1.1. INTRODUCTION

In the modern world, people rely on technology for convenience and consume various foods with side effects. Urbanization and changing lifestyles have led to a preference for ready-made junk food. Globalization has influenced eating habits, making people consume high-calorie fast foods, known as junk food (Shridhar et al., 2015). This results in less physical activity, higher body mass index, increased waistline, and obesity, leading to metabolic disorders and diseases. Hyperglycemia, or high blood sugar, is a common problem caused by high carbohydrate intake, sugary drinks, and low-protein diets. Hyperglycemia can also result from prolonged high carbohydrate levels, physiological conditions, genetics or diabetes. The symptoms of diabetes were first mentioned in 1552 BC by Egyptian physician Hesy-Ra and Greek physician Arateus, who noted frequent urination (Ramachandran et al., 2017). The cause of high blood sugar was discovered when Claude Bernard identified liver glycogenolysis in 1857, linking diabetes to excess glucose production by the liver. Increased obesity, sedentary lifestyles, diet, and heredity were also identified as causes (Ahmed, 2002). Later, it was established that the pancreas plays a key role in maintaining blood sugar levels. Two primary hormones, insulin and glucagon, secreted by the pancreas' β-cells, regulate blood glucose (Giugliano et al., 2008). Insulin helps keep blood glucose levels in check by reducing glucose production in fasting states and allowing glucose into body cells after meals. Glucagon increases glucose production in the liver (Aronoff et al., 2004; Ramnanan et al., 2011). Reduced insulin secretion, decreased glucose use, increased glucose production, islet dysfunction, and insulin resistance lead to hyperglycemia (Giugliano et al., 2008). Recently, epigenetic factors like DNA methylation and histone modifications have also been linked to diabetes (Kaimala et al., 2022). Prolonged hyperglycemia leads to prediabetes or impaired glucose tolerance and diabetes, with an annual conversion rate of 3% to 11% (DeFronzo et al., 2015). Untreated hyperglycemia can cause severe complications, including damage to the eyes, kidneys, nerves, and heart (Giugliano et al., 2008; Michelle Mouri and Badireddy, 2023).

Causes of hyperglycemia (WHO, 2019)

(I) Impaired glucose regulation (IGT and IFG) and

(II) Diabetes mellitus

(I) Impaired Glucose Regulation: Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG)

Impaired glucose tolerance (IGT) is when the two-hour glucose level is between 140 mg/dL and 199 mg/dL after taking 75 g of glucose in an oral glucose tolerance test. This means the patient cannot effectively lower their glucose levels even 2 h after consuming glucose. IGT is also known as postprandial hyperglycemia but is not high enough to be classified as diabetes. It is mainly caused by poor insulin response in skeletal muscles (James et al., 2021). IGT can be detected by measuring glucose levels before and after the oral glucose tolerance test.

Impaired fasting glucose (IFG) is when fasting glucose levels are between 100-125 mg/dL. This happens because the liver cannot properly reduce glucose production at night due to poor insulin secretion and sensitivity (Meyer et al., 2006). Both IFG and IGT indicate higher than normal blood glucose levels, which fall between normal glucose regulation and diabetes (Nathan et al., 2007; IDF, 2021). Globally, 10.2% of people have IGT, and 5.7% have IFG. The Western Pacific region has the highest IGT rate at 12.9%, followed by Africa (12.6%), North America and the Caribbean (11.2%), the Middle East and North Africa (11.2%), South and Central America (10.9%), Europe (7.1%), and Southeast Asia (5.4%). For IFG, South and Central America has the highest rate at 10%, followed by Southeast Asia (8.8%), Africa (8.0%), North America and the Caribbean (8.3%), the Middle East and North Africa (6.1%), Europe (3.3%), and the Western Pacific (2.5%).

(II) Diabetes mellitus

Diabetes mellitus (DM) is a metabolic disorder marked by high blood glucose levels due to the dysregulation of carbohydrate, lipid, and protein metabolism. The term "diabetes mellitus" comes from the Greek word "diabetes," meaning "siphon" (to pass through), and the Latin word "mellitus," meaning "sweet" (Lingaraju, 2022). Normal blood glucose levels range from 70-99 mg/dL. Levels between 100-125 mg/dL are considered prediabetic. A person is diagnosed with diabetes when fasting blood glucose levels exceed 125 mg/dL (≥7 mM/L) or reach 200 mg/dL (>11.10 mM/L) 2 h after a meal (WHO, 2019). According to the American Diabetes Association (ADA, 2018), a

person is diabetic if their plasma blood glucose is 200 mg/dL two h after consuming a 75 g glucose load. Another criterion is a random blood sugar level exceeding 200 mg/dL. Chronic hyperglycemia from DM is associated with damage, dysfunction, and failure of various organs and tissues, including the retina, kidneys, nerves, heart, and blood vessels (Alam et al., 2015). Currently, four diagnostic tests are recommended to confirm diabetes:

1. Fasting plasma glucose concentration
2. Plasma glucose detection or oral glucose tolerance tests (OGTT) with a 75 g glucose load
3. Glycosylated hemoglobin concentration (HbA1c)
4. Random blood sugar levels accompanied by signs and symptoms.

