



Diabetes Mellitus – Pathophysiology & Herbal Management

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Article Information

Received 14 May 2017
Received in revised form 19 Oct 2017
Accepted 21 October 2017

Keywords:

Diabetes Mellitus,
Hyperglycemia,
Metabolic disarray,
Hypoglycemic agents,
Herbal formulations

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Abstract

Diabetes Mellitus (DM) is a metabolic disorder characterized by the occurrence of unceasing hyperglycemia each immune-mediated (Type 1 diabetes), insulin resistance (Type 2), gestational or others (surroundings, hereditary defect, infection as well as assured drugs). Here be tons of chemical agents available to control and to treat diabetic patients, but total recovery from diabetes has not been reported up to this date. The modern oral hypoglycemic agents produce undesirable side effects. Plants by virtue of its composition of containing multiple constituents developed during its growth under various environmental stresses providing a plethora of chemical families with medicinal utility. Herbal formulations are becoming popular now days particularly in the treatment of diabetes due to lesser side effect and low cost. This review focuses on the potential of different polyherbal formulation in the treatment of diabetes and also reviews their pharmacological investigations.

1 Introduction

A cluster of metabolic ailments exemplified through hyperglycemia termed as diabetes mellitus results from deficiency in insulin discharge, insulin attainment, or equally¹. Diabetes mellitus is not a single disorder but it is a group of metabolic disorder characterized by chronic hyperglycemia, resulting from defects in insulin secretion. Increased thirst, increased urinary output, ketonemia and ketonuria are the common symptoms of diabetes mellitus, which occur due to the abnormalities in carbohydrate, fat, and protein metabolism, and protein metabolism. When ketones body is present in the blood or urine, it is called ketoacidosis, hence proper treatment should be taken immediately, else it can leads to other diabetic complications.

The pancreas is an organ positioned after the abdomen where insulin is prepared. The pancreas hold bunch of cells named islets. Inside the islets, beta cells build insulin as well as liberate it into the blood.

If beta cells don't produce enough insulin, or the body doesn't respond to the insulin that is present, glucose builds up in the blood instead of being absorbed by cells in the body, leading to prediabetes or diabetes. Prediabetes is a condition in which

blood glucose levels or A1C levels—which reflect average blood glucose levels—are higher than normal but not high enough to be diagnosed as diabetes. In diabetes, the body's cells are starved of energy despite high blood glucose levels².

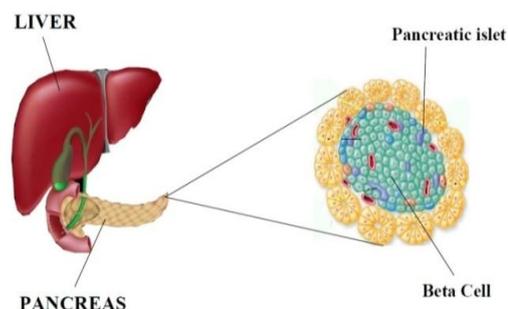


Fig.1: Islets inside the pancreas enclose beta cells, which construct insulin plus discharge it into the blood

Diabetes mellitus is aggravated by and associated with metabolic complications that can subsequently lead to premature death.^[3] The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.

1.2 Etymology

The word 'diabetes' is derived from the Greek word "Diab" (meaning to pass through, referring to the cycle of heavy thirst and frequent urination); 'mellitus' is the Latin word for "sweetened with honey" (refers to the presence of sugar in the urine). It is reflection that the Greeks name it so owing to the extreme amount of urine formed via diabetics attracted flies and bees³.

2 Classifications

Diabetes is classified into two main types: type 1 diabetes & type 2 diabetes. Gestational diabetes a third type is seen only in pregnancy.

2.1 Type 1 diabetes (moderate production of insulin)⁴

Type 1 diabetes is an autoimmune disease in which the β -cells of the pancreas do not produce sufficient insulin, a hormone which helps use blood sugar (glucose) for energy. The cells become starved of energy and there will be excess of glucose in the blood. This is then followed by life threatening conditions of hypoglycemia, low blood sugar, and hyperglycemia, high blood sugar. When hypoglycemia develops, cells do not get enough glucose and patients suffer of confusion, loss of consciousness, and coma. Even death can results when the brain is deprived of glucose for too long⁵.

