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REVIEW OF LITERATURE

Review of literature pertaining to the present study "**Hypoglycemic Effect of Bitter Gourd (*Momordica charantia L.*) on Prediabetics and Type II Diabetics**" is discussed under the following headings:

A. Prevalence of diabetes - A rising global burden

B. Prevalence of prediabetes - A silent killer

C. Etiology of diabetes and prediabetes

- **a. Age**
- **b. Family history**
- **c. Central obesity**
- **d. Physical inactivity**
- **e. Dietary habit**
- **f. Cigarette smoking**
- **g. Alcohol consumption**
- **h. Stress**

D. Management of diabetes – Food based approach

E. Hypoglycemic effect of bitter gourd- Recent trends

A. Prevalence of diabetes - A rising global burden

The prevalence of diabetes is rising all around the globe as an epidemic, in adults between the ages of 20 and 79 worldwide, for 2012, it was 382 million and is expected to affect 592 million people by 2035. It is estimated that 175 million people have undiagnosed Type II diabetes. In 2013, the top five countries that had more than 10 million people with diabetes were China, India, The United States of America, Brazil and The Russian Federation. Diabetes affects people in both urban and rural settings worldwide with 64 per cent of cases in urban areas and 36 per cent in rural (IDF, 2014).

The major part of increase will occur in developing countries. There will be a 42 per cent increase from 51 to 72 million in the developed countries and a 170 per cent increase from 84 to 228 million in the developing countries. Thus, by the year 2025, 75 per cent of people with diabetes will reside in developing countries as compared with 62 per cent in 1995. In 2025, the countries with the largest number of people with diabetes are India, China and the U.S.

WHO (2015) fact sheet reveald that

- In 2014, the global prevalence of diabetes was estimated to be 9 per cent among adults aged above 18 years.
- In 2012, an estimated 1.5 million deaths were directly caused by diabetes .
- More than 80 per cent of diabetes deaths occur in low- and middle-income countries.
- WHO projects that diabetes will be the 7^{th} leading cause of death in 2030.

Table I reveals the prevalence of diabetes in south-east Asia region according to WHO 2014.

TABLE I

PREVALENCE OF DIABETES IN SOUTH-EAST ASIA REGION

Country	2000 (N)	2030 (N)
Bangladesh	3,196,000	11,140,000
Bhutan	35,000	109,000
Dem. People's Rep. of Korea	367,000	635,000
India	31,705,000	79,441,000
Indonesia	8,426,000	21,257,000
Maldives	6,000	25,000
Myanmar	543,000	1,330,000
Nepal	436,000	1,328,000
Sri Lanka	653,000	1,537,000
Thailand	1,536,000	2,739,000
Total	46,903,000	119,541,000

Among the top 10 countries/territories with the largest number of diabetic adults, the five are in Asia. China tops the list with 90.0 million followed by India which has 61.3 million persons affected by diabetes. The numbers are estimated to rise to 129.7 million and 101.2 million, respectively by 2030. These estimates are likely to be underestimations as the prevalence data are mostly available for urban areas and reports from rural areas are scanty (Unwin *et al.,* 2011).

Chen *et al*., (2012) discussed that for the past three decades, the number of people with diabetes has increased more than two fold globally, making it one of the most significant public health challenges to all countries. Type II diabetes and prediabetic are increasingly prevalent among children, adolescents and younger adults. The causes of the epidemic of Type II diabetes are embedded in a very complex group of genetic and epigenetic systems interacting within an equally complex societal framework that determines behavior and environmental influences.

The overall total predicted increase in numbers with diabetes from 2010 to 2030 is 54 per cent, at an annual growth of 2.2 per cent, which is nearly twice the annual growth of the total world adult population. Thirty-six percent of the anticipated absolute global increase of 154 million people with diabetes is projected to occur in India and China alone (Shaw *et al.*, 2010).

The recent burden of metabolic risk factors of chronic diseases study conducted in 199 countries worldwide to assess the national, regional and global trends in diabetes reported that the age standardized adult diabetes prevalence was 9·8 per cent (8.6–11.2) in men and 9.2 per cent (8.0–10.5) in women in 2008, up from 8.3 per cent (6.5–10.4) and 7.5 per cent (5.8–9.6) in 1980 (Danaei *et al*.,2011).

Prescribing and Primary Care Team (2013) disclosed that in 2013, 2.7 million or six per cent of the adult population had diagnosed diabetes in England, an increase of 137,000 people since 2012.

In developing countries, diabetes affects the people in the middle and productive years of their lives. In these countries, three-quarters of all people with diabetes are under 65 years of age and 25 per cent of all adults with diabetes are younger than 44 years of age. In developed countries, more than half of all people with diabetes are older than 65 and only 8 per cent of adults with diabetes are younger than 44 (IDF, 2013). In developing countries, the majority of people with diabetes are in the age range of 45–64 years and in the developed countries, the majority of people with diabetes are aged above 65 years (Chinyere *et al.,* 2010). In developed countries most people with diabetes are above the age of retirement, whereas in developing countries those most frequently affected are aged between 35 and 64 years (Tabish, 2007).

An upsurge in number of early-onset diabetes cases is also responsible for the development of various diabetic complications due to longer disease duration, however data on the prevalence on diabetic complications across the whole of India is scarce (Kaveeshwar and Cornwall, 2014).

Diabetes is a common condition and its frequency is dramatically rising all over the world. Diabetes prevalence and diabetes-related deaths are rising in most parts of the world, at least partly fuelled by the worldwide increase in excess weight and adiposity. According to Danaei *et al*., (2011) diabetes is a life-threatening condition, worldwide 3.2 million deaths are attributable to diabetes every year. One in 20 deaths is attributable to diabetes, 8,700 deaths every day and six deaths every minute. At least one in ten deaths among adults between 35 and 64 years old is attributable to diabetes. Three-quarters of the deaths among people with diabetes aged less than 35 years are due to their condition.

Roglic and Unwin (2010) reported that the highest number of deaths attributable to diabetes is expected to occur in countries with large populations around 1,008,000 deaths in India, 575,000 in China, 231,000 in The United States of America and 182,000 in The Russian Federation.

A major shift is underway in the developing world, in which deaths from communicable diseases like malaria and tuberculosis have declined sharply and chronic diseases like cancer and diabetes are on the rise. The pattern is linked to economic improvement and more people living longer, but it has left governments in developing countries scrambling to deal with new and often more expensive ways to treat illnesses (http://www.who.int/chp/chronic_disease_report/full_report.pdf).

Mohan *et al., (*2007) explain that “Asian Indian Phenotype” that refers to certain unique clinical and biochemical abnormalities in Indians which include increased insulin resistance, greater abdominal adiposity *i.e.*, higher waist circumference despite lower body mass index, lower adiponectin and higher high sensitive C-reactive protein levels. This phenotype makes Asian Indians more prone to diabetes and premature coronary artery disease. At least a part of this is due to genetic factors. However, the primary driver of the epidemic of diabetes is the rapid epidemiological transition associated with changes in dietary patterns and decreased physical activity as evident from the higher prevalence of diabetes in the urban population which in recent times is also seen in rural areas.

In India the disease was recognized from Vedic Age (6^{th} century). The Vedas are the first appearance of the literature in the world. The physicians among Hindu monks recognized that the urine from diabetic patients tasted sweet, although it was not until the 18^{th} century that the sweet tasting substance was identified as the sugar glucose and the word mellitus or honeyed was added (Chaudhury and Rafei, 2001). Between 5th and 6th century AD, two notable Indian physicians Susrutha and Charaka first reported the association of Polyuria with sweet tasting substance in urine and named the condition as *"madhumeha"* (means urine tasting like honey and attracts ants) which is still remembered among Indians (Dwivedi and Daspaul, 2013).

Ancient Indian texts make mention of the disease "*Madhumeha*" which would correspond to the modern term "Diabetes mellitus", suggesting that diabetes must have been present in India even before 2500 BC. Although, there is no evidence as to how prevalent the condition was (Weaver and Narayan, 2008).

Diabetes has emerged as a major healthcare problem in India. According to Diabetes Atlas published by the International Diabetes Federation (IDF), there were an estimated 40 million persons with diabetes in India in 2007 and this number is predicted to rise to almost 70 million people by 2025. The prevalence of diabetes in the age group of 20 to 79 years stood at nearly nine per cent of the population in India.

Furthermore, Anjana *et al.,* (2011) revealed that Indians are genetically predisposed to the development of coronary artery disease due to dyslipidaemia and low levels of high density lipoproteins these determinants make Indians more prone to development of the complications of diabetes at an early age (20-40 years) compared with Caucasians (>50 years) and indicate that diabetes must be carefully screened and monitored regardless of patient age within India.

