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POTENTIAL HERBS AGAINST DIABETES MELLITUS - AN UPDATE

Sheetal Singh [*1], Avijit Mazumder [1] and G. S. Chakaraborthy [2]

Noida Institute of Engineering and Technology (Pharmacy Institute) [1], Greater Noida - 201306, Uttar Pradesh, India.
Parul Institute of Pharmacy and Research [2], Parul University, Vadodara - 391760, Gujarat, India.

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Correspondence to Author:
Sheetal Singh

Noida Institute of Engineering and Technology (Pharmacy Institute), Greater Noida - 201306, Uttar Pradesh, India.

E-mail: singhsheetal781@gmail.com

ABSTRACT: Diabetes or Madhumeha as per Ayurveda is a disease in which there is improper functioning of insulin and as a result, the sugar level in the blood increases. Diabetes may cause heart problem, kidney failure, blurred vision if not treated timely with proper medication. Medicinal plants have been used since ancient times for the treatment and management of diabetic mellitus (DM) in traditional medicine systems of many cultures throughout the world. Traditional Medicines derived from medicinal plants are used by about 60% of the world's population. Recently, the World Health Organization (WHO) recommended the use of medicinal plants for the management of DM and further encouraged the expansion of the frontiers of scientific evaluation of hypoglycemic properties of diverse plant species. This review focuses on Indian Herbal drugs and plants used in the treatment of diabetes, especially in India.

INTRODUCTION: Diabetes mellitus is increasing alarmingly worldwide and is defined as the abnormal glucose tolerance, which affects pancreatic beta cells functions and sensitivity leading to the progression of diabetes and its related complications. It is a chronic disorder of carbohydrate, fat, and protein metabolism characterized by increased fasting and postprandial blood sugar level and an increased risk of vascular complications. Anti-diabetic drugs treat diabetes mellitus by lowering glucose levels in the blood. Though different types of oral hypoglycaemic agents are available along with insulin for the treatment of diabetes, there is increased demand by patients to use natural products with antidiabetic activity.

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Diabetes mellitus is one of the common metabolic disorders characterized by hyperglycemia due to an absolute or relative deficiency of insulin and results in significant morbidity and mortality. Diabetes, by itself, increases the production of tissue-damaging oxidative stress [1]. Therefore, in diabetes, the oxidative stress is referred to as a case of double jeopardy for any beta cells that survive the disease.

Mainly three types:

- ✓ Type 1 (insulin-dependent DM = IDDM)
- ✓ Type 2 (Non insulin dependent DM = NIDDM)
- ✓ Gestational diabetes

Type I diabetes (insulin dependent) is caused due to insulin insufficiency because of lack of functional beta cells. Patients suffering from this are therefore totally dependent on an exogenous source of insulin while patients suffering from Type II diabetes (insulin independent) are unable to respond to insulin and can be treated with dietary changes, exercise and medication [2]. Type II

diabetes is the more common form of diabetes, constituting 90% of the diabetic population.

Diabetes mellitus type 2 is a disease of insulin resistance by cells. Treatments include agents which increase the amount of insulin secreted by the pancreas, agents which increase the sensitivity of target organs to insulin and agents which decrease the rate at which glucose is absorbed from the gastrointestinal tract [3].

Gestational diabetes(GDM) has been defined as any degree of glucose intolerance with onset or first recognition during pregnancy, to differentiate it from pre-diagnosed type 1 or type 2 diabetes or maturity-onset diabetes of the young (MODY) in women that get pregnant. Pregnancy is a condition characterized by progressive insulin resistance that begins near mild pregnancy and progressive through the third trimester. The placenta produces human chorionic somatomammotropin (HCS, formerly called human placental lactogen), bound and frees cortisol, estrogen, and progesterone. HCS stimulates pancreatic secretion of insulin in the fetus and inhibits peripheral uptake of glucose in the mother. As the pregnancy progresses and the size of the placenta increases, so does the production of the hormones, leading to a more insulin resistant state. Patient with GDM is at higher risk for excessive weight gain, preeclampsia, and cesarean sections. Infants born to mothers with GDM are at higher risk for macrosomia, birth trauma, and shoulder dystocia [2]. After delivery, these infants have a higher risk of developing hypoglycemia, hypocalcemia, hyperbilirubinemia, respiratory distress syndrome, polycythemia, and subsequent obesity, and type 2 diabetes. So management of GDM is very important [4].

