	2006	18-80	19.5	4.1	7.0
Ramachandran et al	2006	>20	18.6	7.4	-

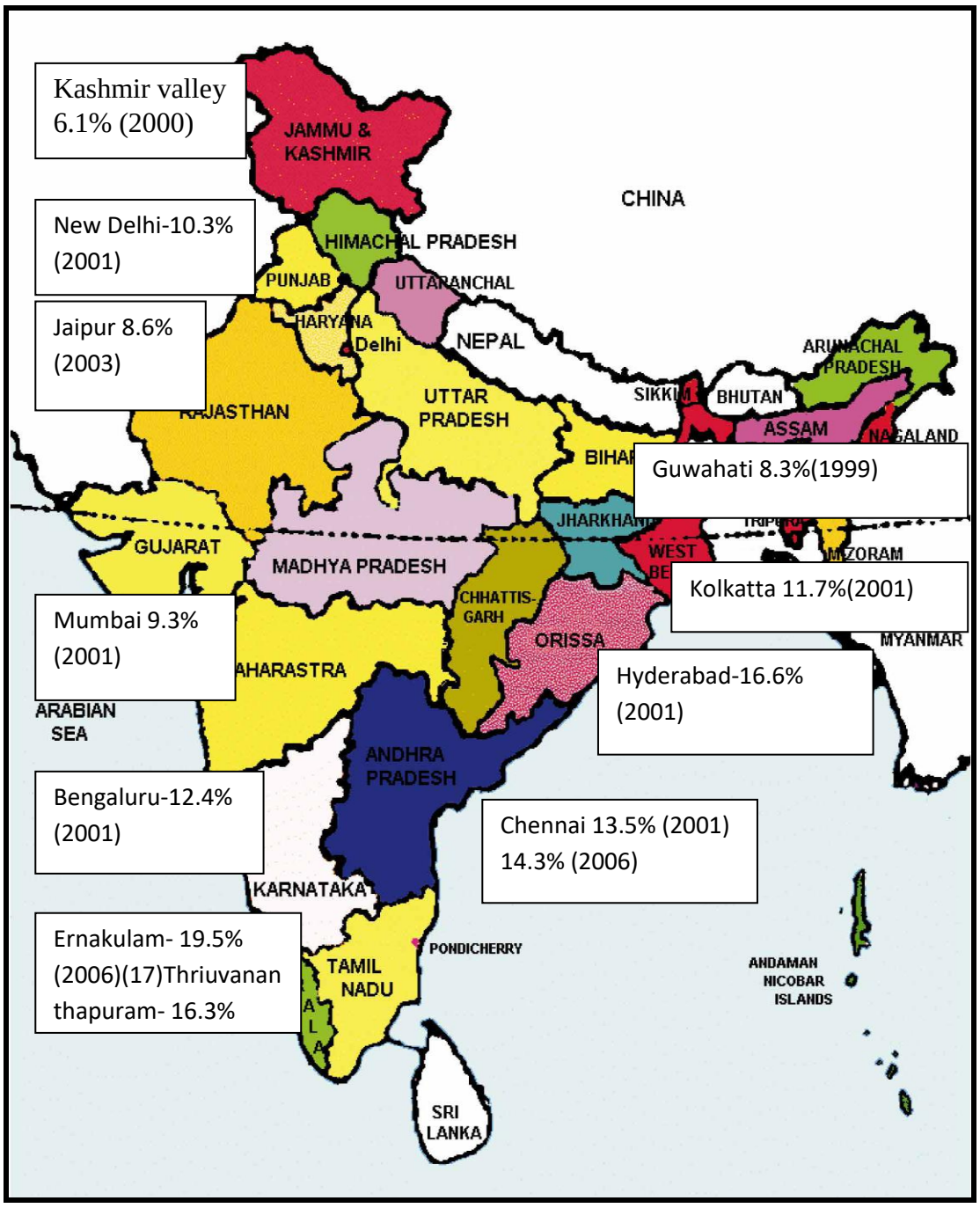
FIG 2.5: WEIGHTED PREVALENCE OF DIABETES AND PREDIABETES IN URBAN AND RURAL POPULATION OF INDIA



Source: (ICMR-INDIAB, 2015)

Fig. 2.6 is a map of India showing the States where population-based studies have been done and it also shows the prevalence of type 2 diabetes reported in different regions of India (Mohan et al., 2007).

FIG 2.6: MAP OF INDIA SHOWING RECENT POPULATION BASED STUDIES SHOWING THE PREVALENCE OF TYPE 2 DIABETES IN DIFFERENT PARTS OF INDIA



(Sources: Mohan et al., 2007)

In the urban Indian middle class, more than a quarter of patients with diabetes are undiagnosed and the status of control is low (Gupta et al., 2015). 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).

Region wise: Alarming situation in Gujarat

Gujarat pips 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). As per the recent health profile report, the number of diabetic persons in Gujarat are 1,61,578 which is 20.5 per cent of the total 7,87,435 population screened. A multicentric ICMR funded study reported 1.73% overall prevalence (3.7% of urban and 1.9% of rural) in Ahemedabad (Ramaiya et al., 1990). No such large community based research was conducted in Gujarat after 1970.

According to National Programme for Prevention and Control of Cancer, Diabetes, cardio-vascular Diseases and stroke (NPCDCS, 2014), **Gujarat had the second highest prevalence of diabetes (more than 50 lakhs)** after Tamilnadu . It is diabetic capital of India. Prevalence of diabetes and hypertension in various cities of Gujarat is given in Fig 6 and also the need for early diagnosis and management to reduce complications Screening India's Twin Epidemic (Site)–Diabetes Mellitus And Hypertension (SITE, 2015).

TABLE 2.3 : 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)

TABLE .2.4: PREVALENCE OF DIABETES AND HYPERTENSION

TYPES	DM (%)	HT (%)
Known cases	21.5	26.9
Newly diagnosed cases	9.4	25.1
Overall prevalence	28.9	45.3
Patients with both (DM+HT)	16.7%	
Family history	38.1%	
Overweight/obesity	75.6%	
HbA1c≥7	73%	

(SITE, 2015)

Few studies carried out in Gujarat are summarized wherein prevalence of diabetes among industrial urban population was found to be 5% to 21% in an around Vadodara

TABLE 2.5: DEPARTMENTAL STUDIES ON PREVALENCE OF DIABETES

Year	Author	Place	Type of Population	Prevalence (%)
2011	Shah & Chandorkar	Vadodara,	Urban (MSU)	6.8% males
2011	Khalsa & Iyer	Ahemedabad	OPD	21.76
2008	Desai & Iyer	Vadodara, Godhra	Urban Urban	12 18.8
2007	Mathur & Iyer	Vadodara	Industrial	6.4
2006	Shah & Mehan	Vadodara	Industrial	15.3
2004	Pandya & Mehan	Vadodara	Industrial	10.4
2002	Dholakia & Iyer	Vadodara	Urban	9.5
2002	Gujarati & Mani	V.V. Nagar	Urban	5.3
2000	Desai & Mani	Vadodara	Industrial	7.4

Pathophysiology

Insulin is the principal hormone that regulates the uptake of glucose from the blood into most cells of the body, especially liver, muscle, and adipose tissue. Therefore, deficiency of insulin or the insensitivity of its receptors plays a central role in all forms of diabetes mellitus (ADA, 2014)

The body obtains glucose from three main places: the intestinal absorption of food, the breakdown of glycogen, the storage form of glucose found in the liver, and gluconeogenesis, the generation of glucose from non-carbohydrate substrates in the body (Shoback et al., 2011). Insulin plays a crucial role in maintaining glucose levels in the body. Insulin can inhibit the breakdown of glycogen or the process of gluconeogenesis, it can stimulate the transport of glucose into fat and muscle cells, and it can stimulate the storage of glucose in the form of glycogen (Shobback et al., 2011)

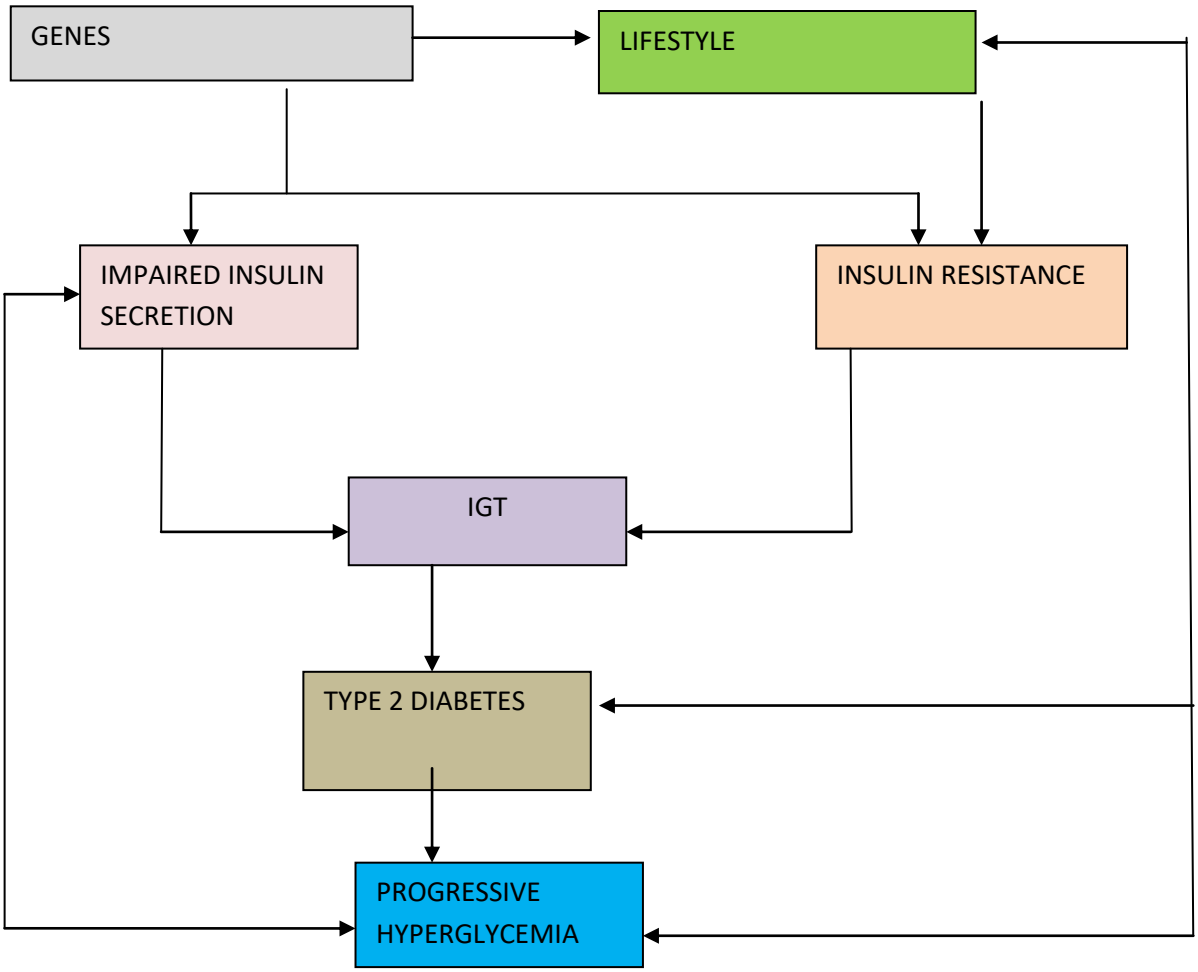
Insulin is released into the blood by beta cells (β-cells), found in the islets of Langerhans in the pancreas, in response to rising levels of blood glucose, typically after eating. Insulin is consumed by around two-thirds of the cells of the body to absorb glucose from the blood for use as fuel, for conversion to other required molecules, or for storage. Lower glucose levels lead to decreased insulin release from the beta cells and result in the breakdown of glycogen to glucose. This process is chiefly controlled by the hormone glucagon, which works in the opposite manner against insulin (Barrett et al., 2012).

If there is deficiency of insulin, if there is insulin insensitivity or insulin resistance or if there is defective insulin, then glucose will be absorbed poorly by the body cells that require it, and it will not be stored properly in the liver and muscles. The net result is rise in the blood glucose levels, poor protein synthesis, and other metabolic derangements such as acidosis (Shobback et al., 2012).

When the glucose concentration in the blood remains high for long time, the kidneys will reach a threshold of reabsorption, and there will be glucose excretion in the urine (glycosuria) (Murray et al., 2012). This increases the osmotic pressure of the urine and arrests the reabsorption of water by the kidney, leading to increased urine production (polyuria) and increased fluid loss. The volume of the blood lost will be replaced osmotically from water occupied in body cells and other body compartments,

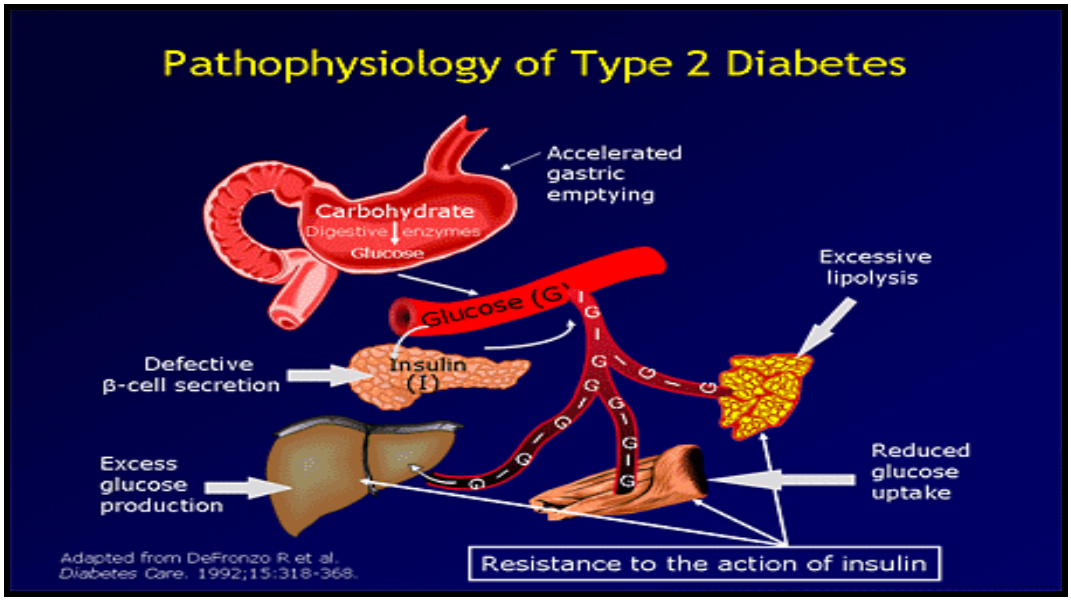
resulting in dehydration and increased thirst (polydipsia) (Shoback et al, 2011).

FIG 2.7 : PATHOGENESIS OF TYPE 2 DIABETES CHARACTERIZED BY IMPAIRED INSULIN SECRETION AND INSULIN RESISTANCE



The main pathophysiological features of type 2 diabetes are impaired insulin secretion and increased insulin resistance. The impairment of pancreatic β cell function shows progression overtime in type 2 diabetes although aging, obesity, low energy consumption, alcoholism, smoking, etc are independent risk factors for the cause of type 2 diabetes mellitus.

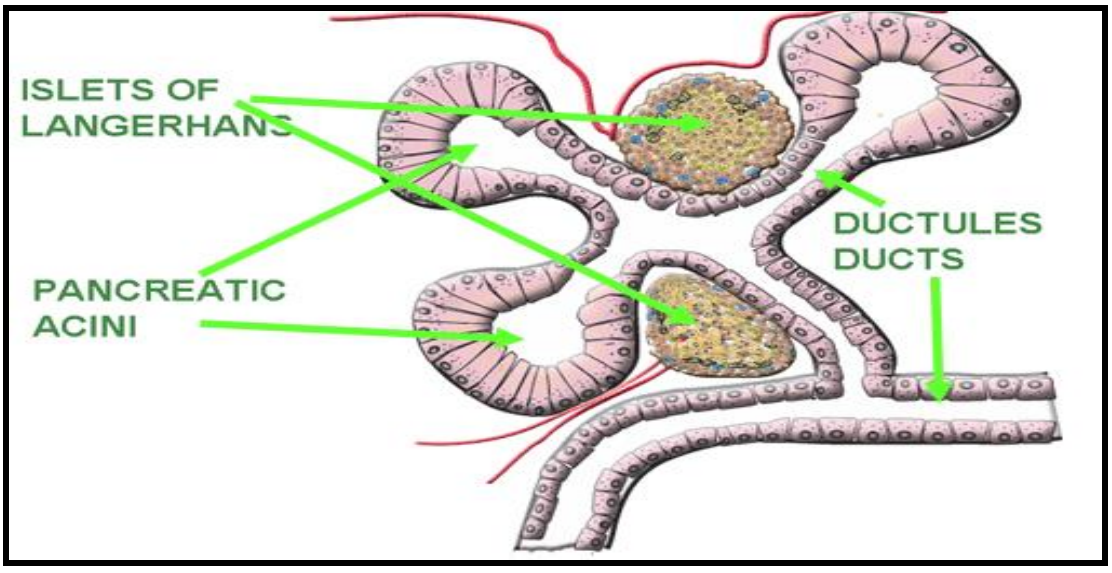
FIG 2.8: PATHOPHYSIOLOGY OF TYPE 2 DIABETES MELLITUS



(Source: Defronzo et al., 1992)

Often symptoms are not severe, or may be absent, and consequently hyperglycaemia sufficient to cause pathological and functional changes may be present for a long time before the diagnosis is made. On the other hand, other chronic features of diabetes mellitus include progressive development of the specific complications of retinopathy with potential blindness.

