CHAPTER 1

Introduction

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1.1 Diabetes mellitus

Diabetes presents a complex health issue in the contemporary era, encompassing a diverse range of chronic metabolic illnesses characterized by the common manifestation of elevated blood glucose levels. Diabetes mellitus (DM) is a prevalent global health concern characterized by insulin resistance[1], progressive β-pancreatic cell dysfunction, endocrine abnormalities[2], elevated glucose levels, and disruptions in carbohydrate, protein, and fat metabolism[1]. Additionally, low-grade inflammation is commonly associated with this condition[3].

1.2 Types of DM

Primarily, DM classification consists of two types: Type-1 diabetes mellitus (T1DM), commonly known as an insulin-dependent diabetes, and Type-2 diabetes mellitus (T2DM), which is also referred to as a non-insulin-dependent diabetes. Furthermore, the World Health Organization (WHO) has included two additional kinds of DM, namely Type-3 diabetes mellitus,commonly known as maturity-onset diabetes of the young(MODY), and gestational diabetesin pregnant women, also known as Type-4 diabetes mellitus.

1.2.1 Type 1 diabetes mellitus

T1DM is a chronic autoimmune disorder in the pancreatic β-cells characterized by inadequate production of insulin and subsequent elevated blood glucose levels [4]. T1DM is marked by the body's inability to release sufficient insulin or a complete absence of insulin production, resulting in inadequate management of blood glucose concentrations [5–6]. In individuals diagnosed with T1DM, the pancreatic β-cells, which are essential to the secretion of insulin, experience significant impairment or complete destruction. This is accompanied by an elevated presence of lymphocytes infiltrating the affected area. When the two aforementioned

elements are conjoined, there is a reduction in the body's production and secretion of insulin. Insufficient levels of insulin result in the inability of the β-cells of the pancreas to adequately regulate blood glucose levels within their established normal range [7]. T1DM has a significant impact on a considerable number of individuals worldwide, necessitating careful monitoring to mitigate the risk of severe complications such as cardiovascular and renal diseases, eyesight loss, and stroke. Insulin therapy is the primary approach for managing T1DM, involving the administration of exogenous insulin as a substitute for endogenous insulin. Regrettably, this approach is inadequate for attaining optimal blood glucose regulation in a significant number of patients [8].

1.2.2 Type 2 diabetes mellitus

On the other hand, in cases where the human body generates insulin but encounters difficulties in its utilization or has developed insulin resistance, it is classified as T2DM [5]. There are two primary factors that are essential to the development of T2DM. These factors include insulin resistance detected in peripheral tissues (such as skeletal muscles and adipose tissues) and insufficient secretion of insulin by pancreatic β-cells [9–10]. There are numerous elements that contribute to the inability of the body to sustain a balanced level of blood glucose in individuals with T2DM. Specifically, elevated levels of pro-inflammatory cytokines and free fatty acids hinder the transportation and storage of glucose in muscle and adipose tissue cells. Furthermore, it is worth noting that renal glucose production in the body is augmented, resulting in an elevated synthesis of fatty acids and glucose [7]. The condition places a significant strain on individuals with diabetes as well as on the healthcare system. Currently, the global community is observing a widespread occurrence of diabetes mellitus. On a global and national scale, DM, together with its associated comorbidities, represents a significant and complex health danger that is of utmost importance in current times. It is the leading etiology of end-stage renal disease (ESRD), non-traumatic lower limb amputations,

and visual impairment in adults. Additionally, it is associated with increased susceptibility to cardiovascular disorders [11]. The disease progression is associated with various risk factors, including elevated blood glucose levels, obesity, hypertriglyceridemia, bad dietary patterns, physical inactivity, age-related changes, familial predisposition, as well as psychological aspects such as stress, anxiety, and depression [12]. Given its escalating global prevalence, it is anticipated that this condition will continue to be a prominent contributor to both illness and death in the coming years. The treatment and maintenance of T2DM necessitate the use of insulin therapy in combination with metformin and other glucose-lowering medications [13].

1.2.3 Maturity onset diabetes of the young (MODY)

MODY is a hereditary manifestation of diabetes, the leading and most challenging health hazard recently. The hepatocyte nuclear factor 1 α (HNF1α) gene undergoes a mutation, resulting in the causation of β-cell dysfunction [14]. MODY is attributed to genetic abnormalities in the autosomaldominant gene, which result in impairment of insulin production. MODY is characterized by decreased glucose tolerance resulting from insulin insufficiency in individuals who are not obese. The severity of decreased glucose tolerance and the treatment techniques employed exhibit variation between the 14 kinds of MODY 1–14. MODY, which is mostly attributed to mutations in the HNF1α gene related to it, represents one of the most commonly identified forms of diabetes. In Japan, a prevalent method for identifying children with MODY is through a urine glucose monitoring program in schools, which is primarily employed due to the observed low renal threshold for glucose [15].

1.2.4 Gestational diabetes

This type of diabetes is characterized by hyperglycemia, or raised blood glucose levels, in pregnant women. This phenomenon exclusively manifests during the period of gestation in certain women, potentially impacting the well-being of both the maternal figure and the developing fetus. Obesity, a familial predisposition to diabetes, and an older mother are just a few factors that affect the onset of this condition. T2DM and ischemic heart disease have been found to be linked [16]. It is typically identified during the 2nd-3rd trimester of pregnancy in individuals who have no previous history of diabetes prior to the gestational period. According to the literature, this particular problem is widely recognized as the most prevalent occurrence during pregnancy [17]. The management of this illness can be achieved through the use of two treatments, namely insulin therapy and lifestyle modification. This includes the incorporation of nutritional therapy [18].

1.3 Statistics of DM

On a global scale, estimates of the prevalence of diabetes suggest that more than 500 million individuals are affected by this condition, constituting approximately 10.5% of the adult population worldwide [19]. According to estimates, the prevalence of diabetes among adults aged 18 and above was approximately 8.5% in 2014. According to estimates, the mortality rate attributed to diabetes is projected at around 1.5 million individuals, with around 48% of these deaths affecting individuals below the age of 70 [20]. According to available data from 2017, the prevalence of T2DM was believed to be 462 million individuals worldwide, with a corresponding worldwide incidence rate of 6059 cases per 100,000 people [21]. The International Diabetes Federation has reported a significant discovery, revealing that the global prevalence of diabetes stands at 537 million individuals, which corresponds to approximately one-tenth of the global population. In the year 2021, it is projected that one individual will succumb to diabetes every five seconds. Impaired glucose tolerance (IGT) is

well recognized as a significant hazard component in the development of T2DM, with a global prevalence of around 541 million people. By the year 2021, it is projected that diabetes will emerge as the primary cause of mortality in Southeast Asia, resulting in an approximate loss of 747,000 lives [22]. In light of the World Health Organization (WHO) report dated November 10, 2021, diabetes is responsible for an estimated 1.5 million global deaths, positioning it as the ninth major reason for death in the year 2019. The prevalence of this condition is observed in approximately 80% to 90% of individuals diagnosed with diabetes. The global prevalence of diabetes among adults is approximately 9.2%, with variations observed across different age groups, genders, and populations. There are currently 425 million people living with diabetes worldwide, according to estimates. However, this estimate is anticipated to increase significantly to 629 million by the year 2045.Death rates due to diabetes are rising day by day. Diabetic complications and renal disease killed almost 2 million people worldwide this year (WHO, 2019) [20].The projected figure for this numerical value is anticipated to increase to 7079 by the year 2030.

