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A Review: Role of Medicinal Plants in the Management of Diabetes Mellitus

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ABSTRACT

Diabetes mellitus (DM), or simply diabetes, is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced. This high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger). Conventionally, diabetes has been divided into three types namely: Type 1 DM or insulin-dependent diabetes mellitus (IDDM) in which body fails to produce insulin, and presently requires the person to inject insulin or wear an insulin pump. This is also termed as "juvenile diabetes". Type 2 DM or non-insulin-dependent diabetes mellitus (NIDDM), results from insulin resistance, a condition in which cells fail to use insulin properly, with or without an absolute insulin deficiency. This type was previously referred to as or "adult-onset diabetes". The third main type is gestational diabetes which occurs when women without a previous history of diabetes develop a high blood glucose level during her pregnancy. It may precede development of type 2 DM. Currently available pharmacotherapy for the treatment of diabetes mellitus includes insulin and oral hypoglycemic agents. Such drugs acts by either increasing the secretion of insulin from pancreas or reducing plasma glucose concentrations increasing glucose uptake and decreasing gluconeogenesis. However these current drugs do not restore normal glucose homeostasis, insulinoma and they have to take rest of life. Various herbal drugs have been also proved effective due to their beneficial contents in treatment of diabetes. diabetes, its complications, goals of management, and synthetic and herbal treatment of diabetes.

Keywords: Insulinoma, hyperinsulinemia, adiponectin, Momordica charantia.

I. INTRODUCTION

The most prevalent endocrine condition, diabetes mellitus (DM), affects about 100 million people globally (6% of the population). It is brought on by the pancreas' inability or lack of ability to produce enough insulin, which causes variations in blood glucose levels. Numerous biological systems, including blood vessels, the eyes, kidneys, hearts, and nerves, have been proven to be harmed by it[1]. Insulin dependent diabetes mellitus (IDDM, Type I) and non-insulin dependent diabetes mellitus (NIDDM, Type II) are the two forms of diabetes mellitus**.** While Type II diabetes is characterized by peripheral insulin resistance and defective insulin secreting cells, Type I diabetes is an autoimmune illness that causes a localized inflammatory response in and around islets that is followed by the selective death of insulin-secreting cells. secretion of insulin[2]. Diabetes mellitus increases the risk of numerous consequences, including peripheral and cardiovascular illnesses, stroke, neuropathy, renal failure, retinopathy, blindness, and amputations[3]. Mostly, drugs are used to treat symptoms and preserve lives. The secondary goals are to prolong longevity by removing different risk factors and to prevent long-term diabetic problems. For patients with type 1 diabetes, insulin replacement therapy is the cornerstone of care, but for type 2 diabetes, dietary and lifestyle changes are the cornerstones of management and treatment [4]. For the treatment of diabetes, a variety of hypoglycemic medications are also available, including biguanides and sulfonylureas. But none of these drugs are perfect because of their harmful side effects, and long-term usage might occasionally result in a decrease in response. [5]. The primary drawback of the medications that are already on the market is that they have adverse effects and must be taken continuously.[6]. Worldwide, medicinal plants and their bioactive components can be used to treat diabetes, particularly in nations with limited access to traditional anti-DM medications Additionally, a

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number of experimental models are available to evaluate plant[7]s antidiabetic efficacy. Therefore, the goal of this review is to learn more specific information on diabetes mellitus, including its clinical manifestation, epidemiological information, complications, and current diabetic treatments.

Table of List:-

s.no	Name of the plant	Common name	Family	Used
1.	Pterocarpus santalinus	Red sandalwood	Fabaceae	ameliorates diabetes mellitus via anti-inflammatory pathways and enhancement of insulin function.
2.	Brassica juncea	Chinese mustard	Brassicaceae	mentioned in Ayurveda for treatment of diabetes
3.	Swertia punicea	Ganyancao and Zihong	Gentianaceae	to cure Fever and diabetics Mellitus
4.	Gymnemasylvestre	Gurmar	Asclepiadaceae	in the control of blood glucose in insulin-dependent diabetes mellitus
5.	Ricinus communis	Costor oil plant	Euphorbiaceae	used in traditional medicine such as abdominal disorders, arthritis, backache, muscle aches, bilharziasis, chronic backache and sciatica, chronic headache, constipation,
6.	Combretum micranthum	Kinkeliba	Combretaceae	use Combretum micranthum for high blood pressure, stomach upset, and many other conditions