FIG. 2.9: THE STRUCTURE OF THE PANCREAS WHICH HOUSES ISLETS OF LANGERHANS



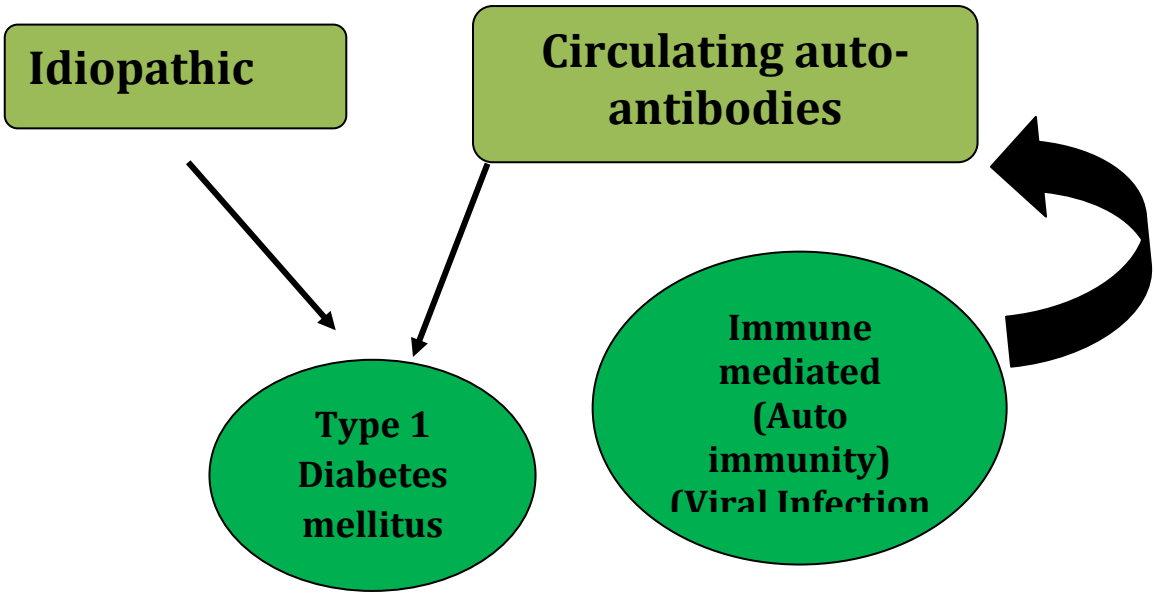
Environmental factors in the pathogenesis of type 2 diabetes

Aging, obesity, deficient energy consumption, alcohol drinking, smoking etc are independent risk factors causing type 2 diabetes. Obesity (particularly visceral fat obesity) due to a lack of physical activity is accompanied by a decrease in muscle mass result in insulin resistance, and is linked with increase in the number of middle and high aged patients. The changes in dietary energy sources, mainly the increase in fat intake, the increase in the consumption of simple sugars, the decrease in starch intake, and the decrease in dietary fiber intake contribute to obesity and cause impairment of glucose tolerance. Mild obesity to moderate obesity (Body mass index (BMI) < 25) lead to 4 to 5 fold increase in risk of developing diabetes, if accompanied by the increase in abdominal fat.

Etiology causes, sign and symptoms and complications of diabetes

The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs. Diabetes mellitus may present with classical characteristic features such as blurring of vision, excessive thirst (polydypsia), excessive feeding (polyphagia) excessive urination (polyuria), and weight loss.

FIG 2.10 MANAGEMENT OF TYPE I AND TYPE II DIABETES MELLITUS



Symptoms

Hyperglycemia
Excessive thirst
Frequent Urination
Significant Weight Loss
Electrolyte disturbances

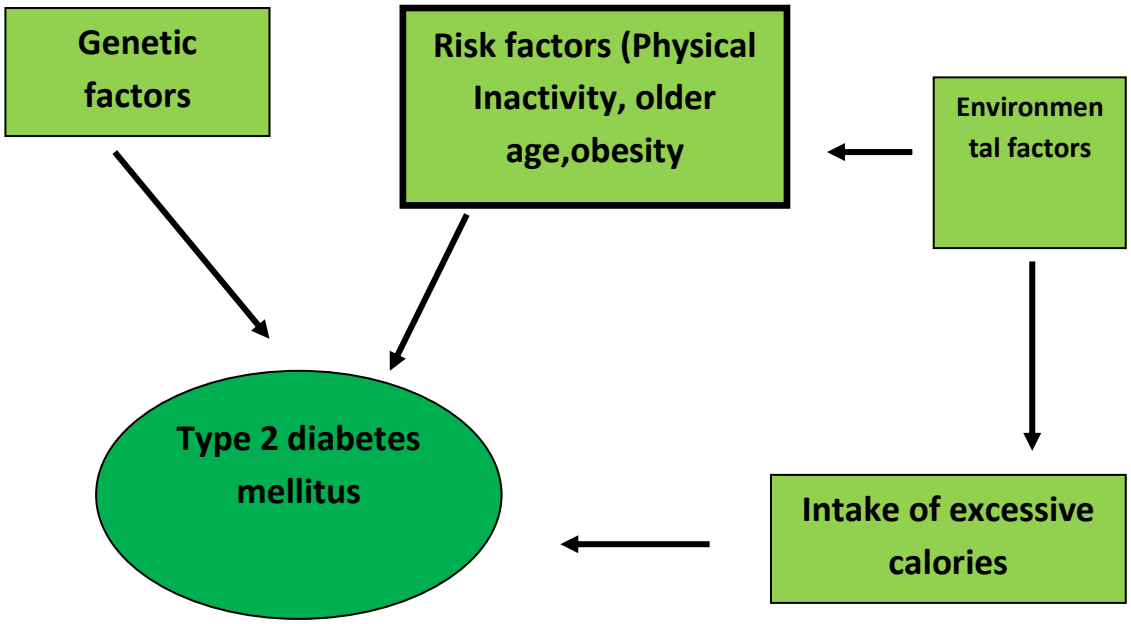
Ketoacidosis Macrovascular diseases
Coronary artery disease
Peripheral vascular disease
Cerebrovascular disease
Microvascular disease
Retinopathy
Nephropathy
Neuropathy

MEDICAL MANAGEMENT

Daily blood glucose monitoring
A1c testing
Medications
Insulin injections/pumps
Rapid-acting
Short acting
Intermediate-acting
Long-acting Mixtures

NUTRITION MANAGEMENT

- Synchronization of insulin action with preferred food intake; consistency in timing and amount of CHO intake
- Adjust pre-meal insulin doses based on CHO content of the meal



SYMPTOMS	CLINICAL FINDINGS
Hyperglycemia **Excessive thirst** **Frequent Urination** **Significant Weight Loss** **Polyphagia**	abnormal pattern of insulin secretion and action Decreased cellular uptake of glucose and increased postprandial glucose Increased release of glucose (gluconeogenesis) by liver in early morning hours

MEDICAL MANAGEMENT

Diagnosis

- FBG> 126 mg/dl
- Non Fasting glucose > 200mg/dl
- Oral GTT > 200 mg/dl

Monitoring

- Blood glucose
- HbA1c

Medications:

Sulphonylureas, Biguanides, Incretins, Thiazolidinedions etc.

NUTRITION MANAGEMENT

- Lifestyle strategies (food/eating activity) that improve glycemia
- Nutrition educatiion (CHO counting and fat modification
- Blood glucose monitoring to determine adjustments for food or medications.

Causes of the rise in prevalence of diabetes

Type II Diabetes Mellitus as a common and complex disease has been characterized by the following causes:

a) **Obesity**

Obesity is also considered a key risk factor for T2DM. The relation between increasing body mass index (BMI) and greater weight gain and risk of developing diabetes is most prevalent among Asians, suggesting that lower cut off BMI values are required to identify Asians at a higher risk of diabetes (Shai et al. 2006). BMI cut off point for Indians for any cardiometabolic risk factors is 23 kg/m2 in both sexes, whereas that of waist circumference (WC) is 87cm for men and 82cm for women (Mohan et al., 2007).

b) **Abdominal adiposity**

There is a preferential abdominal adiposity in Indians despite the amount of general adiposity (Ramachandran et al., 2002).

c) **Imbalance of human metabolism**

Changes in work patterns from heavy to sedentary type of work with increase in urbanization, mechanization, and improved transport have made an impact on human metabolism and it is associated with T2DM (Zimmet et al., 2001).

d) **Genes**

Since 2007, genome-wide association studies has circulated around 20 genes (like TCF7L2, HHEX, CDKAL1, SLC30A8 etc.) proving a strong association (odds ratio ranging between 1.2 to 1.5) with T2DM (Sladek et al., 2007; Scott et al., 2007; Zeggini et al., 2007).

e) **Ethnicity**

The interethnic differences (differences in prevalence of T2DM among Europeans, Americans, Chinese, and Asian Indians) in insulin resistance may have an environmental or genetic reason. The main acquired factors that

increase insulin resistance in all ethnic groups include factors such as obesity, sedentary lifestyle (inactive life style), diet rich in animal products, and aging (Abate and Chandalia, 2001). The so called "Asian Indian Phenotype" makes Asian Indians more susceptible to diabetes and premature coronary artery disease due to genetic factors (Mohan et al., 2007).

f) **Early life**

Early life influences the risk of developing diabetes such as poor growth in uterus and childhood growth spurt appear to be important in determining the risk of diabetes, and related vascular complications (Ekoé et al., 2001). In Indian population in rural areas, pregnant motheres are substantially underfed in terms of protein intake, leading to small, low birth weight babies who are more prone to diabetes and the metabolic syndrome, when they grow up. Their body fat exceeds that of the normal birth weight subjects (Barker BJP, 1998).

g) **Low level of awareness**

There is lower level of awareness in rural population as compared to urban population thus adding to the severity of the condition.

Complication

Long duration of diabetes mellitus is associated with an increased prevalence of microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular diseases (coronary artery disease, peripheral vascular disease, and atherosclerosis). With the rising prevalence of diabetes, the number suffering from the vascular complications of diabetes will also increase. Several studies have shown that the prevalence of microvascular and macrovascular complications were more in Asians in comparison to Europeans (Chowdhary and Lasker 2002).

Micro & Macro Vascular Diabetic Complications

T2DM is a metabolic disorder, potentially affecting organ damage such as eyes, heart, kidney and limbs which ultimately leads to heart attack, kidney failure and limb amputation. The damage of these organs can be completely prevented if diagnosed early and treated. Significant proportion of people with newly diagnosed T2DM may have multiple complications at the time of diagnosis because diabetes may not be detected for a long time (UKPDS-34, 1998)

In patients with T2DM, the risk of diabetic complications has been strongly associated with previous hyperglycaemia and any decrease in HbA1c levels may reduce the risk of complications and there is zero risk in those with normal HbA1c level (<6%). Metabolic control of diabetes is also strongly linked with predominant microvascular complications such as retinopathy, nephropathy and neuropathy (Stratton et al., 2000).

The diabetic complications are related to blood vessels and are classified into small vessel disease associated with the eyes, kidneys and nerves (microvascular disease), and large vessel disease involving the heart and blood vessels (macrovascular disease). Advanced Glycated End Products (AGE) are involved in the development of micro and macro complications related to DM

Risk factors

The risk factors causing diabetes mellitus are well established which can be categorized into Modifiable and Non-Modifiable risk factors.

Modifiable Risk Factors

Obesity

Obesity is defined as a condition when adipose tissue deposits more than normal level of total body weight. Its aetiology is multifactorial involving genetic, environmental, metabolic and lifestyle issues. Development of obesity is associated with risk factors of morbidity and mortality like diabetes, hypertension, dyslipidemia, cardiovascular diseases and cancers (WHO, 2009). Obesity is rightly called " Mother of all Chronic Degenerative Diseases". Visceral obesity has been associated with increased insulin resistance, hyperinsulinemia, increased blood pressure and dyslipidemia (Wang et al., 2006).

Above all, Asians and South Asians could be classified as 'metabolically obese' because they have several metabolic abberations but they are categorized as non-obese by conventional BMI standards. These non-obese people usually have high body fat; abdominal adiposity; fat deposition; and thick truncal fat in South Asians. These body characteristics, individually or in combination, contribute to increased insulin resistance, dyslipidemia, hyperglycemia seen commonly in South Asians (Misra and Khurana, 2008).

Classification of Overweight and Obesity

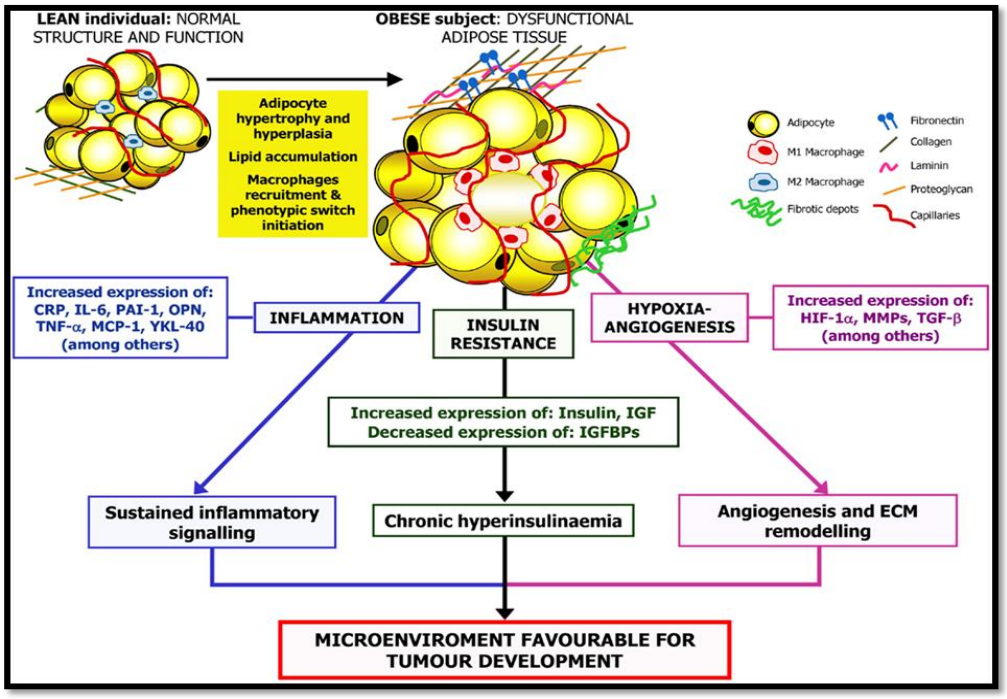
Body Mass Index (BMI) is commonly used to classify overweight and obesity in adults. The classification of overweight and obesity, according to BMI is shown in table as recommended by WHO (2003). The classification is merely based on the linkage of mortality with BMI. As there is evidence of the relative increase in adiposity in Indians, it is sugested that BMI cut off for non-communicable disease should be reduced for Indians and Asians to about 23Kg/m2 or even lower (WHO/IASO/IOTE, 2000). But WHO expert committee referred to this as a "public

health action point" at a BMI of 23 Kg/m^2 (WHO, 2004). BMI and body fat content differs with body built up and proportion of fat deposited. However BMI does not differentiate between muscle weight and weight associated with fat.