The incidence of diabetes is increasing at a concerning pace. Over the course of the previous three decades, there has been a notable surge in the prevalence of diabetes, with a significant majority of individuals affected by this condition residing in developing nations. Individuals that experience social disadvantages within a certain nation are particularly susceptible to the aforementioned sickness [23]. According to estimates, 80 million people in Southeast Asia were predicted to have diabetes in 2017, and by 2045, that number is expected to climb significantly to 151 million people.The prevalence of diabetes in India is currently estimated to impact over 62 million individuals, constituting a proportion of more than 7.1% of the adult population. The mean age of onset is 42.5 years. Approximately one million individuals in India succumb to diabetes annually. The elevated prevalence can be attributed to a confluence of genetic vulnerability and the adoption of a high-calorie, sedentary way of life

among the expanding middle class in India. Chinese (8.4%) and Malays (11.3%) had lower diabetes prevalence rates than Indians (12.8%) [23].Body mass index (BMI), lack of physical exercise, excessive alcohol intake, genetic and epigenetic susceptibility, and cigarette smoking are among the factors that can influence insulin expression and function [21].DM arises from a multifaceted interplay of genetic, behavioral, and environmental determinants. The metabolic dysregulation that is linked to DM leads to secondary pathophysiologic alterations in various organ systems.By producing and secreting insulin, β-cells in the pancreas play a crucial role in maintaining blood glucose levels [24]. Hyperglycemia causes β-cells in the pancreas to die off (a process called apoptosis), leading to abnormalities in insulin secretion as well as glucose uptake [25].

India, a nation currently undergoing significant socioeconomic advancement and urbanization, bears a substantial portion of the worldwide burden of diabetes. Recent research findings indicate a swift progression of disease from impaired glucose tolerance to diabetes in the southern regions of India. In these areas, the occurrence of diabetes among adults has escalated to around 20% in urban communities and approximately 10% in rural communities [23]. The glycemic outcome in treated individuals deviates significantly from what is expected due to the notable discrepancy in the accessibility and affordability of diabetes care, coupled with limited awareness of the condition. Younger ages at the beginning and suboptimal glycemic management are factors that are likely to contribute to an increased incidence of vascular problems. Although it is not feasible to directly reverse economic prosperity in India, it is indeed possible to mitigate the consequences of the swift lifestyle transformations that accompany economic growth. These consequences can be effectively addressed and controlled through the implementation of culturally appropriate approaches, such as Ayurveda and yoga. By doing so, the escalating burden of diabetes can be alleviated [26]. The prevalence of diabetes in India is a growing concern, as approximately 8.7 percent

of those aged 20 to 70 are affected by this condition. The increasing prevalence of diabetes can be attributed to several factors, including rapid urbanization, the adoption of unhealthy lifestyles, poor dietary choices, tobacco consumption, and an extended life expectancy [20]. The global expenditure on diabetes and its associated consequences amounts to an estimated $966 billion. This expense continues to rise steadily, mirroring the increasing prevalence of both diabetic and pre-diabetic individuals worldwide [22].

1.4 Symptoms of DM

The symptoms of DM are observed,such as polyuria, turbidity in urine, polydipsia, polyphagia, weakness, cramps on walking, loss of libido, weight loss, joint pain, burning sensation in hands and feet,laziness,and excessive sleep [27].

1.5 Mechanism

1.5.1 Glucose metabolism (Inadequate and defective insulin secretion)

The transportation of glucose throughout the plasma membrane holds significant importance in biological processes [28]. The body uses glucose, which serves as the main energy source for its metabolic operations, to produce lipids, proteins, and carbs through metabolic processes.Among the numerous procedures that make up glucose metabolism are glycolysis,glycogenesis, glycogenolysis, and gluconeogenesis [29]. The circadian rhythm regulates blood glucose levels. In human beings, the optimal metabolic response to glucose occurs during the early hours of the day. This phenomenon arises due to the predominant activation of pancreatic beta cells during the morning hours, coupled with a substantial increase in glycogen storage throughout the evening period. In the postprandial period, adipose tissue exhibits a heightened sensitivity to the effects of insulin. The cycle of glucose metabolism consists of many daily patterns of energy consumption[30]. Typically, the fasting blood glucose concentration following a period of 3-4 hours without food intake falls within the range of 80-90 mg/dl. The average postprandial blood sugar level can increase to

approximately 120-140 mg/dL; however,usually, the body's feedback process takes two hours to return glucose levels to normal. In instances of severe malnutrition, the physiological mechanism known as gluconeogenesis facilitates the production of glucose within the human body. Hyperglycemia, or elevated blood glucose levels, causes the body to release insulin. At the same time, blood glucose levels fall as glucose is moved from the extracellular area into the intracellular compartment. On the other hand, a decrease in blood glucose secretion causes the production of glucagon, which increases blood glucose levels.As a result, it is possible to infer the clinical significance of the fact that inadequate and defective insulin secretion is the root cause of DM [30].

1.5.2 Glucose transport and defect in transport activity

Carrier proteins help to facilitate assisted diffusion, which is a controlled mechanism for transporting glucose across cellular membranes. Various types of glucose transporters exist, with glucose transporters (GLUT1–5) being of utmost significance. These cellular processes exhibit sensitivity to various metabolic stressors, such as stress hormones, growth factors, hypoxia, and hypoglycemia. Numerous signaling pathways are involved in the control of transporters. The process of glucose transport is essential for providing cells with the necessary energy or fuel required for metabolic activities. There are times when stress-related factors like growth hormones, toxins, the kinase signaling pathway, and inflammation can change the shape, expression, location, synthesis, and activity of transport proteins that control how glucose moves through the body. Certain alterations in glucose transport can either promote or exacerbate illnesses such as diabetes [31]. Defects and deficiencies in glucose transport and clearance are significant diseases associated with the development of T2DM and reduced glucose tolerance. People with T2DM are less able to move glucose through their bodies and get rid of it. People with T2DM are diagnosed based on an examination of the glucose transporter GLUT4, which depends on the presence of insulin.

Individuals diagnosed with T2DM have impaired glucose uptake in many bodily regions, including the brain, skeletal muscles, andvisceral adipose tissue. These specific areas are considered the most accurate markers for assessing insulin resistance [32].

1.5.3 Hormonal regulation for glucose metabolism

The secretion of glucagon and insulin from the pancreas controls the maintenance of levels of plasma glucose. The secretion of glucagon is stimulated by the condition of hypoglycemia through the activation of pancreatic α-cells. This activation then initiates processes such as glycogenolysis, gluconeogenesis, and lipolysis. The ultimate goal of these processes is to reestablish a blood glucose level that is within the normal range. On the other hand, in reaction to increased blood glucose levels, the pancreatic β-cells generate insulin, which facilitates the uptake of glucose for metabolic functions [33]. One of the primary factors exacerbating hyperglycemia in individuals with T2DM is the diminished production of insulin and the inability of the β-cells of the pancreas to meet the required levels. The etiology of continuous pancreatic β-cell failure is believed to be attributed to persistent elevations in plasma glucose levels, while strong insulin therapy has demonstrated the ability to enhance pancreatic β-cell responsiveness to glucose, insulin, and glucagon [34]. The activation of PI3K/Akt signaling cascades occurs upon the binding of insulin to insulin receptors. Insulin signaling triggers glycogen synthase kinase 3 (GSK3) activation in adipose tissues and skeletal muscle cells. This activation leads to the inhibition of glycogen production and makes it easier for vesicles carrying GLUT-4 to translocate to the cell membrane, thereby promoting glucose uptake. When the insulin signaling cascade is turned on in adipocytes, hormone-sensitive lipase (HSL) protein is stopped from working, which slows down the process of lipolysis. Furthermore, it has been observed that gluconeogenesis is impeded, although protein synthesis and lipogenesis are boosted [33].