Classification of Diabetes Mellitus

The World Health Organization released the first widely recognized categorization of diabetes mellitus in 1980 [8], and it was updated in 1985 [9]. The primary or idiopathic diabetes mellitus, which is the subject of our discussion, is the most prevalent and significant kind. It needs to be distinguished from secondary diabetes mellitus, which encompasses hyperglycemia types linked to There are known causes for the death of pancreatic islets, including inflammatory pancreatic disorders, iron overload (hemochromatosis), surgery, tumours, and specific acquired or inherited endocrinopathies [12]. The classification includes various forms of hyperglycemia as well as the clinical stages and etiological types of diabetes mellitus [10]. A person's diabetes type is frequently determined by the conditions that existed at the time of diagnosis, and many people with diabetes are difficult to categories into a single class [11]. Hyperglycemia is likely a common trait across a broad set of illnesses that make up primary diabetes mellitus [11].

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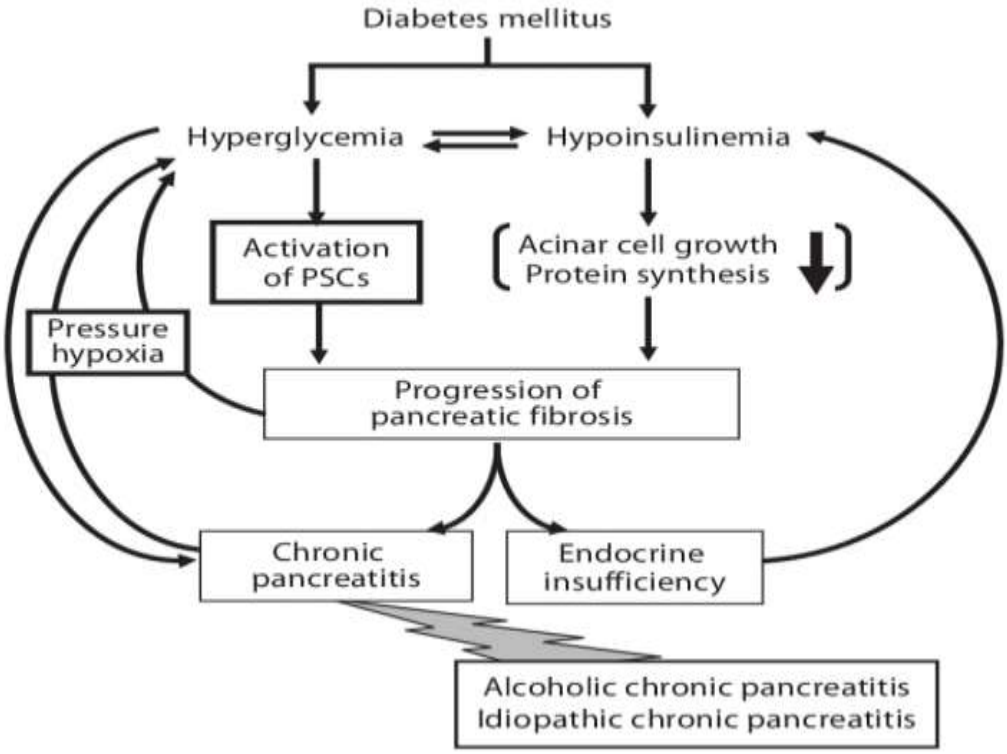

1.Insulin Dependent Diabetes Mellitus (Type1 IDDM)

Formerly known as juvenile-onset or ketosis-prone diabetes, this type of diabetes mellitus is also known as autoimmune diabetes. The patient may also present with symptoms of other autoimmune diseases, including Addison's disease, Hashimoto's thyroiditis, and Graves disease [13]. Insulin-dependent diabetes mellitus (IDDM), another name for type I diabetes mellitus, is primarily seen in children and young adults. Its onset is typically abrupt and can be fatal [16]. Anti-glutamic acid decarboxylase, islet cell, or insulin antibodies that recognize the autoimmune mechanisms that result in beta-cell death are typically present in type 1 [17]. Type 1 diabetes (caused by b-cell breakdown, which typically results in a complete lack of insulin) (American Diabetes Association, 2014) The rate at which beta cells are destroyed varies greatly amongst individuals; in some, it happens quickly, while in others, it happens more slowly [14]. Insulin secretion is severely reduced or absent as a result of the pancreatic ß-islets' loss. Insulin injections are necessary for treatment [16]. When fasting diabetic hyperglycemia is first discovered, 85–90% of people with Type 1 diabetes mellitus have immune destruction markers, such as islet cell auto-antibodies, auto antibodies to insulin, and auto antibodies to glutamic acid decarboxylase (GAD) [15]. Although the precise origin of diabetes mellitus is still uncertain, auto-antibodies that damage beta-islet cells have been linked to the autoimmune process in the majority of cases [16].