TABLE:2.6 : CLASSIFICATION OF OBESITY BASED ON BMI

Classification	BMI (Kg/m^2) WHO cut off	BMI (Kg/m^2) South Asian cut off	BMI (Kg/m^2) Asia-pacific cut off
Underweight	<18.5	<18.5	<18.5
Normal	18.5-24.9	18.5-22.9	18.5-22.9
Overweight	≥ 25.0	23.0-24.9	23-24.99
Pre-obese	25.0-29.9	25.0-27.9	
Class I	30.0-34.9	28.0-30.0	25-29.9 (Grade I)
Class II	35.0-39.9	30.0-34.9	≥30 (Grade II)
Class III	≥ 40	≥ 35.0	

FIGURE 2.11 : LIFECYCLE: OBESITY-THE PROPOSED LINKS



Prospective studies documenting the weight loss and development of diabetes suggest that reducing weight loss significantly reduce risk of diabetes (Resnick et al., 2000; Moore et al., 2000).

Another study prove that a continuous positive association of all markers of obesity (body- mass index, waist size and waist-hip ratio) causes major coronary risk factors such as hypertension, diabetes and metabolic syndrome while waist hip ratio also link with lipid abnormalities (Gupta et al., 2007).

Lifestyle Modifications

DM is considered a disease of major lifestyle disorder today. Changes in lifestyle and habits of people have badly influenced health today. Faulty habits have led to 1% rise in people with NCDs. More than 80% cases of coronary heart disease and 90% cases of type 2 diabetes, could potentially be avoided through changing lifestyle factors such as physical inactivity, low fibre and high GI diets. Environmental and lifestyle changes resulting from industrialization and urbanization may be responsible for the increasing incidence of diabetes.

Lifestyle modification focusing on the reduced intake of saturated fat and cholesterol intake, weight loss and increased physical activity has been shown to improve the lipid profile in diabetic patients. Lifestyle intervention including MNT, increased physical activity, weight loss, and anti-smoking result in improved lipid levels (American Diabetes Association, 2011). Studies show that lifestyle modification was nearly twice as effective as the medications (58% and 31% relative reductions respectively) (Knowler et al., 2002).

Smoking and Tobacco

Tobacco smoking increases risk of macrovascular complications in adults with T2DM. Carbon monoxide and nicotine are the two chemicals in tobacco smoke that affect the heart adversely.

Diabetes smokers have increased risk of morbidity and premature death linked with the premature development of macrovascular complications (American Diabetes Association, 2011).

Alcohol

Prolonged consumption of alcohol develops peripheral neuropathy. Alcohol provides empty calories as it doesn't contain protein or fats which may make a diabetic overweight or obese (Iyer et al., 2008).

The Dietary Guidelines for Americans (2011) recommends no more than two drinks per day for adult men and one drink per day for adult women. Alcoholic beverages can have both hypo- and hyperglycaemic effects in patients with diabetes, depending on the amount of alcohol acutely ingested (https://www.cnpp.usda.gov/sites/default/files/dietary_guidelines_for_americans/ExecSumm.pdf).

Plasma Lipids and Lipoproteins Levels

It has been reported that T2DM patients have an 'antherogenic lipid pattern' comprising of increased levels of total cholesterol, LDL-C, VLDL-C, hypertriglyceridemia and reduced levels of HDL-C (Mooradian, 2009).

Dyslipidemia normally coexists with diabetes. In Asian populations with no family history of diabetes, it was found that subjects with IFG and/or IGT had poor lipid profiles, with higher prevalence of elevated TG and its combination with reduced HDL-C than normal individuals. TG, non-HDL-C and TC to HDL ratio were positively associated with FPG or 2 hour PG levels, the association of glucose with TC was not as clear as that with TG (Zhang et al., 2009).

Hypertension

High blood pressure and high blood cholesterol are the primary risk factors for many diseases including type 2 diabetes. Not only do they affect heart vessels but they are two key components in the development of metabolic syndrome, multiple symptoms including obesity, a high fat diet and lack of physical activity. Metabolic syndrome increases risk of heart disease, stroke and diabetes (www.diabetes.about.com).

In San Antoni Heart Study, the odds ratio of diabetes was 2.21 more for individuals with pre hypertension than for those with normal blood pressure (95% Cl 1.63-2.98)

after adjusting for age, sex and ethnicity (Mullican et al., 2000; Gress et al., 2000). The table 2.7 gives cut offs by JNC VII classification.

TABLE 2.7: : CLASSIFICATION OF BLOOD PRESSURE FOR ADULTS

CATEGORY	SBP/DBP (mmHg)
Normal	<120/80 mmHg
Pre hypertension	120/80-140/90 mmHg
Stage 1 hypertension	140/90-160/100 mmHg
Stage 2 hypertension	>160/100 mmHg

(Source: Joint National Committee-VII (JNC VII), 2004)

TABLE 2.8: CLASSIFICATION OF HYPERTENSION CARDIOVASCULAR RISK

Other Risk Factors and Disease History	Blood Pressure (mm Hg)		
	Grade 1 SBP 140-159 or DBP 90-99	**Grade 2 SBP 160-179 or DBP 100-109**	**Grade 3 SBP ≥ 180 or DBP ≥ 110**
No other risk factors	Low	Medium	High
1-2 risk factors	Medium	Medium	High
≥ 3 risk factors or TOD or ACC	High	High	High

(Source: WHO, 2003)

Physical Inactivity

The primary marker of the epidemic of dibetes is the rapid epidemiological shift associated with reduced physical activity (Anjana et al., 2015). Phase I of ICMR-INDIAB study conducted in four states of Tamilnadu, Maharashtra, Jharkhand and Chandigarh reported that urban population was more sedentary worker than rural (65% vs 50%, $p<0.001$). Also males were significantly more active than females ($p<0.0001$). It was indicated that urgent steps should be taken to promote physical activity in Indian population to uproot twin epidemic of diabetes and obesity in India (ICMR-INDIAB, 2015). Physical activity and weight control are critical factors in diabetes prevention in subjects with both normal and impaired blood glucose regulation (Hu et al., 2001).

Dietary Habits

The primary cause of the epidemic of diabetes is the rapid epidemiological shift associated with changes in dietary patterns and decreased physical activity. Unhealthy eating or junk food contributes to obesity. Too much fat, insufficient dietary fiber, and too simple carbohydrates contribute to diagnosis of diabetes. Misra and Gulati (2014) suggested that whole grains are rich in dietary fiber, starch, fat, antioxidant nutrients, minerals, vitamin and phenolic compounds that have been associated with the reduced risk of obesity, insulin resistance, dyslipidemia, T2DM, heart diseases.

Gestational Diabetes

Gestational diabetes affects about 4% of pregnant women. It begins when hormones from the placenta make the insulin resistant. Many women who have gestational diabetes type 2 diabetes years later. Their babies are also at some risk for developing diabetes later in life (www.diabetes.about.com).

Non-modifiable risk factors

Family History

It appears that people who have family members who have been diagnosed with type 2 diabetes are at a greater risk for developing diabetes themselves. The prevalence among offspring with one diabetic parent was reported to be 36%, which increased to 54% when there was a positive family history of diabetes. When both parents had diabetes, the prevalence rate increased further (62%).

Several studies in India and abroad have shown that nearly 75% of the T2DM patients have first degree family history of diabetes. Insulin resistance has been reported to be a characteristic feature of Asian Indians (Ramachandran, 2007).

Genetics

Since 2007, genome-wide association studies has revolved around 20 genes (like TCF7L2, HHEX, FTO, CDKAL1, SLC30A8 etc.) showing strong corelation (with

odds ratio ranging between 1.2 to 1.5) with T2DM (Sladek et al., 2007 and Zeggini et al., 2007).

The so called "Asian Indian Phenotype" refers to certain unique clinical and biochemical abnormalities in Indians which include increased resistance of insulin, greater abdominal adipose tissues i.e., higher waist circumference irrespective of lower body mass index, lower adiponectin and increased highly sensitive C-reactive protein levels. This phenotype makes Asian Indians more susceptible to diabetes and premature coronary artery disease. Even though the prevalence of micro vascular complications of diabetes like retinopathy and nephropathy are comparatively less in Indians, the prevalence of premature coronary artery disease is much higher in Indians compared to other ethnic groups (Mohan et al., 2007).

Age

It is a fact the with old age, the risk of type 2 diabetes increases. Even a thin elderly person, may be predisposed to diabetes. Scientists prove that the pancreas doesn't pump insulin effectively as it did when the person was younger. Also the cells become more insulin resistant with age (www.diabetes.about.com).

Low/High Birth Weight (Intra-Uterine Environment Exposure)

Low birth weight is regarded as a risk factor for T2DM. Harder et al (2006) found that low birth weight (<2500g) was associated with increased risk of T2DM in comparison to a birth weight of >2500g (Odds Ratio-1.32, 95% CI:1.06-1.64). High birth weight (>4000g), as compared with a birth weight of 4000g, was associated with increased risk to the same extent (OR-1.27, 95CI: 1.01-1.59). These results indicate that there is exists a relation between birth weight and risk of developing T2DM.

Ethnicity

The interethnic differences (like differences in prevalence of T2DM among Europeans, Americans, Chinese and Asian Indians) in insulin resistance may have an environmental or genetic explanation. The main acquired factors that seemingly increase insulin resistance in all ethnic groups include obesity, sedentary lifestyle, diet

rich in animal products, and aging (Abate and Chandalia, 2001). Indians have high genetic risk for diabetes as an ethnic groups (Ramachandran, 1992).

Current trends in the treatment of diabetes mellitus

Glycemic goals in diabetic is a balancing act between hypoglycaemia, hyperglycaemia and the development of chronic complications. Management of this disease includes carefully managing the diet, exercising, lifestyle alterations, taking oral diabetes drugs or injections of insulin.

Diabetes mellitus is a disease directly related to carbohydrate, lipid and protein metabolism, so nutrition has always played an integral role in its management describing dietary prescription in the form of Medical Nutrition Therapy (MNT) (American Diabetes Association, 2014).

There are two main goals of treatment

1) Reduction of mortality and morbidity (as a result of diabetic complications)

2) Maintetnance of quality of life

Pharmacological

Drug Therapy

Diabetes is a multidimensional disorder and its management needs firm adherence to the prescribed treatment plan. The contemporary treatment of diabetes is focused on controlling blood glucose to a normal level. The common agreement on management of type II diabetes is changes in lifestyle along with proper diet and weight control. However, antidiabetic drugs are needed as these measures cannot provide satisfactory results. Conventional antidiabetic drug therapy includes insulin injections and oral hypoglycemic drugs to control the blood glucose level.

Many drugs are now available to treat T2DM. However, many side-effects such as hypoglycemia, lactic acid intoxication and gastrointestinal upset, etc. have been reported in patients (Li et al., 2004). Drugs and their side effects are presented in table 2.10.

These include drugs helping pancreas produce more insulin, making tissues more sensitive to insulin, or improving the liver's response to insulin.

TABLE 2.9: PHARMACOLOGICAL THERAPY FOR TYPE 2 DIABETES MANAGEMENT

Lifestyle changes should be the first-line therapy for most individuals with type 2 diabetes		
When lifestyle changes alone have not achieved or maintained glycemic goals	→	Add metformin Preferred initial pharmacologic therapy if tolerated and not [illegible]
For newly diagnosed individuals who are markedly symptomatic and/or have elevated glucose levels or A1C	→	Consider insulin therapy with or without other agents
If noninsulin monotherapy (OAD) at maximal tolerated dose(s) does not achieve or maintain A1C target over 3 months	→	Add: A second oral agent Or A GLP-1 receptor agonist or Basal insulin
Due to the progressive nature of type 2 diabetes, insulin is eventually needed Insulin therapy should not be delayed		

(Source: ADA, 2016)

TABLE 2.10 : SYNTHETIC DRUGS AND THEIR SIDE EFFECTS

Agent	Mechanism	Site of action	Advantages	Side effects
Sulphonylureas	Stimulating insulin production by inhibiting the KATP channel	Pancreatic beta cells	Effective and Inexpensive	Hypoglycaemia and weight gain.
Metformin	Decreases insulin Resistance	Liver	Weight loss Does not cause Hypoglycaemia	Nausea and diarrhoea. Hypoglycaemia occurs when combined with sulfonylurea or insulin
Thiazolidinedione	Reduce insulin resistance by activating PPAR-γ	GI tract	Low risk	Increased liver enzymes, weight gain, oedema, mild anaemia
α-glycosidase inhibitors	Reduces intestinal glucose absorption	Fat, muscle	Decreases postprandial plasma triglyceride levels	Diarrhoea, abdominal pain, flatulence; Serum levels of transaminases increases at doses

Non-pharmacological

Diet

Medical Nutrition Therapy

Medical Nutrition therapy (MNT) is fundamental for the effective management of type 2 diabetes and the advice provided should be scientific and eventually adjusted for the individual, keeping in mind their cultural preferences, beliefs and lifestyle.

Diet plays a major role in the prevention & reduction in the complications of all forms of diabetes mellitus (Chandalia, 1999). Diet high in simple carbohydrates and fats results in T2DM in the later stages of life. Therefore dietary restriction in the form of diet composition, amount, distribution and timing of food intake is an essential factor in management of T2DM individuals. The ATP III recommends limiting the intake of carbohydrates to <60% in individuals with triglyceridemia and low HDL-c levels. Dietary management in the form of weight loss is the cornerstone in the management of T2DM subjects.

Diet that enhances glycemic control have high dietary fibre, low to moderate dietary fat and moderate high value proteins. High fibre foods like oats, pectin, bran reduce the postprandial blood glucose levels and have been reported to reduce choleseterol. The ADA recommended a moderate increase in the intake of dietary fibre to 20 to 35 g per day as it reduces cholesterol- soluble fiber (Manisha et al., 2000).

A study carried out by Chandalia (2000) stated that 50g of fibre per day improved glycemic control, reduced hyperinsulinemia and decreased plasma lipids.

Diabetes is primarily a disorder of carbohydrate metabolism, but with progression of the disease, protein metabolism is also affected. A high protein diet lowers postprandial blood glucose in persons with type 2 diabetes and improves the overall glucose control (Gannon et al., 2003). In individuals with type 2 diabetes, ingested protein improves insulin response without increasing plasma glucose concentrations (Wycherley et al., 2010).

A study carried out by Miller et al (2003) found a significant reduction in HbA1c and improvement in HDL-C concentration with low glycemic index foods. According to WHO, glycemic index (GI) is important in planning healthy diet as low GI foods help to control blood sugar levels by stabilizing the rise in blood glucose (Franz, 2003).

Antioxidants are substances that neutralize or reduce reactive oxygen species and therefore significantly delay or prevent oxidative damage. Atherosclerosis develops due to the oxidation of lipids in plaque formation. Fruits including berries and vegetables are rich sources of antioxidants such as Vitamin E, Vitamin C, polyphenols, flavonoids and carotenoids beneficial in lowering LDL-c in humans by 7%.

The ideal macronutrient composition of the diet in the management of hyperglycaemia in type 2 diabetes is still not clear with studies showing contradictory results, but the importance of total energy intake and weight loss is significant. Table 2.11 gives guidelines for diet planning in T2DM.

TABLE 2.11: GUIDELINES FOR PLANNING A DIET IN DIABETES

Nutrient	Recommendation
Energy	• 25-30 kcal/kg ideal body weight • Needs to be reduced in obesity and increased in underweight.
Protein	• 0.8 g/kg body weight • Additional needs to be met during pregnancy, location and period of growth.
Fat	• 20-25% of total calories • Saturated fatty acids- 6-7% of total calories • Polyunsaturated fatty acid - 6-7% of total calories • Mono unsaturated fatty acids- 6-7% of total calories • Ratio of omega 6:omega 3- 4:1 • Cooking oil - 0.5kg/person/month • Cholesterol intake - 300 mg/day • The choice of cooking oil should be either ➢ One with moderate quantity of linoleic acid (groundnut/rice bran/sesame oil) ➢ One with high amounts of linoleic acid (safflower/sunflower/cotton seed /corn oil)
Carbohydrates	• 55-56% of total calories • Encourage complex carbohydrate such as cereals, pulses and whole grains. • Restrict refined carbohydrates such as sugar, honey and jaggary.
Dietary fibre	• 30-40 g/day
Salt	• Below 6 g/day • Needs to be reduced to 4g/day in case of hypertension , renal failure and heart problems.
Alcohol	• Restrict

(Source: API-17CP Guidelines, 2007)

Carbohydrates

The total amount of carbohydrates consumed is the primary determinant of postprandial blood glucose. Effective management of carbohydrates intake should be the important for the optimal glycemic control. Carbohydrates should be about 55-65% of total energy intake. Low-carbohydrate diets show improvements in glycemic control if associated with weight loss. Day to day consistency in carbohydrate intake results in improved glycemic control and diets very low in carbohydrate should not be encouraged since this could eliminate vitamins, minerals, fibre and energy rich foods. Current recommendations are that carbohydrate and MUFA's together should compose 60-70% of daily calorie intake. The exact ratio of carbohydrates and MUFA's is not specified while individualization is recommended (American Diabetes Association, 2015).