1.6 Pathophysiology of DM

1.6.1 Oxidative stress

High glucose concentrations have the potential to induce the generation of free radicals. A major factor in the pathophysiology of DM is the generation of free radicals, or reactive oxygen species (ROS), and the consequent development of oxidative stress.Reactive oxygen species (ROS) production, which subsequently results in oxidative stress, is the most important factor influencing the advancement of DM. This includes the presence of superoxide free radicals, hydrogen peroxide, and singlet oxygen, as well as nitrogen-based free radicals like nitric oxide and peroxynitrite [35]. The utilization of ROS has been found to have deleterious effects on cellular components, including DNA damage, damage to mitochondria and other organelles, misfolding of proteins, and malfunction of neural synapses [36–37]. Oxidative stress has been observed to lead to an increase in glutathione levels and an elevation in lipid peroxidation [38]. Advanced glycation end products (AGEs), which are known to cause several problems in people with DM, cause reactive oxygen species (ROS) to form and to start caspases working [39]. It has been suggested that the onset of DM is associated with the generation of ROS. This is because ROS causes adipocytes to lose mitochondrial proteins and DNA. The stimulation of glucolipotoxicity in β-cells of the pancreas leads to the initiation of oxidative stress and impairment of mitochondrial activity, which in turn result in the release of cytochrome c, activation of caspases, and ultimately apoptosis in the cells [40]. Oxidative stress occurs as a result of the formation of highly oxidized and glycated low-density lipoproteins (LDL) during DM, which causes the activation of apoptosis and autophagy. Apoptotic cell death in the context of DM is observed in various cells, including pancreatic β-cells [41], cardiomyocytes, endothelial cells, renal cells, and even neurons [42]. Autophagy has the potential to confer both cytoprotective and harmful effects on cell viability in the context of DM. In times when blood glucose levels are

elevated, autophagy may compromise endothelial progenitor cell function and cause endoplasmic reticulum and mitochondrial oxidative stress.Consequently, this blocks the production of fresh blood vessels. Diabetes-related heart and liver tissue loss has been linked to increased autophagy activity. However, in certain circumstances, autophagy might have diminished influence as a mediator of cellular damage [43], and instead, it could potentially yield advantageous outcomes. The process of autophagy may be needed to get rid of misfolded proteins and mitochondria that don't work right. This would keep beta cells from breaking down and causing diabetes. The occurrence of autophagy deficiency due to haploinsufficiency of the necessary Atg7 gene has been found to be connected with enhanced insulin resistance accompanied by higher lipid levels and inflammation [44].

1.6.2 Insulin resistance

A major characteristic of DM is the diminished efficacy of insulin in its action on target tissues, particularly muscle, liver, and adipose tissue. This phenomenon arises from an association between genetic predisposition and obesity [45]. Insulin resistance is a concept that is subject to relativity, as excessive levels of insulin in the bloodstream can effectively restore normal levels of glucose in the plasma. Insulin resistance hinders the ability of insulin-sensitive tissues to effectively utilize glucose and leads to an elevation in hepatic glucose production, hence contributing to the occurrence of hyperglycemia. The primary factor contributing to elevated levels of fasting plasma glucose (FPG) is an increase in hepatic glucose production, while postprandial hyperglycemia is mostly caused by reduced peripheral glucose use. Within the context of skeletal muscle, it has been observed that the reduction in nonoxidative glucose use, specifically glycogen synthesis, is more pronounced compared to oxidative glucose metabolism via glycolysis [46].

The levels of insulin receptors and tyrosine kinase activity within skeletal muscle exhibit a reduction, which is likely a consequence of hyperinsulinemia rather than an inherent

underlying dysfunction [47]. Hence, it can be inferred that the primary factor contributing to insulin resistance is the presence of "postreceptor" abnormalities in the process of insulin-regulated phosphorylation and dephosphorylation [48–49]. One possible consequence of a failure in PI-3-kinase signaling is a decrease in the translocation of GLUT4 across the plasma membrane. As a result, it is possible that hyperinsulinemia may enhance insulin action via these mechanisms, potentially increasing the development of diabetes-associated diseases like atherosclerosis [50].

The growth of adipocyte mass results in elevated amounts of systemic free fatty acids and other compounds released by fat cells. Higher production of free fatty acids and some adipokines has been linked to the generation of insulin resistance in both skeletal muscle and hepatic cells [51].

As an illustration, it was observed that free fatty acids have a negative impact on glucose utilization within skeletal muscle while concurrently stimulating glucose synthesis in the liver and impairing the functioning of β-cells. In addition to the aforementioned point, it is worth noting that adiponectin, a peptide that enhances insulin sensitivity, has a decrease in levels in individuals with obesity. This reduction in adiponectin levels has the potential to contribute to the generation of insulin resistancevia the liver. The presence of adipocyte products along with adipokines can induce an inflammatory condition, potentially elucidating the reason behind the frequently seen elevation of inflammation markers like IL-6 and C-reactive protein in individuals with DM [48].

1.6.3 Impaired insulin secretion

The secretion of insulin and its sensitivity are interconnected. The release of insulin experiences an initial rise as a reaction to insulin resistance, with the purpose of maintaining normal glucose tolerance. At the onset, the impairment in insulin secretion is minimal and specifically affects the secretion of insulin in response to glucose stimulation. The

continuation of sensitivity to non-glucose secretagogues, like arginine, is seen. Over time, the abnormalities in insulin secretion evolve to a state characterized by significantly insufficient levels of insulin secretion [46, 52].

1.6.4 Increased hepatic glucose and lipid production

The incapacity of high insulin levels to efficiently suppress gluconeogenesis is reflected in the liver's insulin resistance, leading to elevated blood glucose levels during fasting and reduced glycogen storage from the liver after a meal. The amount of glucose produced by the liver increases noticeably in the early stages of diabetes development.This is thought to happen after insulin secretion problems, such as insulin resistance via the skeletal muscle [53].

The course of T1DM is contingent upon the pace at which the immune-mediated breakdown occurs in the pancreatic β-cells. Diabetic ketoacidosis (DKA) is a severe illness observed in diabetic individuals (Fig. 1). The human body exhibits an accelerated breakdown of adipose tissue beyond the typical rate, which subsequently leads to the liver's conversion of fat into ketones, resulting in acidification of the bloodstream. DKA is a common occurrence in pediatric and young adult populations due to the loss of β-cells, often serving as the initial presentation of this disease [9]. The condition has a steady progression, characterized by a concurrent rise in fasting plasma glucose concentrations.

However, as a result of a progressive decline in insulin production, individuals develop a reliance on exogenous insulin when faced with extreme hyperglycemia and ketoacidosis. In addition, as a result of the seriousness and advancement of T1DM, individuals afflicted with this condition rely entirely on insulin therapy [9]. The pathophysiology of T2DM is defined by both insulin deficiency and insulin resistance, which have been connected to the presence of inflammatory cytokines in the plasma and elevated fatty acidlevels. These factors contribute to impaired glucose transport into related target cells, heightened lysis of fat, and

enhanced hepatic glucose production [54]. The occurrence of elevated blood sugar levels, known as hyperglycemia, is a result of excessive glucagon release from alpha cells and insufficient insulin secretion from beta cells. In the context of T2DM, the condition is identified by the inability of patients to enhance insulin production as a compensatory response to insulin resistance, resulting in elevated glycemic levels [54].

Due to its gradual and silent progression and occasionally occurring low hyperglycemia, T2DM has the potential to go undetected during its early stages. The manifestation of additional symptoms such as polydipsia, weight loss, fuzzy eyesight, and growth retardation is observed in the later andmore advanced phases of the progressionof diabetes. The etiology of this particular kind of diabetes is believed to be influenced by both hereditary and environmental factors. Diabetes frequently exhibits associations with a range of lifestyle factors, including inadequate dietary habits, an older age, insufficient physical activity, a familial history of diabetes, excessive body weight, and prior gestational diabetes mellitus in women, as well as pathophysiological disorders such as atherosclerosis, hypertension, and dyslipidemia [9].

Gestational diabetes mellitus refers to the diagnosis of diabetes mellitus or impaired glucose tolerance during the second-third trimester of pregnancy. During the earlier stages of pregnancy, it has been observed that fasting and postprandial blood concentrations are lower than the typical values. However, in the third trimester, there is a significant exponential increase in blood glucose, which serves as confirmation of the presence of gestational diabetes mellitus [9].

