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Overview of diabetes and its curative approach using medicinal plants: A narrative review

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Abstract

Diabetes mellitus is a long term, diverse metabolic illness with a complex pathophysiology. Hyperglycemia, which stems from anomalies in either insulin secretion or insulin action or both, is its defining feature. Metabolic dysfunctions involving proteins, carbohydrates, and fats originate from hyperglycemia, which can express itself in a variety of ways. The main cause of diabetes related morbidity and mortality is long term hyperglycemia, which frequently results in a variety of microvascular and macro vascular diabetic complications. The main biomarker for determining diabetes diagnosis is hyperglycemia. The increase in prevalence rate, high expense of treatment, common side effects of oral antidiabetic medications is a global health challenge. Therefore, medicinal plants could be a viable ways to maximize its utilization in both food and medicine for management of diabetes and its complications. This review discussed the classification of diabetes, its pathophysiology, approved drugs and several medicinal plants that are used to manage diabetes.

Keywords: Diabetes mellitus; Hyperglycemia; Endocrinopathies; Gestational diabetes; Medicinal plants

1. Introduction

The human body has a glycemic homeostasis that operates around-the-clock to keep the balance of glucose levels in the blood and in each and every cell. Since glucose is the primary source of energy for human cells and is converted via the Krebs cycle into pyruvate to produce ATP (adenosine tri phosphate) as the final energy product, which is essential for human cells to operate (Dashty, 2013). A glucose channel that is only opened by insulin permits glucose to enter the cell. In order to allow glucose from the bloodstream to enter the cells, insulin, a hormone generated by the beta cells in the pancreas, is necessary. The extra glucose is then stored as triglycerides in adipose tissues and as glycogen in the liver once the cells have used it all. The process of turning glycogen into glucose, known as glycogenolysis, occurs in these stores when the body requires energy (Melzer, 2011). The hormone glucagon, which is likewise made by the pancreas, is responsible for this process. Because the brain cannot endure prolonged energy supply restriction, hyperglycemia, which happens when blood glucose levels are high, is harmful and can result in death or coma. The symptoms of hypoglycemia and hyperglycemia are similar in many ways, including drowsiness, fatigue throughout, and loss of vision. However, there is one significant distinction: in cases of hypoglycemia, the patient's skin becomes wet and cold with profuse sweating, in contrast to cases of hyperglycemia, where the patient has dry, warm skin without perspiration because the patient is experiencing dehydration as a result of the excessive diuresis brought on by the high glucose levels in his blood circulation. The bloodstream can store glucose when there is an insulin deficit or high levels of insulin resistance. When this occurs, the cells become hungry and begin to seek out alternative energy sources (Stringer et al., 2015).