Pathophysiology: Many tissues contain insulin receptors to which insulin binds reversibly. The biological response of insulin can be altered by either a change in receptor affinity for insulin or a change in the total number of receptors. Changes in the receptors can occur due to obesity and chronic exposure to high insulin levels. Both lead to an increase in the number of receptors, down-regulation. An acute deficiency of insulin leads to unstrained hepatic glycogenolysis and gluconeogenesis with a consequence increase in hepatic glucose output [5]. Glucose uptake is decreased in insulin-sensitive tissues & hyperglycemia ensures. Metabolic disturbances, infection, or acute illness increase the secretion of counter-regulatory hormones glucogon, cortisol, catecholamine, and growth hormone. All these will further increase hepatic glucose production. Most of the carbohydrates in food are converted within a few hours to the monosaccharide glucose, the principal carbohydrate found in blood and used by the body as fuel [6].

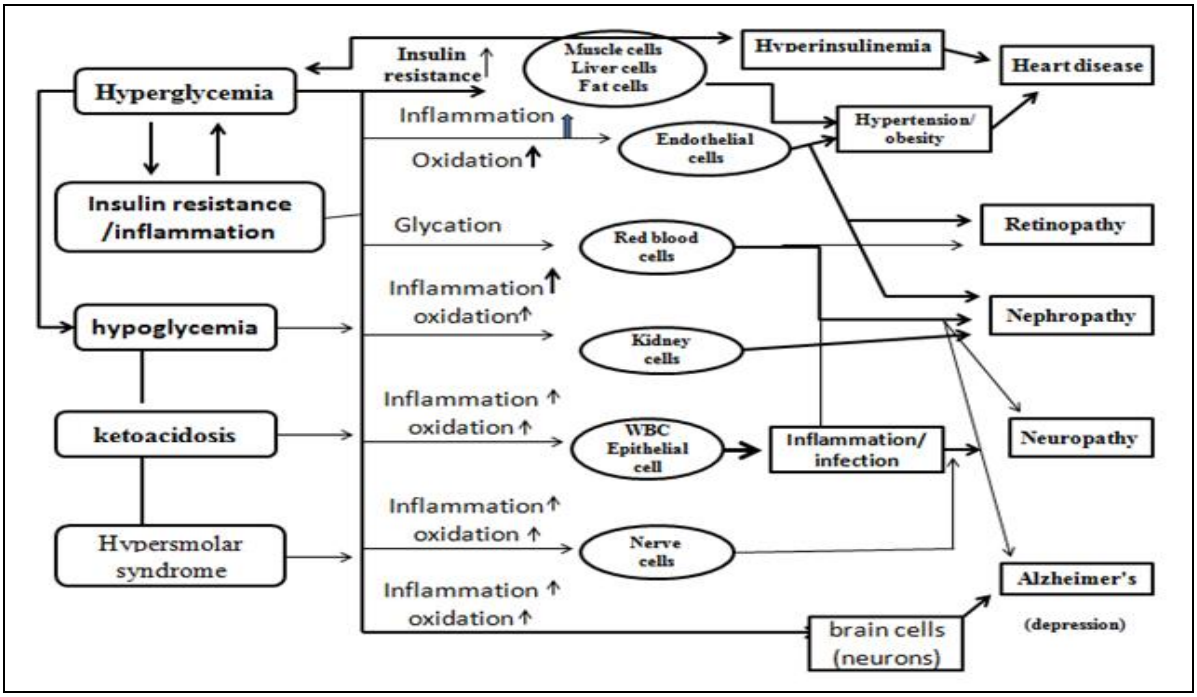


FIG. 1: PATHOGENESIS OF TYPE 2 (CELLULAR LEVEL)

The most significant exceptions are fructose, most disaccharides (except sucrose and in some people lactose) and all more complex polysaccharides, with the outstanding exception of starch. Insulin is released into the blood by beta cells (β-cells) found in the Islets of Langerhans in the pancreas, in response to rising levels of blood glucose, typically after eating. Insulin is used by about two-thirds of the body's cells to absorb glucose from the blood for use as fuel, for conversion to other needed molecules, or storage. Insulin is also the principal control signal for the conversion of glucose to glycogen for internal storage in liver and muscle cells. Lowered glucose levels result both in the reduced release of insulin from the beta cells and the reverse conversion of glycogen to glucose when glucose levels fall [7].

