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# Management of diabetes: Current treatments and their alternatives

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***Abstract*---**Diabetes is the ninth largest cause of death globally and one of the most common lifestyle diseasesIt is the outcome of an intricate interaction between inherited and environmental factors. Obesity, urbanization, and genetic mutations are examples of internal and external variables that may raise the chance of getting diabetes. This paper seeks to review the various treatment, mechanism of action, and various formulations and doses available on the market to treat diabetes in the current era. It will also concentrate on the most promising novel therapeutic approaches now being examined in clinical trials, as well as the financial implications of such therapies in future markets. The high cost and severe adverse effects of allopathy treatment, most people continue to rely on it owing to a lack of knowledge about herbal medication, such as which herbs or species are used to treat diabetes and at what dose. Most of these drugs are particularly targeted on DPP4, AM2A, PPARA, GLP-1, SGLT2, and PTPN9. The study shows that flavonoids and terpenoids are the main constituents and show potential anti-diabetic effects in the herbal drug.

***Keywords*---**diabetes mellitus, beta cells, treatment, marketed formulation, brand name, dose, patents.

## Introduction

Diabetes Mellitus (DM) is one of humanity's earliest diseases, having been written about 3000 years ago in an Egyptian book. Type 1 and 2 diabetes were first distinguished in 1936, and type 2 Diabetes Mellitus was classified as a metabolic syndrome in 1988 (1). It has risen dramatically in recent years, and 42.2 crore individuals worldwide suffer from diabetes, with 15 lakh people dying each year, the majority of them residing in developing countries (2). Diabetes, often known as diabetes mellitus, is a situation in which the body's capacity to manage blood sugar levels is impaired. Diabetes is a chronic metabolic illness due to high blood sugar levels that can affect the kidneys, heart, eyes, lower limbs, nerves and blood vessels. It's done when the pancreatic islet β-cells don't create enough insulin to keep the blood glucose, or sugar level, under control (3).

Understanding the pathophysiology is necessary for the effective treatment of diabetes. Thus, type 1 diabetes is an autoimmune disorder in which T-cells ruin 70-90% of the pancreatic Beta-cells, leading to insulin deficiency. Currently, the only available treatment is insulin administration. However, type 2 diabetes is a complex disease. In this, there is a reduction of glucose receptors on β-cells, causing them to respond to greater glucose concentrations or relative β-cell insufficiency, or a decrease in the number of insulin receptors, resulting in insulin resistance, This kind of diabetes is particularly common in people who are overweight and do not engage in physical activity. Only 1% of all cases are suffered from Gestational diabetes and Maturity-onset diabetes of the young (MODY)(4).

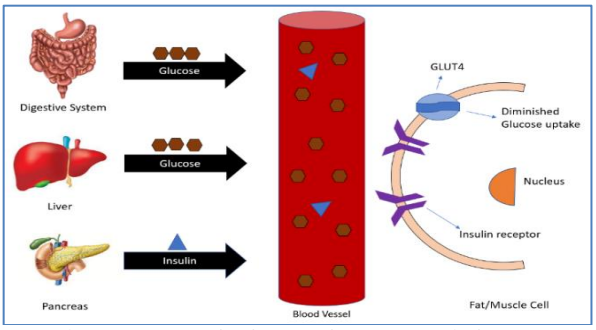


Figure 1. Pathology ofType-1 Diabetes

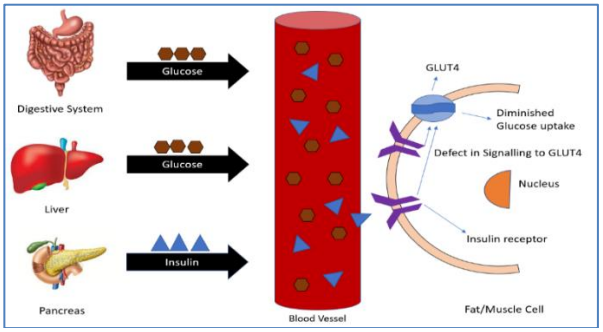


Figure 2. Pathology of Type-2 Diabetes

## Existing treatment

### Lifestyle changes

Diet and physical exercises are the two primary energy balance regulators and base treatment in the management of diabetic patients. Getting enough sleep is also crucial for maintaining and improving our health and energy levels (5). In order to maintain good physical and mental health, patients should be urged to sleep for at least seven hours each day. Sleep deprivation exacerbates dyslipidemia, insulin resistance, hyperglycemia, and hypertension, whereas having 6 to 9 hours of sleep improves cardiometabolic risk factors. Patients with obstructive sleep apnea should be referred to a sleep specialist for diagnosis and treatment (6).