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2. Diabetes

Hyperglycemia, a physiologically abnormal state defined by persistently increased blood glucose levels, is a feature of diabetes mellitus (DM), or simply diabetes. The persistent and varied symptoms of hyperglycemia include abnormalities in the metabolism of carbohydrates, fats, and proteins. Hyperglycemia is caused by abnormalities in either insulin secretion or insulin action, or both. Diabetes presents in a variety of ways and progresses in a complex manner with a complex pathophysiology (Banday et al., 2020), (Karalliedde & Gnudi, 2016). Numerous physiological organs are impacted by hyperglycemia and the resulting metabolic dysfunctions of protein, fat, and carbohydrates, which interfere with their regular operation. The adverse effects of hyperglycemia and its accompanying metabolic abnormalities on the normal structure and function of the micro and macro vasculature, which are at the foundation of organ structure and function throughout the body, are the primary cause of these disruptions, which develop gradually over time. Complications in the micro and macro vasculature are caused by structural and functional changes in the organ system vasculature (Mauricio et al., 2020), (Labazi & Trask, 2017), (Chawla et al., 2016). These issues impact body organs, including the eyes, kidneys, heart, and nerves, causing organ damage, dysfunction, and eventually organ failure. Retinopathy is the result of eye-related issues, and eventually progresses to blindness. Nephropathy and possible renal failure are caused by issues related to the kidneys. Coronary heart disease and hypertension are problems of the heart. Neuropathy, which can be peripheral or autonomic, is caused by issues related to the nerves. Long-term peripheral neuropathy is frequently accompanied by foot infections, including ulcers that necessitate amputations and Charcot joint (osteoarthropathy), whereas cardiovascular, gastrointestinal, and genitourinary (including sexual) dysfunctions are typical manifestations of autonomic neuropathy (Boulton, 2019), (Ahmad, 2016). One of the main causes of diabetes-related morbidity and death is atherosclerotic cardiovascular disease, which is a combination of cerebrovascular illness, peripheral arterial disease, and coronary heart disease (Low et al., 2016), (Wang and Reusch, 2012). Diabetes has become one of the most significant and difficult health problems facing the humanity of the modern world due to its rising global prevalence. The rapid economic advancement that has resulted in urbanization and the adoption of contemporary living patterns has coincided with a rise in the prevalence of diabetes in most parts of the world (Arena et al., 2017), (Hu, 2011). An estimated 463 million adults in the world, or 9.3% of all adults, have diabetes as of the year 2019. These adults range in age from 20 to 79 years. It is predicted that by 2030, this figure would rise to 578 million, or 10.2% of the adult population worldwide, and that by 2045, it will reach 700 million, or 10.9% of the adult population worldwide. The estimated prevalence of diabetes in men and women worldwide in 2019 is 9.6% and 9.0%, respectively, for the total population of each gender (Esen and Okdemir, 2020). Additionally, an estimated 4.2 million adults aged 20 to 99 died from diabetes-related complications in 2019, and the cost of treating diabetes-related health issues is anticipated to be at least 760 billion USD, or 10% of all spending on adults (Banday et al., 2020). According to estimates, more than 20 million live births (1 in 6 live births) were impacted by pregnancy-related diabetes in 2019 (McCance and Casey, 2019).

2.1. Pathophysiology of diabetes and classification

The classification of diabetes mellitus (DM) is thus arbitrary but nonetheless informative and frequently impacted by the physiological parameters present at the time of evaluation and diagnosis as the disease has a complex pathophysiology and diverse presentation. The classification that is now in use is based on both the etiology and the pathophysiology of the disease and is helpful for determining the necessary therapy as well as clinical disease assessment. This categorization divides diabetes into four basic categories: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), and diabetes brought on by or linked to a particular illness, pathology, or disorder (Baynes, 2015), (WHO, 2019), (Banday et al., 2020).

2.2. Type 1 diabetes mellitus

T1DM, often referred to as type 1A diabetes mellitus, insulin-dependent diabetes mellitus (IDDM), or juvenile-onset diabetes, accounts for around 5–10% of all diabetes cases (Karalliedde and Gnudi, 2016). It is an autoimmune condition distinguished by the T-cell-mediated death of pancreatic beta-cells, which causes an insulin shortage and, eventually, hyperglycemia (Katsarou et al., 2017), (Tai et al., 2016), (Rathod, 2022). Despite the fact that the pathogenesis of this autoimmunity is still not fully understood, it has been discovered that both hereditary and environmental variables play a role. Most often occurring in infants and children (juvenile onset), the rate of development of this pancreatic β-cell-specific autoimmunity and the illness itself is rapid. It may however occur gradually in adulthood (late onset). The eventual course of this disease is frequently defined by the diversity in the rate of immune-mediated death of the pancreatic cells. The abrupt death of β-cells in some children and teenagers can result in the development of diabetic ketoacidosis (DKA), which is frequently referred to as the disease's initial symptom. Others experience a very slow evolution of the disease with only a slight rise in fasting blood glucose levels, which only becomes severely hyperglycemic with or without ketoacidosis in the presence of physiological factors such as severe infections or the beginning of other ailments. In some other situations, such as in adults, β-cells may still have some function to emit only

the amount of insulin necessary to prevent ketoacidosis for a long time. But as their insulin deficit worsens, these people develop insulin dependence, which leads to the development of severe hyperglycemia and ultimately ketoacidosis (Banday et al., 2020). Even though this type of diabetes has a diverse course, those who have it develop severe or complete insulin deficiency at an early age and depend on insulin therapy to survive.