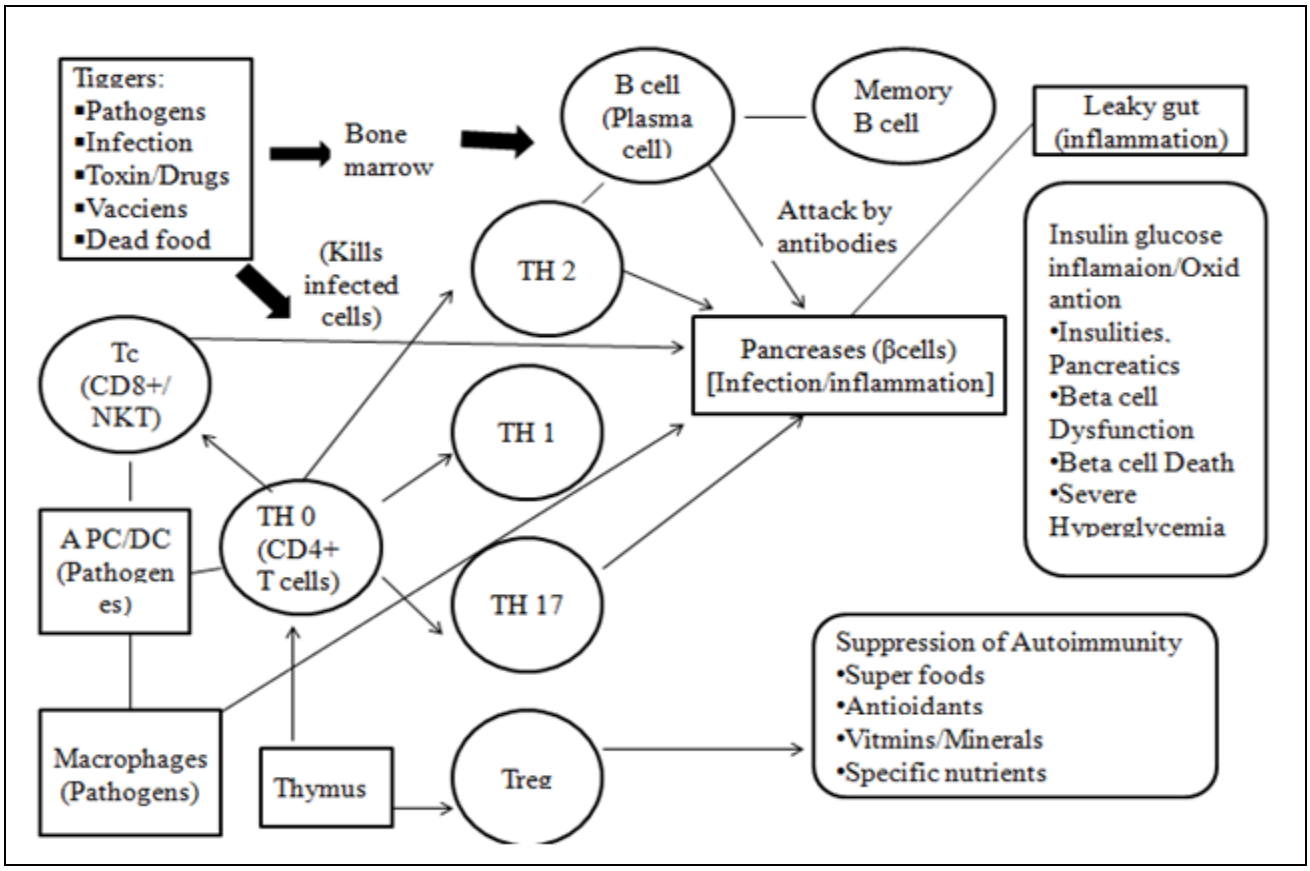


FIG. 2: TYPE 1 DIABETES AUTOIMMUNE DISEASES PATHOGENESIS

Treatment of Diabetes Mellitus: Controlling blood sugar (glucose) levels is the major goal of diabetes mellitus treatment to prevent complications of the disease. Type- 1 diabetes is managed with insulin as well as dietary changes and exercise. Type-2 diabetes may be managed with non-insulin medications, insulin, weight reduction, or dietary changes. Diabetes mellitus may also be managed by lifestyle changes. Antidiabetic drugs are those drugs which lower blood glucose levels and are effective orally [8].

Recent Advancement in Diabetes Mellitus: Advances in diabetes technology have helped to improve the outcomes of the management of T1DM.

Intranasal Insulin Delivery: soluble insulin administered intranasally is rapidly absorbed when given along with a detergent substance to facilitate adsorption. A single dose of intranasal insulin acutely improved memory in memory-impaired older adults with AD or mild cognitive impairment (MCI) and also improved memory and cognitive function with multiple treatments of patients with AD or MCI [9].

Insulin Pumps and Continuous Subcutaneous Insulin Infusion: insulin pump devices have become smaller and increasingly more sophisticated in their functionality. Insulin is delivered through a cannula placed subcutaneously and replaced with a 72 h frequency [10]. Insulin

pumps have Rapid-acting insulin analogs are not approved for use in pregnancy. Intensive diabetes management can be achieved in children, adolescents, and adults, either with the use of continuous subcutaneous insulin infusion or with multiple daily injections [11].

Continuous Glucose Monitoring (CGM) Systems: CGM system provides continuous insight into glucose levels throughout the day and night. The device displays information about glucose direction and rate of change, providing users additional information to help with their diabetes management [12].

The three Food and Drug Administration (FDA)-approved CGM systems all use the subcutaneous space and measure glucose in interstitial fluid (IF). CGM use in all age groups over time.