A. Epidemiology of diabetes mellitus

Diabetes mellitus is a global disease affecting billions of people worldwide, with cases rising from 422 million in 2014 to 537 million in 2021. The number of cases is projected to increase to 643 million by 2030 and 783 million by 2045. In 2021, the Western Pacific region had the highest number of diabetes cases, with about 206 million people affected and 2.3 million deaths. Southeast Asia had the second highest number, with 90 million individuals and 747,000 deaths in 2021. The number of adults with diabetes in Southeast Asia is expected to reach 113 million by 2030 and 151 million by 2045 (IDF, 2021).

Other regions also have significant numbers of diabetes cases: the Middle East and North Africa have 73 million affected individuals, Europe has 61 million, North America and the Caribbean have 51 million, South and Central America have 32 million, and Africa has 25 million. According to the International Diabetes Federation (IDF, 2021), three out of four adults with diabetes live in low and middle-income countries, and the prevalence is rising rapidly (WHO, 2021). In 2019, diabetes was the ninth leading cause of death globally, with an estimated 1.5 million deaths. A recent survey by the IDF in 2022 found that over 476 million indigenous people from 5000 distinct groups in over 90 countries are affected by diabetes. As a result, diabetes has become one of the most common health emergencies, impacting billions of people worldwide.

B. Types of Diabetes Mellitus

Diabetes comprises many disorders including hyperglycaemia. Generally, there are two types of diabetes: Type I and Type II DM. However, with the increasing prevalence of diabetes, several reasons have been found to be associated with diabetes that do not fit in the general category or account for the entire spectrum of diabetes phenotypes. The World Health Organisation has therefore classified diabetes into various sub-types. Based on the aetiological and clinical stages of diabetes the following classification has been made (Table 1).

Table 1. Sub-types of diabetes (WHO, 2019)

Types	Characteristics
Type-I	Destruction of β-cells of the islet of Langerhans (mostly immune-mediated); absolute or total insulin deficiency. Mostly common in childhood and early adulthood. Requires insulin for control and survival
Type-II	Various degrees of β cell destruction and insulin resistance, mainly due to obesity and overweight.
Hybrid form of diabetes	
Slowly evolving to immune-mediated	Has a GAD autoantibody; slowly evolving to Type I type of Diabetes.
Ketosis-prone type II diabetes	Family history of Type II diabetes; Negative for GAD antibody, but are more prone to ketoacidosis
Other specific types	
Monogenetic diabetes	Caused by specific gene mutations
Exocrine pancreas	Tumors or Trauma or inflammation of the pancreas
Endocrine disorders	Excess secretion of some hormones may decrease the secretion of insulin
Chemical-induced diabetes	Administration of a few chemicals impairs insulin secretion or sometimes destroys the b cell.
Infection leading to diabetes	Some viruses are directly linked with B-cell destruction

Other genetic abnormalities	Chromosomal abnormalities or many genetic disorders increase the risk of diabetes
Unclassified diabetes	Diabetes that does not fit any of the other specific types.
Hyperglycaemia first detected during pregnancy	
Diabetes mellitus in pregnancy	Type I or Type II diabetes first detected during pregnancy
Gestational diabetes mellitus	Hyperglycemia below the range for diabetes in pregnancy. The fasting plasma glucose 92-125 mg/dL (5.1–6.9 mM/L or 1-hour post-load plasma glucose 180 mg/dL ≥ 180 mg/dL (10.0 mM/L) or 2-hour post-load plasma glucose 153-198 mg/dL (8.5–11.0 mM/L)

(i) Type-I Diabetes mellitus

Type-I diabetes mellitus (TIDM) is a chronic physiological disorder characterized by hyperglycaemia or high glucose level in the blood. Destruction of islets of the pancreas with less or no production of insulin is the primary hallmark of TIDM. TIDM is characterized by deficient insulin production and requires daily administration of insulin (WHO, 2011). It occurs mainly when the human immune system destroys its pancreatic β-cells. It mainly occurs at the early onset (childhood) of life, and adolescence and 84% of people living with TIDM are adults (Centers for Disease Control and Prevention, 2014). TIDM decreases the life expectancy up to 13 years (Livingstone et al., 2015). However, the rate of β-cells destruction varies from individual to individual (Hagopian et al., 1993).

a) Aetiology

The destruction of β-cells can be caused by various mechanisms. Typically, a biomarker, autoimmune response, or a strong genetic component is detected in the serum of patients, indicating that it is generally immune-mediated. During early childhood, an autoantibody targeting β cells, often insulin, appears. Several autoantibodies, such as those against insulin, glutamic acid decarboxylase (GAD65),

islet antigen-2 (IA-2), and zinc transporter 8 (ZnT8), as well as various associated genes that regulate immune responses, are found in individuals with TIDM (Patterson et al., 2014; Shojaeian et al., 2018). Individuals with specific HLA genotypes, particularly HLA-DQ8 and HLA-DQ2, which encode MHC proteins, have an increased risk of developing autoantibodies and ultimately TIDM (Eisenbarth, 2007; Gianani et al., 2010). Type 1 Diabetes Mellitus may result from a genetic trigger, environmental factors, or a combination of both. Additionally, it has been reported that individuals born in the spring are more susceptible to TIDM (Atkinson et al., 2015; Katsarou et al., 2017).