2.3. Type 2 diabetes mellitus

About 90–95% of all instances of diabetes are Type 2 diabetes mellitus (T2DM), also known as non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes (Schoenberg and Drungle, 2001). Insulin resistance and β-cell dysfunction are the two major insulin-related abnormalities that characterize this kind of diabetes (Brunetti et al., 2014). A decrease in the sensitivity of cells in peripheral tissues, especially those in the muscle, liver, and adipose tissue to insulin is the result of disruption of several cellular pathways, which causes insulin resistance. Reduced insulin sensitivity in the early stages of the disease causes β-cells to hyperfunction, resulting in an increase in insulin secretion as a compensatory mechanism to maintain normoglycemia. As a result, hyperinsulinemia, or high amounts of circulating insulin, prevents hyperglycemia. Nevertheless, over time, the increased insulin secretion by β-cells is unable to fully make up for the declining insulin sensitivity. Additionally, β-cell function starts to deteriorate, and β-cell dysfunction finally results in an insulin shortage. Because of this, normoglycemia cannot be sustained, and hyperglycemia emerges. In most circumstances, the release of insulin is adequate to avoid the development of DKA despite the fact that insulin levels are lowered (Seddik et al., 2019). DKA, however, can happen under extremely stressful circumstances, such as those brought on by infections or other pathophysiological situations. Atypical antipsychotics (second-generation antipsychotic drugs), corticosteroids, and sodium-glucose co-transporter-2 (SGLT2) inhibitors are among medications that may cause DKA (Hirsch and Emmett, 2018), (Muneer and Akbar, 2020). Patients with T2DM frequently do not need insulin therapy at the time when the disease start or even subsequently, throughout their lifespan, if there are no severe physiological stress circumstances present (Chaudhury et al., 2017), (Furman et al., 2019).

T2DM advances very gradually and asymptomatically, with even mild hyperglycemia developing over years. As a result, it goes largely undiagnosed until the advanced stages of the disease, when classic symptoms associated with severe hyperglycemia, such as weight loss, growth impairment, blurred vision, polyuria, and polydipsia, appear. In conclusion, a combination of inherited (polygenic) predispositions and significant environmental impacts can be used to define the pathogenesis/etiology of this kind of diabetes, which is complex and involves numerous known and unknown causes. Growing older, being obese, having a family history of diabetes, being physically inactive, and adopting modern lifestyles have all been linked to T2DM more commonly. Contrary to T1DM, however, no correlation between this illness and genes implicated in the immune response, including autoimmunity, has been discovered. As a result, there is no immune-mediated pancreatic β-cell death (Eizirik et al., 2020). Due to its impact on the development of insulin resistance through its effect on tissues' sensitivity to insulin, obesity plays a significant role in the homeostatic regulation of systemic glucose. As a result, most but not all T2DM patients are overweight or obese (Wondmkun, 2020). Because the increased body fat content, a sign of obesity, is a major risk factor for T2DM, both the total quantity and the distribution of body fat determine the emergence of insulin resistance and, ultimately, hyperglycemia. T2DM patients frequently have hypertension and lipoprotein metabolic abnormalities, which are marked by elevated triglycerides and low levels of high-density lipoproteins (HDLs), which will ultimately cause the onset of various microvascular and macro vascular complications over time. This is because T2DM has a strong correlation with increased body fat content or obesity.