Type 1 occurs in childhood, mainly due to destruction of pancreatic β -cell islets through autoimmune-mediated, resulting in absolute insulin deficiency. it is a lifetime (chronic) ailment with elevated intensity of sugar (glucose) in the blood. The rate of cell damage is somewhat inconsistent in this type of diabetes being hasty in some persons (chiefly infants and children) and deliberates in others (primarily adults). Several patients, mostly kids and youngsters may begin with ketoacidosis as the first symptom of the disease. Hyperglycemia and prolonged absence of insulin may lead to ketoacidosis, which is accumulation of ketones in the blood when the body uses fat for energy instead of glucose. This is because fatty acids cannot be converted into glucose at steady state. Ketones make the blood acidic and slow down all body functions. This also leads to a coma and eventually death^{1, 6}.

2.2 Type 2 diabetes (weakened reaction to insulin or β -cell dysfunction)⁴

Type 2 diabetes mellitus is a complex endocrine and metabolic disorder. Type 2 is more associated with an adulthood and elderly people, which are mainly due to insulin resistance or abnormal insulin secretion. In addition, hypertension and dyslipidemia (high triglyceride and low HDL-cholesterol levels; postprandial hyperlipidemia) often are present in these individuals. This is the most common form of diabetes mellitus and is highly associated with a family history of diabetes, older age, obesity and lack of exercise⁷.

Overweight and obesity are major contributors to the development of insulin resistance and impaired glucose tolerance. When β cells have not longer able to secrete sufficient insulin to overcome insulin resistance, impaired glucose tolerance progresses to type-2 diabetes. Abnormalities in other hormones such as reduced secretion of the incretin glucagon-like peptide 1 (GLP-1), hyperglucagonaemia, and raised concentrations of other counter-regulatory hormones also contribute to insulin resistance, reduced insulin secretion, and hyper glycaemia in type 2 diabetes⁵.

2.3 Gestational diabetes

Gestational diabetes mellitus (GDM) is defined as any abnormal carbohydrate intolerance that begins or is first recognized during pregnancy. It does not exclude the possibility that unidentified glucose intolerance have preceded the pregnant state. It is often diagnosed in middle or late pregnancy. Because high blood sugar levels in a mother are circulated through the placenta to the baby, gestational diabetes must be controlled to protect the baby's growth and development.

Gestational diabetes mellitus is defined by glucose hypersensitivity of inconsistent sternness with beginning of initial identification in pregnancy. Hyperglycemia in pregnancy is found to be related through diverse motherly as well as prenatal undesirable outcome. Their offspring will contain a lifetime raise possibility of glucose fanaticism, stoutness plus metabolic disorder while the mother will contain an elevated threat of metabolic disorder and diabetes in the future⁸.

3 Symptoms

Common symptoms include the following⁵:

- Indistinct visualization
- Abnormal dehydration
- Recurrent urination
- Slow-healing incisions
- Baffling weariness
- Hasty mass loss (Type 1 diabetes)
- Erectile dysfunction^[5]
- Excessive thirst
- Feeling very tired much of the time
- Very dry skin
- More infections than usual
- Tingling or numbness in the feet or toes.

Some of the risk factors for getting diabetes include being overweight or obese, leading a sedentary lifestyle, a family history of diabetes, hypertension (high blood pressure), and

low levels of the "good" cholesterol (HDL) and elevated levels of triglycerides in the blood.

4 Pathophysiology

The principal hormone that regulates the uptake of glucose from the blood into most cells of the body, especially liver, muscle, and adipose tissue is insulin. Hence its deficiency or the tactlessness of its receptors depicts a vital task in the entire type of diabetes mellitus. Beta cells (β-cells), found in the islets of Langerhans in the pancreas, release insulin into the blood in response to rising levels of blood glucose, typically after eating. About two third of the body's cells use insulin for glucose absorption from the blood for use as fuel, for conversion to other needed molecules, or for storage. Decreased insulin release from the beta cells and the breakdown of glycogen to glucose is an outcome of lower glucose levels.

The hormone glucagon primarily controls this process, which acts in the converse manner to insulin. If the amount of insulin available is insufficient, if cells respond poorly to the effects of insulin (insulin insensitivity or insulin resistance), or if the insulin itself is defective, then glucose will not be absorbed properly by the body cells that require it, and it will not be stored appropriately in the liver and muscles. The net result is steadily elevated intensity of blood glucose, reduced protein synthesis, plus additional metabolic derangements, such as acidosis. while the glucose concentration in the blood vestiges elevated above time, the kidneys will achieve a portal of reabsorption, excretion in the urine (glycosuria)⁹ (Fig.- 2a,2b & 2c).