Glycemic Index and Glycemic Load

The glycemic index (GI) is defined as the incremental positive area coming under blood glucose curve of 50g of carbohydrate from a test food divided by the incremental area of 50 g of reference food. A high GI is above 70, medium GI is 56-69 and low GI is below 55. The role of GI in type 2 diabetes is not clear with the evidence of low GI diets reducing glycosylated haemoglobin (HbAIc) by 0.5% (Opperman et al., 2004), while recent randomized controlled trials suggest no benefit of low GI diet. The studies on effects of GI on blood glucose levels are limited. Some studies show that low glycemic index diets cause significant reduction in HbA1c and improvement in HDL-C concentration (Brand-Miller et al., 2003) and positively association of glycemic load with the development of T2DM (relative risk 1.47) in women (Sculze et al., 2004). Thus low GI foods can be identified and incorporated in the diets of T2DM patients. The glycemic load (GL) of a food is obtained by multiplying the GI of a food by the number of grams available carbohydrate in the food . A high level GL is above 20, medium 11-19 and low below 10. The long term sustainability of low GL diets is still not known.

Dietary Fibre:

Individuals with diabetes can be advised to include 25-30 g of fibre per day, with adequate inclusion of soluble fibre. Studies have shown that consuming a high-fiber diet (50g fiber/day) reduces glycemia, hyperinsulinemia and lipemia in T2DM subjects (Franz et al., 2002). Several studies have found the increased intake of whole grains and dietary fiber to be beneficial (Schulze et al., 2004; Meyer et al., 2000).

Sucrose:

Sucrose consumption from 10% to 35% of the total energy in the diet was associated with positive glycemic response when substituted for isocaloric amounts of starch (Nadeau et al., 2001) According to Food and Drug Association (FDA) approved non-nutritive sweetners within the accepted daily limits can be used.

Protein:

Protein intake does not alter long-term insulin requirements (Brinkworth et al., 2004). Thus recommendations for protein intake in diabetic individual is similar to a normal person, except when the protein choice is high in saturated fatty acids or in patients with diabetic nephropathy, a protein intake of less than 0.8 g/kg/day is recommended.

Dietary Fat:

Epidemiological studies have shown a relationship between high fat intake, high saturated fat intake and elevated HbAIc levels (Kodama et al., 2009). Since diabetic patients are at increased risk for cardiovascular diseases (CVD) it is important to consider nutrition interventions for the prevention and treatment of CVD involving low intake of saturated and trans-fatty acid and dietary cholesterol. The American Diabetes Association and the National Cholestrol Education Program's Adult Treatment Panel III have recommended that the serum LDLcholestrol goal be <100mg/dl, HDL Cholestrol; >60 mg/dl; and Triglycerides : <150mg/dl. To achieve this goal, food with a high content of saturated fatty acids and cholestrol should be limited (Krauss et al., 2000). Recommendations for PUFA

compose 10% of daily energy intake. The recommendations for polyunsaturated fatty acids are 0.5-1.0 g/day (American Diabetes Association, 2015).

Fruits and Vegetables

It has been established that increasing intake of fruits and vegetables, high in antioxidants and fibre help to reduce many of the risk factors associated with diabetes, including obesity.

Micronutrients and Vitamins

Multiple micronutrient deficiencies are likely to prevail in individuals with poorly controlled diabetes (Franz et al., 2003). Deficiencies of certain minerals, such as potassium, magnesium, zinc and chromium may predispose the individual to carbohydrate intolerance. Studies on chromium supplementation in diabetes management has mixed results and thus should not be recommended in diabetes management.

Some of the daily requirement of these elements are as follows; Iron 100mg per day for male, 15mg for female per day; Zinc 15mg/day, Mn 2.5-5mg/day, copper 2-3mg/day; chromium and Selenium -9.950.2mg/day.

Alcohol Intake

Physicians need to advice diabetic patients on alcohol intake on an individual basis. It should discouraged for pregnant, patients with pancreatitis and those having severe hypertriglyceridemia. Alcohol intake may cause hypo or hyperglycaemia depending on the amount consumed.

Antioxidants

Observational studies have shown a association between dietary or supplemental consumption of antioxidants and prevention of disease states but large placebo-controlled clinical trials have failed to show a benefit and, in some instances, have suggested adverse effects (Franz et al., 2002).

Combined analysis of 14 studies that met inclusion criteria revealed that dietary antioxidant supplementation (vitamin C or E) could not interfere with the

pathogenesis of insulin resistance. However, HbA1C levels were significantly reduced by antioxidant supplementation, suggesting that antioxidants may have some benefit against the complications of type 2 diabetes mellitus (Akbar et al., 2014).

Lifestyle Modifications

Lifestyle modification focusing on the reduction of saturated fat and cholesterol intake, weight loss (if indicated), and increased physical activity improve the lipid profile in diabetic patients. Lifestyle intervention, including MNT, increased physical activity, weight loss, and anti-smoking, should improve lipid levels (American Diabetes Association, 2011).

MNT should emphasize lifestyle changes that would improve glycaemia, dyslipidemia and blood pressure. Intensive lifestyle programs involving participant education, individualized counselling, reduced dietary and fat intake, regular physical activity and frequent participant contact are necessary to produce long term weight loss of 5-7% (Franz et al., 2002).

Physical Activity

Exercise and physical activity reduce the risk of diabetes, improve insulin sensitivity, independent of weight loss, acutely lower blood glucose, and are important in long term maintenance of weight loss (Franz et al., 2002; Lindstorm et al., 2003).

Physical activity can help lose weight. Modest weight losses of 5-10% were associated with significant improvements in HbA1c levels, blood pressure, HDL cholesterol, and plasma triglycerides) in T2DM patients. Risk factor was even greater with losses of 10-15% of body weight (Wing et al., 2011).

Dm and quality of life: tools for assessment

Direct parameters

Blood Glucose: Utility for diagnosis or screening

Diagnostic criteria for diabetes includes 3 measures- Fasting Blood Sugar (FBS), Post Prandial Blood Sugar (PP2BS) and Random Blood Sugar (RBS). Hyperglycemia through any of these has to be confirmed by any of these tests. Glycosylated Hb is not recommended at the time of diagnosis. The American Diabetes Association gives cut off values for blood glucose in the table (ADA, 2015). Screening for type 2 diabetes would allow earlier recognition of cases for early intervention but whether this would result in improved long-term outcome is unknown.

Acute and chronic complications of diabetes mellitus occur because of poor short term and long term glycemic control due to obesity, hypertension and dyslipidemia. In a series of studies over two decades Mani et al (1987-2003) established the importance of glycemic control using food based approaches (Rai and Mani, 1997; Parikh and Mani, 2001; Mani et al., 1997).

Glycosylated haemoglobin (HbA1c)

This blood test is useful to estimate the average control of blood glucose in the last 90 days. Glycosylated haemoglobin (HbA1c) can be performed any time of the day and does not require any special preparation such as fasting.

Proteins react with glucose in the blood to form glycated products. The extent of glycation depends on the concentration of glucose and the reactive groups on the protein.Clinically, proteins with long life like haemoglobin are more important as they reflect the exposure to glucose over a period of time (WHO, 2002). These properties have made it the gold standard for assessing glycaemic control in people with diabetes and is considered as an option for assessing glucose tolerance in undiagnosed diabetic people. Cost of estimation and non availability of standardization are some of its limitations. The cut off values for HbA1c in diabetes is given in Table 2.12.

TABLE 2.12 : CLASSIFICATION FOR GLYCATED HAEMOGLOBIN IN DIABETES MELLTUS

HbA1c	Control	Inference
> 7.6	**Poor Control**	**Action suggested**
6.8-7.6	**Fair control**	
5.5-6.8	**Good Control**	Goal
4.2-5.5	**Excellent**	Near Normal/ Non Diabetic level

(Source: ADA, Position statement 2008)

TABLE 2.13: CATEGORIES OF INCREASED RISK FOR DIABETES AND PREDIABETES

Categories	**Values**
Prediabetics (Fasting Blood Sugar)	100-125mg/dl
Diabetics (Fasting Blood Sugar)	≥126mg/dl
Pre Diabetics Post Prandial Blood Sugar	≤140mg/dl
Diabetics Post Prandial Blood Sugar	140-199mg/dl
Prediabetics (HBA1c)	5.7-6.4%
Diabetics (HBA1c)	≥6.5%

TABLE 2.14: : DIAGNOSTIC CUT- OFFS FOR TYPE 2 DIABETES MELLITUS

Diagnosis	**Criteria**
Diabetes	Fbs: ≥ 126 Mg/Dl Rbs: ≥ 200 Mg/Dl Pp2bs: ≥ 200mg/Dl
Pre-Diabetes Impaired Fasting Glucose (Ifg) Impaired Glucose Tolerance (Igt) Normal	Fbs: 100-125 Mg/Dl Pp2bs: 140-149 Mg/Dl Fbs: < 100 Mg/Dl Pp2bs: < 140 Mg/Dl

(ADA, 2011)

TABLE 2.15 : DIAGNOSIS CRITERIA FOR DIABETES

Variable	Criteria	
FPG	≥126 mg/dL (7.0 mmol/L) * Fasting is defined as no caloric intake for ≥8 hours	100-125 mg/dL (5.6-6.9 mmol/L)
2-hr PG	≥200 mg/dL (11.1 mmol/L) during OGTT (75-g) * Using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water	140-199 mg/dL (7.8-11.0 mmol/L)
A1C	A1C ≥6.5% (48 mmol/mol) * Performed in a lab using NGSP-certified method and standardized to DCCT assay Random	5.7-6.4% (39-46 mmol/mol)
PG	≥200 mg/dL (11.1 mmol/L)) In individuals with symptoms of hyperglycemia or hyperglycemic crisis	

(ADA, 2016)

Blood Pressure

Raised blood pressure modifies the structure of the arteries resulting in stroke, heart disease, kidney failure and other diseases. The risk is high not only in hypertensive people but also in those with average, or even below average range. Diet, especially excessive salt and alcohol, lack of exercise and obesity raise blood pressure, and these effects worsen with age. In developing and developed countries, in most adults blood pressure is higher than the ideal level. In the high income countries only 7% of deaths caused by high blood pressure occur under 60 years of age, while in African Region this increases by 25% (WHO, 2009). The table 2.16 gives cut- offs by JNC VII classification.

TABLE 2.16: CLASSIFICATION OF BLOOD PRESSURE FOR ADULTS

CATEGORY	SBP/DBP (mmHg)
Normal	<120/80 mmHg
Pre hypertension	120/80-140/90 mmHg
Stage 1 hypertension	140/90-160/100 mmHg
Stage 2 hypertension	>160/100 mmHg

(Source: Joint National Committee-VII (JNC VII), 2004)

Cholesterol

Cholesterol is the name of a group of fats called lipoproteins that are part of the body's metabolism. Lipoproteins play an important role, but too much of cholesterol becomes harmful.

Low-density lipoproteins (LDL),

LDL or "bad" cholesterol, can lead to a build-up of cholesterol in the arteries. In general, the lower the LDL the better. Many people with diabetes may use a drug called statin, which reduces LDL and helps reduce the risk of damage to blood vessels.

High-density lipoproteins (HDL)

HDL or "good" cholesterol, helps remove cholesterol from the body. In general, the higher amount of HDL is better.

Triglycerides

TG are another kind of blood fat that is the risk factor for a heart attack or stroke if the levels are too high (http://www.diabetes.org).

Major risk factors (exclusive of LDL cholesterol) that modify LDL goals

Cigarette smoking, hypertension (BP >140/90 mmHg/ on antihypertensive drugs), low HDL cholesterol (<40 mg/dl), family history of premature coronary heart disease (CHD in male first degree relative <55 years; CHD in female first degree relative <65 years)

- Age (men >45 years; women >55 years)
- HDL cholesterol >60 mg/dl is beneficial (“negative” risk factor). Its presence removes one risk factor from the total count (ATP III guidelines)

TABLE 2.17: CLASSIFICATION OF BLOOD LIPID LEVELS

	Range	**Classification**
S. Total cholesterol	< 200 mg/dl	Desirable
	200-239	Borderline
	>240	High
S. LDL-C	<100 mg/dl	Optimal
	100-129	Near or above optimal
	130-159	Borderline high
	160-189	High
	≥ 190mg/dl	Very high
S. HDL-C	<40 mg/dl	Low
	≥60 mg/dl	High
S. Triglycerides	<150 mg/dl	Normal
	150-199	Borderline high
	200-499	High
	≥500	Very high

(Source: ATP-III Guuidelines, NCEP,)

Indirect Parameters

Health Related Quality of Life (HRQOL)

Quality of life is an important aspect in diabetes because poor quality of life leads to low self-care, which in turn leads to worsened glycemic control, increased risks for complications, and exacerbation of diabetes overwhelming in both the short run and the long run.

Quality of life is an important aspect in diabetes because poor quality of life leads to diminished self-care, which in turn leads to worsened glycemic control, increased risks for complications and deterioration of diabetes in both the short run and the long run. Thus, it is apparent that quality of life issues are important and predict how well an individual would be able to handle his disease and maintain his long term health and well-being. It is also important for the assessment of perception of burden of patients of his chronic disease condition, to see the trends of health overtime and quantification of the effect of treatment (Vigneshwaran et al., 2013).

It is well recognized fact that diabetes mellitus is associated with increased morbidity and mortality. But, impact of this disease on functional health status and sense of wellbeing is still not well established. The apparent difference between one's expectations and one's actual physical, emotional, and social functioning is HRQOL. As one might predict, people with diabetes rate their HRQOL significantly less favorably, on an average than people without diabetes. The concept of HRQOL and its determinants have evolved since the 1980s to encompass those aspects of overall quality of life that can be clearly shown to affect either physical or mental health (Gandek et al., 2004).

Research has suggested that individuals with diabetes have reduced HRQOL compared to the general population, but better HRQOL than individuals with many other chronic illnesses (Rubin and Peyrot, 1999). However, most of the studies on diabetes and HRQOL have been conducted in developed countries where there is access to better health care facilities. In developing countries, the morbidity is associated with diabetes and HRQOL of these patients. However, HRQOL studies of the diabetic patients in developing countries are rare.

Complementary and Alternative Medicine

Complementary medicine refers to therapies that are used along with conventional medicine, while "alternative" medicines are therapies that are used in place of conventional medicine (WHO, 2002). The use of CAM is about 65% in India (WHO, 2002). Although scientific evidences exist regarding some CAM therapies, more well-designed scientific studies are needed to assess regarding the safety and efficacy of these therapies for the disease or condition for which they are used. Common dietary supplements used for diabetes are presented in the table 2.18. Foods or dietary components that may provide a health benefit beyond basic nutrition are known as functional foods. Biologically active components identified in these foods impart therapeutic effects. There are several botanical products and food ingredients which have proved to be beneficial in prevention of various NCDs including T2DM.

TABLE 2.18: COMMON DIETARY SUPPLEMENTS USED FOR DIABETES

Name	Possible effect and evidence
Chromium	Improvement in HbA1c levels, glucose tolerance, beneficial effect on insulin and cholesterol levels in subjects with T2DM (Bahijiri et al., 2000) ; Hypoglycaemic effect in T2DM patients (Bahijiri et al., 2000)
Alpha-Lipoic acid	Increase in glucose uptake, decrease of fasting insulin and improved insulin sensitivity in T2DM patients (Konradet al., 1992; Jacob et al., 1999).
Vanadium	Decrease in FBS, HbA1c, hepatic glucose production, increase in insulin mediated glucose-mediated glucose uptake and insulin sensitivity in T2DM patients (Cohen et al., 1995; Boden et al., 1996; Goldfine et al., 2000; Halbertstem et al., 1996).
Magnesium	Improvement in HbA1c levels, glucose tolerance, beneficial effect on insulin and cholesterol levels in subjects with T2DM (Paolisso et al., 1993). Decrease risk of diabetes in normal individuals (Larsson, 2007; Schulze et al., 2007)
Vitamin E	Improvement in glycemic control in IDDM and NIDDM and decrease in FBS (Paolisso et al., 1993)
Coenzyme Q10	Improved glycemic control in T2DM patients (Hodgson et al., 2002; Kolahdouz et al., 2013)

Indigenous foods in the management of diabetes

Some of the botanical products used for the diabetes treatment are mentioned below.

a) Coccina cordifolia

In a double-blind, placebo-controlled, randomized trial, 1g alcoholic extract of the herb *Coccina cordifolia* was supplemented for 90 days, resulting in 16% decrease in the fasting, 18% decrease in postprandial and HbA1c values of the experimental group compared with that of the placebo group (Kuriyan et al., 2008).