3. Gestational diabetes mellitus (GDM)

GDM is categorized as any level of glucose intolerance or diabetes discovered when a woman is pregnant, typically in the second or third trimester. The above definition also included any undiagnosed T2DM that could start before or happen at the beginning of pregnancy. Women who are pregnant have gestational diabetes (GDM), which is distinct from any other form of diabetes and often goes away shortly after delivering or terminating the pregnancy (McIntyre et al., 2019), (McKenzie-Sampson et al., 2018). The blood glucose levels rise during the third trimester of pregnancy and are referred to as gestational diabetes mellitus (GDM) when they reach diabetic levels. During early pregnancy, both the fasting and post-prandial blood glucose levels are typically lower than normal. GDM is responsible for more than 90% of all occurrences of diabetes and related complications that happen during pregnancy (Saravanan et al., 2020), (Goldenberg et al., 2016) . The prevalence of GDM is significantly influenced by the populations being studied, with its frequency ranging from 1% to 14% of all pregnancies (Erem et al., 2015). Additionally, GDM has been linked to a higher lifetime chance of developing T2DM (Kramer et al., 2019). The chance of developing GDM rises with age, obesity, past pregnancies that resulted in large babies, and any prior episodes of impaired glucose tolerance or GDM (McIntyre et al., 2019), (Sreekanthan et al., 2014).

4. Other forms of diabetes

Besides T1DM, T2DM, and GDM, several other kinds of diabetes have been identified to be linked to a number of other illnesses, including numerous pathologies and several disorders, though in smaller proportions relative to the overall diabetic incidence scenario. The most common of these kinds of diabetes include endocrinopathies, exocrine pancreatic diseases, diabetes resulting from monogenic deficiencies in β-cell function, and those arising from genetic defects in insulin action.

4.1. Diabetes caused due to the monogenic defects in β-cell function

Only 0.6–2% of all occurrences of diabetes are caused by monogenic abnormalities in β-cell function, which mostly comprise neonatal diabetes and maturity-onset diabetes of the young (MODY).

4.2. Maturity-onset diabetes of the young

MODY is a genetic, metabolic, and medically heterogeneous category of primarily non-insulin-dependent diabetes caused by mutations in a number of particular genes involved in pancreatic beta-cell function. These mutations impair glucose sensitivity and accompanying insulin secretion with little to none, if any, problems in insulin action. As the name implies, MODY has an early beginning, with impaired glucose tolerance and hyperglycemia typically appearing before the age of 25, and it is frequently misinterpreted as T1DM or T2DM (Delvecchio et al., 2020), (Urakami, 2019). Less than 2% of all cases of diabetes worldwide and between 1 and 6% of cases in children are due to MODY (Amed and Oram, 2016) , (Urakami, 2019). MODY has a phenotype that is shared by all family members with diabetes and has an autosomal dominant inheritance pattern that often entails the vertical transmission of the condition across at least three generations (Oliveira et al., 2020), (Firdous et al., 2018).

5. Neonatal diabetes mellitus

Diabetes that is discovered within the first six months of life is referred to as neonatal diabetes mellitus (NDM), also known as early onset or congenital diabetes. It is an uncommon condition with an incidence rate of 1 per 500,000 to 300,000 people worldwide (1:500,000–1:300,000) (Banday et al., 2020), although a research in Italy found a greater incidence of 1 per 90,000 live births (1:90,000) (Banday et al., 2020). NDM is primarily hereditary in nature, with monogenic abnormalities accounting for 80-85% of cases. It is marked by severe unregulated hyperglycemia and hypoinsulinemia and need exogenous insulin treatment (Xie et al., 2018), (Banday et al., 2020). The genetic anomalies result in increased apoptotic or non-apoptotic cell death, which causes β-cell malfunction and decreased β-cell mass. Additionally, these flaws cause the pancreas and its islets to develop abnormally or, in extremely rare circumstances, they completely disappear, causing decreased insulin secretion and synthesis, hypoinsulinemia, and, in the latter case, a full insulin deficit. Neonatal diabetes is very different from early-onset T1DM and varies from it both in the etiology and form of inborn pancreatic dysfunction, typically occurring during the first six months of life whereas T1DM mainly evolves after six months of life (Banday et al., 2021).