b) Epidemiology

TIDM is a disease that can affect any stage of life. However, it is more common in childhood age (5-7 years). It can also occur in people who are near puberty but very rare in adults. Prevalence of TIDM is seen to be more common in male individuals compared to females. Globally, more than 1.2 million children and adolescents (0-19 years) are living with TIDM in 2021 (https://www.diabetesatlas.org/). Around the globe, TIDM accounts for nearly 10% of all diabetic cases. According to a model study conducted by Gregory et al. (2022), it has been seen that 8.4 million people were living with TIDM worldwide and of which 18% were from the younger section (0-20 years), 64% were from the range of median age (21-59 years) and 19% were from older section (60 years or above). The prevalence of diabetes is predicted to increase by 2040 to nearly, 13.5-17.4 million people suffering from TIDM. According to the data of IDF (2021), TIDM among adolescents (0-19 years), Europe 294 thousand (0.1 % of the region's adolescent population) constitutes the highest number of adolescents affected. In Southeast Asia, 244 thousand (0.04% prevalence) adolescents are affected by TIDM, followed by North America and the Caribbean having 193 thousand affected adolescents (0.1%), and Middle East and North America 192 thousand (0.06% prevalence). In South and Central America, 121 thousand adolescents (0.01%) were affected followed by Western Pacific 107 thousand (0.01%) and Africa 59 thousand (0.01%).

c) Symptoms

TIDM is a complicated disease showing various symptoms. The major symptoms include polyuria or frequent urination in large quantities. Other notable symptoms include abnormal thirst and dry mouth, sudden weight loss, muscle bulk, lack of energy, itchiness around the genital area, yeast infection, tiredness, and constant hunger. In addition, it, blurred vision, loss of appetite, fruity-smelling breath and urine, high temperature accompanied by nausea or vomiting, and bedwetting may also be an indication of TIDM (Roche et al., 2005; IDF, 2021).

(ii) Type-II Diabetes mellitus

Type-II Diabetes Mellitus (TIIDM) accounts for 90% of diabetic cases and typically begins as insulin resistance until the pancreas slowly loses its ability to produce insulin. It is a metabolic disorder that mainly occurs when the body cannot regulate carbohydrate, lipid, and protein metabolism in our body and results in insulin resistance or a combination of both. It is the most prevalent disease affecting the citizens of both developed and developing countries all around the globe (De Fronzo et al., 2015; Ahmed et al., 2017).

a) Aetiology

Changes in diet and physical activity related to rapid development and urbanization have led to sharp increases in the number of people living with TIIDM. The most influential are lifestyle behaviours commonly associated with urbanization. TIIDM is a multifactorial disease mostly contributed by genetic and environmental factors. Genetically, it is a heritable disease involving many genes. The risk of developing TIIDM is higher when the mother has the disease compared with when the father has the disease. SNP in TCF7L2 showed a strong association with TIIDM, and many other genes such as SLC30A8, FTO CDKALI, and CDKW21. Incretin hormone and gastric inhibitory polypeptide resistance or deficiency, reactive oxygen stress, and hypersecretion of amyloid polypeptide also contribute to the formation of TIIDM. A few environmental factors include unhealthy diet, physical inactive, and sedentary lifestyle (DeFronzo et al., 2015). TIIDM is preventable by maintaining a healthy

weight, BMI less than 25 kg/m^2, and avoiding smoking and alcohol consumption. Research indicates that the majority of cases of TIIDM diabetes could be prevented through a healthy diet and regular physical activity (Rolo and Palmeira, 2006; Giugliano et al., 2008; DeFronzo et al., 2015).

b) Epidemiology

According to the International Diabetes Federation (IDF), approximately 90% of diabetic cases worldwide are Type II Diabetes Mellitus (TIIDM) (IDF, 2023). While TIIDM is primarily observed in adults, its prevalence among children, adolescents, and younger adults is on the rise due to increasing levels of obesity, physical inactivity, and poor diet. An estimated 541 million adults are at an elevated risk of developing TIIDM (IDF, 2023). The Middle East and North Africa exhibit the highest age-adjusted prevalence, reaching 18% among individuals aged 20 to 79 years (IDF, 2023). Once considered rare in African regions, TIIDM has emerged as a significant cause of mortality and morbidity (Motala et al., 2019; IDF, 2021).