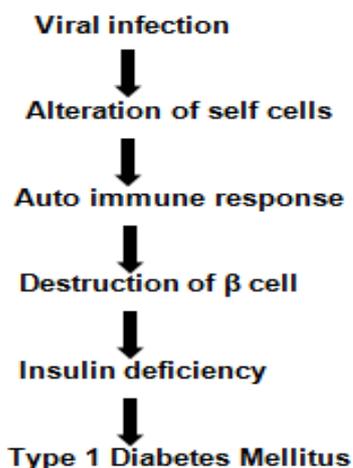


Fig.2a: Schematic diagram representing pathophysiology of type-1 diabetes¹⁰

5 Etiology

5.1 Causes related to type-1 diabetes

Hereditary vulnerability

Genetics plays an essential part in determining who is likely to develop type 1 diabetes. Genes are passed down from biological parent to child. Genes carry instructions for making

proteins that are needed for the body's cells to function. Variations in genes that affect more than 1 percent of a population group are called gene variants.]

Certain gene variants that carry instructions for making proteins called human leukocyte antigens (HLAs) on white blood cells are linked to the risk of developing type 1 diabetes. Some combinations of HLA gene variants predict that a person will be at higher risk for type 1 diabetes, while other combinations are protective or have no effect on risk².

Autoimmune damage of Beta Cells

In this form of diabetes, T cells hit and demolish beta cells. The course of action starts well earlier than diabetes sign emerges and persists following identification. Type 1 diabetes is not identified frequently until major beta cells have by now been damaged. At this peak, an individual wants every day insulin therapy to stay alive.

Ecological aspects

Ecological aspects such as foodstuffs, viruses and pollutants might play a part in the advancement of type 1 diabetes, although the precise character of their function has not been resolute. Few speculations propose that ecological features prompt the autoimmune damage of beta cells in people with a hereditary vulnerability to diabetes. Further hypothesis imply that ecological features play an enduring part in diabetes, yet subsequent to diagnosis².

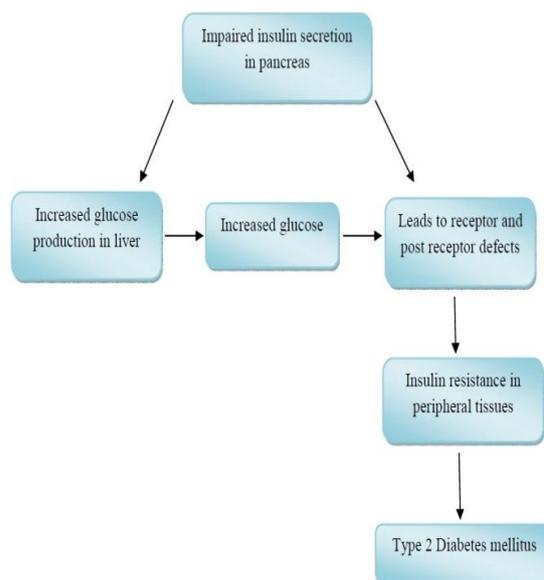


Fig.2b: Pathophysiology of type-2 diabetes¹⁴

5.2 Causes related to type-2 diabetes

Hereditary vulnerability

Genes play a major piece in propensity to type 2 diabetes. Comprising definite genes or mixture of genes might augment or lessen a person's danger for possessing the ailment. The role of genes is recommended by the elevated pace of type 2

diabetes in families and identical twins and extensive deviation in diabetes predominance through traditions. Learnings have revealed that variants of the TCF7L2 gene enhance vulnerability to type 2 diabetes.

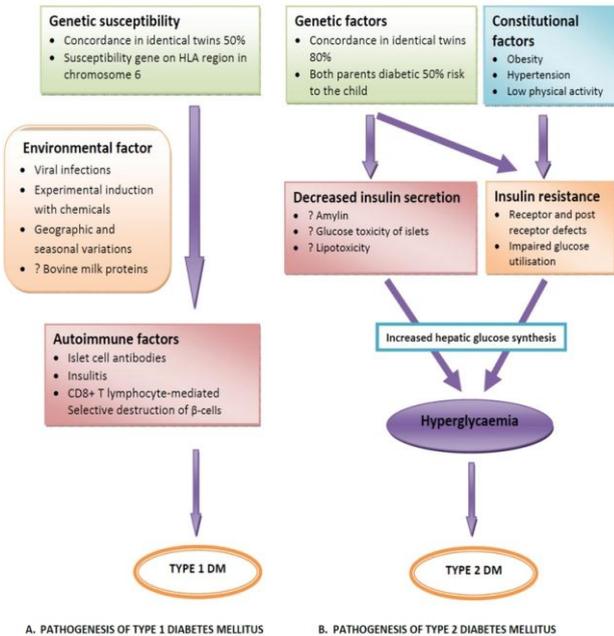


Fig.2c: Schematic mechanism involved in pathogenesis of two main types of diabetes mellitus

