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DIABETES MELLITUS AND ITS TREATMENT ASPECTS IN HERBAL MEDICINE

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ABSTRACT

Diabetes mellitus (DM) is a chronic disease which has clinched the world. More than 300 million people of the world are suffering from this disease and the number is still increasing at a rapid rate as modern medical science has no permanent solution for the disease. Current scenario of the nutraceuticals has increased patient's faith on the traditional medicinal system and world nutraceutical industry is estimated to reach $285.0 billion by 2021. The increasing trend of nutraceuticals in diabetes treatment makes it important to collect the traditional knowledge of medicines under one heading as it can help researchers to formulate new functional foods and nutraceuticals which can either lower down the risk or cure DM. In addition, the discussion of market available food products, their active components and possible health benefits can help the patients to understand the herbal medicines in a better way.

Keywords: Diabetes mellitus (DM), chronic hyperglycemia, Herbal Medicine

INTRODUCTION

Insulin resistance or insufficiency causes diabetes mellitus (DM), a chronic hyperglycemia syndrome. It affects more than 220 million people worldwide, and it is on the rise. expected to affect 440 million by 2030. Diabetes is usually irreversible, and while patients can live a relatively normal life, the disease's late effects result in shorter life expectancy and high medical costs. Microvascular damage, which causes diabetic retinopathy and nephropathy, and macrovascular disease, which causes

coronary artery disease, peripheral vascular disease, and stroke, are examples.

The structure of insulin and how it is produced are discussed.

Insulin is a hormone that is involves in the storage of chemical energy obtained from food and its controlled release. It's made in the beta cells of the pancreatic islets and has a chromosome 11 code for it. The beta version. cell's synthesis, internal processing, and secretion of insulin is characteristic of how the body manufactures and manipulates several peptide hormones. After secretion, insulin enters the portal circulation and is delivered to the liver, which is its major target organ. The liver extracts and degrades about half of the insulin produced; the rest The kidneys break it down. C-peptide is only partially extracted by the liver. (And hence gives a useful indicator of insulin secretion rate), whereas the kidneys breakdown it primarily. A brief overview of glucose metabolism. Blood glucose levels are carefully regulated in health and rarely fall outside the range of 3.5–8.0 mmol/L (63–144 mg/dL) despite the different demands of meals, fasting, and exercise. The fundamental organ of glucose homeostasis is the liver, which absorbs and stores glucose (as glycogen) in the post-absorption stage and releases it into the circulation between meals to match the rate of glucose utilisation by peripheral tissues. The gluconeogenesis process also allows the liver to convert 3-carbon compounds such as glycerol, muscle glycogen (lactate), and protein into the 6-carbon glucose molecule **[1-3]**.

Defination

Diabetes mellitus, a worldwide prevelling condition characterized by hyperglycemia, glycosuria, polyuria, polydipsia, ketoacemia, and a negative nitrogen balance, is currently the most serious life danger **[4]**.

Fasting values are 126mg/dl plasma glucose, and 2 hours after 75g glucose is given, the value is 200mg/dl.

Hyperglycemia results from uncontrolled reduced glucose absorption by skeletal muscle and increased hepatic glucose output, as well as decreased glycogen synthesis. When the renal glucose reabsorption threshold is crossed, glucose spills into urine, causing glycosuria and osmotic diuresis (polyurea). Polydipsia 1is a condition that causes dehydration, thirst, and increased drinking **[6]**.

Polyuria A thorough balance of water intake, renal perfusion, glomerular filtration, tubular re absorption of solutes, and reabsorption of water from renal collecting ducts regulates water homeostasis. Which must be separated from urinary frequency **[7]**.

Taking diuretics is the most prevalent cause of polyuria in adults and children, while

uncontrolled diabetes millutus is the most unusual cause. Although persons with type 2 diabetes may not have particular symptoms, one symptom that is characteristic of the condition is an increase in thirst. Other symptoms that may accompany excessive thirst include frequent urination, unusual hunger, dry mouth, and weight gain or loss **[8]**.