In North America and the Caribbean, approximately 51 million individuals are afflicted with diabetes, with South and Central America hosting 31 million cases (IDF, 2023). The Western Pacific and Europe report 203 million and 24 million cases of diabetes, respectively (IDF, 2023). In Southeast Asia, nearly 90 million individuals are affected by age-adjusted diabetes, while the Asia-Pacific region houses approximately 227 million diabetic individuals as of 2021 (IDF, 2023). Notably, over 60% of global diabetic cases are concentrated in Asia, particularly in countries like China and India, where the prevalence of TIIDM has surged despite relatively low obesity rates (Healthline, 2021). In North American regions alone, over 37 million individuals live with diabetes, with TIIDM accounting for 90-95% of cases (CDC, 2023).

c) Symptoms

During the early stages, individuals often lack noticeable symptoms until they experience health issues related to diabetes. Symptoms typically develop slowly and may be very mild, making them difficult to detect. Common symptoms include increased thirst, frequent urination, fatigue, slow wound healing, blurred vision, and

tingling or numbness in the hands and feet. Additionally, symptoms such as excessive hunger, digestive problems, foot ulcers, gum disease, hearing loss, skin conditions, and urinary tract infections may also signal TIIDM. In later stages, fruity-smelling urine, reminiscent of TIDM, may also be evident (IDF, 2023).

(iii) Hybrid form of Diabetes

Diabetes encompasses more complexity than merely Type I and Type II classifications. Recognizing this challenge has led to the identification of a hybrid form of diabetes known as double diabetes (DD), exhibiting symptoms characteristic of both types. DD involves a combination of beta cell destruction and insulin resistance, often associated with cardiovascular disease. Genetic predisposition, lifestyle factors, and the use of insulin or metformin are primary contributors to DD (Khawandanah, 2019). It presents a blend of Type I and Type II diabetes symptoms, with DD being indicated by the presence of both anti-GAD and IAA antibodies alongside TIIDM characteristics (Olamoyegun et al., 2020). DD may develop in adolescents with Type I diabetes due to weight gain and insulin therapy. Treatment strategy is focused on both the insulin deficiency and insulin resistance, with symptoms including obesity, insulin resistance, and autoimmune diabetes.

(iv) Gestational diabetes mellitus

Pregnancy is a significant life event involving social, psychological, and hormonal changes. It also increases vulnerability to disorders, including gestational diabetes mellitus (GDM). GDM, a common pregnancy complication, involves rapid or sudden hyperglycemia that usually resolves after delivery but can sometimes lead to complications. Women with a history of GDM are at higher risk of developing Type II diabetes later in life (Nicklas et al., 2013; Plows, 2019). GDM is defined as glucose intolerance of varying severity that begins during pregnancy (Schaefer-Graf et al., 2002). Insulin resistance increases from mid-pregnancy through the third trimester, reaching levels similar to those seen in TIIDM (Buchanan et al., 2007; Reece, 2009). In late pregnancy, insulin requirements are high, but pancreatic β-cells may not produce enough insulin, resulting in high blood glucose. To maintain glucose control, the

mother's pancreatic β-cells must increase insulin secretion to counter reduced tissue sensitivity to insulin. Normally, β-cells do this, but in women with GDM, insulin production does not increase adequately (Reece, 2009). Inadequate insulin secretion is most evident in late pregnancy. Evidence suggests that β-cell defects in GDM result from the same causes as general hyperglycemia, including autoimmune disease, monogenic causes, and insulin resistance (Buchanan et al., 2007).

a) Aetiology

During pregnancy, insulin resistance can result from increased maternal fat and placental hormone effects (Buchanan et al., 2007). Pregnancy hormones such as estrogens and progestins lead to lowered fasting glucose, increased appetite, and fat deposition. Risk factors for gestational diabetes mellitus (GDM) include advanced maternal age, ethnicity, previous gestational diabetes, and a family history of TIIDM (McIntyre et al., 2020). GDM may occur due to a limited pancreatic β-cell reserve, which causes hyperglycemia when insulin secretion fails to meet the demands of pregnancy (Buchanan et al., 2007). Some women with GDM cannot increase insulin production sufficiently to counteract increased resistance (Reece, 2009). Genetic factors, such as single-nucleotide polymorphisms in genes like rs7903146, rs12255372, rs1799884, and rs5219, are linked to GDM risk (Zhang et al., 2013; Bhushan et al., 2021). The development of insulin resistance involves defects in the insulin-signaling cascade receptors and the downregulation of insulin receptor substrate-1 (IRS-1) (Avramoglu et al., 2006; Abdulellah et al., 2018). GDM is associated with the upregulation of genes in placental cells, impacting immune response, organ development, and cell death regulation (Nielsen et al., 2014). Susceptibility genes like potassium voltage-gated channel KQT-like 1 and glucokinase are involved in β-cell function and GDM (Xie et al., 2024). Minor β-cell deficiencies during pregnancy-induced stress contribute to maternal insulin resistance.