The recent NFHS 3 data, which studied urban and rural residents (all women aged 15–49 and all men aged 15–54) in 29 states of India during the year 2005-2006, reported that more than two percent of men and women had self-reported diabetes mellitus. The number of women who had diabetes mellitus ranged from 282 per 100,000 women in Rajasthan to 2,549 per 100,000 women in Kerala. In five other states (Tamil Nadu, Goa, Tripura, West Bengal, and Delhi) the number of women with diabetes mellitus was relatively high (above 1,500 per 100,000 women).Only five states had diabetes mellitus prevalence levels below 500 per 100,000 men (Jammu and Kashmir, Mizoram, Himachal Pradesh, Rajasthan and Uttar Pradesh) (IIPS, 2007).

It is estimated that every fifth person with diabetes will be an Indian. The economic burden due to diabetes in India is amongst the highest in the world. The real burden of the disease is however due to its associated complications which lead to increased morbidity and mortality. WHO estimates that mortality from diabetes, heart disease and stroke costs about $210 billion in India in the year 2005. Much of the heart disease and stroke in these estimates was linked to diabetes. WHO estimates that diabetes, heart disease and stroke together will cost about $ 333.6 billion over the next 10 years in India alone (Yesudian *et al*., 2014).

As the tenth largest economy in the world, India spends approximately 5 per cent of its GDP on healthcare. The private sector plays a significant role in healthcare delivery and expenditures, while public health expenditures account for an estimated 1 per cent of GDP. With a current population of 1.2 billion, India is expected to overtake China as the world's most populous country by 2030. In India, there is a gradual transition from infectious to chronic diseases, as the population grows older, richer and more urbanized. Sedentary lifestyles and increased consumption of high-fat foods such as fast food are contributing to the growing prevalence of chronic diseases like hypertension and diabetes (India Disease Incidence and Prevalence Report, 2013).

Muthukumar (2013) elucidated that rapid urbanization and industrialization have produced advancement on the social and economic front in developing countries such as India which have resulted in dramatic lifestyle changes leading to lifestyle related diseases. The transition from a traditional to modern lifestyle, consumption of diets rich in fat and calories combined with a high level of mental stress has compounded the problem further. There are several studies from various parts of India, which reveal a rising trend in the prevalence of Type II diabetes in the urban areas.

A National Urban Survey in 2000 observed that the prevalence of diabetes in urban India in adults was 12.1 per cent per cent. Recent data has illustrated the impact of socio economic transition occurring in rural India. The transition has occurred in the last 15 years and the prevalence has risen from 2.4 per cent to 6.4 per cent. During the period 1971–2000, studies from different parts of India reported a 10-fold increase in the incidence of diabetes in urban India (from 1.2 per cent in 1971 to 12.1 per cent in 2000) (Gupta *and* Misra, 2007, Joshi *et al*., 2008 and Ramachandran and Snehalatha, 2009).

Diabetes accounts for 1.09 lakh deaths in a year. Diabetes mellitus is responsible for 11.57 lakh years of life lost due to the disease, and for 22.63 lakh DALYs during 2004. The estimated number ofDALYs attributable to diabetes was 20.72 lakh in the year 2000. The estimates of number of DALYs in the present study were 22.63 lakh (ICMR, 2004).

The National Urban Survey conducted across the metropolitan cities of India reported similar trend: 11.7 per cent in Kolkata (Eastern India), 6.1 per cent in Kashmir Valley (Northern India),6 11.6 per cent in New Delhi (Northern India), and 9.3 per cent in West India (Mumbai) compared with (13.5 per cent in Chennai (South India), 16.6 per cent in Hyderabad (south India), and 12.4 per cent Bangalore (South India) (Kaveeshwar and Cornwall , 2014).

Given the burden of Type II diabetes and its complications, much attention has been given to prevention, beginning with identifying at-risk individuals prior to diagnosis. This has led to the designation of “prediabetes,” which is an intermediate form of dysglycemia on a spectrum ranging from normal to overt diabetes (Abraham and Fox, 2013).

B. Prevalence of prediabetes - A silent killer

According to Mason *et al.,* (2007) people who developed diabetes, increased glucose values were seen as early as 13 years before diagnosis, although glucose values seemed to be tightly regulated within the normal range until 2–6 years before diagnosis, when an abrupt increase was found. Other studies have confirmed this pattern of glycaemic changes.

Currently, prediabetes is a term covering two possible heterogeneous condition by the presence of Impaired Fasting Glucose (IFG) and/or Impaired Glucose Tolerance (IGT) that has not yet reached the thresholds for diagnosable Type II diabetes. Prediabetes raises short-term absolute risk of Type II diabetes by 3- to 10-fold. Seventy-nine million people-35 per cent of the US population-have prediabetes, and it is estimated that up to 70 per cent of people with prediabetes may develop Type II diabetes during their lifetimes (Centers for Disease Control and Prevention, 2011).

The prevalence of prediabetes currently estimated that over 330 million people worldwide and expected to raise to at least 470 million in 2030 (IDF, 2011). Worldwide, the number of people with IGT is estimated to be 280 million; by 2030, projections are that 398 million individuals will have IGT.

According to the National Health and Nutrition Examination Survey (NHANES), in 2005-2006, 34.6 per cent of US residents had prediabetes. Of these individuals, 19.4 per cent had IFG only, 5.4 per cent had IGT only, and 9.8 per cent had both IFG and IGT. Of these individuals with prediabetes, only 4.8 per cent reported receiving a formal diagnosis from their physicians. None received oral antihyperglycemic agents, while the percentage who received a physician recommendation for exercise or diet was 31.7 per cent and 33.4 per cent respectively (Karve and Hayward, 2010).

Health Survey for England (HSE) results found that there has been a significant increase between 2003 and 2011 in the proportion of people aged 16 or older with prediabetes, from 11.6 per cent in 2003 to 35.3 per cent in 2013. The researchers found that predictors of prediabetes in 2003 and 2011 included:

- being 40 years or older
- being of south Asian ethnicity
- having a high body mass index (BMI) of 25 or over
- having been diagnosed with high blood pressure
- being socioeconomically deprived (being in the second most deprived quintile) (www.nhs.uk)

National Diabetes Statistics Report (2014) opined that prediabetes is a precursor to diabetes, evidence shows that people with prediabetes also have an increased risk of developing heart disease and stroke. Data from the telephone-based New Mexico (NM) Behavioral Risk Factor Surveillance System (BRFSS) show that 7.8 per cent or 122,500 of NM adults aged 18 and older had diagnosed prediabetes in 2012-2013.

Age-sex-standardized prevalence estimates (95 per cent) of prediabetes and unknown diabetes were considerably higher in the northeast (SHIP-TREND: 43.1 per cent; 40.9–45.3 per cent and 7.1 per cent; 5.9–8.2 per cent) than in the south of Germany. The regional differences of prediabetes and unknown diabetes are in line with the geographical pattern of known diabetes in Germany (Tamayo *et al.,* 2014).

Although about 33 per cent of U.S. adults have prediabetes awareness of this risk condition is low. Less than 10 per cent of U.S. adults with prediabetic report that they have ever been told that they have prediabetes (Cowie *et al.*, 2011).

Data for adults with prediabetes who have never been tested for diabetes or who have not been told that they are at risk of developing Type II diabetes are not included. State estimates of prediabetes awareness range from 4.4 per cent in Vermont to 10.2 per cent in Tennessee. These estimates are consistent with analyses of national data that suggest an awareness of prediabetes is low (Geiss *et al*., 2010).

North Carolina Department of Health and Human Services (2013) reports that the measured national prevalence for prediabetes of 35 per cent is applied to the North Carolina population age 20 years and above, then more than 2.5 million North Carolinians may have prediabetes. However, only about 630,000 North Carolinians (about 9 per cent of the population) report having been diagnosed with prediabetes by a health professional and almost 1.9 million North Carolinians may have prediabetes but are unaware of their condition.

Japan Epidemiology Collaboration on Occupational Health study conducted among 47,172 men and 8280 women aged 20–69 years revealed that prevalence of pre-diabetes was 14.1 per cent in men and 9.2 per cent in women. Prevalence of these glucose abnormalities increased with advancing age, especially during mid 40s and 50s (Uehara and Akihiko, 2014)

Asian Indians who live in the U.S. have a 20 per cent higher prevalence of having prediabetes than those residing in India, but Indian residents have a 50 per cent higher prevalence of Type II diabetes compared with those in the U.S.

Recognition of prediabetes is critical, given the risk of progression to diabetes. Identifying individuals with prediabetes offers the opportunity tomodify their risk prior to development of significant squeal. Preventing diabetes remains a challenge but one that is both feasible and imperative. Close surveillance of rising prediabetes prevalence is critical to projecting the future burden of diabetes and the resources that will be required to combat diabetes going forward (Abraham and Fox, 2013).