Additional studies (Kamble et al., 1998; Khan et al., 1980) have documented the hypoglycaemic effect of *Coccina cordifolia.*

b) Ipomoea batatas (Caiapo)

Caiapo was supplemented at 4g dose level once daily for 12 weeks and it recorded decrease in HbA1c, FBS and blood cholesterol levels (Ludvik et al., 2004). This study

highlights the benefits of Caiapo on plasma glucose as well as cholesterol levels in T2DM patients.

c) Trigonella foenum-graecum (Fenugreek Seeds)

Fenugreek seeds (*trigonella foenum graecum*) are high in soluble fibre, which helps lower blood sugar by slowing down digestion and absorption of carbohydrates. Fenugreek seeds are a rich source of vitamins, minerals and antioxidants, which protect the body cells against damage caused by free radicals (http://www.diabetes.co.uk/natural-therapies/fenugreek.html). Fenugreek produced a significant decrease in fasting blood glucose levels, TC, LDL, TG and an improvement in glucose tolerance test (Sharma and Raghuram, 1990). Gupta et al (2001) showed that fenugreek seeds improves glycemic control and insulin resistance also in hypertriglyceridemia.

d) American Ginseng

Studies have shown that diabetics who consume ginseng (American spices) before an oral glucose tolerance test had lower blood-glucose levels. The results suggest that cosuming ginseng before a meal could lower post prandial blood-sugar levels (Grover et al., 2002).

e) Gymnema Sylvestre

Diabetics who consumed gymnema for 18-20 months had lower blood-sugar levels and a significant number of patients discontinued conventional oral medications (Grover et al., 2002).

f) Momordica charantia (Bitter melon)

This is the most popular vegetable herbal resource and is often used as folk medicne to treat diabetes (Arvigo and Balick, 1993). A homogenised suspension of the vegetable pulp of *Momordica charantia* to 100 moderate NIDDM subjects caused a significant reduction of postprandial serum glucose in 86% patients and fasting glucose in 5% patients (Ahmad et al., 1999).

In a clinical trial, water soluble extract of the fruits of *M.charantia* significantly reduced blood glucose levels in nine NIDDM patients on 50 gm OGTT.

Some of the studies carried out elsewhere and in the department using other indigenous foods have been shown in Table 2.19 and 2.20.

TABLE 2.19: COMMONLY USED ANTIDIABETIC FOODS IN THE INDIGENOUS SYSTEM OF HEALTH CARE

Botanical name	Active principle	Possible mode of action	Form and dosage	Authors
Aegle marmelos (BIlva Bael fruit/Bengal quince)	Marmin and marmelosin	Improves digestion reduces blood sugar and urea	Juices of leaves	Krishnan (1968), Santhoshkumari and Devi (1990), Shiva (1998)
Azadirachta indica (Indian liliac, Neem)	Bitter principles nimbin, nimbinin, nimbidin	Lowers blood glucose	Juices of leaves, bark and flowers, seed oil	Siddiqui (1942), Murthy et al (1978), Pillai and Santhakumari (1981), Shiva (1998)
Curcuma longa Saffron turmeric	Turmerone curcumin	Blood purifier	powder	Tank et al (1989)
Embilica officialis (Indian gooseberry/Amla)		Stimulates pancreas	1tbsp of amla juice with a cup of bitter gourd juice	Upadhyay et al (1996), Joshi & Iyer (2009)
Eugenia Jambolana (Blank plum/berry, Jambul)	Jamboline- a glucoside	Prevents pathological conversion of starch to glucose	Jambu seeds	Lal and Chaudhary (1968), Kohli (1983), Kohli and Singh (1993), Upadhyay et al (1996)
Ficus bengalensis (Banyan Tree)		Lowers blood sugar, cholesterol and urea	Infusion of bark	Chopra and Chopra (1955), Shrotri and Aiman (1960), Joglekar (1962), Vohra et al (1969)
Momordica charantia (Bitter gourd)	Momordicine- a bitter glucoside anthelmintic principle	Increases glucose uptake in the liver cells acts as a plant insulin	Fruits, leaves and roots	Lal and Chaudhary (1968), Upadhyay et al (1996), Kavikumar et al (1997)
Ocimum sanctum (Tulsi Holy basil)	Eugenol	Reduces blood glucose, uric acid, total amino acid, TC, TG,	Leaves	Agrawal et al (1996), Rai et al (1997)
Trigonella foenum graecum (Fenugreek)	Mucilaginous fiber, trigonelline -an alkaloid	Lowers TC and TG	Seeds (25g per day)	Raghuram et al (1993), Shiva (1998)

General mechanism(s) of action of medicinal plants with antidiabetic property

Different mechanisms of action of medicinal plants with anti-diabetic have been extensively described (Etuk et al., 2001). These include

- inhibition of renal glucose reabsorption (Edddouks et al., 2004),
- stimulation of insulin secretion from beta cells of islets of Pancreas and inhibition of insulin degradative processes, reduction in insulin resistance (Das et al., 1996).
- Enhancing the peripheral utilization of glucose, correcting the impaired hepatic glycolysis and limiting its gluconeogenic formation similar to insulin (Yaheya, 2009)
- Stimulation of insulin secretion (Esmaeili and Yazdanparast, 2004) and
- Also, protective effect on the destruction of the beta cells and improvement in digestion along with reduction in blood sugar urea has been documented (Kim et al., 2008).
- Prevention of pathological conversion of starch to glucose, and inhibition of β-galactocidase, α-glucocidase and alpha-amylase with ability to lower cortisol has also been reported (Ghalap and Kar, 2003)
- Antioxidant activity of antidiabetic plant against oxidative stress, involved in pancreatic ß-cell dysfunction has been reported as one of the mechanisms of action of antidiabetic plants .

TABLE 2.20: EFFICACY OF VARIOUS FUNCTIONAL FOODS USED IN THE MANAGEMENT OF TYPE II DIABETES (HUMAN STUDIES)

Investigators	Functional Food	Dose/Duration	Results
Pandit (2009)	Garden Cress Seeds	3g/d (28 days) on 41 NIDDM subjects	↓ HbA1c-4.7%;TG-71%;TC,LDL,HDL-NS
Khan et al (2003)	Cinnamon	1,3, 6g/day (40 days)-short term on 60 NIDDM subjects	↓ FBS-18-29%
Ziegenfguss et al (2006)	Cinnamon	500mg/d (90 days) long term	83% subjects showed ↓ FBS-8%
Srivastava et al (1993)	Momordica charantia	Dried powder and aq. extract of 5g/d (1-3 times a day for 21 days	↓ extract-Av bl sugar-54% ↓ dry powder Av bl sugar-25%; HbA1c-27%
Iyer and Mani (1989)	Curry leaves	1g/d for 1 month on 30 NIDDM	Transient decrease in glycemic and other parameters
Rai et al (1997)	Ocimum Sanctum	1g/day for 1 month on 27 NIDDM	↓ FBS-21%, HbA1c-11%,TC-11%,LDL-14%, VLDL-16%, TG-16%
Iyer and Desai (2008)	150ml Panchatantra drink	150ml/d for 45 days on 25 T2DM	↓ FBS-7%, HbA1c-3%
Joshi and Iyer (2008)	Amla	35g/d for 60 days	↓ Gly. profile-no change, TC-5.8%, LDL-9.4%, ↑ HDL-5.5%
Venugopal and Iyer (2010)	Barley grass powder	1.2g/d(capsules) for 60 days on 23 NIDDM subjects	↓ FBS-10.8%, HbA1c-5.2% ↓
Venugopal and Iyer (2010)	Kodari seeds	40g/d for 28 days on 30 T2DM subjects	HbA1c-1.2%, FBS-no change
Venugopal and Chug (2015)	Insulin plant leaf powder	1g/d (4 capsules) for 45 days on 27 T2DM subjects	↓ FBS-13.8%, HbA1c-5.13%, PPBS-12.3%, TG-16.2%, ↑ HDL-9.8%

TABLE 2.21: STUDIES DONE ON VARIOUS FUNCTIONAL FOODS AND THEIR EFFECT ON TYPE II DIABETES

Author	Year	Supplement	Duration	Amount	Major findings
Venugopal & Iyer	2010	Barley grass powder (capsule)	60d	1.2g/d	↓FBS, HbA1c, TC, LDL-C, Non-HDL-C and ↑HDL-C
Desai & Iyear	2008	Panchratna juice Fresh Processed	45d 90d	150 ml 150 ml	↓FBS & HbA1c ↔FBS & HbA1c, ↓TG, ↑HDL
Joshi & Iyer	2005	Amla	60d	35g/d	↔FBS, GHb ↓TC, LDL, non HDL ↑HDL.
Mani et al	2001	Spirulina	120d	2g/d	↓GLC, TL, HbA1c, Non HDL, Apo B ↑HDL, Apo A, A1:B.
Rai & Mani	1997	Tulsi	30d	1g/d	↓ Fructosamine, GLC, Total AA, TC, LDL, TG, VLDL.
Iyer & Mani	1990	Curry leaves	30d	12g/d	↓FBS,↔PPBS,TC,TG
Mani & Mani	1987	Wheat bran	60d	11g/d	↓FBS, PP ↔ GSP,TC
Mani et al	1992	Cereal pulse mix	60d	100g/d	↓TG, LDL, FBS,TC, ↑HDL ↑HDL

Traditional anti-diabetic plants might provide new oral anti-diabetic compounds, which can combat the problem of the high cost and poor availability of the current medicines among many rural populations in developing countries. Plant drugs are frequently considered to be less toxic, safe and free from side effects than synthetic ones (Malaviya et al., 2010).

In India, indigenous remedies have been used in the folk lore medicines for the treatment of diabetes mellitus since the time of Charaka and Sushruta (6th century BC). The World Health Organization (WHO) has listed 21,000 medicinal plants around the world. Among these, 2500 species are in India and out of these about 800 plants have been reported to show antidiabetic potential (Patil et al., 2011).

India produces maximum quantity of medicinal herbs as it is enriched with a wide diversity of agro-climatic conditions and is called ***botanical garden of the world.*** Pharmacological and clinical trials of medicinal plants show that these plants possess anti- diabetic effects via repair of β-cells of islets of Langerhans (Kaushik et al., 2005).

Indian medicinal plants to treat diabetes

Diabetes mellitus is one of the common metabolic disorders affecting about 2.8% globally and is expected to cross 5.4% by the year 2025. Since ancient time, herbal medicines have been the highly demanded source of medicine therefore, they have become a part of modern, high-tech medicine (Patel et al., 2012). Overall, from the review, the antidiabetic activity of medicinal plants is due to the presence of polyphenols, flavonoids, terpenoids, coumarins and other constituents which show improved blood glucose levels. Table 2.22 shows the information about scientific name, family, parts of the plant used to treat diabetes and their mode of action/Observation.

TABLE 2.22: LIST OF PLANTS HAVING ANTIDIABETIC ACTIVITY

S. No	Plant part	Name of plants
1	Aerial parts	*Artemisia pallens, Bidens pilosa, Bixa orellana, Teramnus labialis*
2	Bark	*Cinnamomum zeylanicum, Croton cajucara*
3	Bulb	*Allium cepa, Allium sativum*
4	Flower	*Cassia auriculata, Gentiana olivier, Musa sapientum*
5	Fruit	*Carum carvi, Coriandrum sativum, Embellica officinalis, Juniperus communis, Momordica charantia, Xanthium strumarium*
6	Leaves	*Aloe barbadensis, Annona squamosa, Averrhoa bilimbi, Azadirachta indica, Beta vulgaris, Camellia sinensis, Cassia alata, Eclipta alba, Eucalyptus globulus, Euphrasia officinale, Ficus carica, Gymnema sylvestre, Gynura procumbens, Ipomoea aquatica, Mangifera indica, Myrtus communis, Memecylon umbellatum, Morus indica, Ocimum sanctum*
7	Rhizome	*Nelumbo nucifera*
8	Roots	*Clausena anisata, Glycerrhiza glabra, Helicteres isora, Pandanus odorus*
9	Seed	*Acacia arabica, Agrimony eupatoria, Lupinus albus, Luffa aegyptiaca, Lepidium sativum, Mucuna pruriens, Punica granatum*
10	Stem	*Amaranthus spinosus, Coscinium fenestratum*
11	Tubers	*Ipomoea batata*
12	Whole plant	*Abies pindrow, Achyranthus aspera, Ajauga iva, Aloe vera, Anacardium occidentale, Andrographis paniculata, Capsicum frutescens, Cryptolepis sanguinolenta, Enicostemma littorale, Ficus religiosa*

(Bhushan et al., 2010)

TABLE 2.23: SOME ANTI-DIABETIC MEDICINAL PLANTS AND THEIR MODE OF ACTION/OBSERVATION

Botanical Name	**Family Family**	**Parts used Parts**	**Observation/ Mode of action**
Adhatoda zeylanica	Acanthaceae	Leaf	Significant improvement in blood glucose level in alloxan induced Diabetic rats.
Aloe vera	Liliaceae	Leaf	Shows anti- diabetic activity in streptozotocin induced diabetic rats
Aegle marmelos	Rutaceae	Fruit	Improves functional state of the pancreatic ss-cells and partially neutralized the damage caused by STZ to the pancreatic Islets
Aegle marmelos	Rutaceae	Leaf	Modulates the activity of enzymic and nonenzymic antioxidants and increases the defense against damage in diabetic rats caused by ROS, effectively reduced the oxidative stress induced by alloxan and produced a reduction in blood sugar

Although early onset complications of diabetes can be controlled by oral hypoglycaemic drugs/insulin treatment, it reverts back causing late onset complications in many patients. Furthermore, clinical uses of the oral hypoglycemic drugs carry unpleasant side effects such as severe hypoglycaemia, lactic acidosis, peripheral oedema and abdominal discomfort (Bolen et al., 2007). Therefore, the search for more effective and less toxic new antidiabetic agents is on.

AEGLE MARMELOS

The plant *Aegle marmelos (L) Correa* is popularly known as bael in India is a spine tree belonging to the family Rutaceae. It grows up to a height of 3- 6 metres. It has oval shaped leaves and the flowers emit pleasant fragrance. The medicinal properties of this plant have been described in the ancient Ayurvedic literature. As per Charaka (1500 B.C.), bael is the only drug that has been longer or better known by the inhabitants of India than any other drug. It is popular medicinal plant in Ayurvedic and Siddha systems of medicine and folk medicines which is used to treat a wide variety of disorders. In Ayurveda Bael is termed tridosh har- remedy for three disturbances- bile, wind and phlegm (Chakravarty et al., 2010). *Aegle marmelos* (Bilva) is considered as an incarnation of Lord Shiva himself and it is one of the sacred trees in Hindu religion having spiritual powers. Bilva tree is said to have endowed from Goddess Sri Maha Lakshmi and Sri Sooktham acclaim Goddess Lakshmi as…

"Aadithya varnae tapassodhi jaatho
Vanaspathi stava vrukshotha bilvaha
Tasya phalani tapasaanudantu
Mayaantha raayaashcha baahya alakshmeehi"

The translation of this stotra is given below. "Oh Lakshmi, your complexion is like that of a morning Sun, a vanaspathi (trees bearing fruits without blossoming) called by name Bilva was brought forth by your pious authority. Your favour through your fruits may drive my misfortunes and poverty both internally (ignorance) and externally. It is believed that one who does penance under the Bilva tree and meditate on Goddess Sri Maha Lakshmi will be showered upon with fulfilment of all desires" (Sharma et al., 2007). Shiva and Parvathi are worshipped with offerings of bael leaves since ancient time (Rathore, 2009). Bael acts as a cooling agent having useful medicinal properties. It is a deciduous sacred tree, associated with Gods. This tree is popular in Shiva and Vishnu temples also popularly known as temple garden plant. It can be grown in every house. Its leaves are trifoliate which symbolize the Thrimurthies- Brahma, Vishnu, Shiva. Leaves bear spear shape which is compared to trisoolam the weapon of Lord Shiva. The tree is also sacred to the Jains. The 23rd Tirthankara, Bhagwan Parasnathji attained wisdom under a Bael tree (Chakravarty et al., 2010) . The leaflets are given to devotees as prasad in Shiva temples and as Tulsi

in Vishnu temples. The leaves and fruits of *Aegle Marmelos* plant can be seen in Figure 2.12 and 2.13.