5.1. Endocrinopathies

Diabetes can be brought on by a number of endocrinopathies that are caused by or arise from the improper functioning of different hormones. For example, Cushing syndrome, acromegaly, pheochromocytoma, glucagonoma, and hyperthyroidism, which are caused by the overproduction of the hormones cortisol, growth hormone, norepinephrine (and epinephrine), glucagon, and thyroid, respectively, are endocrinopathies that involve the overproduction of hormones that partially or completely antagonize the function of insulin. When one of these endocrine illnesses already has a deficiency in insulin secretion and/or action, diabetes linked with it typically develops as well (Banday et al., 2020). Somatostatinoma, which causes the oversecretion of somatostatin, and primary hyperaldosteronism are two endocrinopathies that can cause diabetes by inhibiting insulin production (Jennings and Hanley, 2017). Once endocrinopathies are handled or cured, diabetes caused by a variety of endocrinopathies typically disappears.

5.2. Exocrine pancreatic pathologies

Although it has been established that a number of exocrine pancreas disorders can lead to diabetes, their influence on the disease's overall incidence of the condition is negligible, accounting for less than 0.5% of all cases. These include genetic hemochromatosis, secondary hemochromatosis, cystic fibrosis, pancreatic neoplasia, trauma (fibrocalculous pancreatopathy), infection, and chronic pancreatitis (adenocarcinoma and glucagonoma) (Uc et al., 2016). With the exception of pancreatic neoplasia, all of these pancreatic illnesses only result in diabetes when they are severe enough to induce widespread pancreatic damage that affects the islets of Langerhans and results in a significant loss of β-cell

mass and impairment of β-cell function (Kleeff et al., 2017). Even in the absence of any loss of β-cell mass, pancreatic neoplasia-associated diabetes still exists. (Banday et al., 2020).

5.3. Infections

It is recognized that a number of viral infections result in β-cell malfunction, mostly through β-cell death, and hyperglycemia, which eventually manifests as overt diabetes. These include mumps, coxsackie virus B, adenovirus, and CMV infections. Congenital rubella syndrome, which is brought on by the rubella virus, has also been strongly connected to diabetes, but this diabetes is typically accompanied by the presence of T1DM-specific immunological markers such as human leukocyte antigen (HLA) and others (Banday et al., 2020). A very high rate of T2DM has been found among people with hepatitis C infection, and chronic hepatitis C virus infection and fibrosis advancement have both been linked to insulin resistance (Ballestri et al., 2016).

5.4. Drug or chemical induced

It is known that a number of substances can cause diabetes. These substances either inhibit insulin secretion or synthesis, which is mostly caused by the loss of beta cells, or they cause insulin resistance by decreasing the sensitivity of tissues to insulin (Latek et al., 2019). Only those who are vulnerable get diabetes as a result of an increase in insulin resistance caused by a medicine or chemical. Additionally, these substances may exacerbate or heighten hyperglycemia in people who already have overt diabetes. The following medications and substances are known to cause diabetes: glucocorticoids, diazoxide, thiazides, 2-receptor agonists (salbutamol and ritodrine), nonselective -adrenergic antagonists, dilantin, and hormones such as growth hormone (in very high doses), thyroid hormone (thyroxine/triiodothyronine), somatostatin and others (Banday et al., 2020). Additionally, there are ϒ-interferon, protease inhibitors such as indinavir, nelfinavir, ritonavir, and saquinavir, nicotinic acid, and β-cell toxins like streptozocin (streptozotocin), cyclosporine, rodenticides like vacor and pentamidine, as well as a number of antipsychotic medications.

6. Other genetic syndromes associated with diabetes

Along with the previously stated hereditary disorders, there are other factors that are frequently linked to an increase in the prevalence of diabetes. Included among these are, among others, Down's syndrome, Turner's syndrome, Wolfram's syndrome, Klinefelter's syndrome, Huntington's chorea, Friedreich's ataxia, myotonic dystrophy, Laurence-Moon Biedl syndrome, Porphyria, and Prader-Willi syndrome (Bilous et al., 2021), (Banday et al., 2020).