2. Non-Insulin Dependent Diabetes Mellitus(Type2 Niddm)

Adult-onset diabetes is another name for type 2 diabetes mellitus. The American Diabetes Association (2014) [18] describes the increasing insulin secretary malfunction against the backdrop of insulin resistance. Insulin resistance is a common feature in people with this kind of diabetes [19]. The main causes of morbidity and death from diabetes are the long-term issues in the kidneys, eyes, nerves, blood vessels, and eyes that affect both types of people . The predisposing factors are multifunctional and include obesity, sedentary lifestyle, ageing (affecting middle-aged and older adults), and genetics (Ross and Wilson 2010). Patients with these conditions are more likely to experience macrovascular and microvascular problems [20,21].

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3.Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is the term used to describe glucose intolerance that develops for the first time or is identified during pregnancy [22]. Gestational Diabetes Mellitus (GDM) is the term used to describe women who acquire Type 1 diabetes mellitus during pregnancy as well as women who have undiagnosed asymptomatic Type 2 diabetes mellitus that is discovered during pregnancy [23]. Pregnancy-related diabetes that is not clearly over diagnosed as diabetes is known as gestational diabetes mellitus (GDM) [24]. In the long run, children born to mothers with gestational diabetes mellitus are more likely to acquire obesity and type 2 diabetes in later life, a phenomena linked to the consequences of intrauterine exposure to hyperglycemia. The condition may develop during pregnancy and then go away after delivery.

4. Other Specific Type (Monogenic Types)

Hepatocyte nuclear factor (HNF)-1a, a hepatic transcription factor, has mutations on chromosome 12 that cause the most common type of monogenic types of diabetes. They also called them beta cell genetic abnormalities. The early onset of hyperglycemia (usually before the age of 25) is a common characteristic of several kinds of diabetes. These conditions can also be known as maturity-onset diabetes of the young (MODY)[9], maturity-onset diabetes in youth, or defects of insulin action; exocrine pancreas diseases, which are linked to other endocrinopathies (such as acromegaly); and pancreatic dysfunction brought on by medications, chemicals, or infections [23]. therapy for HIV/AIDS or after organ Less than 10% of DM cases are made up of these [8].

REVIEW

The review work was carried out by thorough searching of different research articles and patents from different online journals from PubMed, Google scholar, Science direct etc. The literature of scientifically validated plants are also collected which are having good antidiabetic property.

Pterocarpus santalinus (Fabaceae)

The plant, also referred to as red sandalwood, is extensively distributed throughout South India. It is made up of many chemical components, including triterpenoids, flavonoids, anthocyanins, saponins, tannins, phenols, and carbohydrates[25]. Santalin is the primary active ingredient in the plant. Moreover, it has pterocarpol, pterocarptriol, ispterocarpolone, and pterocarpo-diolones containing cryptomeridol and β-eudeslol[26]. It functions as an astringent tonic, aphrodisiac, antihelmintic, and antidiabetic. Additionally, ulcer and inflammation are treated with it. Numerous research that highlight the plant's antidiabetic properties have been published. The plant is traditionally used to treat diabetes by making heartwood drinking cups[27,28]. According to Rao et al., the ethanolic fraction of the plant exhibited hypoglycemic efficacy at a dose level of 0.25 g/kg body weight/day[29]. According to research by Halim and Mishra, streptozotocin-induced diabetic rats who received an aqueous extract of the plant at a dose of 250 mg/kg also received vitamin E, which significantly lowered their blood pressure [30].