Tabak *et al.,* (2012) portrayed that prediabetes is associated with the simultaneous presence of insulin resistance and beta-cell dysfunction abnormalities that start before glucose changes are detectable. Most people with prediabetes do not show symptoms but are considered to be at a high risk of developing heart disease and stroke. Recent research has shown that some long term damage to the cardiovascular system could start even in the prediabetic stage.

Researchers looked at 1,376 Asian Indians and found an overall diabetes and prediabetes incidence rates of 33.1 and 78.9, respectively, for every

1,000 person-years, and a 29.5 prediabetes incidence rate per 1,000 person-years among those with normal glucose tolerance at baseline. The findings revealed that 19.4 per cent and 25.7 per cent of the participants with normal glucose levels at baseline developed diabetes and prediabetes, respectively, while 58.9 per cent of those with existing prediabetes progressed to diabetes (Anjana *et al.,* 2015). Indians also have a higher prevalence of IGT at a younger age than the Chinese population.

A study in Chennai had shown high prevalence of insulin resistance and cardio metabolic abnormalities among healthy adolescents, the rate of which significantly increased in overweight and obese children (up to 85 per cent) (Ramachandran 2008).

Hu (2011) explained that both the thrifty genotype and thrifty phenotype hypotheses appear to have etiological roles in the development of diabetes in Asian populations. While the thrifty genotype hypothesis points to a mismatch between the ancestral genes and modern environment, the thrifty phenotype hypothesis postulates a mismatch between intrauterine and adult life environments.

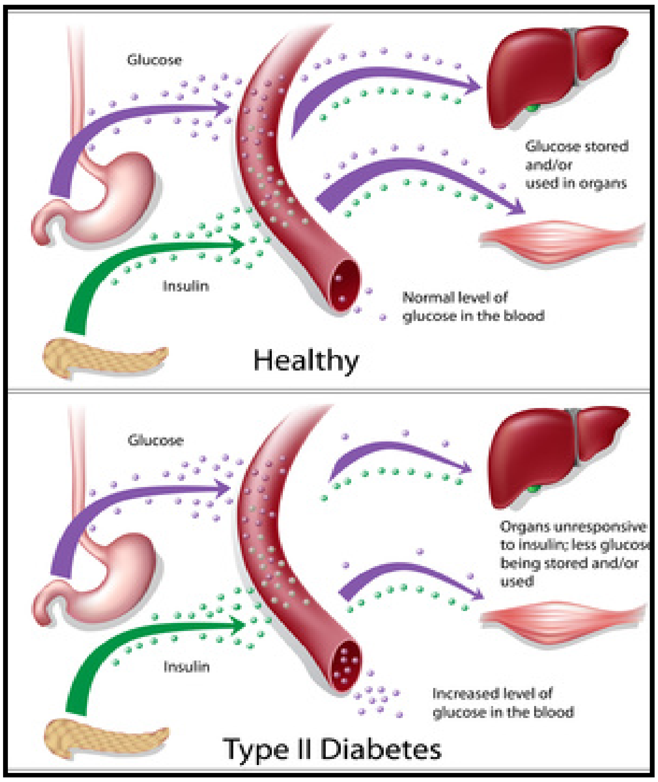
Prediabetes is linked with increased risks of major manifestations of vascular disease, but it remains unclear whether the elevated disease risks depend on development of clinical diabetes. Cross-sectional studies argue in favor of vascular risk effects of mild or moderate hyperglycaemia as there is an excess prevalence of coronary disease in those with fasting or postload hyperglycaemia below the diabetic level. The epidemiological relation between prediabetes and macrovascular disease may be confounded by clustering of vascular risk factors within individuals. Blood glucose in the prediabetic range is modestly correlated with many risk factors, including general and central obesity, blood pressure, triglyceride and lipoprotein levels (Sarwar *et al.,* 2010 and Seshasai *et al.,2011).* People with prediabetes have 20 per cent increased risk of cardiovascular disease compared to their peers with normal blood sugar.

Clinicians may be targeted to facilitate the implementation of screening and early detection programmes, diabetes prevention, self-management counselling, and therapeutic management of diabetes in accordance with the appropriate local guidelines form the backbone of controlling the predicted diabetes epidemic. Early screening and detection of pre-diabetes (especially in pregnant women (Sui *et al.,* 2013) children and adults with BMI ≥25) may yield positive health outcomes in society (Minnie *and* Rattigan 2012).

C. Etiology of diabetes and prediabetes

Ozougwu *et al.,* (2013) described that the development of early onset Type II diabetes mellitus represents a complex interplay between genetic and environmental factors. Under normal physiological conditions, plasma glucose concentrations are maintained within a narrow range, despite wide fluctuations in supply and demand, through a tightly regulated and dynamic interaction between tissue sensitivity to insulin (especially in liver) and insulin secretion.

In Type II diabetes in these mechanisms break down, with the consequence that the two main pathological defects in Type II diabetes are impaired insulin secretion through a dysfunction of the pancreatic β-cell, and impaired insulin action through insulin resistance. The etiology of diabetes in India is multi factorial and includes genetic factors coupled with environmental influences such as obesity associated with rising living standards, steady urban migration, and lifestyle changes (Kaveeshwar and Cornwall 2014).



The highest rates of urbanization (50 per cent) have been in Singapore, Korea, Malaysia, Philippines and Indonesia. China, Pakistan, India and Thailand have intermediate rates (30 per cent) and Bangladesh and Sri Lanka have slow rates of urbanization (Ramachandran *et al.,*2012). The developing countries like India are undergoing rapid urbanisation. Urbanisation is associated with increasing obesity, decreasing physical activity due to changes in lifestyle, diet and a change from manual work to less physical occupations. Urban migration has been linked with increasing prevalence of diabetes. As compared to rural population , urban migrants have higher weight, body mass index (BMI), waist hip ratio (WHR), systolic blood pressure (SBP), cholesterol, HOMA-IR , fat intake while physical activity is less (Huffman *et al*., 2011)

a. Age

The prevalence of diabetes increases markedly with age. Maximum incidence of non-insulin dependent type of diabetes occurs above the age of 35 years. Indians develop diabetes at a very young age, at least 10 to 15 years earlier than the western population. An early occurrence of diabetes gives ample time for development of the chronic complications of diabetes. The incidence of diabetes increases with age. In India, the life span has increased, hence more number of people with diabetes are being detected (Muthukumar, 2013). Diabetes is more likely to affect older people, although there are people of all ages with the disease. Almost 27 per cent of people of age 65 years and older had diabetes in 2010. About 215,000 people younger than 20 years have diabetes (Type I or Type II). This represents 0.26 per cent of all people in this age group (National Diabetes Statistical Report, 2011).

Katikireddi *et al.,* (2011) reported that the rapidly increasing prevalence of Type II diabetes in the youth is highlighted by studies in the Asian populations in native lands and in migrant countries that china showed an 88 per cent increase in prevalence in 35-44 years age group within a period of 6 years. In southern India, the prevalence of diabetes in persons under 44 years has increased from 25 per cent of the total prevalence in 2000 to 36 per cent in 2006.

The rising trend seen in the prevalence of gestational diabetes among Asian women and the increased risk for future diabetes in them may also contribute to the escalating prevalence of diabetes in young people (Ma and Chan, 2009).

Women who develop diabetes while pregnant (gestational diabetes) have a 35 per cent to 60 per cent chance of developing Type II diabetes in the next 10 to 20 years (National Diabetes Statistics Report, 2014). Ahmad *et al.,* (2011) found significant difference between males and females (3.6 per cent Vs 8.3 per cent, $p < 0.05$) diabetic subjects. There was also significant increase in the prevalence of diabetes mellitus with increasing age (age 20-40 years: 3.02 per cent vs > 60 years 16.66 per cent, $p < 0.05$).

Ethnicity is associated with several factors, such as genetic constitution, lifestyle, living environment and anthropometric characteristics. Body composition related to fat distribution is a stronger determinant of the metabolic milieu than BMI. The collaborative analysis of diabetes criteria in Europe/in Asia study group noted that the overall effect of age on the prevalence of diabetes differed considerably between the ethnic groups, even in the subjects with the same BMI (Nakagami, 2003).

b. Family history

Bener *et al.,* (2013) explained that the prevalence of diabetes increases with a family history of diabetes. The risk of a child developing diabetes with a parental history increases above 50 per cent. A high incidence of diabetes is seen among the first degree relatives. Indians have a high genetic risk for diabetes as observed in Asian Indians who have migrated to other countries. They have been found to have a higher rate of diabetes as compared to the local population.