### Diet

Unhealthy foods are now more readily available as a result of substantial changes in the food production, processing, and distribution systems brought on by economic growth and environmental changes (7). It has been advised that a diabetic patient with an obese diet should consume 500 to 1000 kcal less than their energy demands in order to achieve this goal. This weight loss enhances insulin sensitivity, which is a good thing when it comes to glycemic control. Fibre, especially cereal fiber has been proven to improve cardiovascular risk factor control as well as glycaemic control, resulting in a lower risk of cardiovascular mortality in diabetics. In diabetes patients, fibre and whole-grain intake should be similar as recommended to the normal population: roughly 25 g/d for women and 38 g/d for men. Cholesterol, triglycerides, LDL, and HbA1c levels improve when 28 percent - 40 percent of the energy in the diet is consumed as protein. Proteins appear to increase insulin response; hence they are not recommended in hypoglycemic circumstances (8). Diabetes risk was found to increase with increasing heme-iron intake. Diabetes was also increased by larger iron reserves, as indicated by increasing ferritin concentrations. DASH (Dietary Approaches to Stop Hypertension) is a diabetes treatment program that incorporates a low-fat, low-carbohydrate diet (7).

### Exercise

The sympathetic nervous and endocrine systems play a significant role in the maintenance of normal blood sugar levels both at rest and during exercise. Glycogen is the main source of energy for working muscles during exercise. As glycogen supplies are depleted, muscles improve their uptake and use of circulating blood glucose and free fatty acids produced from adipose tissue (9). In several trials, people with T2DM who exercise displayed considerable decrease in HbA1c and depression and enhance metabolic parameters, tissue insulin sensitivity, lipid profile, glycemic and blood pressure control (10). In diabetics, both aerobic and resistance training has been shown to raise glucose uptake and lessen insulin resistance. The improved sensitivity and glucose tolerance last for 12-24 hours and it's best to exercise at least five days or at least 150 minutes a week (5). Intense aerobic exercise raises the plasma catecholamine levels, significantly increasing glucose synthesis, which leads to hyperglycemia and on stopping the exercise, glucose production does not instantly return to normal (9).

**Pharmacological Treatment**

Various types of drugs are available on the market orally or in an injectable form to help diabetics lower their blood sugar levels. Each type operates uniquely.

Table 1. List of Commercialized Antidiabetics Drugs with mode of action and their adverse effects (5)

| S. No. | Drug (Brand Name) | Classification | Mode of action | Side Effect |
|---|---|---|---|---|
| 1 | Miglitol (Glyset), Acarbose (Precose) | Alpha-Glucosidase inhibitory activity | Prevent starches and glucose from being absorbed. | Stomach Pain, Diarrhea, Gas, Abnormal Liver Tests |
| 2 | Repaglinide (Prandin), Nateglinide (Starlix) | Meglitinides | Helps to make more insulin | Hypoglycemia |
| 3 | Pioglitazone (Actos), Rosiglitazone (Avandia) | Thiazolidinediones | Improve insulin sensitivity, Enhance glucose access into cells, tissues, and organs. | Fluid Retention, Weight Gain, Heart Failure, Anaemia, Upper Respiratory Tract Infection |
| 4 | Alogliptin (Nesina), Sitagliptin (Januvia), Linagliptin (Tradjenta), Saxagliptin (Onglyza) | DPP-4 Inhibitors | Stimulate pancreatic islet cells to release insulin | Upper Respiratory Infection, Headache |
| 5 | Glipizide (Glucotrol), Glyburide (Diabeta, Glynase), Chlorpropamide (Diabinese), Glimepiride (Amaryl), Tolazamide, Tolbutamide | Sulfonylureas | Encourage the pancreas to produce more insulin | Hypoglycemia, Weight Gain, Headache, Dizziness |
| 6 | Metformin (Fortamet, Glucophage, Glucophage XR, Glumetza, Riomet) | Biguanides | Inhibit the Glycogenolysis & Enhance the entry of glucose into the cells, tissue, and organ | Diarrhea, Indigestion, Nausea, Vomiting, Gas, Fatigue, Headache |
| 7 | Dapagliflozin (Farxiga), Canagliflozin (Invokana), Empagliflozin (Jardiance) | SGLT2 Inhibitors | Enhance the amount of sugar excreted out through urine | Vaginal, Infections, Urinary Tract Infections (UTI), Changes in Urination |