Epidemiology

According to WHO, From 108 million in 1980 to 422 million in 2014, the number of diabetic patients has surged dramatically. Diabetes is a chronic disease that occurs when the pancreas does not create enough insulin or when the body's insulin is not used efficiently. In comparison to high-income countries, there was only a 5% increase in diabetes-related premature mortality in low- and middle-income countries between 2000 and 2016. In the year 2014, 8.5 percent of persons aged 18 and over had diabetes, and Diabetes was directly responsible for 1.5 million fatalities. in 2019. However, these deaths were Caused by cardiovascular illness, which results in higher-than-optimal blood glucose levels. Tuberculosis, chronic kidney disease, and TB are all diseases caused by tuberculosis. disease, Another 2.2 million died in 2012 as a result of excessive blood glucose levels **[9, 10]**.

The number of persons diagnosed with By 2050, the number of people living with diabetes in the United States is predicted to reach 48.3 million. Between 2000 and 2016, the global risk Between the ages of 30 and 70, the risk of dying from one of the four major noncommunicable diseases (cardiovascular disease, cancer, chronic respiratory disorders, or diabetes) decreased by 18% **[11]**.

Type 1 diabetes Mellitus

Insulin-dependent diabetes, often known as type 1 diabetes, is characterized by a shortage of insulin. that necessitates daily insulin administration. Symptoms include excessive urine excretion (polyuria), Symptoms such as persistent hunger, weight loss, visual problems, and weariness might arise suddenly.

Type 1 diabetes bills for 5% to 10% of all diabetes occurrences, and autoimmune, genetic, and environmental factors are all risk factors for type 1 diabetes. Diabetes mellitus type 1 (T1DM) is a type of diabetes in which the body produces a catabolic condition caused by t lymphocytes (CD4 +CD8) In this condition, circulating insulin levels are low or nonexistent, plasma glucagon levels are high, and pancreatic beta cells fail to respond to all insulin secretory signals cues **[12]**. Then there are the life-threatening situations. hypoglycemia When cells do not receive enough glucose, they develop low blood sugar and hyperglycemia, and high blood sugar and hypoglycemia. and the

patient becomes unconscious or enters a coma, which can lead to death. Hyperglycemia and a prolonged lack of insulin can lead to ketoacidosis, which is an accumulation of ketones in the blood, when the body uses fat for energy instead of glucose. This is due to the fact that fatty acids cannot be turned into glucose at a constant rate **[13]**.

Type 2 diabetics Mellitus

Then there are the circumstances that are life-threatening. hypoglycemia When cells do not receive enough glucose, Hyperglycemia and low blood sugar, hypoglycemia and high blood sugar occur, and the patient falls unconscious or enters a coma, which can lead to death. Hyperglycemia with a prolonged lack of insulin can When the body burns fat for energy instead of glucose, it causes ketoacidosis, or an accumulation of ketones in the blood. This is due to the fact that fatty acids cannot be converted to glucose on a consistent basis, pace **[14]**.

Hyperglycemia is a symptom of the condition, which is caused by a combination of insulin resistance, insufficient insulin production, and excessive or inappropriate glucagon secretion. Inadequate insulin response is seen Insulin resistance is a condition that occurs as a result of the body's response to insulin. compensatory hyperinsulinemia Syndromes are the cause of this. Heart attacks and strokes are examples of cardiovascular illnesses, and hypertension, as well as polycystic ovarian syndrome, non-alcoholic fatty liver disease, Cancers of the liver, colon, breast, and prostate are one of the most common, are caused by syndromes **[15]**.

β-cell dysfunction is characterised by a reduction in the early phase of insulin production during glucose stimulation, and many cases of Before the development of glucose intolerance, type 2 diabetes occurs. Intolerance **[16]**.