6.1. Approved anti-diabetic medications

Currently, oral antidiabetic medications such as sulfonylureas, biguanides, α -glucosidase inhibitors, and glinides as well as insulin are used to manage diabetes. These drugs are expensive and difficult to obtain in impoverished nations. Although insulin therapy and pharmaceutical oral hypoglycemic medicines are the mainstays of diabetes treatment, they have considerable side effects and do nothing to change or slow the progression of diabetic problems (Kaushik et al., 2010). In addition to the high expense of treatment, common side effects of pharmaceutical oral hypoglycaemic medications include hypoglycemia, weight gain, gastrointestinal problems, peripheral oedema, and reduced liver function.

Table 1 Approved Antidiabetic Drugs

Classes	Drugs	Dosage strength	Side effects	Contraindications
Biguanides	Metformin	500-2000 mg daily	Diarrhea, nausea, cramps, vomiting, decreased absorption of vitamin b12, lactic acidosis, weakness	Renal dysfunction, congestive heart failure, hypersensitivity, impaired hepatic function, acute or chronic metabolic acidosis
Sulfonylurea	Chlorpropamide (diabinese) and tolbutamide (orinase).	2.5-5 mg daily	Hunger, weight gain,skin reaction,stomach	Hypesensitivity, sulfa allergy, type 1 diabetes, diabetic ketoacidosis,

			upset,dark coloured urine	complicated gestational diabetes mellitus
Meglitinides	Repaglinide and Nateglinide	120 mg three times daily	Hypoglycemia, headache, respiratory tract infection	Diabetic ketoacidosis,type1 diabetes, co administration with gemfibrozil, hypersensitivity with drug
Thiazolinediones	Rosiglitazone, and Pioglitazone	15 to 30 mg once a day	Edema,weight gain, heart failure	Angina, heart failure
Dipeptidyl peptidase iv inhibitors	Sitagliptin, Saxagliptin, Linagliptin, and Alogliptin	25-100 mg once a day	Upper respiratory tract infection, headache, urinary tract infection	Stevens Johnson syndrome, anaphylaxis, angioedema
Alpha glucosidase	Acarbose, Miglitol, and Voglibose.	Starting dose-25 mg three times daily Maintenance dose-50-100 mg three times a day	Flatulence, diarrhea, abdominal pain, presence of undigested carbohydrates in the G.I.T	Hypersensitivity to the drug, diabetic ketoacidosis, inflammatory bowel disease, colonic ulceration

7. Medicinal plants with anti-diabetic properties

According to ethnobotanical data, more than 800 plants are used traditionally for management of diabetes because of their efficacy, have little side effects, readily available and are reasonably inexpensive (Bilal et al., 2018), (Alhassan et al., 2017). Due to the negative effects of approved oral hypoglycemic medications used to treat diabetes mellitus, there is currently an increasing interest in herbal therapies. The use of medicinal herbs has gained widespread acceptance around the world due to the fact that they are safer and more effective than treatments derived from pharmaceuticals (Khan & Ahmad, 2019), (Sen and Chakraborty, 2017). Many people believe that pharmaceuticals derived from plants and herbal preparations are less harmful and have fewer negative effects than synthetic medications. The potential of these traditional herbs to restore the function of pancreatic tissues by increasing insulin production or repair the activities of insulin receptors is what is thought to be responsible for their antihyperglycemic actions (Patel et al., 2012), (Wickramasinghe et al., 2021). Certain substances lower the glycaemic index of foods by preventing the intestinal absorption of glucose through the inhibition of carbohydrate-digesting enzymes, primarily α-amylases and α-glucosidases (Rasouli et al., 2017), (Lim et al., 2019), (Krishnan et al., 2022). These plants' anti-diabetic qualities could be due to their bioactive components, which include glycosides, alkaloids, terpenoids, flavonoids, carotenoids, etc., all of which are frequently mentioned as having an anti-diabetic impact (Patel et al., 2012), (Tran et al., 2020). Although numerous studies have focused on using phytochemicals to treat diabetes by increasing the production of insulin or its receptors, there have been relatively few studies on the phytochemical inhibition of α-amylase and α–glucosidase (Shanak et al., 2021), (Benayad et al., 2021). It is important to remember at this point that there is no effective treatment for diabetes mellitus (DM), and medications and insulin therapy used to treat the condition are linked to a number of unfavorable side effects (Chikezie et al., 2015). The quest for medicinal plants with antidiabetic properties with the intention of using them for the management of DM was prompted by the unfavorable side effects and high cost of anti-diabetic medicines (Lankatillake et al., 2019), (Chikezie et al., 2015). There have been evaluations of a number of plant species that are used medicinally to treat DM in different parts of the world. Table 1 summarizes the information on the types of extracts, as well as the mechanisms of action, techniques, and references pertaining to the plants that have been studied or reported to have anti diabetic effects in animal models.