TABLE 1: MEDICINAL PLANTS USED FOR DIABETES

S. no.	Plant source	Targeted metabolic pathways	Phytoconstituents
1	*Allium sativum*	Glycogen synthesis, insulin secretion, Cholesterol synthesis, glycogen synthesis	Allyl propyl disulfide, Allicin, apigenin, alliin
2	*Aegle marmelos*	Regeneration of pancreatic β cells and insulin secretion	Aegelin, marmesin, marmelosin
4	*Aloe vera*	Insulin secretion, Carbohydrate digestion and absorption	Leucine, isoleucine, alanin, Cellulose, mannose, Zinc
5	*Alium sepa*	Glycolysis, cholesterol synthesis	S-methyl cysteine sulfoxide, S-allyl cysteine sulfoxide
6	*Agaricus campestris*	Insulin secretion, glycogen synthesis	Furfural, caprylic acid
7	*Areca catechu*	Carbohydrate digestion and absorption	Nitrosamines
8	*Achyranthus aspera*	Carbohydrate digestion and absorption	Betaine, achyranthine, β-ecdysone
9	*Momordica charantia*	Insulin secretion, glycogen synthesis,	Vicine, Polypeptide-P, Momordin, momordicine, charantin
10	*Catharanthus roseus, Vinca rosea*	Free radical scavenging action	Catharanthine, vindoline, vindolinene vinblastine, vincristine
11	*Castanospermum australe*	DPP-IV inhibition	Castanospermine, australine
12	*Curcuma longa*	Free radical scavenging activity, insulin secretion	Ferulic acid
13	*Cassia auriculata*	Insulin secretion, glycogen synthesis	Bis (2-ethyl hexyl) phthalate (DEHP)
14	*Caralluma edulis, Syzygium cumini, Acacia Arabica*	Krebs cycle	Mallic acid, chlorogenic acid
15	*Cassia tora*	Insulin secretion	Torachrysone, toralactone, rhein, alaternin
16	*Camellia sinensis*	Glycogen synthesis, glycolysis, gluconeogenesis, Insulin secretion	Cytrus bioflavonoids (hesperidin, naringin)
17	*Cucurbita pepo*	Free radical scavenging activity	Vitamin A, E
18	*Ficus bengalensis*	Insulin secretion, glycogen synthesis	Leucocyanidin, pelargonidin
19	*Ginkgo biloba*	Insulin secretion, Free radical scavenging activity	Ginkgolides , Kaempferol, isorhamnetin
20	*Gymnema Sylvestre*	Regeneration of pancreatic β cells and insulin secretion	Gurmarin, betaine, choline, trimethylamine
21	*Grape Seed*	Antihyperglycaemic	Procyanidins
22	*Tinospora cordifollia, Barberisaristata*	Glucose transport, carbohydrate digestion and absorption, DPP-IV inhibition	Barberin
23	*Tribulus terrestris*	Insulin secretion and β-cell regeneration	Harmine, pinoline
24	*Trigonella foenum graecum*	Glucose transport, carbohydrate digestion and absorption,	Sotolon [4,5-dimethyl-3-hydroxy-2(5H)-furanone], trigonelline, gentianine, carpaine compounds
25	*Xanthocercis zambesiaca*	Carbohydrate digestion and absorption, insulin secretion	Castanospermine, epifagomine, fagomine