Table 2. Antidiabetic formulation available in the market

| Drugs | Dosage form available | Dose | Brand Name [Manufacturer] |
|---|---|---|---|
| Metformin | Tablet, immediate-release | 500, 850, 1000mg | Fortamet [Lupin Pharmaceuticals Inc.] |
| | Tablet, extended-release | 500, 1000mg & 750mg | Glumetza [Lupin Pharmaceuticals Inc.] Generic |
| | Oral suspension, extended-release | 47.31g/473mL & 500mg/5Ml | Riomet ER [Sun Pharmaceutical Industries, Inc.] |
| | Oral solution | 100mg/mL | Riomet [Sun Pharmaceutical Industries, Inc.] |
| Miglitol | Tablet | 25, 50, 100mg | Glyset [Pfizer] |
| Acarbose | Tablet | 25, 50, 100mg | Precose [Bayer Pharmaceuticals] |
| Repaglinide | Tablet | 0.5,1, 2mg | Prandin [Novo Nordisk] |
| Nateglinide | Tablet | 60, 120mg | Starlix [Ajinomoto] |
| Pioglitazone | Tablet | 15, 30, 45mg | Actos) [Takeda Pharmaceuticals America Inc.] |
| Rosiglitazone | Tablet | 2, 4 mg | Avandia [GlaxoSmithKline] |
| Sitagliptin | Tablet | 25, 50, 100mg | Januvia [MSD Pharmaceutical] |
| Saxagliptin | Tablet | 2.5, 5mg | Onglyza [AstraZeneca] |
| Alogliptin | Tablet | 6.5, 12.5, 25mg | Nesina [Takeda Pharmaceuticals] |
| Linagliptin | Tablet | 5mg | Tradjenta [Eli Lilly] |
| Glimepiride | Tablet | 1, 2, 4mg | Amaryl [Sanofi India Ltd.] |
| Glyburide | Tablet | 1.25, 2.5, 5mg | Diabeta [sanofi-aventis U.S. LLC.] |
| | Tablet, Micronised | 1.5, 3, 5, 6mg | Glynase PresTab [PFIZER] |
| Chlorpropamide | Tablet | 100, 250mg | Diabinese [Pfizer] |
| Glipizide | Tablet | 5, 10mg | Glucotrol [Pfizer] |
| | Tablet, extended-release | 2.5, 5, 10mg | Glipizide ER [Actavis ] |
| Tolbutamide | Tablet | 500mg | Tol-Tab [Sain Medicaments Pvt. Ltd.] |
| Tolazamide | Tablet | 250, 500mg | Tolinase [Pharmacia and Upjohn Company] |

These drugs are also given in combination e.g.- Janumet (Sitagliptin and Metformin), ActoPlus Met (Pioglitazone and Metformin), Avandamet (Rosiglitazone and Metformin), Avandaryl (Rosiglitazone and Glimepiride), Duetact (Pioglitazone and Glimepiride), Glucovance (Glyburide and Metformin), Invokamet

(Canagliflozin and Metformin), Jentadueto (Linagliptin and Metformin), Kombiglyze (Saxagliptin and Metformin), and Metaglip (Glipizide and Metformin).

**Insulin**

Normally 30-50 Units of insulin are secreted daily from a normal adult person but after a meal, more quantity of insulin is secreted by the human pancreas. Insulin is advised for both type 1 and type 2 diabetes. The only type of insulin available presently is synthetic human insulin. Insulin will be provided to diabetes patients in accordance with their meal schedule. It has been found that two to three insulin injections per day provide superior outcomes in controlling a patient's glucose levels with the least amount of eye, nerve, and kidney damage. The location of insulin injection in the body has an impact on blood glucose levels. Insulin shots delivered in the belly act fairly quickly. Insulin enters the bloodstream slowly from the upper arms, and even slower from the buttocks and thighs. However, for type 1 diabetics, mostly subcutaneous insulin injections are advisable. Insulin injections for type 1 diabetic patients improve quality of life and convenience (11).

Insulin comes in a variety of forms that are classified as per its onset and duration of action.

- *Rapid-acting insulin*: It takes effect between 2.5 and 20 minutes after injection, with the peak effect occurring between 1-3 hours and lasting up to 5 hours. Examples- NovoRapid, Humalog, and others.
- *Short-acting insulin*: It takes 30 minutes for them to take effect, thus this injection should be given 30 minutes before eating. Its activity peaks 2–5 hours after injection and can persist up to 6–8 hours. Humulin is a good example.
- *Intermediate-acting insulin*: It appears 60–90 minutes after injection, peaks between 4–12 hours, and lasts for up to 16–24 hours. Examples- Humulin NPH and Protaphane.
- *Long-acting insulin*: These insulins are currently available in Australia. These insulins are shown their action for up to 24 hours. These insulins are generally injected once or twice a day. Eg. Lantus (glargine insulin), Toujeo (glargine insulin) and Levemir (detemir insulin)
- *Mixed insulin*: A blend of either short-acting insulin or rapid-acting as well as intermediate-acting insulin, is known as mixed insulin. Examples-

I. Intermediate-acting insulin and Rapid-acting: Humalog Mix 25 (75% intermediate Humulin NPH, 25% rapid), Humalog Mix 50 (50% intermediate Humulin NPH, 50% rapid), NovoMix 30 ( 70% intermediate Protaphane, 30% rapid)
II. Long-acting insulin and Rapid-acting: Ryzodeg 70:30 ( 30% rapid Aspart, 70% long-acting Degludec)
III. Intermediate-acting insulin and Short-acting: Mixtard 50/50 (50% intermediate Protaphane, 50% short), Mixtard 30/70 (70% intermediate Protaphane, 30% short), Humulin 30/70 (70% intermediate Humulin NPH, 30% short) (3,11).