Gestational diabetes

GDM is caused by insulin resistance and decreased beta cell activity. Pregnancy is a diabetogenic condition that causes insulin resistance. This is most noticeable as the pregnancy progresses towards the second trimester. Hyperglycemia in pregnancy has been linked to a variety of maternal and perinatal negative outcomes. Their offspring will having a significant lifetime risk of glucose obsession, obesity, and diabetes metabolic disease, while the mother will have a metabolic illness and diabetes are more likely to occur in the future. Human placental lactogen, progesterone, cortisol, growth hormone, and prolactin are all placental hormones, key contributors **[17]**. These hormones cause insulin receptor substrate phosphorylation to diminish, resulting in severe insulin resistance **[17]**. Tissue

necrosis factor and other cytokines have also Insulin resistance has been linked to the development. The pancreas should, logically, increase insulin output to meet this requirement. However, in GDM, cell activity deteriorates, notably Insulin secretion is in its initial stages. In a survey of Latina women, it was discovered that GDM, cell activity was When compared to a healthy pregnant control, the risk of death was determined to be 67 percent lower group **[18]**.

Pathophysiology

Hyperglycemia is a risk for diabetic patients. Because multiple causes can typically contribute to the condition, the pathophysiology of DM might be obscure. Hyperglycemia can affect pancreatic beta-cell activity and lead to insulin secretion problems **[19]**. As a result, there is a vicious cycle of hyperglycemia that leads to metabolic impairment. In this setting, blood glucose levels exceeding 180 mg/dL are frequently called hyperglycemic, albeit there is no clear cut-off point due to the multiplicity of mechanisms involved. At increased blood glucose levels, the glucose transporters in the nephron become saturated, causing osmotic diuresis. Serum glucose levels exceeding 250 mg/dL are likely to elicit polyuria and polydipsia symptoms, while the effect is inconsistent **[20]**. Nonenzymatic glycation of proteins and lipids occurs as a result of chronic hyperglycemia. The glycation haemoglobin (HbA1c) test can be used to determine the extent of this. Damage to the retina's tiny blood vessels, kidneys, and peripheral nerves is caused by glycation. Glucose levels that are higher expedite the process **[21]**. The traditional diabetic consequences of diabetic retinopathy, nephropathy, and neuropathy, as well as the avoidable outcomes of blindness, dialysis, and amputation, are all caused by this damage Insulin resistance is caused by excess fatty acids and proinflammatory cytokines, which limit glucose delivery and accelerate fat breakdown. Because the body's response or synthesis of insulin is inadequate, it responds by improperly boosting glucagon, causing to hyperglycemia. While insulin resistance is a part of T2DM, the condition is fully manifested when the patient's insulin production is insufficient to compensate for their insulin resistance **[20, 21]**.

Etiology

T2DM is a complex metabolic condition characterised by high blood sugar levels as the first clinical symptom. Levels for fasting and postprandial plasma glucose are higher in T2DM patients **[22]**. The development Normal glucose tolerance (NGT) to impaired glucose tolerance (IGT) to type 2 diabetes mellitus (T2DM) takes place in stages. The IR and insulin secretion disorders have a connection. causes the progression. To maintain normoglycemia, subjects release insulin from pancreatic cells. The physiologic reaction to insulin varies from person to

person. Even if blood glucose levels and glucose tolerance4 are normal when fasting, most people Those who develop IGT and later T2DM have some IR. Early in the illness process, fasting insulin levels and glucose-stimulated elevations in insulin responses by -cells are sufficient to maintain NGT. IGT patients have higher fasting and postprandial insulin levels, which don't adequately adjust for infrared radiation As islet cell function declines in some persons, compensation fails, resulting in a relative shortage of insulin output **[22]**.

DIAGNOSIS AND INVESTIGATION OF DIABETES

When overt symptoms are present, diabetes is easy to diagnose, A glucose tolerance test is only used in therapeutic situations. However, because there are unique glucose limits for macrovascular and microvascular disease, more precise epidemiological characterization is now possible due to the oral glucose tolerance test. According to epidemiological research, for every person diagnosed with diabetes, there is another who is undiagnosed. The intermediate group of poor glucose tolerance affects a substantially larger proportion of people **[23]**.