Although research have not completely elucidated the pathophysiology of Type II diabetes so far, it is the case that the disease has a major genetic component. Higher concordance rates are found among monozygotic (96 per cent) than dizygotic (DZ) twins in some but not all twin studies, which has been a compelling evidence of a significant genetic component in Type II diabetes. Moreover, 40 per cent of first-degree relatives of Type II diabetes patients may develop diabetes, whereas the incident rate is only 6 per cent in the general population (Sanghera and Blackett, 2012).

Genetic predisposition plays an important part in the risk of developing Type II diabetes. Some 84 per cent of UK adolescents with Type II diabetes have a family history of Type II diabetes while 56–71 per cent have an affected parent or sibling (Shield *et al*., 2009).

Diabetic complications are resulting from an interaction from genes and environmental factors. A family history of diabetes is pointing toward a possible genetic and epigenetic basis for diabetic retinopathy (Maghbooli *et al.*, 2014).

Evidence suggests that family history by itself is most useful for predicting disease when there are multiple family members affected, the relationship among relatives is close, and disease is premature, that is, it occurs at younger ages than would be expected. It has been mentioned that family history information in combination with other known risk factors could be used to provide more personalized information about our risk for common diseases. Yang *et al*., (2010) further suggested that adding a family history of diabetes could provide significant improvements in detecting undiagnosed diabetes.

Family history and diabetes had a graded association in the Sri Lankan population, because the prevalence increased with the increasing number of generations affected. Family history of diabetes was also associated with the prevalence of obesity, metabolic syndrome and hypertension. Individuals with a family history of diabetes form an easily identifiable group who may benefit from targeted interventions (Katulanda *et al.,* 2015).

The combination of gestational diabetes, in utero nutritional imbalance, childhood obesity and over nutrition in adulthood will continue to fuel the epidemic in Asian countries undergoing rapid nutritional transitions (Ramachandran *et al.,* 2010).

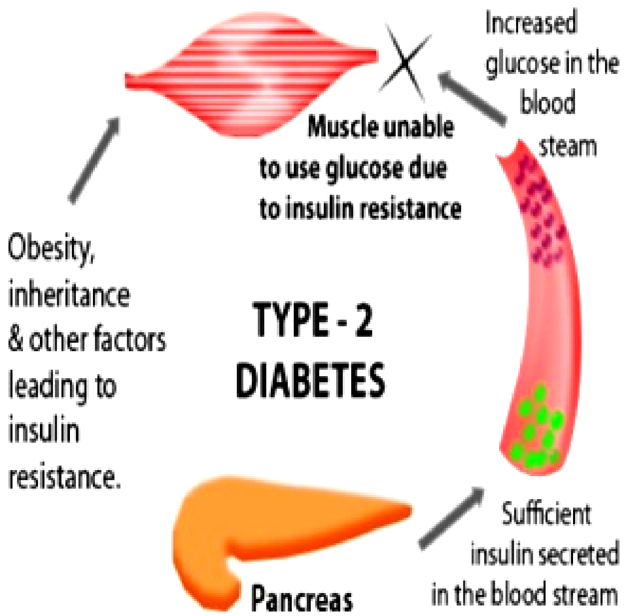
c. Central obesity

Overweight and obesity are driving the global diabetes epidemic, affect the majority of adults in most developed countries and are increasing rapidly in developing countries. If current worldwide trends continue, the number of overweight people (BMI ≥ 25 kg/m^2) is projected to increase from 1.3 billion in 2005 to nearly 2.0 billion by 2030 (Kelly *et al.,* 2008 and Bener *et al.,* 2013).

The worldwide explosion of obesity has resulted in an ever-increasing prevalence of Type II diabetes, a non-communicable disease that has become a scourge of our time, knows no boundaries and currently affects over 370 million people(IDF 2012) . Most patients with this form of diabetes are obese, and obesity itself causes some degree of insulin resistance. Patients who are not obese by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region. Obesity is frequently characterized by systemic inflammation and preclinical evidence links systemic inflammation to β-cell dysfunction (Nichols *et al*., 2007).

Pamidi and Tasali (2012) demonstrated that obstructive sleep apnea, a treatable sleep disorder that is pervasive among overweight and obese adults, has become a novel, modifiable risk factor relevant to insulin resistance and glucose intolerance, and may influence on the development of prediabetes (20 per cent-67 per cent) and Type II diabetes (15 per cent-30 per cent), independent of shared risk factors.

Rapid weight gain occurring in childhood due to a nutritionally rich environment enhances the risk of these adult diseases. A recent collaborative study of prospective data from large numbers of individuals in low and middle income countries, including India, showed that lower birth weight is a risk factor for glucose intolerance (Norris *et al*., 2012).



Asian Indians found to have more insulin resistant as compared to the white population. They have a higher level of insulin to achieve the same the blood glucose control. A cluster of factors consisting of abnormal fats (Dyslipidemia), high blood pressure, obesity, and abnormal glucose levels known as metabolic syndrome is highly prevalent in Asian Indians. Association of obesity with Type II diabetes is well known. Even with an acceptable body weight range, weight gain could increase the risk of diabetes. An excess of body fat specially concentrated within the abdomen has an increased risk of diabetes. The cut-off limit for waist circumference for Indians have been recommended to be 90 cm for males and 80 cm for females. Abdominal obesity is defined by waist circumference above these limits (McCarthy 2010).

Obesity is now viewed as a complex disorder and a major risk factor of linked to increase diabetes, cardiovascular disease and early death (Flegal *et al.,* 2013).

d. Physical inactivity

Numerous epidemiologic studies show that increased physical activity reduces risk of diabetes, whereas sedentary behaviors increase risk (Hu, 2011). In the national health survey, each 2-h/day increment of time spent watching television (TV) was associated with a 14 per cent increase in diabetes risk. Each 2-h/day increment of standing or walking around at home was associated with a 12 per cent reduction in risk.

More recently, study by Bener *et al.*, (2013) showed that only 21 per cent of diabetes patients perform daily physical activities. These results indicate a continuum in the relationship between physical activity levels and diabetes risk. Among sedentary behaviors (TV watching, sitting at work, and other sitting), prolonged TV watching was associated with the highest risk. At least two potential mechanisms account for the positive association between watching TV and obesity and diabetes risk. In fact, those who spend more time watching TV tend to have unhealthy eating patterns characterized by increased consumption of snacks, sugary beverages and fast foods (Hu *et al*., 2003).

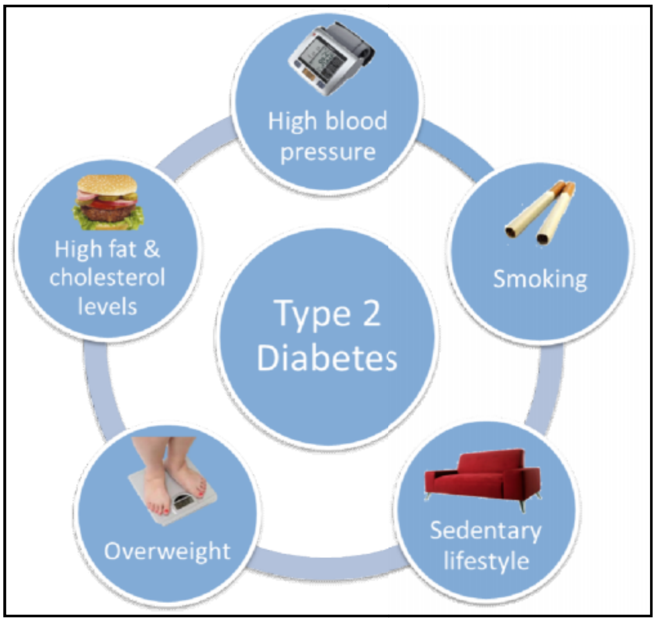
Lack of exercise, a poor diet and smoking were associated with significantly increased risk of diabetes, even after adjustment of the body mass index. The majority of cases of Type II diabetes could be prevented by the adoption of healthier life style practices. Regular physical activity is an important lifestyle factor associated with a reduced incidence of both cardiovascular disease and Type II diabetes (Phielix and Mensink, 2008). Losing weight and taking more exercise could reduce the danger of developing diabetes by nearly 60 percent in people at risk. Lifestyle interventions including moderate to intense physical activity such as walking for two and a half hours every week and exercise for 20 to 30 minutes is effective in preventing the diabetic complications. Physical activity interventions can improve glucose tolerance and reduce the risk of Type II diabetes because it simply help achieve weight loss . Any types of physical activity should be acceptable to the majority of the population. For example, walking, the most popular choice of physical activity, has been shown to reduce the relative risk of Type II diabetes by 60 per cent when walk for 150 min/week, compared to walking for >60 min/week (Wu *et al.,* 2014). It is widely advocated to keep a daily step, which is an effective self-regulatory strategy to successfully promote increased physical activity (Yates *et al.,* 2009)

In prospective cohort studies, exercise improves insulin sensitivity in diabetic patients in the same way as it does in non-diabetic patients. Patients with diabetes have greater insulin resistance which can be mediated by different defects in the glucose metabolism, and some of which would improve with physical exercise. These defects include not only a decreased number of insulin receptors and glucose transporters, but also a reduction in the intracellular enzymes activity (pyruvate dehydrogenase and glycogen synthase) and reduced oxygenation during exercise. Increased physical activity achieves higher mitochondrial enzyme activity and increases insulin sensitivity; however the number of muscle capillaries in diabetic patients with micro vascular complications does not increase or is practically negligible (Sluik *et al.*, 2012).