**Inhaled Insulin**

Afrezza was approved by the FDA in 2014, and it is the only inhaled insulin on the market right now. Recombinant human insulin, known as Afrezza, is adsorbed onto Technosphere particles comprised of the inert excipient fumaryl diketopiperazine. The size of the Technosphere particles allows for improved systemic absorption by delivering insulin to the deep lung. Afrezza has a rapid onset and a shorter duration of effect. Afrezza's median time to peak activity was 53 minutes, and its duration of action was 2.5–3 hours in clinical studies (12).

**Amylin synthetic derivatives**

Amylin is a hormone that occurs naturally similar to insulin that is released by the pancreas. When insulin therapy fails to keep blood sugar under control, an amylin derivative such as pramlintide is recommended. Mimicking incretins: In the United States, exenatide (Byetta) was the first incretin mimic to be approved. It's used to treat type 2 diabetes when metformin or sulfonylurea alone hasn't been enough to keep blood sugar levels under control (13).

**Ayurvedic**

Diabetes mellitus is classified as prameha in Ayurveda. "Pra – meaning excess, Meha – passage of urine" is how the name Prameha is obtained. As a result, Prameha is passing a lot of urine that is turbid in color. Prameha is divided into two categories: Sahaja (Hereditary) and Apathya nimittaja (Unwholesome things such as diet and exercise) (13). Many phytoconstituents obtained from plants, such as flavonoids, alkaloids, terpenoids, and glycosides, are important components in the fight against diabetes. Researchers have discovered that flavonoids like quercetin, myricetin, kaempferol, and genistein protect pancreatic beta cells from damage, stimulate insulin production from beta cells, and promote peripheral tissues' ability to absorb glucose. They also block alpha-glucosidase and alpha-amylase and encourage glycogenesis. It has also been demonstrated that flavonoids are beneficial for conditions associated with diabetes, including retinopathy, diabetic neuropathy, and cardiovascular disease. Several clinical investigations have demonstrated that herbal formulations combining numerous phytoconstituents are more successful in lowering blood glucose levels than single phytoconstituents for diabetic therapy(14). Various decoctions of herbal extract and spices are widely used in our daily life. Several health benefits they provide include antioxidant, neuroprotective, anti-inflammatory, anti-cancer, anti-diabetic, antibacterial and cardiovascular effects(15).

**Marketed Ayurvedic/ Polyherbal Formulation**

Herbs are utilized as decoctions, infusions, tinctures, and powders in Ayurvedic formulations. In Ayurveda, drug composition is based on two principles: (a). Single drug usage (b). Multiple drug usage. Polyherbal formulations are made up of two or more herbs (16). The following are examples of commercialized polyherbal antidiabetic formulations:

- *Cogent-DB plus Tablet*: Manufacturer: Cybele; Terminalia chebula, Trigonella foenum graecum, Phyllanthus emblica, Azadirachta indica, Terminalia bellerica, Rotula aquatica, Curcuma longa, Syzygium cumini, Terminalia chebula, Syzygium cumini, Tribulus terrestris, Phyllanthus emblica, Terminalia bellerica, the combination of 13 herbs has been refined throughout time to address all of the issues associated with diabetes. It's used to treat persistent wounds, diabetic foot infections, and gangrene. It also stops LDL from oxidizing. This is one of the strongest cardiac, neurohormonal, and liver tonics (17).
- *Diabgon capsules*: Chirayata, Kasondi, Shudh Shilajit, Bilva Patra, Indrayan, Safed Musli, Sajjikhar, Giloy, Karela, Jaiphal, Haldi, Neem, Methi, Arjun, Gurmar, Vidarikand, Bimbaphal, Jamun, Baghaphal are among the ingredients of Diabgon capsules. Ayurvedic specialists recommend taking 1 or 2 capsules with water, once in the morning and once in the evening after a meal (18).
- *Madhu Mehari granules*: Vijaysa, Turmeric, Black catechu, Neem, Bitter gourd, Giloy Gurmar, Jamun, and Chitrak are among the ingredients of Madhumehari Granules. 1 Teaspoon, twice daily, with LukeWarm Water, is the single maximum dose (19).
- *Madhu Shoonya Powder*: Shilajeet, Syzygium cumini, Gymnema sylvestre , Momordica charantia, Ocimum basilicum, Withania somnifera, Hibscus rosasinensis, Azadirachta indica, Lallemantia royleana, and Boswellia floribunda are the ingredients. Take 5–10 grams before breakfast and dinner with water (20)
- *Madhumeh Amrit*: Gurmar, Methi, Jamun, Neem, Karela, Vijay sar, Tulsi, and Bel patra are some of the most important ingredients. It also aids in urinary issues (21).
- *Dia-Beta Plus Capsules*: Manufacturer- Jiva ayurveda; Gurmaar, Karela, Tulsi, Ashwagandha, Saptrangi, and Vizaysaar are among the ingredients. Since 5000 BC, diabeta plus has been used. Non-insulin-dependent people should take 2 capsules twice a day, 12 hours before a meal, and insulin-dependent people should take 4-6 capsules twice a day, 12 hours before a meal, with water (22).
- *Dihar*: Curcuma longa, Tinospora cordifolia, Emblica officinalis, Enicostemm, Syzygium cumini, Gymnema sylvestre, Momordica charantia, and Azadirachta indiaca are all included in this polyherbal compound. Strptozotocin (STZ,45 mg/kg iv) caused type 1 diabetic rats showed effective anti-hyperglycemic activity, insulin levels were increased after 6 weeks of Dihar (100 mg/kg) treatment. In diabetic rats, Dihar reduced serum creatinine urea and lipid peroxidation significantly and boosted antioxidant enzyme activity (23).
- *Diabet*: Phyllanthus reticulatus, Strychnos potatorum, Coscinium fenestratum, and Curcuma longa are all included in this polyherbal mixture. At a dose of 500 mg/kg, the substance is effective, although it has no hypoglycemic impact (16).
- *Diasol*: Enicostemma littorale, Foenum graceum, Quercus infectoria Terminalia chebula, Emblica officinalis, Cuminum cyminum, Phyllanthus nerui, Taraxacum officinale, Gymnea sylvestre and Eugenia jambolana plant extracts were used. Previous studies show that Diasol minimizes 63.4