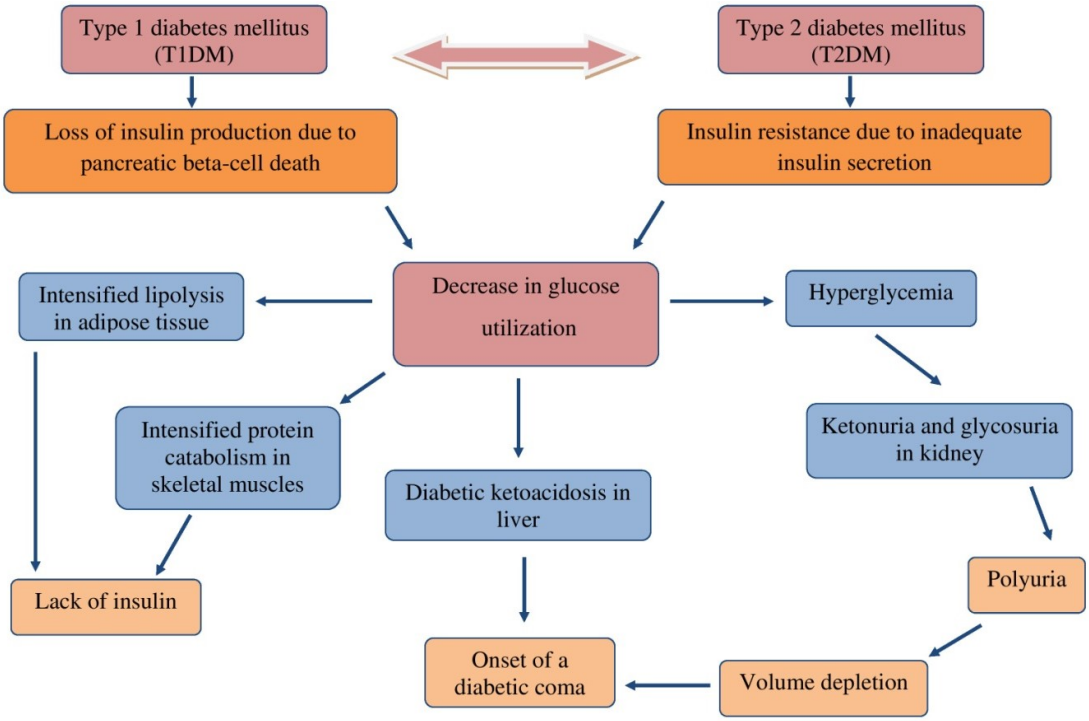

Figure 1 Pathophysiology of diabetes mellitus

1.7 Tests for diabetes

A variety of tests, some of which are described and explained more below, can be used to diagnose diabetes. The individuals in question are:

1. The HbA1C test is a diagnostic method utilized to assessthe glycemic statusof a diabetic patient. The mean glycemic level over a period of two to three months has been found to be both effective and useful in the evaluation of patients with diabetes or those at risk of diabetes-related complications [30].

2. The fasting blood glucose (FBG) test is a diagnostic procedure that measures blood glucose levels after a period of fasting. To ensure precision, the examination is conducted throughout the morning hours, following a fasting duration of around 8 hours. According to reference [55], a blood glucose level exceeding 126 mg/dL is indicative of diabetes.

3. The random plasma glucose measurement involves the collection and subsequent analysis of a blood sample following the ingestion of a meal. Diabetes is often indicated when the blood glucose level exceeds 200 mg/dL [30].

4. The oral glucose tolerance test (OGTT) for diabetic patients is a diagnostic procedure performed in the medical field to assess the rate at which glucose is metabolized in the patient. This test involves the administration of glucose, followed by the analysis of a blood sample to determine the efficiency of glucose clearance. This diagnostic tool is employed for the purpose of screening individuals for T2DM.

5. The measurement of C-peptide assesses the functionality of the pancreatic beta cells. The assessment and examination of urine and serum samples are conducted with the purpose of aiding in the diagnosis and management of DM [30].

6. Autoantibodies, such as islet autoantibodies, insulin autoantibodies, and anti-glutamic acid decarboxylase (GAD) autoantibodies, show that someone with T1DM has an autoimmune reaction. Confirmation of T1DM is established through the detection of autoantibodies specific to diabetes within the bloodstream [30].

1.8 Treatment of DM

1.8.1 Pharmacological agents

Although glycemic control can be improved with lifestyle modifications, pharmaceutical medication is required for the long-term care of DM.In the treatment of T2DM, inhibitors are a category of oral pharmacological agents. These inhibitors encompass various classes, such as bile acid sequestrants, dopamine agonists, meglitinides,sulfonylureas, metformin (a biguanide), oral glucagon-like peptide 1 (GLP-1) receptors,thiazolidinediones,dipeptidyl peptidase IV (DPP-IV) inhibitors, sodium-glucose transport protein 2 (SGLT2) inhibitors, and alpha-glucosidase inhibitors [56].

1.8.1.1 Pharmacological treatment of type 1 diabetes

Insulin therapy serves as the fundamental approach to managing T1DM. Research has led to the utilization of non-insulin supplement medication in laboratory and clinical settings for the purpose of exploring novel therapeutic approaches for diabetes. However, it is worth noting

that metformin, classified as a biguanide, remains the prevailing pharmaceutical agent employed for diabetes management. Occasionally, it is complemented by the administration of amylin analogues, GLP-1 receptor agonists, andSGLT2 inhibitors. These pharmacological drugs have been found to have positive effects and effectively manage T1DM in patients [57].

1.8.1.2 Pharmacological treatment of type 2 diabetes

The pharmacological interventions employed for the management of T2DM patients exhibit several modes of action aimed at ameliorating hyperglycemia through the reduction of blood glucose levels [56].

1. Sulfonylureas are a class of pharmaceutical agents known as insulin secretagogues that have been widely employed in the therapeutic management of individuals diagnosed with DM. The majority of these substances undergo hepatic metabolism, with occasional elimination through renal excretion [56]. Sulfonylureas enhance insulin synthesis by the pancreatic β-cells, independent of blood glucose levels [58].In addition, it has been observed that sulfonylureas have the ability to prevent the release of glucagon, increase insulin sensitivity within peripheral tissues (skeletal muscles and adipose tissues), and decrease insulin clearance via the liver [56].

2. Meglitinides are pharmacological agents that enhance the excretion of insulin from the pancreatic cells, exhibiting a glucose-dependent mechanism. This characteristic aspect of meglitinides serves to mitigate the possibility of experiencing hypoglycemia. The medication has a brief period of efficacy and can be taken in a manner that aligns with the rise in blood glucose levels following a meal [56].

3. Metformin, also known as glucophage, has been found to enhance the sensitivity of the liver to insulin and decrease hepatic glucose production. Furthermore, it has been observed that this intervention leads to a decrease in insulin resistance within the peripheral tissues

through the reduction of free fatty acids, triglycerides, and elevated blood glucose levels [56]. The antihyperglycemic activity of the substance is executed without exerting any influence on the secretion of insulin [59]. Additionally, it enhances the consumption of glucose in the gastrointestinal tract and stimulates the release of GLP-1. Metformin is frequently used as the initial pharmaceutical intervention for diabetic management due to its cost-effectiveness, efficacy, and few adverse reactions [56].

4. SGLT2 antagonists are a type of drug that works on the sodium-glucose transport protein 2 in the renal tubules to stop glucose from being reabsorbed and make more glucose leave the body through urine. Oral anti-diabetic drugs are a category of medications that are prescribed to adult patients diagnosed with T2DM with the aim of reducing blood glucose levels. According to a study [56], it is unaffected by insulin resistance or variations in levels of insulin inside the body.