Table 2 Some Medicinal plants with anti-diabetic activity

S/N	Name of plants and part used	Family	Mechanism of action	References
1.	*Aframomum melegueta*. Aqueous leaf extract	Zingiberaceae	Blocking essential enzymes associated with type 2 diabetes	(Mohammed et al., 2017)
2.	*Allium cepa* (Onion); Onion bulbs.	Alliaceae	Enhance the production of insulin. Compete with insulin for locations in the liver that inhibit insulin.	(Teshika et al., 2019), (Jini and Sharmila, 2020)
3.	*Allium sativum* (Garlic); Garlic gloves	Alliaceae	Enhance the release of insulin. Impede the liver's synthesis of glucose	(Hosseini and Hosseinzadeh, 2015)
4.	*Aloe vera* (Aloe barbedensis); Leaf, pulp and gel.	Aspholedeceae	Stimulate the release or production of insulin. Alter the enzymes' ability to metabolize carbohydrates.	(Abo-Youssef and Messiha, 2013)
5.	Avocado pear (Persea amaricana) seeds. Aqueous extract.	Lauraceae	Prevention of cell death and activation of the P13K/AKT signaling pathway.	(Alhassan et al., 2012), (Ojo et al., 2022)
6.	*Azadirachita indica* (Neem). Ethanolic leaf extract.	Meliaceae	Enhancing insulin release from active pancreatic beta cells	(Akter et al., 2013)
7.	*Carica papaya* linn. Unriped pulp and ethanolic leaves extract	Caricaceae	Delay the onset of hypoglycemic symptoms	(Sunday and Uzoma, 2014), (Vij and Prashar, 2015)
8.	*Catharanthus roseus;* Aqueous Fresh leaf juice.	Apocynaceae	Enhance the liver's capacity to use glucose. Suppress the gluconeogenic enzymes' activity.	(Vega-Ávila et al., 2012), (Govindan et al., 2020)
9.	*Cinnamomum cassie* (Chinese cinnamon); Ethanol stem Bark.	Lauraceae	Increase insulin activity. Increase glycogen synthesis and glucose absorption.	(Thangavelu et al., 2021), (Akbar, 2020)
10.	*Coccinia indica*; Ethanolic Leaves extract.	Cucurbitaceae	Neutralize glucose-6 phosphatase. Increase the activity of glycogen synthase while decreasing the activity of phosphorylase.	(Patil et al., 2011)
11.	*Fiscus bengalensis;* Ethanolic Leaves and bark.	Moraceae	Enhance insulin production. Inhibit the activity of insulinase.	(Kolhe and Rachh, 2018), (Chikezie et al., 2015)
12.	*Gymmema slyvestre* (Gurnar); Ethanolic Leaves.	Asclepiadaceae	Stimulate the rat islets to secrete insulin. Reduce the gluconeogenic enzymes' activity. Regenerate -cells in the process.	(Kolhe and Rachh, 2018), (Chikezie et al., 2015)