percent of blood sugar levels at doses of 125 and 250 mg/kg b.w. (i.p.), proving to be an best antidiabetic polyherbal compound (24).

- *Dianex*: Dianex produced a considerable hypoglycemic effect in diabetic mice. It was given orally in doses of 100, 250, and 500 mg/kg BW for up to six weeks (25).
- *Diashis*: Streptozotocin(STZ) induced hyperglycemia in rats was treated Diashis, showing an excellent antioxidant effect, and also improved the activities of hepatic hexokinase, glucose-6-phosphate dehydrogenase and glucose-6-phosphatase, as well as corrected fasting blood glucose, skeletal muscle glycogen, glycated hemoglobin and liver. The oxidative stress of the liver was improved by 'Diashis,' as seen by increased catalase, peroxidase, and glutathione-S-transferase activities, as well as decreased thiobarbituric acid reactive compounds and conjugated diene levels. There was no metabolic toxicity observed in 'Diashis' (26).
- *Diabrid*: It's mainly for type-2 diabetic patients, dose of 180-280 mg/dl is most effective in mild and moderate diabetic cases after clinical investigations demonstrated that it was well tolerated at high doses. Diabetic patients' body weight and blood pressure were also maintained by the medicine. The kidneys and liver showed no negative effects (27).
- *Diasulin*: Tinospora cordifolia, Scoparia dulcis, Trigonella foenum graecum, Curcuma longa, Momordica charantia, Syzygium cumini, Coccinia indica, Gymnema sylvestre, Emblica officinalis, Trigonella foenum graecum, Cassia auriculata, Trigonella foenum graecum, increases glycolysis while decreases gluconeogenesis, resulting in a reduced requirement for insulin than in untreated rats. It modulates the activity of glucose metabolic enzymes in liver. It also decreased tissue lipids and lipid peroxide production significantly (28).
- *Dia-Care*: Namejav, Jambu beej, Kadu, Himej, Neem chal, Himej, Namejav, Neem chal, Himej, Jambu beej, Kadu, and Sanjeevan Mool. Insulin-dependent people will eventually be free of it. Each phase of the treatment lasts 90 days. 1 teaspoon of the powder is mixed in 1/2 glass of water, thoroughly swirled, then filtered the next day. The filtrate is consumed in the morning, on an empty stomach. Fresh water is poured into the remaining medicine, which is preserved for the entire day and swallowed half an hour before dinner. The medication has a strong bitter flavor (118).
- *Diabetes-Daily Care*: It contains Alpha Momordica 7%, Lipoic Acid, Cinnamon 4%, Chromax, Licorice Root 20% , Fenugreek 50%, Gymnema sylvestre 25%, and Vanadium (29).
- *Diabcap*: Amla, Daru haridra, Dev daru, Harad, Nagarmotha and Bahera are all used in a mixture that helps to reduce blood sugar levels (30).
- *Diabecon*: Gymnema sylvestre is included in this polyherbal composition. Aloe vera, Tinospora cordifolia, Boerhavia diffusa, Abutilon indicum Gmelina arborea, Sphaeranthus indicus, Momordica charantia, Swertia chirata, Asparagus racemosus, Rumex maritimus, Tribulus terrestris, Gossypium herbaceum, Piper nigrum, Berberis aristata Triphala, Commiphora wightii, shilajeet, Ocimum sanctum, Curcuma longa, Phyllanthus amarus has been shown to improve peripheral glucose utilization, hepatic and muscle glucagon content, Beta cell repair and regeneration, and c-peptide levels. It has anti-oxidant properties and

protects Beta cells from oxidative stress. It acts similarly to insulin in lowering glycated hemoglobin levels, modulating the lipid profile and normalising microalbuminuria. Diabecon has also been shown in previous studies to be a safe medicine for diabetic people who want to avoid issues like retinopathy. Diabecon effectively treated and prevented retinal and vitreal hemorrhages (31).Some other antidiabetic herbal formulations are Pancrease formula, Ayubes, Tongyitang Diabetes Angle Hypoglycemic Capsules, Pearl Hypoglycemic Capsules, Diabetes Hypoglucose Capsules etc (32).