5. GLP-1 is synthesized and bound inside the enteroendocrine cells located in the ileum as well as the colon. The discharge of food in the gastrointestinal tract (GIT) is triggered by neural and hormonal factors. The incretin hormone GLP-1 has been shown to boost the secretion of insulin by β-cells of the pancreas and reduce the release of glucagon by α-cells of the pancreas in instances where blood glucose levels exceed the typical range [56].

6. Pramlintide, also known as Symlin, is a pharmaceutical agent that is used for therapeutic purposes. Pramlintide is a pharmacological compound that is chemically derived from amylin, a naturally occurring peptide hormone. Due to its inherent properties, this substance exhibits solubility and is commonly taken via the oral route. The pancreas releases amylin alongside insulin in response to dietary stimulation. According to previous research, it has been observed that this particular intervention has the ability to decrease the release of glucagon after a meal, delay the process of stomach emptying, and inhibit the sensation of hunger [56].

7. Bromocriptine-QR has been shown to have the effect of reducing insulin sensitivity as well as resistance, resulting in a decline in glucose synthesis in the liver and an elevation in glucose disposal. It exhibits a lack of insulin elevation, hence demonstrating efficacy in individuals who possess endogenous insulin production yet exhibit insulin resistance. The use of bromocriptine-QR, either as a single or in combination therapywith other antihyperglycemic medications, has been shown to enhance glycemic levels in individuals diagnosed with T2DM [56].

8. Thiazolidinediones (TZDs) have been shown to effectively mitigate insulin resistance while concurrently stimulating the insulin response. Thiazolidinediones (TZDs) have been shown to improve glycemic management and have the potential to help people with T2DM who have polycystic ovarian syndrome, atherosclerosis, and certain cardiovascular diseases. Nevertheless, the occurrence of adverse effects such as weight gain and osteoporosis can have significant implications, hence restricting its application [56].

DM is a chronic disorder caused by a range of risk factors and significant effects that have a profound influence on the life standards ofindividuals. Still, the use of research studies has made a big difference in improving techniques for predicting the future, diagnosing the disease, treating it, and managing the disease as a whole in all of its forms. Understanding the underlying mechanisms and processes that underlie the development and progression of a medical condition, as well as the ability to accurately determine the likely outcome and identify the specific nature of the condition, have a significant impact on deciding which treatment plan is best to follow. It is noteworthy that pharmacological treatments exhibit varying side effects, yet recent research contributes to the appropriate utilization and integration of these medications. One effective approach to mitigating the risk of developing the condition is adhering to a suitable dietary regimen, engaging in regular physical exercise, and actively monitoring and managing glucose levels to ensure their maintenance within

healthy parameters. In the present time, significant progress has been made in recognizing the metabolic phases of diabetes, leading to notable advancements in the therapeutic approach for this life-threatening condition. Currently, there exist therapeutic approaches that enable the treatment and management of insulin resistance and insulin secretion through the utilization of natural herbs.

1.8.2 Traditional and Ayurvedic medicine

Indigenous, traditional, and folk medicine encompasses a variety of therapeutic modalities, including medicine based on herbs, Ayurveda, Siddha, Unani, traditional Chinese, Islamic, ancient Iranian, traditional Vietnamese, traditional African medicines, and acupuncture, muti, Ifa, and other techniques used globally to treat DM [60]. The prevalence of individuals affected by diabetes mellitus (DM) is on the rise, particularly in developing nations where access to economical and efficacious therapies is limited. Consequently, there is an immediate need to explore alternative therapeutic interventions. Numerous conventional pharmaceuticals have been synthesized based on prototype compounds found in medicinal plants. Metformin, the present oral glucose-lowering pharmacological drug, was derived from the medicinal plant *Galegaofficinalis* L. (Fabaceae) for the treatment of diabetes. *Galegaofficinalis* is known to contain a significant amount of guanidine, which has been identified as a hypoglycemic compound [61]. Advancements in the treatment or prevention of illnesses are dependent upon a more comprehensive understanding of the fundamental molecular pathophysiology and the factors that influence it. Undoubtedly, advancements in the fields of genetics, signal transduction, and the neurology of energy intake as well as metabolism hold the potential to facilitate a more accurate and potentially customized therapeutic strategy, enabling us to focus on the underlying issue.

The utilization of herbal medications has significant importance in accelerating the development of efficacious therapeutic agents. Moreover, it has demonstrated its capacity to

minimize the development of several disorders. There is no indication that people used artificial medicines in the distant past to treat their illnesses, despite the fact that earlier humans began to study diseases and their cures [62]. Still, they had difficulties effectively utilizing the many resources available at the time. Plants and animals were the predominant components observed in their immediate environment. A variety of plants were identified as viable options for use as dietary supplements, with certain species possessing both toxic properties and medicinal significance [63]. With this knowledge in mind, the transmission of herbal remedies occurred across generations as a form of traditional medicine. Herbal medicine has been recognized and utilized since ancient civilizations. This phenomenon can be attributed to the widespread belief that numerous herbal remedies are reputedly devoid of adverse reactions. Moreover, it is an established reality that the process of uncovering the novel synthetic medication is both laborious and financially burdensome. As previously mentioned, herbal remedies have been utilized in every aspect of healthcare since ancient civilizations, and their popularity continues to grow steadily. WHO estimates that more than 75% of people worldwide rely on herbal medicines to stay healthy [64]. According to the WHO, traditional medicine is defined as:

"The health practices, approaches, knowledge, and beliefs incorporating plant, animal, and mineral-based medicines, spiritual therapies, manual techniques, and exercises, applied singularly or in combination to treat, diagnose, and prevent illnesses or maintain well-being."

Herbal medicines have been found to be effective in treating various disorders, with a particular emphasis on investigating the antioxidant and anti-inflammatory properties of these remedies [65–67]. Pharmaceutical companies worldwide are presently engaged in comprehensive research on plant-based substances due to their potential therapeutic properties [68]. Still, among the estimated range of 250,000–400,000 plant species, only 6%

have undergone scientific examination to determine their biological activity, while approximately 15% have been subject to investigation into their phytochemical composition. The topic of herbal medicines presents significant research requirements, particularly in the field of identifying active molecules derived from plant sources, which remains an immense challenge. It is necessary to establish empirical evidence through study to ascertain the superiority of whole herbs and extracted chemicals. Currently, there is a substantial demand to promote the growth of pharmacological interventions that are characterized by better safety profiles, with the aim of effectively addressing a wide range of medical conditions. Consequently, there is an increasing trend towards the pharmacological assessment of diverse botanical species and polyherbal formulations (PHF) employed in traditional medicinal practices [69].

In order to promote health and welfare, the traditional medical system of Ayurveda employs a variety of techniques. The primary objective of Ayurveda healthcare is to restore the equilibrium of the physical, mental, and emotional aspects of individuals, enhancing their well-being, eliminating ailments, and solving existing illnesses. The demand for alternative and herbal medicines among patients is experiencing significant growth, as evidenced by a substantial increase in the number of individuals accessing such treatments [70–72].Ayurveda,which is defined through systematic and fundamental regulation by multiple medicinal plants such as PHF, containing multiple active components, actingon multiple pathways, and targeting multiple targets, is thus having an increasing impact on the development of drugs [73-74]. About 600 plants are thought to have anti-diabetic effects according to the Ayurvedic medical system, which is described in old Indian texts like *CharakSamhita*, *MahdhavNidan*, *AshtangaHridayaChikitsa*, and *AstangSanghra*. A diverse range of active compounds originating from plants, which comprise various phytochemicals,

have consistently shown hypoglycemic activity.These compounds may have applications in the treatment of DM [75–77].

The Indian botanicals that have been extensively studied and are widely recognized for their efficacy in managing diabetes include:*Terminaliabellerica, Swertiachirayita, Terminaliachebula, Allium cepa, Allium sativum,Aloevera, Berberisaristata, Phyllanthusemblica, Trigonellafoenum,Cajanuscajan, Gymnemasylvestre, Caesalpiniabonducella, Ficusbengalenesis, Syzigiumcumini, Momordicacharantia, Pterocarpusmarsupium, Cyperusrotundus*,*Tinosporacordifolia, Cocciniaindica,Annonasquamosa*,*Ocimum sanctum,*etc.