13.	Ginseng (Panax ginseng); Roots and Leaves.	Araliaceae	Carbohydrate digestion and absorption are both slow. Alter the transport of glucose that is mediated by NO.	(Hussain et al., 2021)
14.	*Moringa oleifera.* Aqueous and ethanol leaves extracts	Moringaceae	Increasing the release of insulin from active pancreatic beta cells to increase appetite	(Owens III et al., 2020), (Muhammad et al., 2016), (Irfan et al., 2017)
15.	*Momordica charantia* (bitter melon) fruit juices	Cucurbitaceae	Inhibiting intestinal glucose uptake while stimulating the use of glucose in skeletal muscle.	(Mahmoud et al., 2017)
16.	*Muurrayi komingii* (Cury leaf); Alcholic extract	Rutaceae	Enhance the release of insulin. Increase glycogenesis while reducing gluconeogenesis and glycogenolysis.	(Kolhe and Rachh, 2018)
17.	*Ocimum gratissimum*. Aqueous and ethanolic leaf extract	Labiaceae	Stimulate insulin action	(Casanova et al., 2014)
18.	*Parkia biglobosa*. Ethanol stem bark extract	Fabaceae	Increase glycogen synthesis and glucose absorption.	(Oyedemi et al., 2021)
19.	*Picralina nitida*. Aqueous and ethanol extract of seeds, fruit, stem	Apocynaceae	Inhibit beta cell deterioration	(Erharuyi et al., 2014), (Oguntibeju, 2019)
20.	*Polygala senega*; Rhizomes	Polygalaceae	Reduce the production of hepatic glucose. increase insulin sensitivity	(Chikezie et al., 2015)
21.	*Pterocarpus marsupium*; Aqueous and methanol Bark extract	Falcaceae	Protect the rats' beta cells. Restore healthy pancreatic -cells. increase insulin secretion	(Rahman et al., 2018)
22.	*Sida acuta*. Leaves	Malvaceae	Increase insulin action	(Priya et al., 2021)
23	*Sysygium aromaticum* (cloves). Oleanolic acid extract	Mytaceae	Reduce the gluconeogenic enzymes' activity. Activate the release of insulin	(Kuroda et al., 2012), (Musabayane et al., 2010)
24.	*Syzigium cumini* (Eugenia janbolaria); Seeds, leaves and fruit pulp.	Mytaceae	Activate the kinases that are responsible for peripheral glucose consumption.	(Chikezie et al., 2015)
25.	*Tithonia diversifolia*. Aqueous leaf extract	Asteraceae	It acts on glucose transporter 2 (GLUT 2)	(Chunudom et al., 2020)
26.	*Trigonella foemum-graecum* (Fenugreek); Seeds.	Falcaceae	Slow Carbohydrate digestion and absorption. Increased insulin secretion caused by glucose. Improvement in the action of peripheral insulin.	(Shashikumar et al., 2019)

8. Conclusion

DM is a complex metabolic disease that manifests in a variety of forms, each having a unique pathophysiological basis but frequently as a disorder with conflicting and hard to distinguish features. Each of these different varieties of diabetes is treated and managed differently, but they also have many things in common, just like the condition itself. All of this,

highlights the significance of an accurate and prompt diagnosis of each of these diabetes kinds, as well as the vital importance of an understanding of their pathophysiology. This is crucial in order to protect diabetic patients from potential deleterious consequences of inappropriate, inefficient, or needless pharmaceutical interventions which frequently postpone the desired prognosis and lengthen exposure to hyperglycemia. Long-term hyperglycemia have also been linked to an increased risk of microvascular and macrovascular diabetic complications, which have a negative impact on quality of life and are a major factor in the morbidity and mortality associated with diabetes. The accurate and prompt molecular diagnosis of diabetes in general, and in particular the types of diabetes caused by genetic mutations or associated genetic anomalies, can aid in disease risk analysis, disease prediction, and the timely identification of individuals at an increased risk for the disorder, particularly family members. In these situations, preventive care and predictive molecular/genetic testing can be extremely important. The prevention and management of diabetes need a variety of lifestyle changes and interventions, regardless of the type of diabetes. These include strict nutrition control, physical activity, a change in daily sedentary habits, and the management of obesity. A crucial component of the therapy and control of diabetes mellitus is the use of educational programs to increase public awareness of the disease's pathophysiology and the different risk factors that can be changed to reduce it. We can infer that investigation into the bioactive elements in plant based extracts may be essential to locating chemical substances for potential development of anti-diabetic treatments.

Compliance with ethical standards

Disclosure of conflict of interest

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