FIG:2.12 AEGLE MARMELOS FRUITS

FIG:2.13 AEGLE MARMELOS LEAF

Plant profile

- Botanical Name: *Aegle Marmelos*
- Sanskrit Name: Bilva
- English Name: Bael Tree
- Family: Rutaceae
- Parts of Plant used: Fruit, leaf, root, bark

Scientific classification (Source: Maity et al., 2009)

- Kingdom: Plantae
- (unranked): Angiosperms
- (unranked): Eudicots
- (unranked): Rosids
- Order: Sapindales
- Family: Rutaceae
- Subfam*ily: Aurantioideae*
- Tribe: Clauseneae
- Genus: *Aegle* Corrêa
- Species: *A. marmelos*

Binomial name: *Aegle marmelos* (L.) Corr. Serr.

The names of *Aegle marmelos* in different languages are given in Table 2.24 (Ayurvedic Pharmacopoeia of India, 1999)

TABLE 2.24: NAMES OF AEGLE MARMELOS IN DIFFERENT LANGUAGES

Name	**Language**
Aegle mamelos	Latin
Wood/stone apple, Bengal Quince	English
Mbau Nau, Trai Mam	Vietnamese
Bel, Gudu	Nepali
Toum	Lao (Sino-Tibetan)
Bnau	Khmer
Modjo	Javanese
Oranger du Malabar	French
Ohshit, opesheeet	Burmese
Mojo tree	Indonesian
Pokok Maja Batu	Malay
Mapin, Matum, Tum	Thai
Shreephal, Bilva, Bilwa	Sanskrit
Sir Phal	Old Hindi
Bel, Shreefal	Bengali
Kaveeth	Marathi
Vilva Maram, Vilva Pazham	Tamil
Maredu	Telugu
Bel	Urdu
Billi	Gujarati
Belo	Orissa

Botanical Description

Bael is having only one type of genus (monotypic genus-*Aegle*) (Parmar and Kaushal, 1982). *Aegle marmelos* is a slow-growing and medium in size tree growing 25 to 30 feet in height. The stem is short, thick, soft, flaking bark, and spread out, sometimes having spiny branches, the lower ones drooping. There are sharp, one inch size axial spikes on this tree.

The leaflets are either oval or lancet shaped. It is 4-10 cm long and 2-5 cm wide. Leaves composed of 3 to 5 leaflets in it. The lateral leaflets are without petiole whereas the terminal one has a long petiole which is 1 to 2.5 inch long. Mature leaves release a peculiar fragrance when rubbed. In India flowering occurs in April and May soon after the tender new leaves appear and fruits ripe in 10 to 11 months from March to June of the following year (Parmar and Kaushal, 1982). Flowers occurs in clusters of 4 to 7 along the young branchlets, have 4 fleshy petals. The flowers are greenish white in color and fruit is spherical or oval in shape with a diameter of 2 to 4 inch. Shell is thin, hard and woody in nature, greenish when raw or unripe and yellow when ripe. The pulp of the fruit has 8 to 15 segments, yellow, soft, pasty, sweet, resinous and fragrant. The seeds are small (nearly 1 cm in length) embedded in the pulp, hard, flat-oblong, having woolly hairs each enclosed in an adhesive sac (Lambole et al., 2010). *Aegle marmelos* is one of the most important medicinal plants of India, Burma and Ceylon (Srivastva et al., 1996). It is found as a wild plant all over India and cultivated in north India. The Aegle is a small genus of three species distributed in tropical Asia and Africa belonging to the family Rutaceae and is known as Opesheet, Ohshit. It is termed differently in different languages as well as countries (Orwa et al., 2011).

Soil Type

Aegle marmelos is said to grow best on rich well drained soil, but it has grown well and fruited on the oolitic limestone of southern Florida. It also grows well in swampy, alkaline or stony soils having pH ranging from 5-8. In India it thrives where other fruit trees cannot survive (Sharma and Dubey, 2011).

Tree Management

The tree does well with little fertilizer and irrigation. The spacing between trees in orchards is 6-9 m. Seedlings begin to bear in 6-7 years. Full production is achieved in 15 years. Normally the fruit is harvested when yellowish-green and kept for 8 days during which it loses its green tint. Then the stem easily separates from the fruit. A tree may yield as many as 800 fruits in a season (Venkatesan et al., 2009)

Origin and Distribution

The *Aegle Marmelos* tree has its origin from Eastern Ghats and Central India. It is native to India and is found growing wild in Sub-Himalayan region from Jhelum eastwards to West Bengal, in central and south India. Bael is found growing along foothills of Himalayas, Bihar, Chattisgarh, Uttaranchal, Jharkhand, Gujarat and Madhya Pradesh. It is also grown in some Egyptian gardens in Surinam and Trinidad (Sukhdev, 1975).

Habitat

Bael is indigenous to dry forests, hills and plains of central and southern India, southern Nepal, Sri Lanka, Myanmar, Pakistan, Bangladesh, Nepal, Vietnam, Laos, Cambodia and Thailand. It is cultivated throughout India, as well as in Sri Lanka, northern Malay Peninsula, Java in the Philippines and Fiji Islands (Sukhdev, 1975).

Documented species distribution

Native range: India

Exotic range: Bangladesh, Egypt, Malaysia, Myanmar, Pakistan, Sri Lanka, Thailand (Vaidya and Devasagayam, 2007)

Chemical compounds isolated from plant

Leaf- Skimmianine, Aeglin, Rutin, Y-sitosterol, β-sitosterol, Flavone, Lupeol, Eugenol, Cineol, citral, Glycoside, O-isopentenyl , Halfordiol, Marmeline, Citronellal, Cuminaldehyde phenylethyl cinnamamides, Eugenol, Marmesinin

Fruit- Marmelosin, Luvangetin, Aurapten, Psoralen, Marmelide, Tannin

Bark- Fagarine, Marmin.

Seed- Essential oil: D-limonene, A-D-phellandrene, Cineol, Citronellal, Citral, P-cyrnene, Cumin aldehyde.

Nutritional value

- The fruit is eaten fresh or dried. The leaves and small shoots are eaten as salad greens in many Asian countries. The young shoots and leaf are used as vegetable in Thailand and as seasonal food in Indonesia. These are used to reduce appetite (Farooq, 2005)
- Various studies have been done to know the proximate composition of the leaves, pulp of fruit and seed powder of *Aegle Marmelos*. A study was conducted to analyze values for proximate composition of *Aegle Marmelos* leaf, pulp and seed powder using standard methods and it reported that bael leaf, pulp and seed powder are good source of protein, fat, minerals, crude fiber and energy, rich source of available carbohydrates, dietary fiber and also contain antinutrient content which help in controlling blood sugar (Morton, 1987; Singh et al., 2012).
- Another study reported that *Aegle Marmelos* leaf powder has 10.3g ash, 0.14µg zinc, 2.67µg iron and 1.73µg of chromium in leaf powder (Singh et al., 2012).

Phytochemicals and their Biological Activities in Aegle marmelos

Broadly, *Aegle marmelos* leaves contained γ-sitosterol, aegelin, lupeol, rutin, marmesinin, β- sitosterol, flavone, glycoside, oisopentenyl halfordiol, marmeline and phenylethyl cinnamamides (Narayan and Yadav, 2009). The detailed investigations on isolated compound classes are as under:

Alkaloids

The alkaloids comprise the largest single class of secondary plant substances. Four alkaloids were reported from dry leaves of *A. marmelos* *N*-2-[4-(3',3'-dimethylallyloxy)phenyl]ethylcinnamide,*N*-2-hydroxy-2-[4-(3',3'- dimethylallyloxy) phenyl] ethylcinnamide or marmeline, *N*-4- methoxystyryl cinnamide and *N*-2-hydroxy-2-(4-hydroxyphenyl) ethylcinnamide and aegeline. (Govindachari, 1983).

Initially aegeline was believed to be a sterol but after a critical study it was reported to be a neutral nitrogenous compound.

Recently, series of phenylethyl cinnamides, which included new compounds named anhydromarmeline, aegelinosides A and B were isolated from *Aegle marmelos* leaves as α-glucosidase inhibitors (Phuwapraisirisan et al., 2008). The present result also supports ethnopharmacological and therapeutic use of *Aegle marmelos* as a remedy for diabetes mellitus (Sharma et al., 1981).

A major constituent alkaloid Shahidine, containing an unstable oxazoline core was isolated from the fresh leaves of *Aegle marmelos*. Shahidine showed activity against a few Gram-positive bacteria (Pattnaik et al., 1996). It is reported to be moisture-sensitive and parent compound of aegeline and other amides; however, it is stable in dimethyl sulfoxide. Its structure was studied through spectroscopic analysis. Biogenetically, oxazolines are the precursor of hydroxyl amides and oxazoles contained in plants.

Phenylpropanoids

These are naturally occurring phenolic compounds, having an aromatic ring which is attached with three-carbon side chain. Hydroxycoumarins, phenylpropenes and lignans are included in phenylpropanoids. The most widespread plant The parent compound coumarin itself, occurs in around twenty-seven plant families. Marmesin was also isolated as a new compound from leaves, a constituent of heartwood and root (Kurian, 1992). Aegelenine isolated from the leaves as minor base was reported to be similar to halfordinol, the basic constituent of *Halfordia scleroxyla* (Chatterjee A, 1957; Chatterjee et al., 1971).

Aegeline (N-[2-hydroxy-2(4-methoxyphenyl) ethyl]-3-phenyl-2-propenamide) is a known compound of the bael leaf and utilized as a dietary supplement for a variety reasons (Riyanto et al., 2001) (Lanjhiyana et al., 2012) (Sharma et al., 1981). On distillation, fresh leaves yield yellowish-green oil comprising of marmelosin (typical aromatic odour), marmesinine, β- sitosterol-β-D-glucoside and rutin compounds present in the leaves. Another compound, Marmenol, a new 7-geranyloxycoumarin [7-(2,6-dihydroxy-7- methoxy-7-methyl-3-octaenyloxy)coumarin] was isolated from the leaves of methanolic extract of *Aegle marmelos*.

Terpenoids

The essential oil of *Aegle marmelos (L.) Correa* leaves were studied extensively in India by various inestigators since 1950. α-Phellandrene was found to be the common constituent of the leaf oil, twigs and fruits (Bhati, 1953; Karaway et al., 1980). α-Phellandrene (56%) and p-cymene (17%) were reported from leaf oil by another study also (Baslas and Deshpandey, 1951). Later on, similar results were published on leaf essential oil by many investigators. Various compounds like p-Menth-1-en-3,5-diol (Garg et al., 1995) and γ-Sitosterol was identified and characterized from the leaves (Chakravarti, 1958). Limonene (82.4%) was reported as the main component of *Aegle marmelos* leaves and it was proved to be characteristic marker for identification of *Aegle marmelos* oil samples (Kaur et al., 2006) γ-Sitosterol was identified from the leaves (Chakravarti, 1958).

Tannins

There is as much as 9% tannin in the pulp of wild fruits but found to be less in cultivated type. Tannin is also present in leaves as skimmianine known as 4, 7, 8-trimethoxyfuro-quinoline (Daniel, 2006).

Flavonoids

Flavonoids mainly includes rutin, flavone, flavan-3-ols, flavone glycosides (Sivaraj, 2011). In a study important medicinal plants were investigated on the phytochemical composition of the plants including Aegle marmelos and it reported that highest alkaloids (1.08%), tannins (15.26%), Flavonoid (0.98%) and saponins (2.62%) in found in Aegle marmelos leaves when compared with other plants (Dhandapani and Sabna, 2008). In a study conducted from 18 varieties/accessions of the leaves of Aegle marmelos from all over India, it was found that the crude extracts of *Aegle marmelos* revealed the presence of several biologically active phytochemicals containing highest quantity of alkaloids, flavonoids, and phenols in Pant Aparna variety of *Aegle Marmelos* plant. The GC-MS analysis showed the presence of many bioactive compounds such as flavonoids, alcohols, aldehydes, aromatic compounds, fatty acid methyl esters, terpenoids, phenolics, and steroids that account for antibacterial activity (Mujeeb et al., 2014).

Seed oil

Seed oil is bitter in taste and contains 15.6% palmitic acid, 8.3% stearic acid, 28.7% linoleic acid and 7.6% linolenic acid whereas seed residue contains about 70% protein (Sivaraj, 2011).

Miscellaneous compounds

Praealtin D, *trans*-cinnamic acid, valencic acid, 4-methoxybenzoic acid, betulinic acid, *N*-p-*cis*-& *trans*coumaroyltyramine, montanine, and rutaretin were the bioactive compounds present in methanolic extract of *Aegle Marmelos* leaves (Ali and Pervez, 2004). In addition, rutin, flavan-3-ols, anthrocyanins, lecucanthrocyanins, flavone glycoside and tannins also have been reported from the leaves (Sharma et al., 1981).

Antioxidant and anti-diabetic activity of aegle marmelos (animal studies)

Aegle marmelos is one of the most widely used medicinal plant belonging to the family Rutaceae. The leaf juice of *Aegle marmelos* is used in diabetes and oedema (Jain, 1968).

The aqueous and alcoholic extract of *Aegle marmelos* leaves showed increase in amplitude and force of contractions of frogs' heart similar in activity to that shown by digitoxin. Both these extract stimulated the ventricles of dog's heart as seen from electrocardiograms. The alcoholic extract of the root and fruits of *Aegle marmelos* showed hypoglycaemic activity in albino rats (Harvey, 1968).

In a study the potential antidiabetic effect of *Aegle marmelos* leaf extract in diabetic rats was examined wherein one group of diabetic animals were given insulin injection and another group were fed with *Aegle marmelos* leaf extract orally. This study indicated that the hypoglycaemic activity contained in active principle present in *Aegle marmelos* leaf extract can be compared to insulin treatment (Ponnachan, 1993).

It was reported that aqueous leaf extract (equivalent to 1 gm powder/kg/day) produced significant ($p<0.01$) anti-hyperglycaemic effect within three days in alloxan induced diabetic rabbits while similar treatment in normal rabbits lowered blood glucose level upto 35.3% after 4 hours of administration. Moderate hypoglycaemic effect was recorded even after 12 hours (Rao et al., 1995).

The effect of *Aegle Marmelos* leaf on histological and ultra structural changes in tissues of streptozotocin induced diabetic rats was studied at a smaller dose of 45 mg/kg B.W. The treatment of leaf extract showed improved functional state of pancreatic beta cells of diabetic pancreas. This study indicates the hypoglycaemic property of the leaf extract, via regeneration of damaged pancreas. (Das et al., 1996).

The leaf extract of *Aegle marmelos* was found to be as effective as insulin in restoring blood glucose and body weight to normal levels (Padayatti et al., 1996; Seema et al., 1996). The alcoholic extract of the *Aegle Marmelos* leaves has been reported to have the chemo preventive potential, especially against chemical carcinogenesis (Singh et al., 2000).

The effect of the aqueous, alcoholic and petroleum ether extracts of *Aegle marmelos* for the hypoglycaemic and other pharmacological actions was studied and it was reported that the aqueous and alcoholic extracts at 500 mg/kg dose produce hypoglycaemia in normal fasted rabbits, but the petroleum ether extract did not show such activity (Hema and Lalithakumari, 1999 ; Ogata, 2000).

Antioxidant parameters like reduced glutathione, glutathione peroxidase, glutathione reductase, superoxide dismutase (SOD) and catalase have shown a dose related increase in their level/activity and a decrease in lipid peroxidation following the treatment with *Aegle marmelos* leaf extract (Singh and Banerjee, 2000).

The hypoglycaemic effect of *Aegle marmelos* extract and *Hibiscus rosa sinensis* was studied in glucose induced hyperglycaemic rat for 7 consecutive days, at 250 mg/kg oral dose and it showed significant improvements in its ability to utilize the external glucose load. Average blood glucose showed a decrease by 67% and the efficacy of *Aegle marmelos* was 71% of a standard drug, glibenclamide (Sachdeva et al., 2001).

Glutathione (GSH) is reduced in erythrocyte whereas plasma glutathione-S-transferase (GST) and melondeialdehyde (MDA) are increased in diabetic male albino rats which is reversed to normal level with *Aegle marmelos* leaf extract administration suggesting antioxidant potential of *Aegle marmelos* leaves (Kar et al., 2003).