Herbal remedies have been employed as therapeutic interventions for diabetes, either as single anti-diabetic treatments or in conjunction with pharmacological hypoglycemic agents. The Ayurvedic classic known as the "***SarangdharSamhita***" highlights the concept of synergism as a fundamental aspect of PHF. The therapeutic spectrum of this treatment is extensive, exhibiting a multi-targeted impact, a limited occurrence of adverse effects, and widespread accessibility [78]. A polyherbal formulation (PHF) involves the combination of active components derived from various plants with the aim of treating diseases and mitigating associated negative effects. The concept of the PHF technique, as described in references [79–80], has the potential to significantly enhance the effectiveness of treating medical issues. The addition of PHF has the potential to improve the pharmacological activity of medicinal herbs and simultaneously decrease their concentrations, leading to a reduction in the occurrence of undesirable effects. The utilization of plant formulations and the combination of plant extracts has predominantly been employed as pharmaceutical agents as opposed to their individual usage.The Indian traditional medical system has developed several effective medicines for the treatment of diseases in accordance with advances in medicinal technology [81].For example,Madhumeghachurna, Naval churna, Seenthilchurna,

Avaraikudineer, Vilvakudineer, Abargaparpam, Abrakachendooram,Diabecon, Manomanichooranam, GSPF kwath, PF-4, Dashmoolarishta, and Triphalachurna are used in the treatment of diabetes [82].

Finding a treatment that may effectively treat diabetes, either on its own or in combination with other medicines, remains a difficult task. Therefore, our research aims to develop a polyherbal extract formulation with anti-diabetic properties. This formulation will consist of ethanolic extracts derived from specific plant parts, namely the pericarp of matured fruit from *Terminaliachebula* Retz. (from the Combretaceae family), the pericarp of dried ripe fruit from *Terminaliabellerica*Roxb. (also from the Combretaceae family), the whole herb of *Andrographispaniculata*Nees. (from the Acanthaceae family), the dried stem of *Berberisaristata* DC. (from the Berberidaceae family), the dried leaves of *Nyctanthesarbor-tristis* L. (from the Oleaceae family), and the dried leaves of *Premnaintegrifolia* L. (from the Lamiaceae family).

1.8.2.1 *Terminaliachebula*Retz.

Terminaliachebula, often referred to as black or chebulicmyrobalan, is a botanical species belonging to the *Terminalia* genus. It is indigenous to South Asia, specifically found in regions extending from India and Nepal to the southwestern part of China (Yunnan). Additionally, it can be found in southern areas such as Sri Lanka, Malaysia, and Vietnam. The distribution of this species in India encompasses the sub-Himalayan region, extending from the Ravi River in the west to West Bengal and Assam in the east. This tree grows naturally in Bengal, the central provinces of India, and the northern forests; it is also prevalent in Mysore,Madras, and the southern region of the Bombay presidency [83–84]. Table 1 displays the taxonomic categorization of *Terminaliachebula* and the medicinal uses [84] of its fruit (Fig. 2).

Table 1 Taxonomic classification, common name, phyto-chemical, uses, and therapeutic benefits of ingredient medicinal plants of PHE

Kingdom	Plantae	Plantae	Plantae	Plantae	Plantae	Plantae
Phylum	Tracheophyta	Tracheophyta	Tracheophyta	Tracheophyta	Tracheophyta	Tracheophyta
Class	Magnoliopsida	Magnoliopsida	Magnoliopsida	Magnoliopsida	Magnoliopsida	Magnoliopsida
Order	Myrtales	Myrtales	Lamiales	Ranunculales	Lamiales	Lamiales
Family	Combretaceae	Combretaceae	Acanthaceae	Berberidaceae	Oleaceae	Lamiaceae
Genus	*Terminalia*	*Terminalia*	*Andrographis*	*Berberis*	*Nyctanthes*	*Premna*
Species	*T. chebula* Retz.	*T. bellirica*Roxb.	*A. paniculata*Nees.	*B. aristata* DC.	*N. arbor-tristis* L.	*P. integrifolia* L.
Comm. Name	Harra	Bahera	Kalmegh	Daruharidra	HarSingar	Agnimantha
Phyto-chemicals	Chebulic, gallic, ellagic acids, luteolin, etc.	Tannic, gallic, ellagic,chebulagic acids, etc.	Andrographolide, neoandro-grapholide, etc.	Berberine, oxyberberine, berbamine, etc.	Oleanolic, nyctanthic, tannic acids, etc	Luteolin, linoleic acid, β-sitosterol, eugenol, etc.
Uses	Stomachic, Tonic, Antispasmodic, Anti-inflammatory	Laxative, Astringent, Antipyretic, Anti-inflammatory	Anticancer , Antihepatitis, Antihyperglycemic	Antidiabetic, Antipyretic, Stomachic	Anticancer, Diuretic, Anti-inflammatory	Laxative, Bitter, Pungent
Therapeutic benefits	Diabetes, Digestive, Heart diseases	Hepatitis, Diabetes, Bronchitis	Fever, Torpid liver, Diabetes, Hypertension	Inflammation, Liver diseases	Rheumatism, Liver diseases,Bile disord.	Gonorrhoea, Fever, Tumours, Pile

Table 1continu……

Kingdom	Plantae	Plantae	Plantae	Plantae	Plantae
Phylum	Tracheophyta	Tracheophyta	Tracheophyta	Tracheophyta	Tracheophyta
Class	Liliopsida	Equisetopsida	Asteride	Magnoliopsida	Magnoliopsida
Order	Poales	Malpighiales	Scrophulariales	Ranunculales	Cucurbitales
Family	Cyperaceae	Phyllanthaceae	Scrophulariaceae	Menispermaceae	Cucurbitaceae
Genus	*Cyperus*	*Emblica*	*Picrorhiza*	*Tinospora*	*Citrullus*
Species	*C. rotundus* L.	*E. officinalis*Gaertn.	*P. kurroa*Royle	*T. cordifolia*	*C. colocynthis* L.
Comm.Name	Nagarmotha	Anwla	Kutki	Giloy	Indrayana
Phyto-chemicals	p-Cymol, α-Cyperolone, β-Cyperone,Myristic acid, Oleic acid etc.	Ascorbic, gallic, ellagic acids, pyrogallol, corilagin, etc.	Picroside I-IV, kutkin, apocyanin, androsin, vanillic acid, etc.	Berberine, tinosporine, magnoflorine, jatrorrhizine, etc.	Cucurbitacin, isovitexin, isoorientin, isosaponarin, etc
Uses	Diuretic, Antispasmodic, Carminative, Anti-microbial, Anti-obesity	Laxative, Diuretic, Antipyretic, Liver and Hair tonic, Stomachic	Anticancer , Antifungal, Antidiabetic, Antiasthmatic, Anti-inflammatory	Anti-diabetic, Antispasmodic, Anti-inflammatory, Anti-stress	Anticancer, Diuretic, Anti-bacterial, Anti-inflammatory, Anti-diabetic
Therapeutic benefits	Diabetes, Digestive, Epilepsy, Fever, Heart diseases	Hepatoproective, Antihypercholesterolemia, Cardioprotective	Cancer, Cardiovascular, Diabetes, Hepatoprotective	Immunomodulation, Diabetes, Cancer, HIV	Gastrointestinal, pulmonary, Cancer, Diabetes, Edema

1.8.2.2 *Terminaliabellirica*Roxb.

Terminaliabellirica, commonly referred to as baheda, bahera, behada, beleric, or bastard myrobalan, is a substantial deciduous tree belonging to the Combretaceae botanical family. The tree species under review is frequently found in the plains and lower hills of South and Southeast Asia and is cultivated as a roadside tree in these regions [85]. Table 1 displays the taxonomic categorization of *Terminaliabellirica*and the medicinal uses [86] of itsfruit (Fig. 2).