A total of 60 minutes of physical activity per day is recommended for healthy Asian Indians, in view of the high predisposition to develop Type II diabetes and CVD. This should include at least 30 minutes of moderate-intensity aerobic activity, 15 minutes of work-related activity, and 15 minutes of muscle-strengthening exercises. For children, moderate-intensity physical activity for 60 minutes daily should be in the form of sports and physical activity. This consensus statement also includes physical activity guidelines for pregnant women, the elderly, and those suffering from obesity, Type II diabetes, CVD and other components of metabolic syndrome (Misra *et al.,* 2011)

e. Dietary habit

Kapur, (2007) cautioned that, only a structured lifestyle with diet control and exercise can curb the complications in diabetics. Treatments for diabetes aims at relieving the symptoms of diabetes, preventing long term complications through education, careful dietary management and weight control, medication, physical activity, self testing and foot care (www.eeseehealth.com).



Many developing nations experience rapid economic and social development with concomitant shifts in lifestyle habits and dietary structure. These changes promote over nutrition and positive energy balance. In Middle East and Arab Countries, traditional dietary patterns are being lost as the population adapts to more industrialized and urban food environments. At the same time, built living environments have become increasingly sedentary. These changes have a significant impact on Type II diabetes risks by increasing body weight and central adiposity, and decreasing physical activity. With the rapid pace of nutrition transition, many countries are facing coexisting problems of over and under nutrition, which lead to the double burden of infectious and chronic diseases (Bener, 2011).

Wu *et al.,* (2014) orated that the changes in dietary energy sources, particularly the increase in fat intake, the decrease in starch intake, the increase in the consumption of simple sugars, and the decrease in dietary fiber intake, contribute to obesity and cause deterioration of glucose tolerance. Studies have shown that a low-fiber diet with a high glycemic index is positively associated with a higher risk of Type II diabetes, and specific dietary fatty acids may affect insulin resistance and the risk of diabetes in varying degrees . Total and saturated fat intake is associated with an increased risk of Type II diabetes independently of BMI, but higher intake of linoleic acid has the opposite effect, especially among leaner and younger men.

Frequent consumption of processed meat, but not other meats, may increase the risk of Type II diabetes after adjustment for BMI, prior weight change, and alcohol and energy intake. Soft drinks have also been bounded up with increased risk of

Type II diabetes and metabolic syndrome, because they are directly associated with BMI. The changes in dietary energy sources, particularly the increase in fat intake, the decrease in starch intake, the increase in the consumption of simple sugars, and the decrease in dietary fiber intake, contribute to obesity and cause deterioration of glucose tolerance (Ozougwu *et al.,* 2013).

Accumulating evidence supports that vitamin D may have a potential role in the control of Type II diabetes (Mitri *et al*., 2011 and Nikooyeh *et al*., 2014). Furthermore, vitamin D has influence on the insulin sensitivity by controlling calcium flux through the membrane in both β cells and peripheral insulin-target tissues. In addition, vitamin D supplementation is recognized as a promising and inexpensive therapy, which may decrease the risk of Type II diabetes and improve glycemic parameters in Type II diabetes patients (Wolden *et al.,* 2011).

Improper dietary habits significantly increase the risk for the development of non-insulin dependent diabetes mellitus. Piłaciński *et al.,* (2014) suggested that, diet and alcohol intake patterns are related to the development of obesity. Caffeine induces high levels of cortisol which may promote abdominal fat accumulation. Increased consumption of eggs and saturated fats is associated with significant increase in mortality.

The majority (ranging from 66.85 to 80.4%) of adolescents in the current study did not daily consume breakfast, fruit, vegetables and milk, while a considerable proportion frequently showed unhealthy dietary habits. The WHO Global Strategy for diet and physical activity recommendations call for achieving an energy balance, limiting the energy intake from fats, reducing the intake of free sugars and increasing fruit and vegetable consumption (Musaiger, 2011).

f. Cigarette smoking

Smoking is associated with other unhealthy behaviors that may have an impact on Type II diabetes, such as insufficient physical activity, higher alcohol consumption, and diets low in fruits and vegetables (Agarh, 2008).

Several possible biological mechanisms may explain the association between cigarette smoking and diabetes. Although smokers tend to be leaner than nonsmokers, smoking has been associated with increased risk of central obesity or abdominal fat, an established risk factor for insulin resistance and diabetes. More recent literature showed that the proportion of smokers was above 18 per cent among diabetes and metabolic syndrome patients and there is a trend of smoking increasing within 8 years (AlAli *et al*., 2013)

Cigarette smoking causes specific effect on people with diabetes and is even more intricate and macro vascular and micro vascular complications ensue more quickly in smokers with diabetes (Justin and Sherman, 2005). Cigarette smoking has been associated with development of persistent micro-albuminuria as well as nephropathy in diabetic patients. Smoking can result in devastating health consequences for patients with diabetes. Prevention and treatment of smoking should be of high priority for diabetes care providers.

Smoking is associated with higher energy expenditure and lower appetite, which could explain lower body weight in smokers and weight gain after smoking cessation. Furthermore, although smokers tend to have a lower BMI than nonsmokers, smokers are more likely to have abdominal fat accumulation. Because abdominal obesity is related to insulin resistance and the development of Type II diabetes, it is possible that smokers have a higher risk of type 2 diabetes because of the presence of abdominal obesity (Travier *et al*., 2012). Smoking is linked with deterioration in metabolic control in diabetic patients, which is associated with an increased risk for development of macrovascular and microvascular complications and mortality in diabetes.

A meta-analysis found that current smokers had a 45 per cent increased risk of developing diabetes compared with nonsmokers. Moreover, there was a dose-response relationship between the number of cigarettes smoked and diabetes risk (Willi *et al.*, 2007).

g. Alcohol consumption

Koppes *et al*., (2005) indicated that alcohol consumption is a life style factor that has been suggested to be relevant with respect to the risk of diabetes mellitus. Alcohol intake increases the risk of hyperglycemia and may induce ketoacidosis, lactic acidosis and may contribute to peripheral neuropathy. Moderate to high alcohol consumption was positively associated with incidence of diabetes. A general concept regarding alcohol intake is that it further deteriorates the condition; but interestingly, a Meta-analysis with 12 years of follow up showed that the controlled intake of alcohol (1-2 drinks/day) decreases the risk of diabetes by 30-40 per cent as compared to substantial drinkers.

It was concluded that moderate amounts of alcohol not only increase the sensitivity of insulin, but also increase HDL cholesterol levels while heavy intake of alcohol increases the triglyceride levels and impair carbohydrate and glucose metabolism. Ahmed (2011) also studied the relationship between alcohol consumption and glycemic control and concluded that the relationship is inversely proportional; thus diabetic complications can be minimized by the restricting alcohol consumption.

h. Stress

Stress has a major role to play in the causation and progression of diabetes, particularly in developing countries. Systemic stress may contribute to insulin resistance and play a key role in the etiology of diabetic complications such as cataract, nephropathy, neuropathy, atherosclerosis and obesity. Post-pyramidal oxidative stress is attenuated when dietary antioxidants are supplied together with a meal rich in oxidized or oxidisable lipids (Sies *et al.,* 2005).

Vigersky (2011) reported that diabetes is associated with debilitating micro and macro vascular complications. As Asian populations develop diabetes at a young age, they live long enough to develop the complications too, resulting in high rates of morbidity and early mortality. Cardiovascular disease is a primary cause of mortality and morbidity in both prediabetes and Type II diabetes, the potential mechanism for which is oxidative stress that has important effects on atherogenesis and may contribute to low-density lipoprotein oxidation.

The risk of CVD increases by 3-4 fold in a diabetic person. More than 75 per cent of all mortality among diabetic persons occurs from cardiovascular disease. The UK Prospective Diabetes Study (UKPDS) showed that every 1 per cent increase in HbA1c was associated with 12 per cent increase in heart failure.