b) Epidemiology

According to the International Diabetes Federation estimates (IDF, 2017), GDM affects approximately 14% of pregnancies worldwide, representing about 18 million births

annually. It has been seen that in five years, there is an increased GDM percentage that is approximately 16.6% and about 21 million births are affected with gestational diabetes. The highest prevalence of GDM is seen in Southeast Asia (25.9%) followed by North America and Caribbean (20.7%). South and Central America have a prevalence of 15.8 % followed by Europe which has a prevalence of 15%. Likewise, the Middle East and North America have a prevalence of 14.1% and Africa constitutes about 13%. Gestational diabetes is more frequent in certain ethnic groups than in the general population. The rate of gestational diabetes was also shown to be 5–10 times higher in pregnant Asian women than in white women (Reece, 2009).

c) Symptoms

Most of the time, gestational diabetes does not cause any notable symptoms and is generally asymptomatic. Systematically examining personal and family history and conducting frequent medical examinations are useful for detecting GDM. Possible symptoms in patients with GDM include increased thirst or frequent urination. Additionally, depression, stress, and anxiety may occur (Yogev et al., 2009; Lee et al., 2019). Notable symptoms also include tiredness, blurred eyesight, dry mouth, thirst, genital itching, or thrush (National Health Services, 2022).

C. Complications of diabetes

Diabetes mellitus is a long-term metabolic disorder associated with several clinical problems and complications and sometimes even may lead to death if not medically aided. The severity of the complications mostly depends on the blood sugar level of the person. The prolonged or consistent hyperglycaemia may lead to various complications initiating micro and macrovascular damage.

(i) Acute complications

a) Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) develops when insufficient insulin secretion reduces glucose uptake of the cells. To meet the glucose demand of the body, the liver breaks down fat, a process that produces acids called ketones. When there is a fast production

of ketones, it builds up in the body causing DKA. It is the consequence of a lack of insulin secretion and elevation of counter-regulatory hormones. Accumulation of ketoacids leads to a decrease in serum bicarbonate concentration and retention of these 'fixed acids' leads to the development of high anion gap metabolic acidosis (Dhatariya et al., 2020; CDC, 2022).

b) Hyperosmolar hyperglycemic nonketotic coma

The initiating event in the hyperosmolar hyperglycemic state is glucosuric diuresis, which mainly occurs as a result of high-water loss from the body. Due to low insulin levels, by the action of counter-regulatory hormones, gluconeogenesis, and glycogenolysis is initiated, resulting in hyperglycemia but low uptake of glucose by the cells. The resultant hyperglycemia increases the serum osmolarity and increases the osmotic gradient causing the cells to pull out extra water from the extravascular space. Free water with electrolytes and glucose is also lost through urination. To preserve the intracellular volumes, the brain produces new intracellular solutes known as radiogenic osmoles, to prevent fluid from moving to the extracellular space and to maintain a state of equilibrium. If the serum osmolarity is decreasing too fast and is brain is lacking to eliminate the osmoles at the same rate, then there is a chance of accumulation of fluid in the brain causing a brain edema (Stoner 2005; Adeyinka and Kondamudi, 2022).

c) Hypoglycemia

When the blood glucose level drops below the normal range (≈70 mg/dL), such condition is known as hypoglycemic condition. Hypoglycemia occurs mostly in T1DM, and TIIDM, where there is progressive insulin deficiency. Hypoglycaemia is a result of an imbalance between insulin intake and the body's physiological and behavioural defense against falling plasma glucose concentration. The sulfonylurea class of drugs or insulin is the more common cause of hypoglycemia. Such drugs are hypoglycemic agents, i.e., lower blood glucose level below the normal range of the person thereby leading in decrease of blood glucose below the normal range. This could cause severe organ illness, acute vascular diseases or may even lead to death (Shafiee et al., 2012; Cryer and Arbeláez, 2017).

(ii) Chronic complications

Patients suffering from diabetes for longer periods have the chance of developing chronic complications in the body. A phase of asymptomatic which lasts 4 - 7 years may be seen in patients suffering from DM. By the time it is diagnosed, a lot of complications arise due to the elevated glucose in the blood. This led to the development of chronic complications of diabetes and it remains the major problem in diabetic care.

(iii) Diabetic retinopathy

A serious eye problem may arise due to DM. Involves anatomic changes in retinal vessels. New vessels and connective tissue grow on the surface of the retina or optic nerve head and the development of background lesions has appeared leading to retinal damage (Engerman, 1989).

(iv) Diabetic cardiomyopathy

Cardiovascular complications are the leading cause of diabetes-related morbidity and mortality. Diabetes mellitus is responsible for diverse cardiovascular complications such as increased atherosclerosis in large arteries and increased coronary atherosclerosis, which increases the risk for myocardial infarction, stroke, and limb loss (Boudina and Abel, 2007).

(v) Neuropathy

The nervous system may also be affected due to diabetes. It typically begins with the loss of sensory functions especially, in the lower extremities of the body marked by pain and considerable morbidities. Symptoms include tingling of hands and feet and paralysis. It is a group of clinical disorders, where damage to the peripheral and automatic nervous system occurs (Feldman et al., 2019). It is a common complication in both the types of diabetes.