1.8.2.3 *Andrographispaniculata*Nees.

Andrographispaniculata, sometimes referred to as creat or green chiretta, is a perennial herbaceous plant from the Acanthaceae family. It is indigenous to India and Sri Lanka [87]. The plant in question is extensively grown in regions of southern and southeast Asia, where it has been traditionally regarded as a potential remedy for bacterial infections and certain ailments. The utilization of plant components for various purposes has primarily focused on leaves and roots, with occasional instances where the entire plant is employed [88–89]. Table 1 displays the taxonomic categorization of *Andrographispaniculata*and the medicinal uses [90] of itswhole herb (Fig. 2).

1.8.2.4 *Berberisaristata*DC.

Berberisaristata is a shrub that belongs to the Berberidaceae family and the Berberisgenus of plants. It is also known by other names, including Mara manjal,Indian barberry, chutro, sumbal, and tree turmeric. There are roughly 450–500 shrub species in the genus that can be either deciduous or evergreen. The majority of these shrubs are found in Asia, America, and Europe, in temperate and subtropical regions. The Himalayan regions of India and Nepal are habitatsfor*B. aristata*. Furthermore, this species can be seen in its native environment in the Nilgiri Mountains of southern India and Sri Lanka [91–93]. Table 1 displays the taxonomic classification of *Berberisaristata*and the medicinal uses [93] of itsstem (Fig. 2).

1.8.2.5 *Nyctanthesarbor-tristis* L.

Nyctanthesarbor-tristis, frequently referred to asthe night-flowering jasmine, is a botanical species belonging to the Nyctanthes genus. It is indigenous to the regions of South Asia and Southeast Asia. This particular plant is widely recognized by various names, including night-blooming jasmine, tree of grief, tree of sorrow, coral jasmine (in Burma or Myanmar), harsingar, and parijata (in India). Contrary to its colloquial designation, the aforementioned plant does not belong to the taxonomic genus Jasminum [94–96]. Table 1 displays the taxonomic classification of *Nyctanthesarbor-tristis*and medicinal uses [97] of itsleaf (Fig. 2).

1.8.2.6 *Premnaintegrifolia* L.

The species *Premnaintegrifolia* L. holds significant botanical and therapeutic value, being well recognized and utilized within the Ayurvedic, Siddha, and Unani medical traditions. The species exhibits widespread distribution along the Indian peninsula and the Andaman coast. The occurrence of this phenomenon has also been documented in the plains of Maharashtra, Gujarat, Assam, the Khasi Hills, and Tarai. The species is visible in the Mahanadi delta's tidal-affected areas of land in the state of Orissa. Several synonyms of *Premnaintegrifolia* L. are recognized, including *P. serratifolia* L., *P. corymbosa* (Burm. f.), and *P. obtusifolia* R. Br. (98–99). Table 1 displays the taxonomic categorization of *Premnaintegrifolia*and the medicinal uses [98] of itsleaf (Fig. 2).

1.9 Current drug (PHE) targets for DM

Several plants have been shown in traditional medical systems to be beneficial for the curative purposes of various kinds of systemic illnesses. Traditional medicine confronts a number of major challenges, one of which is a lack of total standardization. Despite the fact that many traditional and indigenous medical systems are more effective than the modern system of medicine, these systems suffer from a lack of thorough uniformity.The World Health Organization (WHO) has put an emphasis on the significance of guaranteeing the

scientific validity of herbal medicines and developing, putting into practice, and ensuring compliance with solid scientific practices [100].

Figure 2 Medicinal plants and crude drugs of PHE.**1**) *Terminaliachebula*, **2**) *Terminaliabellirica*, **3**) *Andrographispaniculata*, **4**) *Cyperusrotundus*, **5**) *Citrulluscolocynthis*, **6**) *Tinosporacardifolia*, **7**) *Berberisaristata*, **8**) *Nyctanthes arbor-tristis*, **9**) *Premnaintegrifolia,***10**) *Picrorhizakurroa*, and **11**) *Emblicaofficinalis*

As previously stated, the herbs possess antioxidant activity, as elucidated in the previously mentioned papers. Therefore, it is possible to incorporate all of these components in order to create a novel PHE with a synergistic impact. The selection of medicinal herbs utilized in this study was focused on their previously documented pharmacological effects, which can be described as follows: The bioactive phytochemicals, antioxidants, and pharmacological activities of *Terminaliachebula* Retz. (TC) have been extensively studied [101–102]. *Terminaliabellirica*Roxb. (TB) has also been investigated for its phytopharmacology, antioxidants, and therapeutic potential [103–104]. Ethnobotanical, phytochemical, and pharmacological aspects of *Andrographispaniculata*Nees. (AP) have been explored [90, 105]. Similarly, *Berberisaristata* DC. (BA) has been the subject of research on its phytochemical composition, antimicrobial properties, antioxidant potential, and clinical updates [106–107]. *Nyctanthesarbortristis* L. (NA) has been examined for its bioactive compounds and its biological activities [108–109]. Lastly, *Premnaintegrifolia* L. (PI) has been studied for its antimicrobial, analgesic, antidiabetic activities, and antioxidant properties [110–111]. The present focus in the treatment of diabetic patients lies in utilizing the potent antioxidant effects exhibited by these medicinal plants.

1.9.1 Phytochemical content

Pharmaceuticals originating from botanical sources are commonly recognized as the primary means of avoiding sickness and mitigating its consequences [66]. Synergistic polyherbal formulations that contain a number of bioactive phytoconstituents may be more effective at treating diabetes because they can target more than one biological pathway [112]. Recent advancements in the field of pharmacology have yielded novel natural medications that exhibit a reduced occurrence of side effects compared to conventional therapeutic interventions. Consequently, individuals afflicted with diabetes now have access to more cost-effective and efficacious treatment alternatives. Scientists have redirected their focus

towards natural products, specifically pharmaceuticals derived from phytochemicals, which are abundantly present in various fruits, cereals, vegetables, and medicinal herbs [113]. The potential advantages of incorporating medicinal plants, with their diverse array of bioactive compounds, into the treatment regimen of individuals with diabetes have been suggested as a means to enhance their overall well-being [114]. Polyherbal medications have gained popularity in Asian cultures and other regions due to their affordability, safety, and therapeutic effectiveness. The enrichment of phytochemicals such as alkaloids, flavonoids, glycosides, and other compound groups with unique modes of action for the treatment of diabetes is the reason for this [112]. Various techniques, such as chromatography and spectroscopy, can be employed to ascertain and approximate the enrichment of phytochemicals in medicinal plants.

Several methods can be used to analyze phytoconstituents, such as high-performance thin-layer chromatography (HPTLC),gas chromatography-mass spectroscopy (GC-MS), liquid chromatography-mass spectroscopy (LC-MS), high-performance liquid chromatography (HPLC), high-resolution mass spectroscopy (HRMS), and others [114].Nowadays, one of the most powerful analytical methods utilized for phytochemical and biomedical determination is called high-performance thin layer chromatography (HPTLC), which is an upgraded variant of the versatile analytical method TLC. This method is regarded all over the world as one of the most effective procedures. Because of advancements in technology, HPLC and HRMS are now possibly used to recognize, investigate, and separate these bioactive molecules [115]. People in today's world are increasingly falling ill as a result of the use of herbal treatments all over the world that contain heavy metals. It is conceivable for heavy metals to be found in pharmaceutical plant materials originating from anthropogenic activities such as agriculture, industrial waste, or natural sources. The presence of these metals should be avoided if possible. The toxicity of heavy metals in the products of medicinal plants has been related to

a broadarea of negative consequences for health, involving the functioning of the liver, kidney, and heart, as well as mortality. There is a lot of evidence that shows how hazardous heavy metals are to humans [116]. Lead (Pb), arsenic (As), nickel (Ni), cadmium (Cd), as well as mercury (Hg), all of which are exceptionally hazardous to human health, tend to build up in internal organs over time [117]. Indeed, proper investigation for heavy metals in plant-based products is vital because the acceptable consumption range for these substances is quite narrow, falling somewhere between adequate quantities and excessive use. In several studies, the most typical technique, inductively coupled plasma mass spectrometry (ICP-MS), was utilized to measure the amount of these heavy metals in herbal products [118]. It is easy to handle, needs a small volume of sample, and has low detection limits.For the purpose of determining the amount of heavy metals present, an approach that first involved microwave acid digestion and then utilized ICP-MS was utilized for this study. In the older scientific literature, the idea of polyhedral formulation is discussed at length. When compared to the use of a single herb, the therapeutic potential of the polyherbal formulation is superior and more extensive due to the inclusion of a greater number of bioactive components in predetermined quantities [115].