Impaired glucose tolerance (IGT)

Only a glucose tolerance test may be used to make the diagnosis, which is confounded by the low repeatability of the test's critical 2-hour value. The patients are diverse; some are fat, others Some people suffer from liver disease, while others are on drugs that affect glucose tolerance. Patients with IGT have the same risk of cardiovascular illness as those who have type 2 diabetes, but they don't acquire the microvascular consequences **[24]**.

WHO criteria for the diagnosis of diabetes are

>7.0 mmol/L (126 mg/dL) fasting plasma glucose >11.1 mmol/L (200 mg/dL) of random plasma glucose **[25]**.

In symptomatic patients, one aberrant in asymptomatic people, a laboratory value is diagnostic; two values are necessary.

It's only in borderline instances A glucose tolerance test is used to diagnose gestational diabetes. required. >6.5 (48 mmol/mol) HbA1c WHO guidelines for the glucose tolerance test Normal Inability to tolerate glucose Diabetes mellitus is a type of diabetes that affects people. two hours after glucose 11.1 mmol/L, fasting 7.0 mmol/L For adults, in a youth, 75 g glucose in 300 mL water equals 1.75 g glucose per kilogram body weight. All that is necessary is a 120-minute fast and a sample. For whole blood, the values are lower. than those for venous plasma. All individuals who fulfil the diabetes criteria are at risk for long-term consequences that can be debilitating **[25]**.

Impaired fasting glucose (IFG)

Fasting plasma glucose between 6.1 and 6.9 mmol/L falls under this diagnostic group benefit of not requiring a test for glucose tolerance Although It isn't always a medical entity, it does imply the chance of diabetes and cardiovascular disease, in the future. IFG and IGT share just a small amount of overlap, as a result, the risks of heart disease and diabetes are not directly equivalent. American Diabetes Association (ADA) has advocated a lower cut-off of 5.6 mmol/L (rather than 6.1 mmol/L), which, if followed, would considerably expand the number of people that fall into this category **[24]**.

Haemoglobin A1c (HbA1c)

HbA1c is a composite assessment of the present blood glucose level of a person over a period of time. The American Diabetes Association has advocated this metric as an alternate diagnostic test for diabetes due to its standardisation. According to the present proposal, a HbA1c level, a level of >6.5% (48 mmol/mol) is considered diagnostic of diabetes, but a level of 5.7–6.4% (39–46 mmol/mol) indicates an increased risk of diabetes. HbA1c can also be used as a diabetes diagnostic test, according to a recent WHO consultation. Unfortunately, there is minimal agreement between IGT, IFG, and HbA1c as prediabetes markers. In addition, many people in a mixed population will test 'normal' on glucose tolerance tests but be diabetes according to HbA1c standards. It makes a lot of people uncomfortable **[21]**.

Sing and symptoms

a) Indistinct visualization
b) Abnormal dehydration
c) Recurrent urination
d) Slow-healing incisions
e) Baffling weariness
f) Hasty mass loss (Type 1 diabetes)
g) Erectile dysfunction
h) Lack of sensation or itching in hands or feet
i) More thirst
j) More hunger
k) Peeing often
l) Dry mouth
m) Loss of consciousness

Significance of identifying prediabetes

Even early phases of prediabetes, such as IFG and IGT, are linked to a high risk of vascular complications, such as cardiovascular disease. More than 316 million people worldwide have diabetes, according to the International Diabetes Federation (IDF). Living with diabetes. persons (6.9%) worldwide who have IGT. More than 70% of them live in low- and middle-income countries. It's also worth noting that one-third of persons with IGT are currently in their productive years,

ranging from 20 to 39 years, and are thus likely to spend many years at high risk of acquiring diabetes and/or diabetic complications1. Reactive hypoglycemia occurs in some people with prediabetes 2-3 hours after a meal. This is a symptom of poor insulin metabolism, which can indicate the onset of diabetes. As a result, having a regular medical check-up in patients who have such symptoms or risk factors for diabetes would lower the risks of having undiagnosed diabetes. It would allow a significant number of people who would otherwise be silent suffers from the metabolic abnormalities linked with diabetes to improve their health **[26]**.