26	*Phyllanthus amarus*	Carbohydrate digestion and absorption	Brevifolin carboxylic acid, ethyl brevifolin carboxylate
27	*Viscum album*	Insulin secretion, glycogen synthesis	Lectins, mistletoe lectin I, II, III, viscotoxin B, cycliton
28	*Vitis vinifera*	Insulinonematic activity	Raisin
29	*Ocimum canum, Coriandrum sativum, Artemisia roxburghiana, Syzygium aromaticum*	Insulin secretion, regeneration of pancreatic β cells	Camphor, eugenol, trans-β-ocimene, geraniol, α-pinene, limonene, p-cymene, 1,8-cineole, thujone
30	*Hericium erinaceus*	Carbohydrate digestion and absorption	D-threitol, D-arabinitol, palmitic acid
31	*Cinnamomum zeylanicum*	Carbohydrate digestion and absorption	L-arabino-D-xylan, cinnzeylanin, cinnzeylanol,

			D-glucan
32	*Opuntia ficus indica*	Carbohydrate metabolism, cholesterol synthesis	Mucopolysaccharide
33	*Taraxacum officinale*	Glucose transport, carbohydrate digestion and absorption	Inulin, laevulin
34	*Helicteres isora*	Insulin secretion, glycogen synthesis	Cucurbitacin B, isocucurbitacin B
35	*Luffa cylindnica*	Insulin secretion, glycogen synthesis	Momordin-a, luffin-a
36	*Salacia reticulate, Salacia oblonga*	Insulin secretion, glycogen synthesis	Kotalanol, salacinol
37	*Arctostaphylos uvaursi*	Insulin secretion, glycogen synthesis	Arbutin, eriolin
38	*Trigonella foenum graecum*	Glucose transport, carbohydrate digestion and absorption	Fenugreek in
39	*Taraxacum officinale*	Glucose transport, carbohydrate digestion and absorption	Gluten, taraxacerin
40	*Swertia chirayita*	Insulin secretion, glycogen synthesis	Amarogentin, swerchirin, chirantin, gentiopicrin
41	*Tribulus terrestris*	Insulin secretion, free radical scavenging activity	Tribulusamides A and B, kaempferol-3-β-D, glucoside, kaempferol-3-glucoside
42	*Casearia esculenta*	Insulin secretion	Leucopelargonidin, dulcitol
43	*Matteuccia orientalis*	Insulin secretion	Matteuorien, matteuorienin matteuorienate A, B, C

Herbal Drugs Used for the Treatment of Diabetes:

(1) *Acacia arabica* (Babhul): The plant extract acts as an antidiabetic agent by acting as a secretagogue to release insulin. Powdered seeds of *Acacia arabica* when administered (2, 3 and 4 g/kg body weight) to normal rabbits induced hypoglycemic effect by initiating the release of insulin from pancreatic beta cells [13]. This plant contains polyphenols, tannins, and flavonoids (for example, quercetin). The presence of these substances with antioxidant properties is an explanation for the anti-diabetic effects of this plant.