(vi) Nephropathy

A renal failure or kidney dysfunction is also seen to be the side effect of diabetes mellitus. Diabetic nephropathy is a clinical syndrome characterized by the occurrence of persistent microalbuminuria (Schena and Gesualdo, 2005).

(vii) Alzheimer's disease

Insulin functions by controlling neurotransmitter release processes at the synapses and activating signalling pathways associated with learning and long-term memory. Impairment in insulin secretion may lead to dementia or more complicatedly to Alzheimer's disease (Kroner, 2009).

D. Available drugs and side effects

To date, six major classes of oral antihyperglycemic drugs are available: biguanides (metformin), sulphonylurea (e.g., tolbutamide), glinides (e.g., repaglinide), thiazolidinediones (e.g., pioglitazone), dipeptidyl peptidase IV inhibitors (e.g., sitagliptin) and alpha-glucosidase inhibitors (AGIs; e.g., acarbose) (Van de Laar, 2008).

(i) Biguanides: Metformin

Metformin (1.1-dimethyl biguanide hydrochloride) belongs to the biguanide class of drugs that are guanidine derivatives. This drug decreases the rate of conversion from prediabetes to diabetes. It also reduces insulin resistance and allows the body to use its own insulin more effectively (Lily and Godwin, 2009). Regular uses of metformin cause digestive side-effects such as diarrhoea, nausea, flatulence, abdominal pain with cramps, abdominal swelling, dysgeusia, vomiting, constipation, and dyspepsia and may also affect the gastrointestinal tract (Bouchoucha et al., 2011).

(ii) Sulfonylureas: Glicazide, Glipizide, Glimepride, Tobutamide, Glibenclamide

All sulfonylureas contain a phenyl-sulfonylurea structure, which exerts a hypoglycemic effect and decrease the glycated hemoglobin A1C (HbA1c) by 1% to 1.25% (Van de Laar, 2008). Sulfonylureas cause insulin secretion regardless of plasma glucose

concentration, by binding to and inhibiting the K- channel on the pancreatic β cell. B-cell membrane depolarizes as a result of potassium efflux which in turn causes calcium channels to open in turn causes an influx of calcium thereby increasing the intracellular calcium which further stimulates insulin secretion. Hypoglycemia may be a possible side effect of the sulfonylurea class of drugs (Costello et al., 2022). Sulfonylurea may also trigger hyperosmolar hyperglycemic non-ketotic coma (Adeyinka and Kondamudi, 2022).

(iii) Glinides: Repaglinide

They are insulin secreting agents or a stimulant of insulin secretion. This class of drugs act through the same mechanism of sulfonylureas class of drugs. They binds and inhibit the potassium channel on the cell membrane of pancreatic beta cells, but the binding affinity is weaker, for which it dissociates faster from the binding site. Glinides, has also equivalent effect on glycated hemoglobin level with that of sulfonylureas but it reduces predominantly the postprandrial blood glucose (Blicklé, 2006; Lioudaki et al., 2017). Due to the shorter binding capacity, this class of drugs specially the nateglinide has reduced risk of hypoglycemia than that of sulfonylureas class of drugs (Hu et al., 2000).

(iv) Dipeptidyl peptidase-IV inhibitors

Dipeptidyl peptidase 4 (DPP-4) inhibitors are a group of antihyperglycemic medications that act through incretin hormone, a gut hormone responsible for glucose homeostasis. Significant risk factors include - coronary disease, heart failure, stroke, and many other cardiovascular conditions (Kasina and Baradhi, 2019).

(v) α-Glucosidase inhibitors

Acarbose: They delay carbohydrate absorption in the gastrointestinal tract and control postprandial hyperglycaemia and provide cardiovascular benefits. These types of drugs basically work in the early stage of diabetes (Lebovitz, (1997).

Side effects: α-Glucosidase inhibitor class of drugs are known to cause genital, and to a lesser extent urinary tract infections, acute kidney injury, diabetic ketoacidosis, bone fracture, and lower limb amputation (Garofalo et al., 2019).

(vi) Sodium-glucose cotransporter-2 (SGLT-2) inhibitors

Empagliflozin, dapagliflozin, and canagliflozin are the main class representatives. They decrease the load of glucose in the body by blocking SGLT-2 in the proximal renal tubule and, therefore, increasing urinary glucose excretion (Lioudaki et al., 2017).

Side effects: Genital, and to a lesser extent urinary tract infections, acute kidney injury, diabetic ketoacidosis, bone fracture, and lower limb amputation (Garofalo et al., 2019). Glucagon-like peptide-1 (GLP-1) agonists: Exenatide, Liraglutide, Dulaglutide, mimic the effect of certain intestinal hormones (incretins) involved in the control of blood sugar.

(vii) Insulin injections

Insulin injections are effective but can cause severe side effects like hypoglycemia and nephropathy (ADA, 2020). Current antidiabetic medications are effective but also have serious side effects. This highlights the need for safer, more accessible, and cost-effective alternatives with fewer side effects. There's growing interest in plant-based products that act as drugs, glucosidase inhibitors, or mimic insulin hormones in the body. These alternatives offer promising potential for managing diabetes with fewer adverse effects.