1.9.2 α-amylase and α- glucosidase enzymes

Pancreatic α-amylase plays a pivotal role as an enzyme in the hydrolysis of dietary carbohydrates, specifically starch, into easily absorbable monosaccharides within the gastrointestinal tract. The α-glucosidases further catalyze the degradation of these compounds into glucose molecules, which are subsequently absorbed and transported into the bloodstream. Hence, the inhibition of α-amylase and α-glucosidase enzymes can effectively impede the process of carbohydrate digestion, leading to a delay in glucose absorption and subsequently resulting in a decline in blood sugar levels [119]. In practical use, medicines such as acarbose, voglibose, and miglitol have been found to block the enzymes α-

glucosidase and α-amylase. However, it should be noted that these drugs are associated with the occurrence of undesirable side effects, including diarrhea,bloating, flatulence, and abdominal discomfort [119]. One therapeutic strategy for reducing postprandial hyperglycemia involves the use of drugs or dietary interventions that can block the activity of enzymes thathydrolyze carbohydrate, including α-amylase and α-glucosidase. This inhibition effectively delays the synthesis or absorption of glucose, thus contributing to the management of hyperglycemia after meals [120].

1.9.3 Free radical scavenging activity

As was previously said, a variety of free radicals, especially reactive oxygen species (ROS), possess the capacity to cause oxidative stress, which is the term used to describe the damage that can be done to cells. The body may be adversely affected by this oxidative stress via both direct and indirect ways. Numerous chronic complications marked by inflammatory processes, such as diabetes, liver cirrhosis [121], autoimmune diseases, oncogenic inflammation linked to tumors, and other inflammatory conditions like ocular damage, cataract formation, Alzheimer's disease, and progressive neurological degeneration [64], have been linked to oxidative stress. The first technique the body uses to fight off infection is the induction of an inflammatory response. Numerous cytokines and chemokines induce and/or amplify this response [122].Cytokines and immune signaling molecules are essential for managing the inflammatory process. To fight inflammation, the body's defense mechanism uses a variety of enzymes, including glutathione peroxidase (GSH), catalase, and superoxide dismutase (SOD). The ability of natural products to protect against excessive oxidative stress through inflammation further emphasizes their role in controlling oxidation by increasing the activity of enzyme-based antioxidants in cells. The response described above to tissue injury [123] is a commonly seen phenomenon that might cause effects if not managed appropriately. Activated T cells produce a vital pro-inflammatory cytokine called tumor necrosis factor-

alpha (TNF-α).Uncontrolled expression of TNF-α can lead to the development of severe and potentially hazardous inflammation. The implementation of antioxidant and anti-inflammatory strategies is crucial in mitigating the negative effects of inflammation and oxidative stress resulting from persistent infectious ailments [124–125].

1.9.4 Gut microbiotadysbiosis

The gut microbial population present in the intestine specifically metabolizes exogenous and endogenous substances into metabolites [126]. The microbiota of the gut and the metabolites have effects both in the gut and in the rest of the body because metabolites produced in the intestine are circulated throughout the body parts [127]. It is important to completely understand the gut-pancreas and gut-liver axes in order to figure out the mechanisms underlying a variety of pancreatic disorders, including diabetes mellitus, acute pancreatitis, cholangitis, chronic pancreatitis, and pancreatic cancer. Effective treatments for diabetes can be found in the metabolites produced by the gut flora. Even though it is unclear how many and which metabolites are associated with gut microbiota, they have either favorable or unfavorable impacts on the onset of diabetes [128]. Before clinical trials of suggested diabetes therapies, research should be done on active metabolites that are changed by precursors and how they work. This will help us learn more about how it works; again, it is a difficult task. The methodical approach of network pharmacology is now being used to find connections between different parts of gut microbiota analysis, such as the gut microbiome, active metabolites, signaling pathways, and targets. Network pharmacology would therefore appear to be a particularly advantageous approach in order to investigate how metabolites associated with the microbiota affect disease.

The phytoconstituents may influence our body physiology through various mechanisms, even through modulation of the gut microbiota and the synthesis of micronutrients [129]. Although eukaryotes and archaea are also included in the term "gut microbiota," bacteria make up the

bulk of this community [130]. Maintaining the diversity and abundance of the human gut microbiota has been found to be important for maintaining intestinal homeostasis [131-132]. This is because the microbiota protects the host from pathogens by competing for niches and nutrients, boosting immune functions, and regulating metabolism. The gut microbiota is a dynamic ecosystem that is constantly changing and interacting with the host in a mutualistic manner. In fact, it may affect host defense, glucose as well as lipid metabolism regulation, and immune system function [129]. Therefore, modulating the gut microbiota may be an effective means of warding off metabolic and inflammatory disorders. Obesity, beta-cell exhaustion, insulin resistance, and T2DM are all conditions that have been linked to changes in the gut microbiota, according to animal studies [133]. Furthermore, observational investigations have demonstrated that there is evidence of altered microbial communities in the gut in prediabetic or DM patients in comparison to healthy subjects, a condition referred to as "gut microbiotadysbiosis" [134-135]. Furthermore, "gut microbiotadysbiosis" may disrupt the equilibrium between commensal species and different types of pathogens, and it may also reduce the release of metabolic SCFAs and antimicrobial molecules like bacteriocins [136]. However, there is now more evidence on the activities of microbial species associated with the gut microbiota's protective effect against DM as a metabolic disorder [137].

1.9.5 Short chain fatty acids content

The preservation of intestinal barrier integrity leads to the attenuation of systemic inflammation, specifically endotoxemia. Acetate, propionate, and butyrate are the main short-chain fatty acids (SCFAs) that are produced, and they have the ability to influence metabolic pathways by supporting a population of gut microbes that are in good condition [138].The gut microbiome may affect the intestinal barrier via signaling pathways other than SCFAs and bacterial toxins [139-140]. There is mounting evidence linking DM and a condition known as

gut microbiotadysbiosis, which compromises the gut wall and encourages the movement of endotoxemia from the intestines into the bloodstream, setting off a cascade of adverse events including inflammation, autoimmunity, and oxidative stress [141]. Changes in the composition and location of gut microbes, especially intestinal bacteria found in the mucous membrane, and metabolic activities may be triggered by microbial dysbiosis [142]. Numerous studies showed that people with different types of DM had an increased abundance of *Firmicutes* and a decreased abundance of *Bacteroidetes*, which had a negative impact on their metabolic regulation of nutrients, their glucose tolerance, and their inflammatory responses [143]. Anti-inflammatory SCFA levels, specifically butyrate, were lower in people with diabetes because they had a decreased abundance of SCFA-producing microorganisms such as *Roseburiaintestinalis* and *Faecalibacteriumprausnitzii* [142-145]. Intestinal bacteria may be more likely to enter the systemic circulation if SCFA synthesis is impaired, which may trigger or exacerbate integrated inflammatory responses [146]. Positive effects of SCFAs for diabetics include lowering serum glucose levels, improving insulin sensitivity, decreasing inflammation, and increasing the production of the protective hormone GLP-1 [3].

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