Brassica juncea (Brassicaceae)

Chinese mustard, also referred to as brown mustard, is a plant that is extensively distributed in Asia, North America, Europe, and Africa. It contains numerous significant chemical elements such as triterpenes, Saponins, alkaloids, flavonoids etc[31]. It has antiscorbutic, diuretic, stimulant, stomachic, antihelmintic, antidysentric, diaphoretic, and antiarthritic properties when taken pharmacologically. In streptozotocin-induced diabetic male albino rats, the plant's aqueous seed extract demonstrated strong hypoglycemic action at dose levels of 250, 350, and 450 mg/kg, according to Thirumalai T et al.

Swertia punicea (Gentianaceae)

The plant is widely accessible in China, Japan, India, Pakistan, and other Asian nations. Important elements like xanthonoids, terpenoids, flavonoids, alkaloids, irridoid glycosides, etc. are present in it. The most prevalent class of these chemicals is called xanthonoids. It has medicinal uses as an antimicrobial, hypoglycemic, antihepatotoxic, anti-inflammatory, and antioxidant. The herb's antidiabetic properties have been the subject of numerous investigations. According to a study cited by Pen and Fang, this plant has a strong hypoglycemic effect [32]. The plant's ethanol extract and ethyl acetate soluble fractions had a hypoglycemic impact on streptozotocin-induced type II diabetic mice, according to Wen L. and Chen J.C.'s report[33].

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Gymnemasylvestre (Asclepiadaceae)

This woody perennial vine is mostly planted in tropical regions of Australia, Africa, and India. Gymnemic acid serves as the plant's primary active ingredient. Flavones, anthraquinones, hentri-acontane, pentatriacontane, α and β chlorophylls, phytin, resins, tartaric acid, formic acid, etc. are other active ingredients[34]. Daisy et al. discovered that the plant's crude extracts and its isolated component dihydroxy gymnemic triacetate demonstrated a strong hypoglycemic effect in a dose- and time-dependent manne[35] in streptozotocin-induced diabetic mice. A study by Liu et al. unequivocally shows that the plant's aqueous extract enhanced insulin production from mouse cells and isolated human islets in vitro without.

Ricinus communis (Euphorbiaceae)

This is a type of perennial flowering plant that grows widely throughout India. It has a variety of chemical components, including glycosides, alkaloids, steroids, saponins, and flavonoids. 45 percent of fixed oil found in seeds and fruits is made up of glycosides of stearic, dihydroxystearic, isoricinoleic, and ricinoleic acids. It is utilised pharmacologically as an antiasthmatic, hepatoprotective, antidiabetic, antioxidant, anticancer, antiulcer, and antibacterial. In the initial screening experiments, Dhar ML et al. observed that the plant's root, stem, and leaves demonstrated hypoglycemic action in albino rats at a dose of 250 mg/kg. According to Poonam Shokeen et al., the plant's roots' ethanolic extract demonstrated strong blood glucose-lowering action in diabetics given alloxan[37].

Combretum micranthum (Combretaceae)

Senegal, Mali, Gambia, and Northwestern Nigeria are frequent places to find this plant. It contains various kinds of chemicals, including tannins, terpenoids, alkaloids, and flavonoids29. It has a variety of pharmacological applications, including antibacterial, anti-inflammatory, and antioxidant ones. In rats with diabetes and sub-diabetes, Aminu Chika et al. reported on the plant's aqueous leaf extract at a dose level of 100 mg/kg having possible anti-diabetic effects[37].

Arbutus unedo (Ericaceae)

This shrub is native to France and Ireland and is evergreen. This plant contains a variety of chemical classes, including organic acids, terpenoids, a-tocopherol, essential oils, and phenolic compounds31. It is used to treat a variety of conditions, including diabetes, inflammation, hypertension, gastrointestinal disorders, dermatological issues, and cardiovascular ailments. The plant's aqueous extract, when administered at a dose of 500 mg/kg to diabetic mice produced by streptozotocin-nicotinamide (STZ-NA), demonstrated a strong antidiabetic activity both in vitro and in vivo[38].