(2) *Aegle marmelos* (Bengal Quince, Bel or Bilva): Administration of aqueous extract of leaves improves digestion and reduces blood sugar and urea, serum cholesterol in alloxanized rats as compared to control [14]. Along with exhibiting hypoglycemic activity, this extract also prevented the peak rise in blood sugar at 1h in oral glucose tolerance test. It cleans and tones up the intestines. Aegeline has antihyperglycemic and anti-hypercholesterolemic action. Phytoconstituents with varied chemical structures including cinnamides like aegeline, coumarins like umbelliferone, furanocoumarins like imperatorin, psoralen and xanthotoxin and others such as limonene, auraptene, *etc*. [15]

(3) *Allium cepa* (Onion): Various ether soluble fractions as well as insoluble fractions of dried onion powder show anti-hyperglycemic activity in diabetic rabbits. *Allium cepa* is also known to have antioxidant and hypolipidaemic activity [16]. When diabetic patients were given a single oral dose of 50 g of onion juice, it significantly controlled post-prandial glucose levels. Quercetin, a major phenolic content.

(4) *Allium sativum* (Garlic): Allicin, a sulfur-containing compound is responsible for its pungent odor and it has been shown to have significant hypoglycemic activity. Aqueous homogenate of garlic (10 ml/kg/day) administered orally to sucrose fed rabbits (10 g/kg/day in water for two months) significantly increased hepatic glycogen and free amino acid content, decreased fasting blood glucose, and triglyceride levels in serum in comparison to sucrose controls [17].

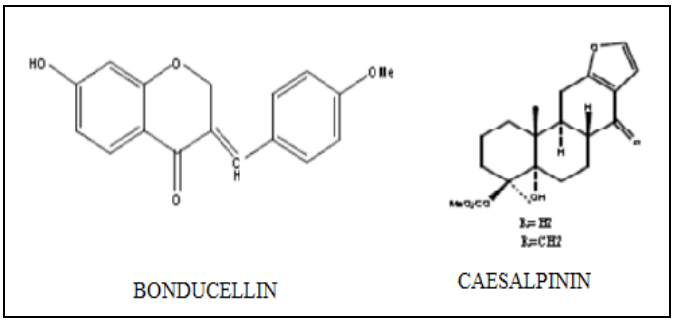
A comparison was made between the action of garlic extract and glibenclamide (600 microg/kg), the known antidiabetic drug. The antidiabetic effect of the extract was more effective than that observed with glibenclamide ($p<0.05$) [18].

(5) *Aloe vera* and *Aloe barbadensi*: *Aloe vera* gel is the leaf pulp or mucilage, aloe latex, commonly referred to as "aloe juice," is a bitter yellow exudate from the pericyclic tubules just beneath the outer skin of the leaves. Extracts of aloe gum effectively increase glucose tolerance in both normal and diabetic rats aloe juice paired student's t-test was used, and 99% confidence limit $p=0.01$ [19]. It contains 8 enzymes: aliiase, alkaline phosphatase, amylase, bradykinase, carboxy-peptidase, catalase, cellulase, lipase, and peroxidase [20].

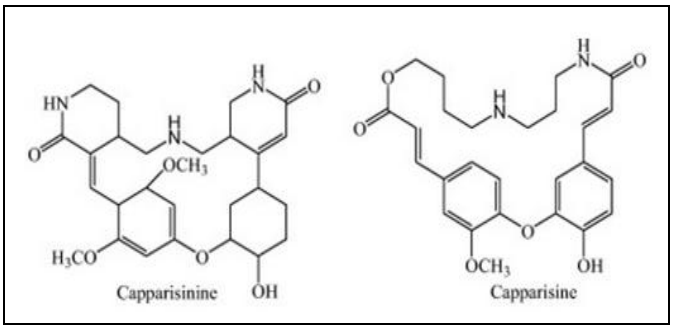
(6) *Azadirachta indica* (Neem): Hydroalcoholic extracts of this plant showed anti-hyperglycemic activity in streptozotocin-treated rats, and this effect is because of the increase in glucose uptake and glycogen deposition in isolated rat hemidiaphragm. *Azadirachta indica* $p<0.05$ [21].