Diabetic neuropathy may be associated with foot ulcers, amputations, non-healing skin wounds, and sexual dysfunction (Sanghera and Blackett, 2012). The neuropathy results in loss of protective sensation in the feet, which leads to callous formation, ulceration and other injury, and may also result in the infection of the skin (e.g. cellulitis) and/or bones of the foot (e.g. osteomyelitis) and gangrene.

Chronic hyperglycemia may cause micro vascular damage to the retinal vessels, resulting in edema and/or hemorrhage into the retina or the vitreous humor because of vascular permeability. In fact, dysglycemia often occurs earlier than the diagnosis of diabetes patients, because nearly 20 per cent of newly diagnosed diabetes patients show evidence of retinopathy.

Epidemiologic evidence has demonstrated that diabetes may elevate the risk of cancer such as colorectal cancer, liver cancer, bladder cancer, breast cancer and kidney cancer which varies depending on the subsites of specific cancers (Larsson and Wolk 2011).

D. Management of diabetes - Food based approach

Diet has powerful effects in every stage of an individual's healthy life. It also plays a significant role in many of the degenerative diseases. Diet plays a seminal role in the prevention and treatment of diabetes (Asif, 2014). Dietary factors play a key role in the development of various human diseases, including cardiovascular diseases and other metabolic diseases, atherosclerosis, hyperlipidemia, thrombosis, hypertension and prediabetes and diabetes.

Bishwajit *et al.,*(2014) opined that rapid urbanization, cross-border trade and advance agrifood technologies have revolutionized Asian food culture marked by considerable decrease in cereal grain and vegetable consumption to high animal based, fat and dairy food consumption. High rate of urbanization has its impacts on people's dietary habit, mode of entertainment, physical activity which together lead to an epidemiological transition where the disease burden is gradually shifting from communicable and infectious diseases to non-communicable chronic diseases. Prevalence of overweight, obesity and other associated diseases like diabetes, cancer, cardiovascular diseases has increased dramatically over past two decades.

The Finnish Diabetes Prevention Study (FDPS) advocated decreasing total and saturated fat intake and increasing fibre density in the diet. In the Diabetes Prevention Program (DPP), dietary goals were to reduce total fat and energy intake. A Mediterranean diet characterized by a high intake of vegetables, fruit, legumes, extra virgin olive oil, nuts, fish, whole grains and red wine also showed a remarkable decrease in the incidence of diabetes in a Spanish study (Schwarz *et al.,* 2012).

Reducing carbohydrates for patients with diabetes improves insulin sensitivity, reduces visceral fat and triglycerides, and increases HDL-cholesterol. Recently, a meta analysis showed that reducing carbohydrates load and glycemic index was associated with a reduced risk of developing Type II diabetes. After weight reduction, maintaining a diet lower in glycemic index and higher in protein was shown to maintain weight loss for a longer duration (Larsen *et al*., 2010).

Maritini *et al.,* (2010) indicated that vitamins and minerals play an important role in glucose metabolism, so understanding the impact of vitamin and mineral deficiencies and the potential utility of supplement is relevant in the management of diabetes mellitus. In order to prevent deficiencies and maintain health, majority of diabetic individuals should receive daily vitamins and minerals within the ranges of recommended value from the consumption of natural food sources and fortified foods.

Consumption of low glycemic index diet resulted in lower glycosylated haemoglobin concentrations. Inclusion of low GI in dietary planning for patients with Type II diabetes mellitus contributes to improvement of glycemic control. A low-glycemic load diet resulted in lower post-prandial insulin and glucose responses and modestly lower fasting insulin-like growth factor-1 (Runchey *et al.,* 2012).

Avoiding carbohydrates of much quantity is a prevention measure in developing diabetes. Energy intakes above 70 per cent from carbohydrates appeared to be a risk factor for diabetes. Meal with high glycemic index and glycemic load value need be avoided and macro nutrients must be balanced (Kyung *et al*., 2009).

Solomon *et al.,* (2010) illustrated that a high glycenic index diet when combined with exercise may delay the onset of Type II diabetes is at-risk individuals but a low GI treatment method will prevent the diabetes onset. Lifestyle induced weight loss improves insulin resistance in pre-diabetic individuals, postprandial hyperinsulinemia is reduced only when a low glycenic index diet is consumed.

Functional food or medicinal food is any fresh or processed food which affects beneficially one or more target functions in the body, beyond adequate nutritional effects, in a way that is relevant to either improved state of health and well-being and/or reduction of risk of disease (Henson *et al.,* 2008).

Phenolic compounds from the finger millet seed coat act as powerful natural inhibitors of alpha glycosidase and pancreatic amylase thereby playing vital role in the clinical management of postprandial hyperglycemia (Shobana *et al.*, 2009).

Dietary fiber from psyllium have been used extensively both as pharmacological supplements, food ingredients, in processed food to aid weight reduction, for glucose control in diabetic patients and to reduce lipid levels in hyperlipidemia (Sartore et al., 2009).

Hooda *et al.,* (2010) indicated that β-glucan in dietary oat lowers glucose and insulin responses by enteroinsular axis and stimulate fermentation. Dietary oat β-glucose improves intestinal and metabolic health in Type II diabetes.

The development of food products that provide benefits beyond their traditional nutritional value has raised academic, industrial and public interest. In recent years, the ability of functional foods to impact metabolic parameters and eventually chronic diseases such as diabetes has been deeply explored. Recent population studies have shown that the high Glycemic Index (GI) food is positively associated with the risk of developing Type II diabetes (Barclay and Lie 2007)

Barley bread based on 50 percent barley flour attenuated a low glycemic index. These findings clearly show that inclusion of barley grains tested in the present work offers new ways of reducing the high glycemic index seen with conventional cereal products. Thus increasing the intake of whole grain products such as barley would increase both total and soluble dietary fiber in the diet and most likely would result in retarding the glucose release. Such products may have a potential use in the dietary management of Type II diabetes (Blaak *et al.,* 2012).

Shirude (2011) speculated that Phytochemical constituents of wheatgrass include alkaloids, carbohydrates, saponins, gum and mucilages. Its water soluble extractive value is found to be greater than its alcohol soluble extractive value. This is because of the chlorophyll content of wheatgrass, which is about 70% water soluble, which brings about the hypoglycemic effect when consumed about 15 g/day.

Cheng *et al.* (2009) demonstrated that stabilized rice bran can lower the level of glycosylated hemoglobin and blood lipids and increase blood adiponectin concentrations in type 2 diabetic subjects. Thus, rice bran represents an important functional nutrient to ameliorate lipid and glycemic anomalies in Type II diabetic subjects.

Kwak *et al.,* (2010) suggested that high level intake of soya products resulted in decreased risk for Type II diabetes in overweight women and post menopausal women. The fermentation of these soybean products changes the bio active components, such as isoflavonoids and peptides, in ways which may alter their efficacy in the treatment of Type II diabetes. The intake of soybeans and fermented soybeans may be associated with the antecedently lower incidence of Type II diabetes in Asians. Ahdab (2014) suggested that consumption of high-isoflavones, soy protein not only lowers glucose level, but also reduces the incidence of cataracts in diabetic rats. The beneficial effects of soy isoflavones were attributed to increased insulin secretion, better glycemic control, and antioxidant protection.

Certain vegetables contains an abundance of polyphenolics, terpenoids, isoflavones, anthocyanin’s, amino acids, minerals, vitamins, and other antioxidants that are associated with protection from cancer, cardiovascular diseases, diabetes and hypertension (Islam, 2011).

Tomé-Carneiro *et al.,* (2013) revealed that grapes contain polyphenols such as resveratrol and flavonols quercetin, catechhin and antholyanine which resulted in reducing hyperglycemia, improving β cell function and protecting against β cell loss in diabetic person. The grape seed extract inhibits the intestinal α-glucosidases and α-pancreatic amylase that may delay carbohydrate digestion and absorption. Recently, this fact has been further documented, where grape seed extract has lowered the postprandial plasma glucose concentration in an acute, randomized, controlled crossover design study, in which healthy subjects received high carbohydrate meal with or without grape seed extract (Sapwarobol *et al., 2012).*

Mangifera indica *Linn.* (*Anacardiaceae*) is a plant that possesses several properties, one of which is hypoglycemia that favors it to control Type II DM in some rural African communities. Mangiferin is one of the active constituents of this plant, besides the polyphenolics, flavonoids, triterpenoids, and other chemical compounds. Therefore, the mangiferin-mediated inhibition of α-glucosidase activity, offers one mechanism for the hypoglycemic effect of this plant (Shah *et al*., 2010).