Cocos nucifera (Arecaceae)

It is abundantly accessible in India's coastal regions and is frequently referred to as coconut. It has a number of significant chemical components, including alkaloids 33, triterpenes, flavonoids, leucoanthocyanidins, phenols, and tannins. It has several pharmacological uses, including those related to analgesia, inflammation management, antimicrobial, antifungal, antioxidant, antiparasitic, antimalarial, and cardioprotective. S. Saranya et al. discovered that the plant's flower extract, at a dose of 300 mg/kg, significantly reduced the risk of diabetes in streptozotocin-induced diabetic rats34. According to Nidhi Tyagi et al., this plant's ethanolic extract had strong anti-diabetic effects in streptozotocin-induced diabetic rats at dosages of 200 mg/kg and 400 mg/kg35.

Sarcopoterium spinosum (Rosaceae)

The Middle East and Mediterranean regions are frequent places to find this plant. This plant contains a number of flavonoids and phenolic chemicals, including catechol, protocatechuic acid, hesperidin, naringin, rutin, galllic acid, and quercetin36. Diabetic patients were historically treated with it. Additionally, it is used to alleviate pain, inflammation, and digestive issues. According to a study published by Dafni et al., the plant's root extract was utilized in Muslim traditional medicine to treat[40].

Etiology of Diabetes Mellitus

The Greek term "aetiologia" is where the word "aetiology" originates. Thus, the science of determining the causes and origins of an illness is known as aetiology, and it encompasses the following:

1. The juvenile-onset (insulin-dependent) form's aetiology is currently thought to be autoimmune.
2. Viruses similar to coxsackieB may potentially contribute to the genesis of diabetes.
3. It has been demonstrated that the mumps and rubella viruses cause morphologic alterations in the islet-cell structure.

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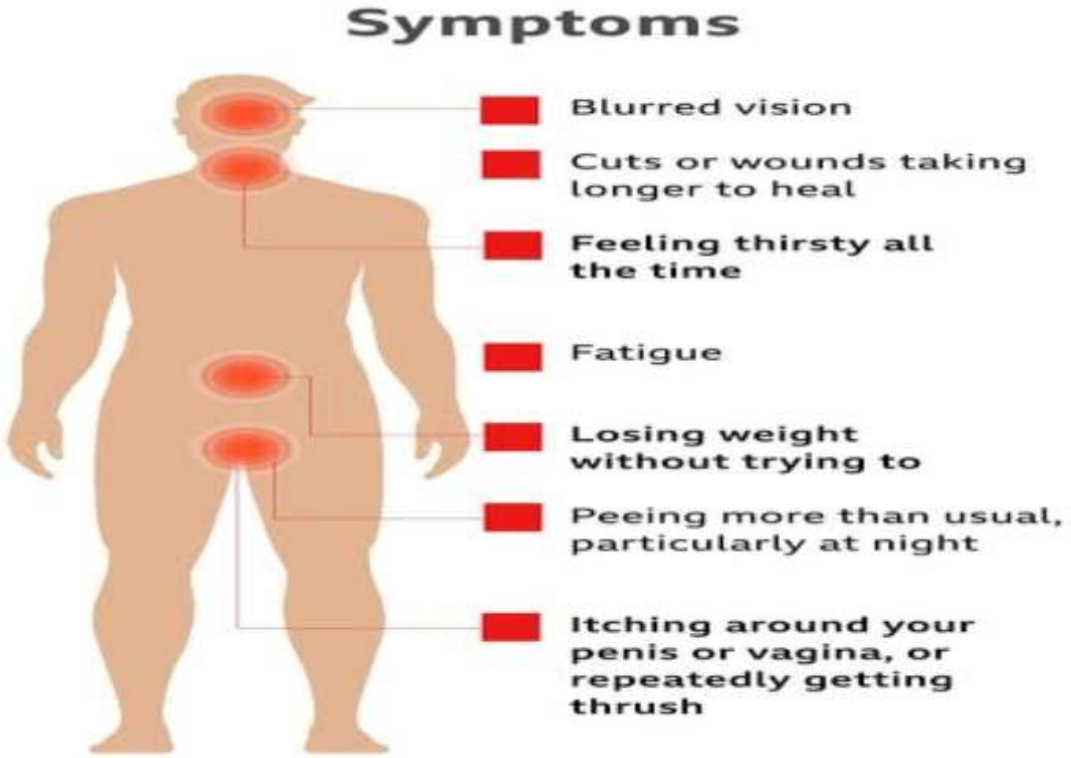
4. There is debate on the genetic component in the genesis of diabetes. Perhaps a genetic characteristic increases a person's susceptibility to any of the aforementioned viruses in the pancreas.