A study reported the hypoglycaemic and antioxidant activity of aqueous extract of *Aegle marmelos* leaves by analyzing the glucose, urea and GST (glutathione-S-transferase) levels in plasma, GSH (glutathione) and MDA (malondialdehyde) levels in erythrocytes of alloxan induced diabetic rats (Upadhya et al., 2004).

A study reported that pre-treatment with *Aegle marmelos* leaf extract at doses of 100mg/kg and 200mg/kg body weight for 35 days showed a significant effect on the activities of marker enzymes, lipid peroxides, lipids, lipoproteins and antioxidant enzymes in isoproterenol treated rats. The effect of extract 200mg/kg was found to be similar to the effect of alpha-tocopherol at the dose of 60mg/kg (Rajadurai et al., 2005).

This antidiabetic effect is probably due to the presence of eugenol and marmesin in bael leaves extract suggesting antioxidant potential of the leaves probably through the mechanism which stimulate the insulin secretion from existing beta cells of the islets of Langerhans (Kamalakkannan and Prince, 2005).

Comparative evaluation of hypoglycaemic activity of some 30 hypoglycaemic Indian medicinal plants from indigenous folk medicines (Ayurvedic, Unani and Siddha systems of medicines) including *Aegle marmelos* was studied in alloxan induced diabetic rats. The results showed that in all the 24 herbal samples including *Aegle marmelos* (vacuum dried 95% ethanolic extracts), significant blood glucose lowering effect close to normal at a dose of 250mg/kg within 2 weeks had been confirmed in alloxan diabetic albino rats. *Aegle marmelos* showed significant hypoglycaemic activity (Sharma et al., 2007).

Phuwapraisirisan (2008), isolated series of phenylethyl cinnamides, which included novel compounds named anhydromarmeline, aegelinnosides A and B from Aegle marmelos leaves reported to be alpha-glucosidase inhibitors. The structures of new compounds were characterized by spectroscopic data and chemical degradation. Among the compounds isolated, anhydroaegeline revealed the most potent inhibitory effect against alpha-glycosidase with IC (50) value of 35.8 mM. This result suggest ethno pharmacological use of *Aegle marmelos* as a remedy for diabetes mellitus (Phuwapraisirisan, 2008),

In vitro antioxidant activity of the methanolic extract of *Aegle Marmelos* leaf was studied using standard methods like DPPH scavenging activity, H_2O_2 scavenging activity and ferrous red*ucing power. In* vitro activity of Methanolic extract of *Aegle marmelos* showed that it has good antioxidant activity with the IC50 value 23±0.08. It thus can be used as potential inhibitor of free radicals (Siddique and Mujeeb, 2010).

It was further reported that aqueous leaf extract of *Aegle marmelos* inhibit primarily the uptake of glucose across rat inverted gut sacs so it also suggested that bael leaves have anti hypoglycaemic (Therasa, 2009; Siddique, 2010).

Aegle marmelos leaves were screened for phytochemicals, antioxidant (DPPH) and polyphenol content (Folin-ciocalteu assay) using a series of solvents. The methanol and water extract of *Aegle marmelos* was found to be rich in ascorbic acid, glutathione, flavonoids, saponins, reducing sugars, turpenoids and polyphenol (2.4g of Gallic acid per 100g of (dry wt.) of extract). Antioxidant activity of water extract was higher (92%) than BHT (81% standard antioxidant). It also exhibited significant radical scavenging activity due to higher content of antioxidants such as tocopherol, glutathione and ascorbic acid in it (Reddy et al., 2012).

A study compared antioxidant activity and phenol content in methanolic extract of the selected parts (leaves, root and stem bark) of *Aegle marmelos*. The total phenolic contents varied from 9.8367 ± 0.0235 to 1.7281 ± 0.049 mg g-1 and total flavonoids content were between 8.248 ± 0.029 to 1.087 ± 0.002 mg g-1.The highest free radical scavenging effect (using DPPH) was observed in leaves with IC50 = 2.096μg/ ml turning to be about 10 times greater than reference antioxidant butylated hydroxy toluene (BHT). Thus it was shown that greater amount of phenolic compounds leads to more powerful radical scavenging effect as shown by methanolic extract of *Aegle marmelos* leaves (Bhalla et al., 2012).

A study was conducted to see the maximum percentage scavenging (DPPH value) for Ascorbic Acid, petroleum ether, chloroform, alcohol, and aqueous extracts (Juice of powdered leaf) of *Aegle marmelos* and it was found to be 94.56 %, 62.56 %, 86.81 %, 76.78 % and 72.74 % respectively at highest concentration. The more potent activity was observed in chloroform extract (AMCL) compare to control group (Modi et al., 2012).

In another study it was found that the various ethanol extract at the concentration of 5, 10 and 15mg/ml respectively of *Aegle marmelos* has antioxidant values of 46.08%, 50.56% and 54.32%. The total phenolic compounds are the bioactive compounds responsible for antioxidant activity. Among the three solvents, ethanol solvent showed maximum extraction of phenolic compounds (1.921mg/g) and distilled water extract showed lowest extraction (1.510mg/g) (Sathya et al., 2013).

In a study it was found that single dose of 10mg/100g aqueous extract of the leaves of *Aegle marmelos* supplemented to alloxan-induced diabetic rats every day morning for one month significantly ($p<0.001$) decreased blood glucose levels and significantly ($p<0.01$) increased body weight changes while in non-diabetic rats. The leaves did not cause any hypoglycaemic effect and body weight changes indicating that they have anti-diabetic activity. Even 20 times high dose of the leaf extracts did not cause any toxicity or mortality. This further indicates high margin of safety. The mechanism behind the effect of leaf extracts appears to be inhibition of glucose-6-phosphate dehydrogenase, hepatic glucose output and control of the elevated blood glucose levels. *Aegle marmelos* leaf is an insulin sensitizer which can be used in the treatment of diabetes. It improves the glycaemic control by stimulating the insulin sensitivity in liver and muscle (Murlidharan, 2014).

TABLE 2.25: SUMMARY OF EFFECT OF VARIOUS DOSAGES OF AEGLE MARMELOS LEAVES ON ANTIHYPERGLYCEMIC ACTIVITY IN VARIOUS ANIMAL MODELS

Sr. No.	Investigators	Dosage	Duration	Findings
1	Ponnachan et al (1993)	250mg/Kg B W leaf extract	1 month	Anti-hyperglycemic activity in alloxan diabetic rats along with decreased cholesterol and blood urea.
2	Paulose et al (1993)	250mg/Kg B W leaf extract	1 month	Leaf exhibited insulin like activity in diabetic rats.
3	Das et al (1996)	50mg/100gm body weight		Improved state of pancreatic cells in streptozotocin induced diabetic rats.
4	Sharma et al (1996)	250and 500mg/kg orally		Produced hypoglycemic effect and increased plasma insulin level. LD_{50} observed greater than 10g/kg at oral administration to rats.
1	Sachdeva et al., (2001)	250mg/Kg B W leaf extract	7 days (short term)	↓ ABS- 67%
2	Sabu and Kuttan (2004)	120mg/ Kg B W methanolic leaf extract	12 days (short term)	↓ RBS- 54%
3	Upadhya et al (2004)	Aqueous leaf extract	one month (long term)	↑ erythrocyte GSH and plasma GST levels, ↓ BS & MDA
3	Narendra et al (2007)	Aegelin 2 isolated from leaf (50mg/Kg BW)	30 days (long term)	↓ TC-24%, TG-55% ↑ HDL-28%
4	Arumugam et al (2008)	1 g/ Kg B W aqueous extract of dry leaf & fresh leaf	3 consecutive days (short term)	↓ RBS-20%(fresh leaf),30% (dry leaf extract)
5	Vijaya et al (2009)	125mg/ Kg B W and 250mg/ Kg B W ethanolic leaf extract & std drug gemfibrozil	7 days (short term)	↓ TC-36.8% ,50.3% ↓ TG-17.7%, 39.01%
6 A	Devi et al (2010)	250mg, 350mg & 450mg/Kg BW AMLE	7days (short term)	↓ TC-8.12%(450mg);TG-10.2%;LDL-23.25%; ↓ VLDL-40.8% HDL-15.7%
6 B	Devi et al (2010)	250mg, 350mg & 450mg/Kg BW AMLE	25 days (long term)	↑ TC-34.15%; TG-35.5%;LDL-34.78% ↑ HDL-36.2%
7	Gohil et al (2010)	400mg/Kg BW ethanolic leaf extract	25 days (long term)	↓ RBS-60%, TC-9.1%, TG-10.25%, LDL-23.81% ↑ HDL-16.2%
6	Prince and Rajadurai (2010)	50, 100 and 200mg/Kg BW leaf extract	35 days (long term)	200mg/kg dose was as effective as 60mg/kg α- Tocopherol-(std antioxidant)
7	Murlidharan (2014)	10mg/100g BW	30 days (long term)	↓ FBS-45%, PPBS-27.4%, Body wt-4.5%

Anti-toxicity Activity

Generally, *Aegle marmelos* is used as folklore medicine and its consumption is considered safe but few studies have been carried out with respect to its efficacy and toxicity. A study was designed to explain the toxicity of *Aegle marmelos* in rats. Total alcoholic, aqueous and methanolic extracts of leaves were used for the toxicity studies. Acute, sub-acute and LD_{50} values were determined in experimental rats. About 50mg/kg leaves were administered intraperitoneally for 14 days and the vital organs such as heart, liver, kidney, testis, spleen and brain were carefully examined by histopathological studies. Pathologically, no abnormalities or histopathological changes were recorded. LD_{50} values were calculated using graphical methods, and it was found that *Aegle marmelos* extracts possess a broad therapeutic window and a high therapeutic index value (Veerappan et al., 2008).

The detailed information presented in this review on the phytochemicals, antioxidant, anti-diabetic and anti-toxic properties of the plant extract might provide detailed evidence for the use of this plant as a remedy for diabetes.

Among the various therapeutic properties of Aegle Marmelos leaves reported by different workers, the most important pharmacological activity of *Aegle marmelos* leaves has been found to be its antidiabetic activity. Still the mechanism of hypoglycaemic action is not clear and may be the result of improvement in the functional status of beta cells, reversing the histologic and ultra structural changes in the pancreas and liver of streptozotocin-induced diabetic rats.

So there is urgent need of correlating the therapeutic activity with the chemical marker of the plant as well as studying the mode of action of that marker compound. Skimmianine and Anhydroaegeline can be used as markers to standardize the plant material with respective to its potential anti diabetic activity.

The development of *Aegle marmelos* as a nutraceutical suggests further preclinical and clinical studies to explore its utility and efficacy in treatment of chronic diseases.

An attempt has been made to review different in vitro models for estimating antioxidant properties of bio active compounds from *Aegle Marmelos.* There are large number of studies showing in vitro antioxidant activity but in vivo studies are still lacking.

Clinical trials using aegle marmelos leaves on diabetic subjects- human studies

Very few studies have been done to explore the therapeutic effect of *Aegle marmelos* leaf with respect to human subjects however antidiabetic activity of the leaf decoction was evaluated. The study was performed in 4 groups having ten NIDDM patients (5gm powder) given for a period of one month daily orally. Pre and post prandial blood glucose level (PPBGL) was estimated and it was found that antidiabetic effect was more significantly marked when it was combined with the oral hypoglycaemic therapy (Yaheya and Ismail, 2009).

In another study T2DM subjects were given sulfonylurea drug alongwith 2g *Aegle marmelos* leaves twice a day or sulfonylurea plus placebo. After 8 weeks, the combined therapy was more beneficial in lowering the level of fasting blood glucose (FBG), PPBG and urinary glucose (Sankhla et al., 2009).

Singh and Kochhar (2012) studied the impact of Aegle Marmelos in 120 NIDDM subjects (4 groups) who were supplemented with 2gms of (bael leaf powder - group II, bael pulp and bael seed powder- group III and group I treated as control) for 3 months and then along with supplementation, nutritional counselling was given for the next 3 months. The results indicated significant reduction in FBS level. There was a significant reduction in total cholesterol and triglycerides and increase in HDL. (Singh and Kochhar, 2012).

Ethanobotanical and various indigenous uses of Aegle Marmelos

The ethnic community of India has played an important role in conservation of several forests and have preserved several flora and fauna in sacred groves of tribal, otherwise these might have been disappeared from natural ecosystems. *Aegle marmelos* is one of few trees which has been conserved since ages (Rawat and Uniyal, 2003).

Aegle marmelos (L.) Correa, one of the most important medicinal plants of India, for its immense low cost, easy accessibility.

In Ayurveda, the ripe fruit has been used for chronic diarrhoea and dysentery, as a tonic for the heart and brain and as a cooling agent during summer. A decoction of the root mainly being used as an ingredient of the Ayurvedic medicine, dashmool. It has

been used to treat melancholy, intermittent fevers and palpitation. The leaves have been given as febrifuge and its paste as a poultice for the treatment of eye disorders and ulcer whereas consumption of fresh leaves have been used for weakness of the heart, dropsy and beriberi.

In a study it was indicated that *Aegle marmelos* can be a good cash crop, showing that the inhabitants earn Rs.2991/annum selling ripe fruits and approximately 30 households are involved in this business (Ajaz-ul-Islam et al., 2013).

The Ethnomedicinal importance of A. marmelos

Ethnomedical information on various parts of *Aegle marmelos* is available from many parts of India and other countries. Available ethnomedical literatures reveal that entire plant, leaf, fruit, stem bark, root and essential oil from fruits of this plant are used in the treatment of various diseases (Fig:2.1 and 2.2). It is given the honor by title of "sriphala" and by associating it with Lord Shiva who is fond of its leaves. Bilva is one of the ingredients of dasmula in which its root is used (Jain, 1989). Around 7000 years back, *Aegle marmelos* was used as a stick by the Babylonian slam. Puppetries and dental oral health and the importance of the bael leaf has been discussed. British pharmacopoeia has included A. marmelos fruit because of its effectiveness against diarrhoea and dysentery (Chopra, 1982). Moreover, Chopra (1982) has appropriately stated that “No drug has been longer and better known, nor more appreciated by the inhabitants of India than the Bael fruit”. Various forms of preparation of leaf for its therapeutic application is presented in Fig 2.14 and 2.15.