Table 3. List of various Herbal Plants as Antidiabetic activity In vivo & In vitro

| Botanical Name (Common Name) | Family | Part | Extract Dose | In Vivo Anti-Diabetic Effects (Dose) | Invitro Anti-Diabetic Effects | Reference |
|---|---|---|---|---|---|---|
| Agaricus bisporus (Mushroom) | Agaricaceae | Fruits | 200 mg/kg | Male Wistar rats/Sprague-Dawley rats (40/50 mg/kg I.M) were stimulated with streptozotocin (STZ). | Shows α-amylase, ß-Glucosidase inhibitory activity | (33)(34)(35) |
| Carum carvi (Caraway) | Umbelliferae | Seeds | 20 mg/kg | Streptozotocin (STZ) induced Male Wistar rats (65 mg/kg, I.V) | Shows PPARα transactivation | (36)(37) |
| Cinnamomum Verum (Cinnamon) | Lauraceae | Bark | 300-600 mg/kg | Streptozotocin (STZ) induced male albino wistar rats (45 mg/kg I.P) | α-glucosidase inhibitory activity, enhance GLUT1 & GLUT4 and activate PPAR | (38)(39)(40) |
| | | | 200-400 mg/kg | Male Sprague-Dawley rats were induced with alloxan. (120mg/kg) | | |
| | | | 1000 mg | Male-Female Patients with type-2 Diabetes | | |
| Cuminum cyminum (Cumin) | Apiaceae | Seeds | 1.2% | Streptozotocin (STZ) induced male albino rats (55 mg/kg I.P) | Shows α-amylase, α-glucosidase & Sucrase inhibition activity | (41)(42) |
| Curcuma longa (Turmeric) | Zingiberaceae | rhizome | 200-400 mg/kg | Alloxan induced male and female wistar albino rats (100-150 mg/kg I.P) | Shows α-amylase, β-glucosidase, α-glucosidase & Sucrase inhibition activity and as Antiglycation activity | (43)(44)(45) |
| Cymbopogon citratus (Lemongrass) | Poaceae | Leaf | 125-500 mg/kg | Male Wistar rats | α-amylase & α-glucosidase inhibitory activity, PPAR agonist, Dpp4 inhibitor and shows Insulin stimulatory activity | (46)(47) |
| Foeniculum vulgare (Fennel) | Apiaceae | Seeds | 150-300 mg/kg | Streptozotocin-induced male swiss albino strain Rats (40 mg/kg IP) show Hypoglycemic, antioxidant effects | Inhibitory action of α-amylase and α-glucosidase | (48)(49) |
| Nyctanthes arbor-tristis Linn. (Harsingar) | Oleaceae | Flower, | 250-750 mg/kg | Normal pelleted food to male mice | α-amylase inhibitory activity | (50) |
| Origanum majorana (Marjoram) | Lamiaceae | Leaf | 250-500 mg/kg | Alloxan induced Wistar albino rats of both sexes (150 mg/kg I.P) | DPP4, PTP1B inhibitory activity | (51)(52) |
| Pimpinella anisum | Umbellifers | Seeds | 5 gm/day | Shows Anti-Diabetic & Antioxidant activity in Both | α-amylase, α-glucosidase, HMG CoA | (53) |

| | | | | | | |
|---|---|---|---|---|---|---|
| (Aniseed) | | | | Male-Female patients with type-2 Diabetes | reductase, and Pancreatic lipase inhibitory activity | |
| Piper nigrum (Black pepper) | Piperaceae | Leaf | 200 mg/kg | Streptozotocin (STZ) induced male Wistar albino rats (50 mg/kg I.P) | α-amylase & α-glucosidase inhibitory activity | (54)(55) |
| Zingiber officinale (Ginger) | Zingiberaceae | rhizomes | 500 mg/kg | streptozotocin (STZ) induced Male Sprague–Dawley rats (55-60 mg/kg I.P) show a higher insulin level and a lower fasting glucose levels in diabetic rats, increased GLUT4, antiglycatiosn, Glucose uptake, antioxidative effects | Inhibited α-amylase and α-glucosidase, PPAR-γ agonist, suppressing TNF-α, enhance insulin-sensitive glucose uptake | (56)(57)(58) |