Herbal treatment for DM

Plant name (Botinicalname /family)	Parts used	BioactivityCompound	Related animal studies
Peepal (Ficus religiosa/moraceae)	Leaves Bark Fruits, Roots,	Non-enzymatic constituents include Flavonoids, glycosides, alkaloids, steroids, saponins, and diet C; enzymatic elements encompass catalase and peroxidase .	Aqueous extract of bark (50 and 100mg In diabetic rats, kg body weight) had a hypoglycemic effect. caused by streoptozotocin. [27-28]
Blackberry (syzygium cumini or eugenia jambolana/myryaceae)	Leaves Root Stem, seeds	Alkaloids , falvonoids, tannins, saponins,sterols,carbohydrate,polyphenols,ellagic acid , salicylic acid,fiber	In alloxan-induced diabetic rats, aqueous extract of syzygium cumini seeds (2.5g and 5g/ Kg frame weight) had a hypoglycemic effect. In alloxan-caused diabetic mice, an ethanolic extract of seeds from Eguenia jambolana (100 mg/kg frame weight) confirmed hypoglycemic Action [29, 30].
Fenugreek (Trigonella foenum Graceum/fabaceae)	Leaves seeds	Saponins,steroids zingerone, gingerol, eugenol cedrane, vanillin, zingerone, methanol extract.	alkaloids extract of In streptozotocin-induced hyperglycemic rats, fenugreek (60 mg/kg body weight) had a hypoglycemic effect [31, 32].
Bitter melon (momordica Charantia/cucurbitaceae)	Pulp,seeds and leaves	Triterpene,proteine,steriod, Inorganic alkaloids, lipids and phenolic chemicals, saponins, charantin, and resins	In normal mice, Aqueous extract of bitter melon decreased the glycemic reaction to each oral and intraperitoneal glucose loading while leaving the insulin response unchanged. At a dose of 20 mg/kg body weight, an aqueous extract powder of fresh unripe whole fruit lowered fasting blood glucose by 48% [33].
Onion Allium Cepa/amary llidaceae)	Whole	Alkaloids, flavonoids, cardiac glycosides, trepenes, steroids, and resins are some of the compounds found in plants.	Amixture of minerals and vitamin extract of onion juice (1ml/100g frame weight) showed hypoglycemic interest in alloxan induced Rats [34, 35]