Symptoms and causes of Diabetes-
Increased thirst and urination;
Increased hunger;
Fatigue;
Blurred vision; numbness or tingling in the hands or feet;
Sores that do not heal; and unexplained weight loss are some of the symptoms associated with diabetes.



• Ketones, a consequence of the breakdown of muscle and fat that occurs when there is insufficient accessible insulin, are present in the urine.[46]

Pharmacological treatments for diabetes
Sulfonylureas: According to reference [47], sulfonylureas were the first commonly used oral hypoglycemic drugs. By binding to particular sulfonylurea receptors on pancreatic βcells, the sulphonylureas stimulate the production of insulin. It is best to take them 15 to 30 minutes before eating.
• **Meglitinide analogues:** Repaglinide and netaglinide, two non-sulfonylurea insulin secretagogues, are analogues of meglitinide. These are derivatives of benzoic acid that increase insulin secretion by binding to distinct non-sulphonylurea receptor binding sites on β-cells.
• **Biguanides:** Biguanides enhance peripheral glucose absorption, notably in skeletal muscle, and decrease hepatic glucose output. The most widely prescribed medication for type 2 diabetes in kids and teenagers is now Motorman, which includes Metformin, Phenformin, and Buformin [47]. The chosen biguanide is metformin.
Alpha-glucosidase inhibitors: Alpha-glucosidase is an enzyme found in the small intestine brush border that breaks down oligosaccharides and disaccharides into monosaccharides. Alpha-glucosidase inhibitors, like acarbose, work by competitively blocking this enzyme. 25–50 mg once daily is the initial dosage; this is increased to 50 mg two or three times per day. It needs to be consumed right away after eating.
• **Thiazolidinediones, such as Glitazone:** These substances work by increasing skeletal muscle and adipose tissue's sensitivity to insulin. It also stops the liver from producing glucose. Partial PPAR-alpha agonist activity is present in pioglitazone. Whereas pioglitazone is taken once daily at a dose of 15 to 45 mg, rosiglitazone is taken in one or two

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split doses of 2 to 8 mg. These medications take 2-4 weeks to start taking effect.

Causes of Diabetes Mellitus

Abnormalities or disturbances in the ß cell's gluco-receptor, causing them to react to increased glucose concentrations or relative ß cell shortages. Either way, there is a reduction in insulin secretion, which could lead to ß cell failure. The fundamental idea behind microvascular illness that causes cerebral hypoxia and the direct consequences of hyperglycemia on the metabolism of neurons.

1.Diminished insulin sensitivity in peripheral tissues due to "down regulation" and a decrease in the number of insulin receptors. Many have normal glycemic levels but are hypersensitive and hyperinsulinaemic; they are also linked to dyslipidemia, hyperuricemia, and abdominal fat. Relative insulin resistance therefore exists, especially at the liver, muscle, and fat levels. It has been suggested that hyperinsulinemia can lead to angiopathy.

2. Excessive glucagon, the hormone that causes hyperglycemia, and obesity lead to a relative insulin deficit, with the ß cells falling behind. Nitric oxide metabolism anomalies have been shown in two models, leading to changes in perineural blood flow and nerve injury.

3. Genetic problems resulting in certain types of diabetes mellitus, such as "maturity onset diabetes of young" (MODY), other endocrine disorders, pancreatectomy, and gestational diabetes mellitus (GDM), are another rare cause of the disease.

4. A particular receptor imbalance may be the cause of diabetes mellitus. Glucagon-like peptide-1 (GLP-1) receptor, peroxisome proliferator-activated (γ) receptor (PPARγ), beta3 (ß3) ardent-receptor, and various enzymes such as α glycosidase and dipeptidyl peptidase IV enzyme, among others, are examples of specializedreceptors .

5. Advanced glycation-end products, protein kinase C, oxidative stress, and the polyol pathway are the main topics of current research on diabetic neuropathy [41].

Diagnosis of Diabetes Mellitus

It is never appropriate to diagnose diabetes in a patient who exhibits no symptoms based on a single aberrant blood glucose reading. If diabetes is diagnosed, the doctor must be certain that the diagnosis is solidified because the patient will have significant, lifetime effects [42]. The following tests can be used to diagnose diabetes mellitus: blood sugar, urine sugar, glucose tolerance test, renal glucose threshold, reduced, increased, and renal glycosuria; cortisone-stressed glucose tolerance test; intravenous glucose tolerance test; and oral glucose tolerance test.