Various insulin injections are available for different stages of diabetes.

a) Short-acting insulin: Works after 30 minutes of injection and lasts up to 4 to 5 h. Examples Novolin R, Humulin R, Afrezza.
b) Rapid-acting insulin: Works within 15 min after injection and lasts up to 4 h. For example, Glulisine, Lispro, and Aspart. These types of insulin are generally injected 15 -20 min prior to meal.
c) Intermediate-acting insulin: This type of insulin is slower than the other two types acting 1 - 3 h after the injection and can last up to 8-12 h. Examples include Novolin N and Humulin N.
d) Long and ultralong acting insulin: Last up to 14-40 h. Examples include garglin, detemir, degludec. The delivery of insulin may be either by injections or pumps. Accompanying insulin treatment, regular blood glucose monitoring, healthy nutrition, and regular exercises may also help to keep blood glucose levels in check.

E. Traditional medicine system as antidiabetic agents

Human societies have been in close contact with the environment since the beginning of human life on Earth. From the shelter to the clothing, food to medicines, plants had been providing man with all his needs. The Indian subcontinent is believed to have the oldest known habitation and is generally known for its oldest practice of traditional medicine and its uses. The history of healing art can be traced back to about 1500 BC (Raj and Gothandam, 2011). The incorporation of plants in curing ailments derived from three medical systems - Ayurveda (Indian system), Greek and Chinese medicine, and Ayurveda emerged as the world's most classic medicinal practice. Ayurveda provides a plethora of information on ethnic folklore practices and traditional aspects of therapeutically important medicines (Mukherjee et al., 2017). Plants are the sources of biologically active compounds and act as an element in the complex equations of healing. According to the WHO (2013), about 80% of the populations of developing countries currently use medicinal plants as remedies. Many currently available drugs (25%) are directly or indirectly derived from plants. The secondary metabolites present in the plants may contribute to the healing property of the plant. Secondary metabolites like polyphenols, terpenes, and alkaloids have been reported to possess many biological properties in various studies, which lie in bioactive phytochemical constituents that produce definite physiological action in the human body.

Plants are well-known in traditional medicine for their hypoglycaemic activities. Medicinal plants have long been used since ancient times for the treatment of diabetes, particularly in developing countries where most people have limited resources and do not have access to modern treatment (Garcia-Olmedo et al., 1987; Oguntibeju, 2019). Available literature indicates that more than 400 plant species are showing hypoglycaemic activity globally (Akah, 2011; Tran et al., 2020; Kasali et al., 2021). Therefore, there has been an increasing demand for plant products with antidiabetic activity due to their low cost, easy availability, and lesser side effects (Mahmun-Rashid et al., 2014). Recently, WHO recommended the use of medicinal plants for the management of DM and further encouraged the expansion of the frontiers of scientific evaluation of the hypoglycaemic properties of diverse plant species (WHO, 2011; Chikezie et al., 2015).

The Bodoland Territorial Council (BTC), now BTR (Bodoland Territorial Region), is a naturally rich area in Assam, located along the northern bank of the Brahmaputra River and the foothills of Bhutan and Arunachal Pradesh. Established in February 2003, it comprises eight districts carved out of Assam: Kokrajhar, Dhubri, Bongaigaon, Barpeta, Nalbari, Kamrup, Darang, and Sonitpur (BTC Accord, 2003). Covering approximately 8,795 square kilometers, it includes the Bodoland Territorial Region governed by the BTC, an autonomous unit under the sixth schedule of the constitution (BTC Accord, 2003). Kokrajhar district serves as the center and headquarters of the BTR and is culturally diverse, home to various ethnic groups like the Garo, Rajbonshi, Rabha, Nepali, Sonowal, and Bodos. Among these, the Bodos are the predominant ethnic group in Kokrajhar district (Census, 2011).

The Kokrajhar district is bordered by Bhutan to the north, the Sankosh River to the west, and the Riverine tract of the Brahmaputra Valley to the south. In the central part of the district, dense forests cover the northern region. The diverse climatic condition nourishes various flora and fauna to co-exist, making it one of the biodiversity hotspot areas. Most of the inhabitants are socio-economically backward. Living far away from cities and towns, tribal communities rely on traditional herbal formulations for their daily healthcare purposes. It has also been seen that the traditional medicine system has also started to decrease due to modernization and urbanization, thereby losing the vital indigenous knowledge that has been passed down by their forefathers. The documentation of medicinal plants and their uses in various diseases has become increasingly urgent because of the rapid loss of the natural habitat of some of these plants due to various anthropogenic activities and the knowledge of medicinal plants needs to be preserved before it is fully vanished. The traditional wisdom of the medicine system developed since time immemorial is the basis on which modern therapeutic drugs are developed. Recently, there has been an increase in new reports on anti-diabetic medications derived from natural ingredients, both from laboratory trials and from studies based on historic or traditional applications of these products for diabetes treatment. Even in the modern era, despite technological advancement, and the development of new drugs, herbal drugs are still preferred by a plethora of people in developmental countries. The medicinal value of plants lies in some chemical substances or phytochemicals of the plant. Medicinal plants exhibit a vast array of