Table 4. Patented instances of herbal anti-diabetic preparations for diabetes treatment

| Title | Inventor | Patent no. | Reference |
|---|---|---|---|
| A mixture of various medicinal herbs for treating diabetes | Mashat et al. | US8993008B1 | (59) |
| Novel anti-diabetic herbal formulation | Pushpangadan et al. | US2007/0042062A1 | (60) |
| An herbal formulation for the prevention and treatment of diabetes and associated complicsations | Krishnan et al. | US8163312B2 | (61) |
| Anti-diabetic and cholesterol-lowering preparation from fenugreek seeds | Murthy et al. | US7815946B1 | (62) |
| Synergistic composition for the treatment of diabetes mellitus | Bhaskaran et al. | US7641925B2 | (63) |
| Pharmaceutically active extracts of Vitex leucoxylon, a process of extracting the same and a method of treating diabetes and inflammatory diseases therewith | Raju et al. | US7780997B2 | (64) |
| Anti-diabetic extract isolated from rauvolfia vomitoria and Citrus Aurantium, and methods of using the same | Campbell-Tofte et al. | US7579025B2 | (65) |
| Preparation, process, and a regenerative method and technique for prevention, treatment, and glycaemic control of diabetes mellitus | Antony et al. | US20080274216A1 | (66) |
| Obtained from the extract of Costus pictus D.don plant and method of preparing the same | Antony et al. | WO2013190572A1 | (67) |
| Method for treating type 2 diabetes with an extract of artemisia | Ribnicky et al. | US6893627B2 | (68) |
| Herbal nutraceutical formulation for diabetics and process for preparing the same | Pushpangadan et al. | US7014872B2 | (69) |
| An anti-diabetic herbal formulation comprising glycine max | Pushpangadan et al. | WO2006/048696A1 | (70) |

**Homeopathic**

Homeopathic medicine is a type of medicine that treats the whole person rather than just the disease or symptom. Homeopathic drugs for diabetes play a supportive function rather than acting as a substitute for standard allopathic medications. Homeopathic diabetes treatments are made from natural ingredients and have no adverse effects. Various homeopathic medications are available on market:

*Abroma Augusta*: Manufacturer- Omkar Herbals; A homeopathic remedy for diabetic patients who are becoming weaker due to the loss of flesh. It can also aid patients with thirst, dry mouth, frequent urination, and increased appetite. Many diabetic patients also have insomnia as a result of excessive blood sugar levels, they also benefit from Abroma Augusta.

*Jambolanum Or S. Cumini (Black Plum)*: Manufacturer- SBL Pvt Ltd; Jambolanum is the most effective natural homeopathic treatment for diabetics. It is an excellent blood purifier. Diabetes patients also feel increased thirst and urination. It also works well for the treatment of long-standing ulcers in diabetic patients.

*Uranium Nitricum*: Manufacturer- Hering Pharma; The homeopathic medication Uranium Nitricum protects against high blood sugar levels, high blood pressure and fatty liver disease. Additionally, it is beneficial for abdominal bloating, reduces frequent urination and eases urine pain (71).

*Conium*: Manufacturer- Hering Pharma; Numbness in the feet and hands, as well as nerve damage caused by high blood sugar levels, can be treated with conium medications. It also keeps muscle weakness in the lower body. Poisonous hemlock is another name for conium. It is extremely poisonous. As a result, it protects against neuromuscular disorders caused by high glucose levels.

*Phosphoric Acid*: Manufacturer- ICL Group; When patients have frequent urination, the homeopathic practitioner may recommend phosphoric acid. If the urine color is milky, it means there is a lot of sugar in it. Phosphoric acid can treat diabetes when it is in its early stages (72).

**Others Treatment**

**Oral vaccination**

Mucosal-induced immunization is used to treat a variety of disorders caused by an immune response to non-self or self-antigens. Type-1 diabetes is an autoimmune illness, and oral vaccination is used to reduce autoimmune and allergy conditions. Oral vaccination must be given repeatedly to control disease because they went through the stomach's harsh environmental conditions, oral vaccinations must provide protection. M.I. Husseiny and colleagues present an oral vaccination that uses live attenuated Salmonella to deliver autoantigens and immunomodulatory cytokine genes to immune cells in the gut mucosa at the same time. It is a Salmonella-based type 1 diabetes vaccine that has shown promise in non-obese diabetic mice (73–75). In both naive and immune animals,

Cholera Toxin B(CTB) an oral vaccination, can effectively reduce systemic T-cell reactivity. We now report that feeding adult nonobese diabetic (NOD) mice modest quantities (2–20μg) of human insulin conjugated to CTB can successfully reduce beta cell loss and clinical diabetes (76).

**Pancreas transplantation**

The pancreas, which is located near the stomach, is the major organ for insulin synthesis. Because the pancreas cannot manufacture insulin in people with type 1 diabetes, pancreatic transplantation is used. The patient's donor pancreas is usually surgically inserted and his old pancreas is kept inside, producing enzymes that help the body digest food but not insulin. When a patient has a new kidney or pancreas transplant, modern diabetes management tools are used. However, pancreatic transplantation is a dangerous procedure. Each patient must consider the risks and advantages of treatment. The following advantages of pancreas transplantation; without insulin, the patient may be able to maintain a normal blood glucose level. Many diabetes-related side effects are delayed or eliminated after pancreatic transplantation. (77) People with nerve damage usually recover after receiving a pancreas transplant rather than getting worse. The patient's body treats the new pancreas as an antigen, and the immune system's antibodies assault the transplanted pancreas, which is one of the downsides of pancreas transplantation. As a result, transplant patients may take potent immunosuppressive medicines to suppress their immune systems, preventing the new pancreas from rejecting. However, suppressing the immune system has side effects such as decreased resistance to various diseases such as bacterial and viral infections, as well as cancer (74).