Another study was carried out to investigate the antihyperglycemic mechanisms of syringin, an active principle purified from the rhizome and root parts of *Eleutherococcus senticosus* (Ginseng). STZ-diabetic rats showed an increased release of β-endorphin from the adrenal medulla after receiving a bolus intravenous injection of syringing. Abhar and Schaalan (2014) concluded that the decreased plasma glucose, in the diabetic rats lacking insulin, is mediated by the effect of β-endorphin on peripheral micro-opioid receptors.

Diet supplemented with flax and pumpkin seeds mixture ameliorated the antioxidant enzyme activities in diabetic subjects and significantly reduced malonaldialdehyde levels (Makni *et al.*, 2010).

Sour cherry juice beneficially alters serum glucose, blood pressure, glycosylated haemoglobin, lipid profile in Type II diabetes. It has been found that sour cherries contain high levels of anthocyanine that posess insulin releasing stimulatory properties on pancreatic β cell (Jafari *et al.*, 2008).

Daily dietary supplement with bioactivities from whole blueberries improved insulin sensitivity in obese and insulin resistant persons. Insulin sensitivity was enhanced by blue berry bioactivities without significant inflammatory biomarkers (Stull *et al.*, 2010).

Nuts have a healthy nutritional profile such as high mono unsaturated fatty acids, polyunsaturated fatty acids, good source of protein and rich in fibre, vitamins and minerals. Nuts have minimal effects on diminishing post prandial glycemic response in Type II diabetes (Kendall *et al.*, 2010). Omega-3 fatty acids supplementation in Type II diabeteshas a favorable impact in lowering triglycerides and VLDL-cholesterol, and reducing blood pressure and inflammatory markers (Bradberry and Hilleman, 2013).

Gymnemasylvestre (leaves) 30 percent, *Tinosporacordifolia* (stems) 15 per cent, *Azadirachtaindica* (leaves) 10 per cent, *Phyllanthusemblica*(fruits) 20 per cent, *Curcuma longa* (roots) 10 per cent and *Aeglemarmelos*(leaves) 15 per cent and four gram of mixed powder should be given to the patient, twice a day with water (Narayana and Subhose, 2005).

Tulsiisan effective treatment for diabetes by reducing blood glucose levels. Another study showed that tulsi's beneficial effect on blood glucose levels is due to its antioxidant properties (Tewari *et al*., 2012).

Inclusion of fenugreek in the daily diet in amount of 25-100g can serve as an effective therapy in the clinical management of diabetes (Gupta and Verma, 2015).

Anti-hyperglycemic effect of the extracts, powder and gum of *Trigonella foenum-graecum* seeds and leaves have been linked to delayed gastric emptying caused by the high fiber content, inhibition of carbohydrate digestive enzymes and stimulation of insulin secretion (Chauhan *et al*., 2010).

Hypoglycemic effect by bitter principle of *Aloe vera* in the rats is mediated through stimulation of synthesis or release of insulin from the beta-cells of Langerhans (Singh, 2011)

Mushrooms with immune-modulating polysaccharides are used as delicious food or as healthpromoting food supplement (nutraceutical) or as drug in limited geographic regions. These functional mushrooms might have a particularly high impact for prevention or curative of diabetes more than in other species (Perera and Li, 2011).

Garlic is a species in the onion genus. It belongs to the family *Amaryllidaceae*. This is a perennial herb cultivated throughout India. Allicin, a sulfur-containing compound is responsible for its pungent odour and it has been shown to have significant hypoglycemic activity. This effect is thought to be due to increased hepatic metabolism, increased insulin release from pancreatic beta cells and/or insulin sparing effect (Padiya *et al.,* 2011). Daily treatment of diabetic rats with an extract of raw garlic (500 mg/kg of 60 kg wt) for even weeks significantly lowered serum glucose cholesterol and triglyceride levels.

Spices are the common dietary adjuncts that contribute to the taste and flavour of foods. Besides, spices are also known to exert several beneficial physiological effects including the antidiabetic influence. Among the spices, fenugreek seeds *(Trigonellafoenum graecum*) and ginger (*Zingiberofficinale*) have been reported to be hypoglycaemic (Srinivasan,2005).

Cinnamon oil was useful in treatment of Type II diabetes mellitus. It was found to decrease fasting glucose tolerance, plasma c-peptide, serum triglyceride, total cholesterol, blood urea nitrogen level in diabetic subjects (Ping *et al.*, 2010).

Diabetes prevention studies have demonstrated that diet composition is another important factor to prevent the development of Type II diabetes. Epidemiological studies have suggested that the risk of diabetes can be increased or decreased owing to dietary factors. The dietary factors which may increase the diabetes risk are consuming excessive amounts of refined grains, sugar-sweetened beverages, red and processed meat and alcohol, and those with the opposite effects are the intake of whole-grain cereal, vegetables, dairy, legumes, nuts, independently of body weight change (Landaeta-Diaz *et al.,* 2013).

A large number of prevention studies concerning dietary factors have been conducted in many countries during the past several years. Studies from China, Japan and India aimed at examining the effects of reducing fat, refined carbohydrates and alcohol and increasing fibre intake on the development of Type II diabetes (Wu *et al*., 2014).

The cost of diabetes care is high and increasing worldwide. The economic burden is very high, especially in developing countries, and more so in the lower economic groups, who spend 25 per cent 34 per cent of their income on diabetes care (Kapur, 2007).

Kumpatla *et al.,* (2013) suggested that to reduce the disease burden that diabetes creates in India, appropriate government interventions and combined efforts from all the stakeholders of the society are required.

Recently, some researchers had manifested an increasing interest towards traditional medicinal plants. Many traditional plants have been identified to have hypoglycemic activities and were cost effective and affordable (Abhar and Schaalan*,* 2014).

E. Hypoglycemic effect of bitter gourd-Recent trends

Over 1000 herbal products have been used by various cultures to lower blood glucose and treat diabetes. Among them, *Momordica charantia* is the most popular herbal resource (Rahman *et al.,* 2011)

Fruits and leaves of most wild *Momordica* species are consumed as vegetables and have a similar bitter taste and almost identical medical uses. It has been used as a traditional antidiabetic remedy in eastern countries for many years (Zhu *et al.,* 2012).

Scientific name : *Momordica charantia*
Kingdom : Plantae
Division : Magnoliophyta
Family : Cucurbetaceae
Genus : Momordica
Species : Charantia
Duration : Annual

Some common names of *M.charantia* include bitter melon, papilla, bitter gourd, salsamino, corrila or karela, hanzal, assorossie, ampalaya, nigauri or goya, pare, kho gua, sora, balsam apple and balsamina (Singh *et al.,* 2011).

Bitter gourd is a popular vegetable in some Asian countries. Fresh bitter gourd is used as a nourishing food. It contains 93.8 per cent water, 0.9 per cent protein, 0.1 per cent lipid, 3.3 per cent dietary fiber, 20 kJ energy per 100 g and a small quantity 0.05 per cent of vitamin C . It is a good source of phenolic compounds (Islam *et al.*, 2011).

Momordica charantia originated on the Indian subcontinent and was introduced into China in the 14^{th} century. It is also used in native medicines of Asia and Africa particularly for enhancing the digestion, metabolism, blood circulation, immunity and robustness. According to Ayurvetha, and Indian System of Medicine, bitter guard causes vatta, reduces kuph and pitta and controls fever, blood impurities and jaundice. Moreover, this vegetable is beneficial in curing liver diseases, skin ailments and other windy complaints (Ariyawansa, 2011).

Traditional medicine of Brazil believes that bitter gourd is used for treating tumors, wounds, rheumatism, malaria, leucorrhea, inflammation, menstrual problems, diabetes, colic, fevers, worms, and also used as an abortions inducer as well as an aphrodisiac agent (Maiti *et al.*, 2012).

Folk wisdom has it that bitter gourd helps to prevent or counteract Type II diabetes. A scientific study at the Jawaharlal Institute of Postgraduate Medical Education and Research, India proved that consumption of bitter gourd could significantly increase the insulin sensitivity. Most of the scientific studies suggest that a regular consumption of bitter gourd certainly can circumvent various health related problems either by its prophylactic or therapeutic actions (Anilakumar *et al.,* 2015).

In the latest count, approximately 228 different compounds with proven medicinal properties acting alone or in combination with other, have been isolated from bitter melon fruit, seeds, leaves, stems, pericarps, endosperm, callus tissues and cotyledons (Singh *et al.,* 2011). Among the most actively studied constituents shown to improve glycemic control include charatin, polypeptide-P, vicine, momordin and similar derivatives (eg. momordinol, momordicilin, momorcharin,momordicin).