Fatness and Physical Sluggishness

Physical sluggishness and fatness are stoutly linked via growth of type 2 diabetes. When these hazardous features are nearby the people who are genetically susceptible to type 2 diabetes are more vulnerable. Difference among caloric ingestion along with physical activity can lead to fatness which cause insulin resistance and is frequent within public with type 2 diabetes. Fundamental heaviness, within which an individual have surplus abdominal fat, is a foremost hazard issue not merely for insulin resistance as well as type 2 diabetes however also for heart plus blood vessel ailment furthermore termed cardiovascular disease (CVD). This surplus “abdomen stout” produces hormones along with additional materials that be able to cause dangerous unremitting consequences inside the body like harm to blood vessels.

Insulin Resistance

Ordinary situations in public who are heavy or overweight contain surplus abdominal fat, as well as are not bodily energetic. Muscle, fat, as well as liver cells impede reacting correctly toward insulin, forcing the pancreas to balance through generating superfluous insulin. Blood glucose intensity resides within the usual array, as long as β - cells are capable to generate adequate insulin. However as insulin production wane since β - cell dysfunction, glucose intensity increases foremost to pre-diabetes or diabetes.

Irregular Glucose Production through the Liver

An abnormal increase in glucose production by the liver also contributes to high blood glucose levels in some people with diabetes. Generally, the pancreas discharges the hormone glucagon when blood glucose as well as insulin intensity is small. The liver is stimulated by glucagon and produces glucose which is released into the bloodstream. Glucagon levels drop, when blood glucose and insulin levels are high after a meal and the liver stores surplus glucose intended for later, as needed. In several populaces with diabetes, glucagon intensity reside elevated than required. Elevated glucagon intensity cause the liver to generate unwanted glucose, which throw in to elevated blood glucose intensity².

6 Complications

6.1 Acute complications¹¹

- Diabetic ketoacidosis
- Hyperglycemia hyperosmolar state
- Hypoglycemia
- Diabetic blackout
- Erectile Dysfunction
- Respiratory contagion
- Periodontal sickness
- metformin associated lactic acidosis, MALT

6.2 Chronic complications¹²

- Diabetic retinopathy
- Diabetic nephropathy
- Diabetic neuropathy
- Macrovascular diseases (CHD, peripheral vascular disease, stroke)

6.3 Other complications and associated conditions

- Impaired growth and development
- Hypothyroidism
- Hyperthyroidism
- Celiac disease
- Vitiligo
- Primary adrenal insufficiency (Addison’s disease)
- Lipodystrophy (lipoatrophy and lipohypertrophy)
- Necrobiosis lipoidica diabetorum
- Non-alcoholic fatty liver disease
- Infections seen in patients with diabetes

- k) Limited joint mobility
- l) Edema

7 Diagnosis

Following tests are employed in diagnosing of diabetes

Random plasma test

This is the simplest test that requires no fasting prior to the test. Blood glucose of 200 or more than 200mg/dl possibly specify diabetes but have to be confirmed again.

Fasting plasma glucose test

The FPG is most reliable when done in the morning. The test requires eight hours fasting. If your fasting glucose level is 100 to 125 mg/dL, you have a form of prediabetes called impaired fasting glucose (IFG), meaning that you are more likely to develop type 2 diabetes but do not have it yet. A level of 126 mg/dL or above, confirmed by repeating the test on another day, means that you have diabetes¹².

Oral glucose tolerance test (OGTT)

This test is carried out when random plasma glucose test is 160-200 mg/dl and the fasting plasma test is 110-125 mg/dl. This blood test estimates body's response to glucose is estimated. Fasting of at least eight but not more than 16 hrs is required in this test. Fasting glucose intensity is resolute furthermore provide 75 gm of glucose, 100 gm for pregnant women. Every 30 minutes to one hr for two or three hrs the blood is tested. If the glucose level at two hrs is less than 140 mg/dl, then this test is normal. A diabetes diagnosis is confirmed with the fasting level of 126 mg/dl or greater and two hour glucose level of 200 mg/dl or Higher.