Active constituents of neem leaf extract include isomeldenin, nimbin, nimbinene, 6-desacetyllnimbinene, nimbandiol, immobile, nimocinol, quercetin, and beta-sitosterol

(7) *Caesalpinia bonducella*: Both the aqueous and ethanolic extracts showed potent hypoglycemic activity in chronic type II diabetic models. The aqueous and 50% ethanolic extracts of *Caesalpinia bonducella* seeds showed antihyperglycemic and hypolipidemic activities in streptozotocin (STZ)-diabetic rats. bonducella was effective at $p<0.005$. [22]. The whole plant of *Caesalpinia bonducella* contain all major chemical constituents such as Steroidal Saponin, Fatty Acids, Hydrocarbons, Phytosterols, Isoflavones, Aminoacids, and Phenolics [23].



(8) *Capparis decidua*: Hypoglycemic effect was seen in alloxanized rats when the rats were fed with 30% extracts of *Capparis decidua* (*C. decidua*) fruit powder for 3 weeks. phytochemicals including alkaloids (capparisinine, capparisine, stachydrine, isocodonocarpine), phenolics, flavonoids, sterols and fatty acids [24].

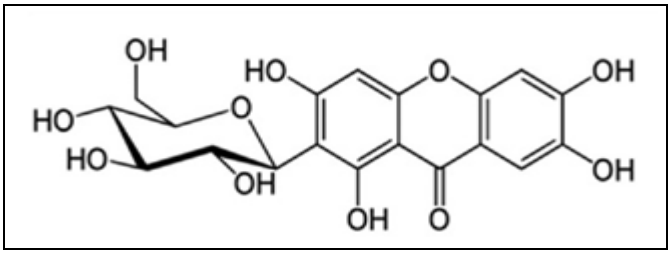


(9) *Coccinia indica*: Dried extracts of *Coccinia indica* (*C. indica*) (500 mg/kg body weight) were administered to diabetic patients for 6 weeks. These extracts restored the activities of enzyme lipoprotein lipase (LPL) that was reduced and glucose-6-phosphatase and lactate dehydrogenase, which were raised in untreated diabetics [25].

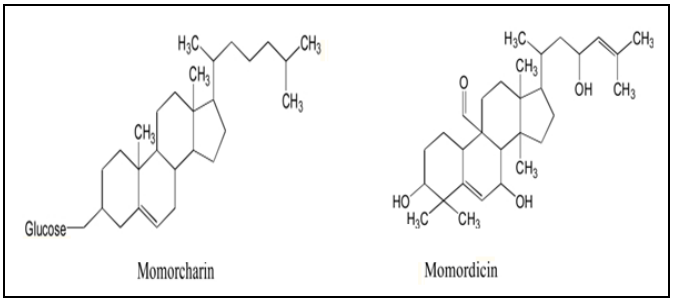
Extract of Coccinia contains triterpenes, alkaloid, flavonoid, B-carotene, which is responsible for the hypoglycemic activity.

(10) *Neugenia jambolana* (Indian Gooseberry, Jamun): Antihyperglycemic effect of the aqueous and alcoholic extract, as well as a lyophilized powder, shows a reduction in blood glucose level. In mild diabetes (plasma sugar >180 mg/dl) it shows 73.51% reduction, whereas in moderate (plasma sugar >280 mg/dl) and severe diabetes (plasma sugar >400 mg/dl) it is reduced to 55.62% and 17.72% respectively [26]. The seeds are claimed to contain alkaloid, jambosine, and glycoside jambolin or antimellin, which halts the diastatic conversion of starch into sugar and seed extract has lowered blood pressure by 34.6%, and this action is attributed to the ellagic acid content [27].

(11) *Mangifera indica* (Mango): The leaves of this plant are used as an antidiabetic agent in Nigerian folk medicine, antidiabetic activity was seen when the extract and glucose were administered simultaneously and also when the extract was given to the rats 60 min before the glucose [28]. Mango is a rich source of various polyphenolic compounds, mangiferin.