FIG 2.14 : THERAPEUTIC USES OF THE VARIOUS PARTS OF AEGLE MARMELOS PLANT

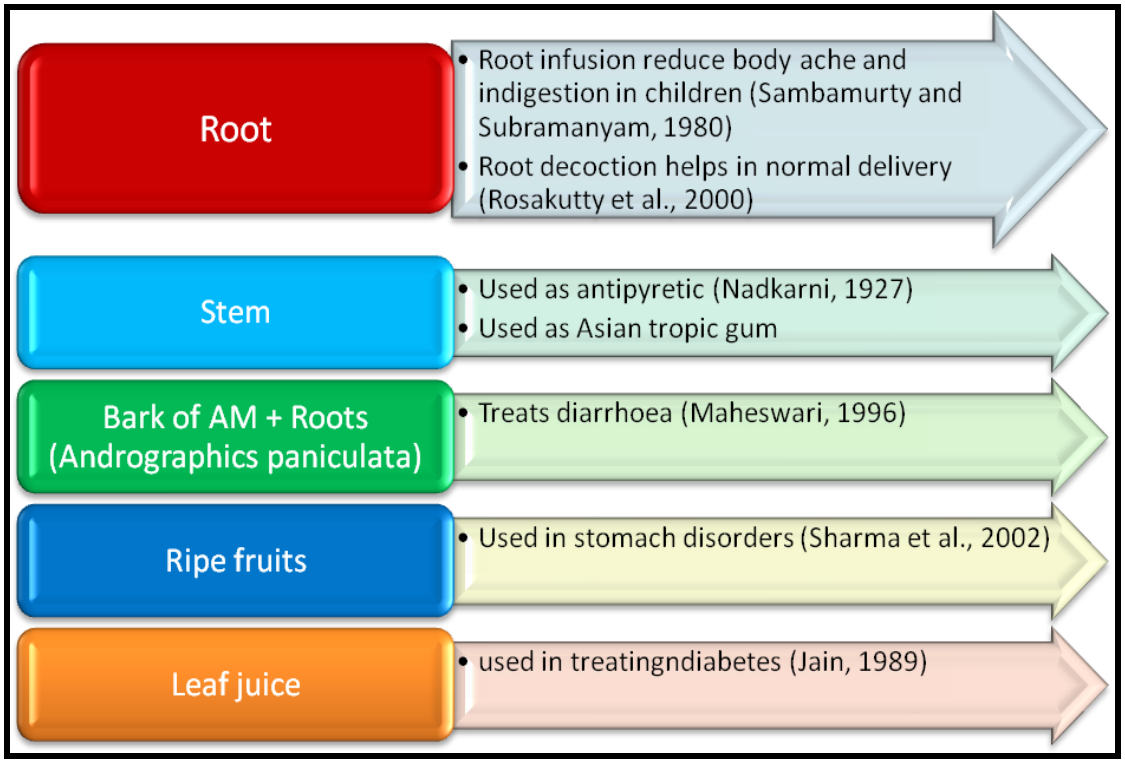
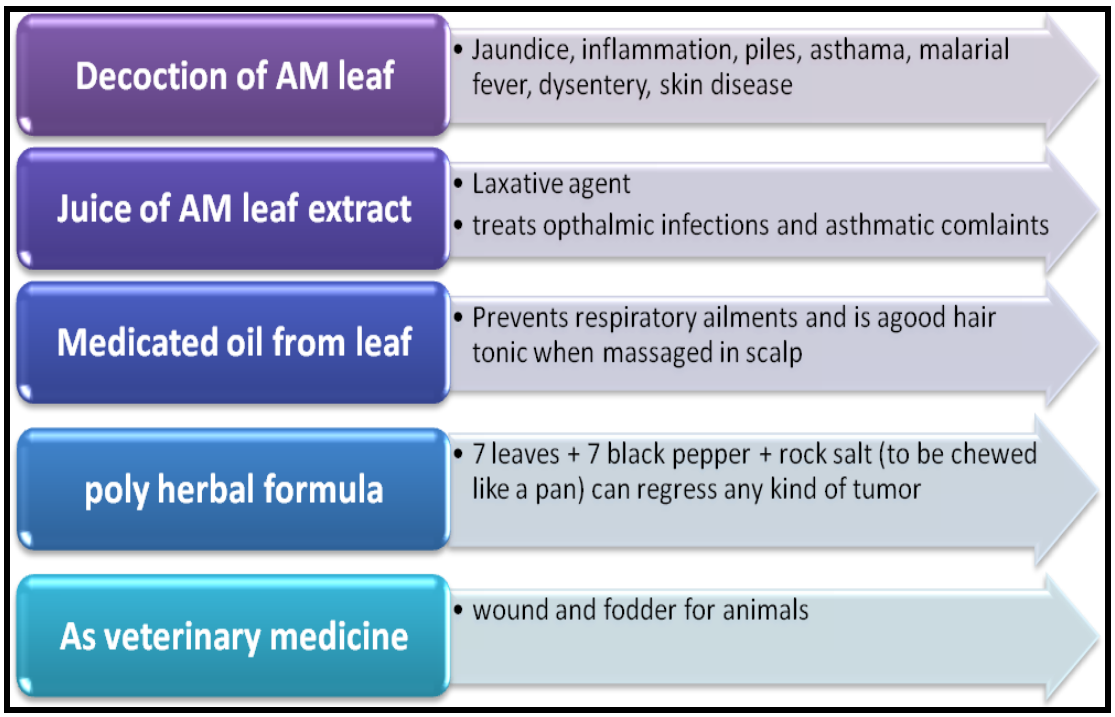


FIG 2.15: VARIOUS THERAPEUTIC FORMS OF AEGLE MARMELOS LEAF



(Gaur , 1999; Jain, 1995)

Ethanobotanical Studies

Various uses of Aegle Marmelos leaf mentioned in Ayurvedic Pharmacopeia of India is given in Table 2.26 below.

TABLE 2.26: VARIOUS ETHANOBOTANICAL STUDIES DONE ON AEGLE MARMELOS

Ethanobotanical Use of Aegle Marmelos Leaf	References
Opthalmic	Nadkarni, 1976 ; Chopra et al., 1955; Singh and Pandey, 1980, Singh et al., 1994
Anti-inflammatory	Reddy, 1986
Digestive disorders	Tripathi et al., 1996; Pant and Pandey, 1995, Mohan and Singh, 1996; Maheshwari and Singh, Ahmad and Chaghtai, 1982
sprains	Chandra et al., 1987
Diabetes	Hemadri and Rao, 1989, Pushpalata et al., 1990, Badhe and Pandey, 1990, Kumar and Pandey, 1990, Kumar et al., 1993, Ponnachan et al., 1993, Paulose et al., 1993, Singh and Prakash, 1994, Das et al., 1996, Sharma et al., 1996, Sachdeva et al., 2000, Sachdeva et al., 2001, Upadhya et al., 2004 and Murlidharan, 2014
Wound healing and skin application	Joshi et al., 1980, Singh and Singh., 1985; Reddy et al., 1988, 1998
Sunstroke	Singh and Prakash, 1994
influenza, malaria, acute rheumatism	Ghosh, 1986
De-worming	Maheshwari et al., 1980; Mohan and Singh, 1996
Throat infection	Aminuddin and Girach, 1993
Antipyretic	Singh, 1997

(ICMR, 2004)

Ethno-medicinal use of Aegle marmelos leaves by traditional healers

Various studies have documented the indigenous folklore use of Aegle Marmelos leaves by the traditional or local healers/ *Vaidyas* in various communities of India. These studies show the dependence of the ethnic people on the herbal remedies using *Aegle Marmelos* in their everyday life. Generally, the people are found to be having strong faith in traditional medicine. Most of them are found to consume only herbal medicine throughout their life. Traditional knowledge of such kind demands serious conservation steps.

The plant uses practised by tribal people still need to be examined in order to popularise these authenticated practices; to preserve indigenous knowledge; to integrate or blend it with scientific knowledge so that practitioners, health professionals and healthcare users may benefit from a wider range of traditional healing practices which are environmentally favourable and not threatening.

Table 2.27 shows indigemous uses of Aegle Marmelos in various ailments by traditional healers in various communities of India.

TABLE 2.27 : INDIGENOUS USES OF AEGLE MARMELOS LEAF BY TRADITIONAL HEALERS IN VARIOUS COMMUNITIES IN INDIA

Investigators/Year	Dosage	Methods	Place of Work	Findings
Thakur et al., 2013	2 grams of fresh leaves	Ethno-botanical survey of medicinal plants used by tribes	Manipur block, Chattisgarh	Everyday chewing of 2g leaves of aegle marmelos to cure jaundice and skin diseases
Chaudhary and Upadhya 2012	5 leaves of Aegle Marmelos chewed with 2-3 pepper every day empty stomach	Survey work	Bhil tribe	Chewing Aegle Marmelos leaves with pepper for the treatment of jaundice
Chakravarty and Kalita 2012	all the remedies are based on fresh juice, powder, fresh leaf paste or decoction in water	survey to cure diabetes in the form of a questionnaire and personal interviews	Nalbari district of Assam	Aegle Marmelos Leaf powder is taken with cow's milk daily to cure diabetes.
Tripathi et al., 2000	100 ml juice	Attempt was made to link the traditional practice with the relevant scientific information to determine the validity of the practices	55% tribal belt of Bihar (Andhaura block of Kaimur district)	Leaf Juice taken orally once a day to treat diabetes, found to be effective and scientifically confirmed.
Das and Chaudhary, 2012	Dosage depends mostly on the intensity of the disease and the age of the person concerned	Information was collected in the form of a field survey mainly from the medicine men, village headmen and the aged and experienced people.	tribal villages of Tripura (north)	1 cupful extract made from Bael leaves and *Cajanus cajun* with water taken in the morning empty stomach in combination with molasses in jaundice.
Devi, 2011		Survey of locally available antidiabetic plants used through comprehensive questionnaire format	Meitei Community of Manipur	Among 53 plants used by traditional healers leaves of the aegle marmelos was used for the cure of diabetes.
Hossain et al., 2012	No fixed dose	Formulations used for treatment of various diseases by the Assam-trained Kaviraj were explored in this study.	Dhaka district, Bangladesh	Equal amount of *Aegle marmelos* leaves and *Azadirachta indica* A. (Neem) are macerated together and applied to acnes once daily. for 20 minutes each time to cure acne.

Other Pharmacological Activities of Aegle Marmelos (Dutta et al., 2014)

a) Antiulcer Activities

Oxidative stress usually leads to gastric ulcer. Luvangetin prevents ulcer formation by lowering oxidative stress in the gastro duodenal mucosa. The phenolic compounds are potent antioxidants and believed to have powerful antiulcer activities (Bandyopadhyay et al., 2002).

b) Antioxidant activity

Administration of bael leaf extracts showed dose–related increase in their antioxidative activity such as reduced glutathione, glutathione peroxidase, glutathione reductase, super oxide dismutase (SOD) and catalase and a decrease in lipid peroxidation.

Leaf extract (dose-200 mg/kg) was found to be as effective as natural antioxidant alpha tocopherol (60mg/kg) in isoproterenal (ISO)-treated rats (Chakrabarti et al., 1960). The antioxidant activity or free radical scavenging activity in the leaf is attributed to the presence of phytochemical such as flavonoids, alkaloids, sterols, tannins, phlobatannins and flavonoid glycosides. (Rajadurai and Prince, 2005). The antioxidant potential of bael leaves increases the level of (GSH) in erythrocyte and decrease of plasma glutathione-S-transferase (GST) and malondialdehyde (MDA) in male albino rats The antioxidant potential of bael leaves brings back the level to normal (Upadhya et al., 2004).

c) Antimalarial activity

Malaria caused by Plasmodium falciparum causes about 2 million deaths annually. Also, the species gradually get resistant to existing anti-malarial drugs which complicates the treatment of this dreadful disease. The alcoholic extracts of the bael leaves have been tested for antimalarial activity against the NK65 strain of Plasmodium berghei. The leaves have shown activity in the in-vitro system (Misra et al., 1999).

d) Antidiabetic activity

The plant extracts have a multidirectional antidiabetic action that significantly lowers the blood glucose levels and glycosylated hemoglobin and shoots up the plasma insulin as well as liver glycogen in diabetic rats (Kamalakkanan et al., 2003). It has been noted that oxidative stress of the body is closely associated to diabetes and related complications (Ceriello, 2006) with cardiovascular as well as renal disorders.

e) Anti-inflammatory activity

Due to the presence of Lupeol and Skimmianine in the leaves, the anti-inflammatory, analgesic and antipyretic activities of the organic extracts of the bael leaves have now been established (Arul et al., 2005; Getha and Varalakshmi, 2001). Activation of histamine receptor is crucial for allergic and asthmatic manifestation. The alcoholic bael leaf extract, containing Lupeol and Citral contradicted the histamine–induced contractions and demonstrated positive chain, inhibits H1-receptor activity and histamine mediated signal (Getha and Varalakshmi, 2001) and relaxant effect in isolated guinea pig ileum and tracheal is observed.

f) Antifungal activity

Essential oil extracted from the bael leaves shows potent antifungal activity against animal and human fungi like: Trichophyton mentagrophytes, T. rubrum, Microsporum gypseum, M. audouinii, M. cookie, Epidermophyton floccosum, Aspergillus niger, A. flavus and Histoplasma capsulatum (Jain, 1977).

The germination of any spore (bacterial or fungal) is associated to free Ca^{+2} ion available in the medium as well as within the cytoplasm of microbes. Bael leaf essential oil may inhibit spore germination via interference with the Ca^{+2-}dipicolonic acid metabolism pathway.

g) Antibacterial activity

Aegle Marmelos leaf extracts have been found to be active against several bacterial strains. The essential oil of the leaf inhibits the growth of Escherichia coli (Joshi and Magar, 1952). Aeromonas sp., Pseudomonas salanacearum and Xanthomonas vesicatoria by blocking protein synthesis either at transcription or translation level

and/or peptide-glycan synthesis at membrane level due to the presence of bioactive compounds such as Cuminaldehyde and Eugenol.

h) Antiviral activity

In a study, the IC_{50} values of leaves, stem, stem bark, fruit, root, root bark and purified compound Marmelide were reported to be 1000, 500 to 1000, 250 to 500 and 62.5 µg/ml, respectively, whereas, the IC_{50} of Ribavirin (a standard antiviral agent) was 2000 µg/ml for the same viruses and at the same time period (Badam et al., 2002). Thus, marmelide is the most effective virucidal agent interfering with early events of its replicative cycle ((Badam et al., 2002). The mechanism of action is that bael extracts act upon the early stages of viral replication with minimum host cytotoxicity opposite to a virucidal chemotherapeutic agent, ribavirin, acting during the later stages of viral replication accompanied with side effects.

i) Anticancer activity

Hydro- alcoholic extract of bael leaf at the dose of 400 mg/kg shows the greatest antitumor effect on the animal model of Ehrlich ascites carcinoma (Jagetia et al., 2003). It inhibited in-vitro proliferation of human tumour cell lines including the lecukenic K562, T-lymphoid jurhat, Beta lymphoid Raji, Erythro leukemic HEL (Lampronti et al., 2003). The plant extract manifests cytotoxicity against tumor cell lines in brine shrimp lethality assay and methyl thiazolyl tetrazolium (MTT) based assay. The extract also reflects anti-proliferative activity on MCF7 and MDA-MB-231 breast cancer cell lines (Lambertini et al., 2005). Skimmianine present in the leaf extract exerts apoptosis thereby killing the tumor cells (Jagetia et al., 2003).

j) Radioprotective activity

Aegle Marmelos leaf extract at the dose of 5 µg/ml exhibited radio protective effect on animal models by reducing multiple micronuclei produced as a result of irradiation with different doses of gamma-radiation leading to on cultured human peripheral blood lymphocytes (HPBLs). This radio protective effect was due to antioxidant effect causing the scavenging of radiation–induced free radicals (Jagetia et al., 2003). Identical experiment was conducted in Swiss albino male mice. The mice were administered with various intraperitoneal single doses of the extract. The optimum

radio protective dose of the extract has been found to be five consecutive doses of 15 mg/kg body weight ((Jagetia et al., 2003).

k) Antihyperlipidaemic activity

Pre-treatment with 100 mg/kg and 200 mg/kg doses of the bael leaf extract for 35 days have shown significant improvement in the activities of marker enzymes, decrease of lipid peroxides, plasma lipids and lipoproteins in isoproterenol-treated rats, suggesting its antihyperlipidaemic effect (Rajadurai and Prince, 2005).

Ethanolic extract of bael leaves also improved serum cholesterol and triglyceride level in triton treated hyperlipidemia rat (Vijaya et al., 2009). This extract also improves glucose utilization.

l) Other activities

Leaf extract (1 gm/kg) of *Aegle marmelos* was examined to study the regulation of thyroid hormone in male mice. Leaf extract affected serum levels of both T (3) and T (4), it could decrease only 62% of T (3) concentration suggesting its possible use in the control of hyperthyroidism (Kar et al., 2003).

Aegle Marmelos plant acts as a 'filter' for removal of chemical pollutants by absorbing poisonous gases from the atmosphere and turning them neutral. It is also known as ‘Climate Purifiers’ because it releases huge amount of oxygen in sunlight in comparison to other plants. The tree is also recognized in the class of ‘Fragrant’ species, as the flowers and volatile vapors nullify the bad smell of decaying organic matter or refuge and thus help our life from bacterial attack by neutralizing the bad odor of air (Agarwal, 1997).

FIG 2.16: VARIOUS MEDICINAL PROPERTIES OF AEGLE MARMELOS PLANT

SUMMARY

The prevalence of modern lifestyle diseases such as Type 2 diabetes is on the rise in developing countries. The burden of T2DM is huge considering the cost of diagnosis and treatment. In developing countries such as India, due to economic constraints providing modern medical healthcare is still a far-reaching goal.

Less than 1% of the medicinal plants out of 2,50,000 has been screened pharmacologically with regards to DM. Therefore, it is urgent to look for alternatives in herbal medicine for diabetes as well.

The goals of all the system of medicine irrespective of its group are the same which is service to mankind or pateints. Research in alternative medicine will assist in safe and effective medical claims and outcomes.

Aegle marmelos may impart health benefits when it is used as functional food products and should be regarded as a potential nutraceutical resource and food additive because of its various attributes like typical colour, flavour and texture in the future. These results are useful for developing and improving the quality of bael leaf. It is quite evident from this review that *Aegle marmelos* contains a number of phytoconstituents which imparts its usefulness for various therapeutic purposes. The extracts of this important medicinal plant can become the main form of health care for not only the poor tribal community of India but can also form an integral part of primary health care or an alternative therapy to the allopathic system of medicine. In an era when traditional knowledge is gaining recognition, these indigenous plants can serve as healthy, cheap and readily available options in place of more sophisticated, costlier and ill effects causing synthetic medicines.