HbA1C (A1C or glycated hemoglobin test)

This test can be used for the diagnosis of both prediabetes and diabetes. Average blood glucose control for the past 2 to 3 months is measured. Moreover this test is more convenient as no fasting is required. When the A1C is 6.5% or higher, diabetes is diagnosed¹³.

Fructosamine test

The main component of plasma proteins is albumin. Since albumin too includes open amino clusters, non-enzymatic response among glucose within plasma occurs. Thus, glycated albumin be able to equally serve up like a indicator to examine blood glucose. Glycated albumin is generally taken to present a fair measure of regular blood glucose concentration greater than a time of 1 to 3 weeks.

Gestational diabetes

It is also diagnosed based on plasma glucose values measured during the OGTT. Blood sugar levels are checked four times during

the test. If your blood sugar levels are above normal at least twice during the test, you have gestational diabetes¹².

8 Management

Diabetes mellitus being a persistent ailment for which there is no identified treatment excluding very explicit situation. Maintaining blood sugar levels since close toward normal being the attention towards management, exclusive of causing stumpy blood sugar. This be able to generally consummate by means of a well diet, work out, mass loss, along with employment of suitable drugs (insulin during the case of type 1 diabetes; oral drugs, as well as probably insulin, during type 2 diabetes)⁹.

The importance of regular follow-up of diabetic patients with the health care provider is of great significance in averting any long term complications. Studies have reported that strict metabolic control can delay or prevent the progression of complications associated with diabetes. Results of large randomized trials involving patients with type 1 diabetes or newly recognized or established type 2 diabetes show that control of glycemia delays the onset and slows the progression of micro vascular complications, including nephropathy, retinopathy, and neuropathy. The needs of diabetic patients are not only limited to adequate glycemic control but also correspond with preventing complications; disability limitation and rehabilitation. Some of the Indian studies revealed very poor adherence to treatment regimens due to poor attitude towards the disease and poor health literacy among the general public.

The diabetic managing of diabetes mellitus being an accompaniment of lifestyle management and has a affirmative result on long term fitness along with quality of life. Diebetic managing seeks on best metabolic control with creating equilibrium among food ingestion, bodily motion in addition to medicine in the direction of evading problems. The dietary objective in type 2 diabetes is for improved glycemic and lipid levels and weight loss as appropriate.

9 Treatments

Medicines employed to extravagance diabetes act consequently through lessening blood sugar levels. Here are a number of diverse classes of anti-diabetic medicines.

9.1 Herbal treatment for diabetes

Herbal drugs have been employed from the time of the beginning of human beings on this earth and as a consequence is approximately as old as time itself.^[15] Even though here are numerous synthetic medications designed for patients, however it is the reality that it has in no way been account that someone had recovered completely from diabetes. The present oral hypoglycemic agents generate adverse consequence. Therefore, during the recent times great considerations have been aimed on the antidiabetic potential of

therapeutic foliage plus their herbal formulation in the management of ailment. Substitute to these synthetic agents various herbal plants with hypoglycemic assets are identified since crosswise the planet. 21,000 plants have been listed by

the World Health Organization (WHO), which are utilized for therapeutic rationale around the world. Several therapeutic plants with possible antidiabetic actions accounted with their promising mode of action have been listed below^{16, 17} (Table-1):