Treatment of Diabetes Mellitus

The goal of treatment is to treat the underlying cause and administer frequent high doses of insulin. Once the condition is under control, the need for insulin returns to normal. The goals of managing diabetes mellitus can be accomplished by:

1. To bring the diabetic's disrupted metabolism as close to normal as possible while maintaining comfort and safety.
2. To stop or postpone the disease's short- and long-term risks from getting worse.
3. To give the patient the information, inspiration, and resources they need to take charge of their own informed care.

A. Types of Therapy Involved In Diabetes Mellitus

1. Stem cell therapy

Studies have indicated that T2DM patients' persistent inflammations and insulin resistance may be mostly caused by monocytes and macrophages [28]. One new approach that aims to manage or correct immunological dysfunctions is stem cell educator therapy [43]. Using a closed-loop system, patients' blood is collected; lymphocytes from the whole blood are purified; adherent cord blood-derived multi-potent stem cells (CB-SCs) are co-cultured with the purified lymphocytes in vitro; and the educated lymphocytes—not the CB-SCs—are then infused back into the patient's circulation [43].

2. Antioxidant therapy

Patients with type 2 diabetes have been treated for oxidative stress using a range of antioxidants, including vitamins, supplements, active ingredients derived from plants, and medications with antioxidant properties. Vitamins C, E, and β carotene are the best supplements to prevent oxidative stress and its consequences. [44] Antioxidants are crucial because they reduce the chance of diabetes and its consequences**.**

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B. Dietary Management

Sufficient energy content Both patients with diabetes and those without it should follow appropriate dietary guidelines, such as:

1. Well-balanced in terms of fats, proteins, and carbohydrates; in every situation, limiting the amount of carbohydrates consumed is essential.
2. Should try to resemble normal as much as possible
3. Food intake should be divided into regularly spaced meals of similar size
4. Reduce total calorie intake by decreasing both fat and carbohydrate
5. Patient must be advised to be constant in his dietary habits from day to day.

c. Newer Insulin Delivery Devices

Many advancements have been achieved to establish strict glucose control and to make insulin delivery easier and more accurate. These include pen devices, insulin syringes, insulin pumps that are implanted, inhaled insulin, and various insulin administration methods.

D. Oral Hypoglycemic or Antidiabetic Agents

In 1957, biguanide phenformin—a clinically beneficial drug—was created concurrently with sulfonylureas. Dipeptidyl peptidase-4 (DPP-4) inhibitors are the newest of the newer strategies that have been continuously investigated and have recently produced thiazolidinediones, meglitinide analogues, α-glucosidase inhibitors, and others [45].

Important Features of Oral Hypoglycaemic Agents

Diabetes mellitus is regarded as a modern disease that has a significant influence on morbidity, morality, and the individual's quality of living. Diabetes mellitus is a common side effect of Cushing syndrome. It is brought on by a prolonged exposure to glucocorticoids and manifests as a variety of clinical symptoms, including central obesity, weakness in the proximal muscles, hirsutism, neurophysiological disturbance, autonomic neuropathy, autonomic complication, digestive issues, and dental issues. [45].

II. CONCLUSION

The term diabetes mellitus includes several different metabolic disorders that all, if left untreated, result in abnormally high concentration of a sugar called glucose in the blood. Diabetes mellitus type 1 results when the pancreas no longer produces significant amounts of the hormone insulin, usually owing to the autoimmune destruction of the insulin-producing beta cells of the pancreas. Diabetes mellitus type 2, in contrast, is now thought to result from autoimmune attacks on the pancreas and/or insulin resistance. The pancreas of a person with type 2 diabetes may be producing normal or even abnormally large amounts of insulin. The main goal of diabetes management is, as far as possible, to restore carbohydrate metabolism to a normal state. To achieve this goal, individuals with an absolute deficiency of insulin require insulin replacement therapy, which is given through injections or tablets. Insulin resistance, in contrast, can be corrected by dietary modifications and exercise. Other goals of diabetes management are to prevent or treat the many complications that can result from the disease itself and from its treatment.

Conflict of interest

The authors declare that there is no conflict of interest in publication of this paper.

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