(12) *Momordica charantia* (Bitter Gourd): Extracts of fruit pulp, seed, leaves, and the whole plant was shown to have hypoglycemic effect in various animal models [29]. The active constituents are momocharin and momordicin, which is believed to possess insulin-like chemical structure and properties.



(13) *Ocimum sanctum* (Holy Basil): The aqueous extract of leaves of *Ocimum sanctum* showed a significant reduction in blood sugar level in both normal and alloxan-induced diabetic rats [30]. Oral administration of plant extract (200 mg/kg) for 30 days led to a decrease in the plasma glucose level by approximately 9.06 and 26.4% on 15 and 30 days of the experiment, respectively. Eugenol has been found to lower the blood glucose level.

(14) *Phyllanthus amarus* (Bhuiawala): Methanolic extract of plant reduced the blood sugar in alloxanized diabetic rats. Oral administration of *Phyllanthus amarus* ethanolic leaf extract (400 mg/kg body weight) for 45 days showed significant ($P<0.05$) reduction in blood glucose (310.20 to 141.0 mg/dl) and an improvement in body weight in diabetic mice compared with untreated diabetic mice [31].

(15) *Pterocarpus marsupium*: The hypoglycemic activity of this extract is because of the presence of tannates in the extract. Flavonoid fraction from *Pterocarpus marsupium* has been shown to cause pancreatic beta-cell regranulation [32]. Marsupin, pterosupin and liquiritigenin obtained from this plant showed antihyperlipidemic activity the ethanol extract of *Pterocarpus marsupium* blood glucose by $p<0.001$ [33].

(16) *Trigonella foenum graecum:* (Fenugreek) 4-hydroxyleucine, a novel amino acid from fenugreek seeds increased glucose-stimulated insulin release by isolated islet cells in both rats and humans [34]. Oral administration of 2 and 8 g/kg of plant extract produced dose-dependent decrease in the blood glucose levels in both normal as well as diabetic rats. The P-values, less than or equal to 0.05 ($P\leq0.05$), has been fixed as the level of significance.

(17) *Tinospora cordifolia* (Guduchi): Oral administration of the extract of *Tinospora cordifolia* (*T. cordifolia*) roots for 6 weeks resulted in a significant reduction in blood and urine glucose and in lipids in serum and tissues in alloxan diabetic rats [35].

Besides, tinosporin, isocolumbin, palmatine, tinocordiside, cordioside, and β-sitosterol compounds present in stem and root, which are also reported to possess antidiabetic, antihyperlipidemic, and antioxidant properties.

(18) *Camellia sinensis* (Green Tea): The effects of a green tea catechin-enriched extract on lipid and glucose homeostasis and decipher its probable mode of action by using the fructose-fed Hyper-triglyceridemic insulin-resistant golden Syrian hamsters as an animal model.

Oral administration of a green tea extract is capable of improving glucose and lipid metabolism in an insulin-resistant hamster model induced by a high-fructose diet [36]. It contains alkaloids.

(19) *Brassssica juncea*: The aqueous seed extract of *Brassica juncea* has potent hypoglycemic activity in the male albino rat. Isorhamnetin has been reported to be the major antidiabetic flavonol of *Brassica juncea*. Statistical significance * $P<0.001$ [37].

CONCLUSION: Diabetes mellitus is a syndrome, initially characterized by loss of glucose homeostasis resulting from defects in insulin secretion, insulin action both resulting in impaired metabolism of glucose and other energy-yielding fuels such as lipids and proteins. Many traditional plant treatments for diabetes are used throughout the world. Plant drugs and herbal formulations are frequently considered to be less toxic and free from side effects than synthetic ones.

From this, we know that aqueous extract of some plant was significantly decreased in the level of SGPT, SGOT. Main plants are *Azadirachta indica*, the bark of *Semecarpus anacardium* exhibit $p<0.05$. The ethanol extract of *Pterocarpus marsupium* blood glucose by $p<0.001$, so it is more effective than others.

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