Table 1: Medicinal plants with possible antidiabetic activity

Botanical Name	Common Name	Part Used	Active Constituent	Mode of Action
<i>Aegle marmelos</i> ¹⁶	Bael ¹⁸	Leaf ¹⁹	Aegelin ²⁴	Augments consumption of glucose each via straight stimulation of glucose uptake otherwise via the arbitration of improved insulin discharge and have strong antioxidant activity, which can account for the hypoglycemic potential
<i>Allium cepa</i> ¹⁶	Onion ²⁰	Bulb ²¹	Quercetin ²⁵	Lessens oxidative strain as well as conserve pancreatic beta cell reliability ²⁶
<i>Azadirachta indica</i> ²³	Neem ²²	Leaf and bark ²³	Quercetin, rutin, and nimbidin ²⁷	β cells rejuvenation ¹⁶
<i>Brassica juncea</i> ¹⁶	Indian mustard ²⁸	Seed ²⁹	Isothiocyanate glycoside singrin ¹⁵	Hepatic glycogen and glycogenesis mass is increased and the activity of glycogen phosphorylase and gluconeogenic enzymes is repressed, directs the reduction in glycogenolysis and gluconeogenesis ¹⁶
<i>Cajanus cajan</i> ³¹	Pigeonpea ³¹	Leaves ³¹	Two globulins, cajanin and concajanin ³⁰	Plasma glucose extent is lowered ¹⁶
<i>Eucalyptus globules</i> ³²	Blue gum ³³	Leaves ³²	Polyphenols, proanthocyanidins, anthocyanins ³²	Hamper α-glucosidase ³²
<i>Aloe vera</i> ³⁴	Aloe ³⁵	Gel from leaves ³⁵	Barbaloin ³⁶	Stimulate production and/or discharge of insulin from pancreatic beta cells ¹⁷
<i>Catharanthus roseus</i> ¹⁶	Madagascar periwinkle ³⁷	Leaf ¹⁶	Indole alkaloid (vincristine) ¹⁵	Raise mobilization of glucose ¹⁵
<i>Cryptolepis sanguinolenta</i> ¹⁵	Anantmul ¹⁵	Stem ³⁸	Cryptolepine ¹⁵	Glucose uptake is enhanced by 3T3-L1 cells ¹⁵
<i>Olea europia</i> ¹⁵	Olive ¹⁵	Leaf ³⁹	Oleuropeoside ¹⁵	Potentiates glucose, stimulation of insulin discharge and escalates peripheral uptake of glucose ¹⁵

9.2 Polyherbal formulation for diabetes

Dihar

✓ A polyherbal formulation holding eight diverse herbs *Syzygium cumini*, *Momordica charantia*, *Emblica officinalis*, *Gymnema sylvestre*, *Enicostem*, *Azadirachta indica*,

Tinospora cordifolia and *Curcuma longa*.

✓ Literatures revealed that combination of these eight herbs shows effective Anti-hyperglycemic activity in

Streptozotocin (STZ,45 mg/kg iv single dose) induced type 1 diabetic rats.

Diasol

✓ Holds plant extracts of *Eugenia jambolana*, *Foenum graecum*, *Terminalia chebula*, *Quercus, infectoria*, *Cuminum cyminum*, *Taraxacum officinale*, *Embllica officinalis*, *Gymnea sylvestre*, *Phyllanthus nerui* and *Enicostemma littorale*.

✓ Previous investigation showed Diasol produced 63.4 % reduction of blood glucose level in a dose of 125 and 250 mg/kg b.w i.p and proved to be effective antidiabetic polyherbal formulation.

Dia-Care

✓ Containing Sanjeevan Mool; Himej, Jambu beej, Kadu, Namejav, Neem chal is a herbal formulation alleged to be efficient for together Type 1, Type 2 diabetes surrounded by 90 days of treatment and heals within 18 months.

✓ With 1/2 glass of water, approx. 5 grams (1 tea spoon) powder is blend stirred well set aside overnight and filtered. The filtrate is taken in the morning on empty stomach.

Diabeta

✓ A formulation obtainable in the capsule type is an anti-diabetic among mixture of verified anti-diabetic equipped with strong immunomodulators, antihyperlipidemics, anti-stress and hepatoprotective of plant source include *Gymnema sylvestre*, *Vinca rosea*, *Curcuma longa*, *Azadirachta indica*, *Pterocarpus marsupium*, *Momordica charantia*, *Syzygium cumini*, *Acacia arabica*, *Tinospora cordifolia*, and *Zingiber officinale*.

Karmin Plus

✓ Holds *Momordica charantia*, *Azadirachta indica*, *Picrorrhiza kurroa*, *Ocimum sanctum* and *Zinziber officinale* is a local polyherbal formulation.

✓ Banger et al estimated its antidiabetic action and established that on two dosage stage by 200 mg/kg and 400 mg/kg body weight product confirmed efficacy for antidiabetic action.

10 Conclusion

In recent years, diabetes has become a major health problem worldwide, affecting people across all ages, sex, ethnicities, and races, and its prevalence has been increasing at an alarming rate. The associated complications of synthetic drugs have lead to a shift towards locating natural resources showing anti diabetic activity. Thus many different plants have been used individually or in formulations for treatment of diabetes and its complications. The above-mentioned plants have been considered for their possible hypoglycemic actions and the researchers have carried out some preliminary investigations. It

is important to know the active component and their molecular interaction, which will help to analyze therapeutic efficacy of the product and also to standardize the product. Efforts are now being made to investigate mechanism of action of some of these plants using model systems.

10 Conflict of interests

The author declared none

11 Author's contributions

NP and PP carried out literature review and draft the manuscript. AR participated in collection of data. All authors read and approved the final manuscript.

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