Scientists have identified three groups of constituents responsible for blood sugar lowering action of bitter melon; one of these, a compound called charantin which is composed of sitosteryl glucoside & stigmasteryl glucoside and can potentially replace treatment by insulin(Pitipanapong *et al.,* 2007). The bitter melon is believed to improve glucose tolerance in Type II diabetes. Active constituents are believed to be oleanolic acid glycosides and Momordins which prevent absorption of sugar (Mitra and Bhattacharya, 2006).

Charantin a type of triterpenoid in *Momordica charantia* and is a potential substance with anti diabetics properties(Keller , 2012). Studies have reported that this compound is more effective than the oral hypoglycemic agent tolbutamide. Charantin-rich extract is a potential agent for increasing insulin sensitivity in Type II diabetic patients rather than for protecting patients with Type I diabetics against β-cell dysfunction (Wang *et al.,* 2014). Recently, eight new cucurbitanetype glycosides were isolated by bioactivity-guided fractionation that also exhibited a hypoglycemic effect *in vitro.*

Another compound, polypeptide p (plant insulin) found in seeds and fruits of bitter melon is similar to insulin in composition, so it can be of a great benefit in therapy of Type I diabetes (Paul and Raychaudhuri , 2010).

A study in mice revealed that lipid and saponin extracts of melon are more effective in lowering glycated haemoglobin levels and excessive body weight gain than the hydrophilic extract or the whole fruit. White bitter gourd varieties were found to contain significantly lower saponin concentrations (0.25 per cent) compared to green varieties (0.67 per cent). The lipid extract contained higher amounts of conjugated linoleic and linolenic acids i.e up to 65.89 per cent (Habicht *et al.,* 2011).

Study by Nkambo *et al.,(*2013) revealed that the methanolic fruit extract of *M. charantia* exhibited anti-hyperglycaemic effects comparable to those of metformin, in appropriate doses, in alloxan-induced diabetic rats, but the initial effect appears to be offset by the carbohydrate content of the extract. The anti-hyperglycaemic activity increased with an increase in dose of extract.

Bitter melon is believed to exert its hypoglycemic effect through multiple mechanisms involving the stimulation or inhibition of the key enzymes of metabolic pathways. For example, it stimulates the key enzymes of hexose monophosphate pathway and increases the utilization of peripheral and skeletal muscle glucose (Akhtar *et al.,* 2011)

The blood glucose lowering effects of *Momordica charantia* were closely associated with its inhibitory activity against disaccharidase. This effect is important for the treatment of both Type I and Type II diabetic patients and helps to prevent high blood sugar levels after meals. Bitter melon has shown to stimulate glycogen storage by liver and insulin secretion by islets of Langerhans (Zhu *et al.,* 2012). Evidence indicates that bitter melon may decrease hepatic gluconeogenesis, increase hepatic glycogen synthesis, and increase peripheral glucose oxidation in erythrocytes and adipocytes (Hamissou *et al.,* 2013).

Hazarika *et al.,*(2012) have demonstrated that momordicilin a triterpene, is a potent inhibitor of glycogen synthase kinase-3, an enzyme involved in glucose homeostasis and potential target for anti-diabetic compounds.

A study proved that bitter melon could up regulate the significance of glucose transporter 4 (GLUT-4), peroxisome proliferator-activated receptor γ (PPARγ) and phosphatidylinositol 3 kinase (PI3K) by augmenting the glucose uptake and homeostasis (Kumar *et al.,* 2009).

M. charantia appears to act by repairing damaged beta cells, increasing insulin secretion, enhancing insulin sensitivity in peripheral tissue by promoting glucose uptake, inhibition of hepatic gluconeogenesis, decreasing glucose absorption by inhibiting glucosidase and disaccharidases in the intestine, and enhancing the activity of AMP-activated protein kinase (Chaturvedi, 2012).

Indeed some of the constituents of the extract like oleanolic acid 3-O-glucuronide and momordin exert their anti-hyperglycemic effect by inhibiting glucose transport at the brush border of the small intestine. The aqueous extract of the unripe fruit of *M. charantia* has been shown to partially stimulate insulin release from isolated beta cells of the pancreas in rats, while the fruit juice significantly increased the number of beta-cells. *M. charantia* has also been reported to inhibit 11 Betahydroxysteroid dehydrogenase, a potential antidiabetes target (Blum *et al*., 2011).

Kolawole *et al.,*(2011) reported that the methanolic fruit extract of *M. charantia* decreased blood glucose in both normal and diabetic animals, comparable to

10mg/kg of chlorpropramide in doses of 400 to 600mg/kg. Mamun (2011) also found a significant decrease in blood glucose and increase in serum insulin when powdered fruits of the plant were administered to diabetic rats.

Bitter melon (*Momordica charantia*) extract promotes a balanced storage of glucose in the liver as glycogen, supports healthy insulin secretion by the islets of Langerhans, promotes peripheral glucose utilization, and healthy serum protein levels according to *in vivo* and *in vitro* studies. Bitter melon is another botanical that has reduced insulin resistance in animals, partly through its ability to improve the function of insulin receptors in the liver. It also been widely researched in animal studies for its ability to improve glucose and insulin tolerance (Nerurkar *et al.,* 2008).

Popovich *et al.,* (2010) found that bitter melon triterpenoid extract reduces lipid accumulation and adiponectin expression in 3T3-L1 cells. Kumar *et al.,* (2010) reported that the *Momordica charantia* decreases "bad" cholesterol and increases "good" cholesterol. Wan *et al*.,(2011) have also found that *M. charantia* peroxidase can be used for biotransformation of piceatannol into antihyperglycaemic oligomeric stilbenes

Recently, Wehash *et al.*, (2012) stated that bitter melon appears to be exerting in reducing capillary permeability than the fenugreek extract. In general, the increase in capillary permeability is a sign of micro vascular dysfunction at the arteriolar and capillary level, which is a common and severe complication of diabetes. More recently, a detailed antidiabetic mechanism has been reviewed by Joseph and Jini (2013).

Bitter Melon Extract exerts a significant effect on inhibition of cell growth and induction of apoptosis in breast cancer cells mediated by cell cycle and apoptosis regulatory proteins (Ray *et al.,* 2010).

In vitro studies reveals that the bitter gourd proteins (α -and β-monorcharin) have inhibitory effect against human immune deficiency virus (HIV). Leaf extracts have demonstrated broad-spectrum anti-microbial activities against *E.coli, Staphylococcus, Pseudomonas, Salmonella, Streptobacillus* and *Streptococcus*

Bitter gourd Leaf extracts have demonstrated broad-spectrum anti-microbial activities against E. coli, Staphylococcus, Pseudomonas, Salmonella, Streptobacillus and Streptococcus (Patil and Patil, 2011). An extract of the entire plant was shown to have antiprotozoal activity against Entamoeba histolytica (Gupta *et al.,* 2010).

Numerous *in vitro* studies have also demonstrated the anti-cancerous and anti-leukemic activity of bitter gourd against numerous cell lines, including liver cancer, human leukemia, melanoma and solid sarcomas (Fang *et al*., 2012).

Results of Chao *et al.,* (2014) research on mice with sepsis indicated that wild bitter gourd in diets promoted lipid metabolism, reducing fat accumulation, and improving low blood glucose in sepsis. Addition of wild bitter gourd can reduce inflammation biochemical markers or indicators and pro-inflammatory cytokines in the body, hence improving the inflammation responses in mice with sepsis.

In fruit, the pulp portion showed higher anti-oxygenic activity compared than seeds, which may be ascribed to their different phenolic and flavonoid compositions. Ethanol/water extracts of both pulp and seed powders exhibited higher anti-oxygenic activities compared with other solvent extracts when evaluated for anti-oxygenic activity by any of the methods (Kubola and Siriamornpun 2008).

Investigations shown that the fruits and leaves of *Momordica charantia* has rich in phenolics and exhibit high antioxidant activity. It is an effective medicine for diabetic and anemic people and act as good blood purifier. As it has hypoglycemic substance, it helps in bring down the blood sugar and urine sugar levels (Ying *et al*., 2012).

In addition to hypoglycaemic activity, *M.charantia* has been shown to have as an abortifacient. A substance called as quinine may stimulate shrinkage of uterus and may possibly result in abortion (Shah *et al.,* 2013). The most appropriate or effective dose of bitter melon is not entirely clear. Powdered, dried fruit has been dosed in a range of 3–15 g/day. The fresh juice has been used at 50–100 mL/day, and an aqueous decoction of the fruit has ranged from 100 to 200 mL per day. Standardized extract dosing ranges from 100 to 200 mg three times a day (Hudson, 2012).

To date, *M. charantia* has been extensively studies worldwide for its medicinal properties to treat a number of diseases. It is described as a versatile plant worthy of treating almost any disease inflicted on mankind.