**Islet cell transplantation**

It is a sophisticated diabetes management technique. Islets, also known as Langerhans islets, are small clusters of cells found throughout the pancreas. The Langerhans islet comprises a variety of cells, including beta cells, which produce insulin. The pancreas secretes insulin into the bloodstream to digest the food when blood sugar levels rise after eating. The energy source is glucose, which is absorbed from the bloodstream. There are two different methods of transplanting pancreatic islet cells: allotransplantation and auto-transplantation. Donor islet cells are obtained, purified and prepared, and then transplanted into the patient's body. Every infusion requires two injections for patients with an average of 400,000 to 500,000 islets. Following islet cell transplantation, the beta cells within the islet cells begin to produce insulin, and type 1 diabetes patients undergo islet allotransplantation.

Another islet cell transplant procedure is pancreas islet auto-transplantation. This technique is done for patients whose pancreas has been destroyed and no other treatments are available. This islet auto transplanting method is not used by patients with type 1 diabetes. The patient is given anesthesia before the surgeon removes his pancreatic islet. Within hours of the pancreas islets being removed and purified, they are injected into the patient's body. Islet cells produce insulin once they have been transplanted. The patient, however, must rely on insulin shots to keep their glucose levels under control because the creation of

new blood vessels and islet cells is delayed. There is no need to take immunosuppressive medication during pancreatic auto-transplantation. To decrease autoimmune reactions and extend the lifespan of beta cells, patients take a number of drugs before and after the transplant. The liver is currently used for islet cell transplantation, but researchers are looking into different infusion sites to optimize the procedure (78). Islet cell transplantation can result in bleeding and blood clots, and the patient's new islet cells may or may not function properly.

**Gene therapy in the treatment of diabetes**

This technique is utilized when blood glucose levels rise and the patient is at risk of dying if not treated. Gene therapy's main goal was to eliminate the need for daily insulin injections. Ectopic gene expression refers to the expression of genes in cell types outside of their normal range. Tian et al. used a CMV promoter-containing lentivirus to genetically modify epithelial cells to produce a fusion protein when activated by rampamycin, which consists of proinsulin that has been modified to allow furin cleavage and a self-dimerization mutant of FK506-binding protein to produce bioactive insulin (79). Rats were given the chitosan nanoparticle-wrapped expression plasmid pCMV.Ins(human insulin gene under the control of a CMV promoter), which was used to transfect rats via the gastrointestinal tract, Rats' BGLs dropped from 22.12 1.31 mM to 5.63 0.48 mM (80). In mice, Obesity and type 2 diabetes are cured after a single infusion of an adeno-associated viral vector (AAV) encoding the FGF21 (Fibroblast Growth Factor 21) gene (81).

**Conclusions and future trends**

The number of diseases is constantly expanding in today's world, posing a threat to the host's health. Blood glucose levels are controlled using a variety of methods, although each method has its own set of benefits and drawbacks. Allopathy medicines are not bad, they are the ancient method of treatment, cure almost every acute and life-threatening disease, even Doctors-Physicians also recommend these drugs to their patients, give guarantee or assurance for their treatment, and are easily available. Even allopathy medicines are the biggest market share in the world but there are also some drawbacks of allopathy medicines that they are partial treatment means they do not cure the root of the disease, one of the major drawbacks is a side-effect, most of the drugs have side effects and incorrect diagnosis may be fatal. On the other side, Herbal medicines which increase their use of the product over the past few years, and almost 80% of people worldwide rely on herbal drugs. Due to its very few or no side effect, the ability to cure the root cause of ailments, and taking herbal medication not be a fatal condition during incorrect diagnosis. More than 900 compounds with potential antidiabetic activity were discovered in herbs and spices, with the sesquiterpenoids and flavonoids being the two primary chemical families of bioactive molecules discovered. Encapsulated islet cell transplantation also has been proven to be more effective or better than other procedures, with fewer complications.

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**Abbreviation**

DPP4: Dipeptidyl Peptidase-4; AM2A: Pancreatic Alpha-Amylase; PPARA: Peroxisome Proliferator-Activated Receptor Alpha; GLP-1: Glucagon-like peptide-1; SGLT2: Sodium-glucose co-transporter-2; PTPN9: Protein Tyrosine Phosphatase Non-receptor Type 9; GIP: Glucose-Dependent Insulinotropic Polypeptide; VIP: Vasoactive Intestinal Peptide; GABA: Gamma-aminobutyric acid

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