potential therapeutic properties. The therapeutic effect of the plants may be due to the combined effect of secondary metabolites or phytochemicals present in them (Nyamai et al., 2016; Khan et al., 2021). Knowingly or unknowingly, traditional healers try to bring out phytochemicals through different processes of extraction like decoction, perchloration, maceration infusion, etc. (Daimari et al., 2019). Phytochemicals have primary and secondary constituents. Primary constituents include- protein, carbohydrate chlorophyll, etc. while secondary constituents are phenol, flavonoids, terpenoids, steroids, tannins, etc. (Wadood et al., 2013). Phenolics are the compound with one or more aromatic rings and possess antioxidant properties. Tannin has a glucose-lowering potential. Antioxidants are the molecules that scavenge the free radicals generated constantly as a result of oxidative and metabolic stress in the body (Daimari et al., 2020). Many bioactive compounds such as sterols, act as hypoglycemic agents. Besides this, knowing the structure and chemical constituents of the plants is very much needed for the synthesis of drugs or complex chemical substances (Yadav and Agarwala, 2011). The most important of these bioactive constituents of plants are alkaloids, tannins, flavonoids, phenolic compounds, lignin, and other metabolite that are rich in antioxidants. Modern researchers believe that it is better to deliver a product with a specified minimum level of one or more phyto constituent(s), where we can make sure about the quality of the product. Qualitative phytochemical screening will help to understand a variety of chemical compounds produced by plants and quantification of those metabolites will help to extract, purify, and identify the bioactive compounds for useful aspects to human beings (Santhi and Sengottuvel, 2016). Compounds capable of scavenging free radicals, produced as a result of stress by different diseases, possess great potential in ameliorating various diseases, which may give additional benefit to the plant as medicine (Olajuyigbe and Afolayann, 2011). Various in vitro methods are adopted to know the antidiabetic effect of the plants. One of the important strategies adopted by most of the researchers to screen antidiabetic property of the plants is α-amylase and α- glucosidase inhibitory property of the plants. α-amylase and α-glucosidase are important enzymes responsible for the breakdown of carbohydrates into simple sugars. Inhibition of these enzymes can control blood glucose levels being of one of the effective postprandrial control of blood glucose. Because of this, plenty of researchers have investigated the α-amylase and α-glucosidase inhibitory activity of

plants. However, the belief that plants have a lesser side effect or are less toxic would be pointless or ineffective without its proper validation or proof. Proper safety or evidence for safe use for the plant is mandatory for the use of medicinal plants and plants must go through a rigid screening process before using as a drug. Originally, ancestral people most likely tested medicines on themselves and later patients. With the development of pharmacology as a specialization of medical science, a shift to animal experiments occurred (Verpoorte et al., 2006). An accurate estimation of drug mechanism and action often requires considering the whole environment surrounding, in other words, it requires in-vivo analysis. Even the smallest-to-smallest things interact with their environment. Despite the advancement of techniques and different modes of toxicity study, testing on animal models is far better as the animal can be strongly correlated to that of human physiology. The whole animal itself possesses all the pharmacokinetic properties when the test substance route of administration is similar to its intended use (Ifeoma and Oluwakanyinsola, 2013). It also accounts for other physiological processes in an organism that affect toxicity. So, there has been a tremendous resurgence of medicinal plants with fewer ramifications, easy accessibility, economical and better efficacy. The potential of Ayurvedic medicine needs to be explored further with modern scientific validation and approaches for better therapeutic leads.

There is therefore the need to look inwards to search for herbal medicinal plants with the aim of validating the ethno-medicinal use and subsequently qualifying and quantifying its phytochemicals along with toxicity study and testing its efficacy in vivo system.

1.2. SIGNIFICANCE OF THE STUDY

The Bodoland Territorial Region is renowned for its endemic flora and serves as a habitat for numerous medicinal plants. However, there has been limited scientific research conducted in this region of Assam. Therefore, this study was designed to explore the medicinal plants of this area and assess their efficacy in vivo. The objective was to identify new potential antihyperglycemic agents from ethnomedicine. Ayurvedic drugs are predominantly natural and gentle, often claimed to be devoid of side effects. Therefore, if a hyperglycemic treatment could be developed from this system, it could serve as a preferable alternative with potential for clinical trials.

1.3. AIMS AND OBJECTIVES

The present study aimed to study antihyperglycemic properties of traditionally used medicinal plants of Kokrajhar district Assam. The following objectives were taken-

1) To collect and identify traditionally used antidiabetic medicinal plants from Kokrajhar District
2) Phytochemical analysis and antioxidant study of the plants
3) Preliminary anti-hyperglycemic studies of different crude extracts and selection of the best fraction
4) Biochemical and histochemical analysis of antidiabetic effects of the most active fraction of plant