Gum arabic (Acacia nilotica/fabaceae)	**Bark,pods,leaves**	**Tannins gallic acid,alkloides Saponins**	**In alloxan-induced diabetic mice, aqueous extracts of gum arabic leaves had a hypoglycemic effect [37].**
Aloe vera (Barbadensis mill/asphodelaceae)	**Leaves extract**	**Anthraguinoes, Glycosides,vitamins (A,C,E)lipds,sterols,gibberlins,pseudoprototinosaponis AIII,prototinosaponinsAIII**	**Antharquinone extract of leaf pulp of aloevera (300mg/kg body weight)showed hypoglysmeic effect in streptozotocininduc [38]**
Gooseberry (ribes uva-crispa/grossulariaceae	**Whole**	**Tannis,phenoles, alkaloids,flavonoids,gallic acid,corilagin,geranin,ellagic**	**Phenols extract In type 2 diabetic rat models, gooseberry (13.5 mg/kg bodyweight) showed hypoglycemic action [39].**
Mulberry(morinda \sCitrifolia/moraceae) morus alba) and white mulberry	**Leaves, fruits**	**Rutin, isoqurecitrin,astragalin caffeic acid,ethanol,methanol,kaemperfol**	**In type 2 diabetic mouse models, terpenoids and falvonoids extracted from white mulbery solid had a hypoglycemic impact. In stretozotocin- Protine extracts from mulberry leaves (35 mg/kg body weight) had a hypoglycemic activity on diabetic rats effect [40, 41].**
Radish (raphanussativus/brassicaceae)	**Roots and leaves**	**potassium chloride, sodium acetate, acetone, acetic acid, trifluoracetic anthocyanin, potassium chloride**	**In streptozotocin-prompted diabetic rats, aqueous extract of root juice (300mg/kg frame weight) had a hypoglycemic effect [42].**
Coriander Coriandrum sativum/umbellifers	**Leaves roots and seed**	**Flavonoids,steroids ,amino acid saponins and tannis**	**A dose of 200mg/kg and 400mg/kg bodyweight of a methanolic extractof corriander A considerable dose-based drop in blood glucose level was observed [43].**
Cumin (syzygium cumini or cumini or cuminum cyminum/umbelifers)	**Seeds**	**Flavonoids ,antharquinones phytosterol,saponin,steriods,tannins,triterpennoids**	**Hyperglycemia and glucosuria were reduced in normal rats fed 1.25 percent cumin powder for 8 weeks [44].**
Cinnamon (cinnamomum cassia)	**Seeds ,stems**	**Methylhdroxychalcone ,tannins, falvonoids glycosides terpenoids ,coumarins,anthraquinones**	**Cinnamon methanol extracts had a beneficial effect on diabetic rats caused by streptozotocin.(3g/kgbody weight) [45].**
Olives (Oleaeuropaea/Oleaceae)	**Leaves fruits, roots**	**Alkaloids, terpenes, secoridoids, ethanol, oleosides, tyrosol**	**In streptozotocin-induced diabetic rats, Olive leaf aqueous extracts (200 mg/kg body weight) exhibited hypoglycemic effects. Polyphenol extracts of olive leaves (500 mg/kg body weight in tablet form) showed a hypoglycemic activity on streptozotocin-induced diabetic mice impact [46].**
Ginger (Zingiber officinale/Zingiberaceae)	**whole**	**Flavonoids, saponins, tannins, terpenoids, phenols**	**In streptozotocin-induced diabetic rats, an A hypoglycemic effect was observed using an**

			ethanolic extract of ginger garlic powder (500 mg/kg body weight) [48].
Lilac/Neem (Azadirachta indica/Meliaceae	**Leaves, root, stem, flowers, seeds, bark**	**Isoazadirolide, nimbaflavone, nimbandiol, nimbinene, nimbolide, quercetin, quercitrin**	**In Streptozotocin-caused diabetic rats, ether extracts of neem seed (2 g/kg frame weight) showed anti-diabetic properties [49].**
Curry leaves (Murraya koenigii/Rutaceae)	**Leaves**	**Carbohydrates, alkaloids, phytosterols, alcohol, flavonoids, saponins, tannins, glycosides, and are some of the compounds found in plants.**	**In alloxan-triggered diabetic rats, aqueous extracts of curry leaves (three hundred mg/kg frame weight) confirmed anti-diabetic action. In streptozotocin-triggered diabetic rats, dried powdered curry leaves (35 mg/kg frame weight) had hypoglycemic Effects [50].**
Gymnema (Gymnema slyvestre/Asclepiadaceae)	**Leaves**	**Steroids, terpenoids, alkaloids, flavonoids, coumarins, saponins, tannins**	**In streptozotocin-triggered diabetic rats, leaf ethanolic extracts discovered hypoglycemic action [51].**

DISCUSSION

The growing The quantity of diabetic patients, the high expense of medical therapy, the poor treatment outcomes, and public scepticism of today's health-care facilities all point to the modern medical system's still imperfect character. These elements are the primary reasons for people's continued faith in established medical systems. Despite major advancements in T2D research and the introduction of anti-diabetic medicines, no solutions have been discovered. T2D therapies abound in medicinal herbs, which have long been employed in alternative and complementary medicine systems.

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