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FIGHTING DIABETES WITH HERBAL TECHNOLOGICAL DEVELOPMENTS

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ABSTRACT

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia, hyperlipidemia, hyperaminoacidemia, and hypoinsulinaemia which leads to reduce in both insulin secretion and insulin action. It is often connected with the development of micro and macro vascular diseases which include a long term damage, dysfunction and failure of various organs especially the eye, nerves, heart, kidney and blood vessels. Various approaches have been developed for the treatment of diabetes, like insulin management and use of a variety of oral hypoglycemic agents but these synthetic drugs are costly and often associated with high chances of side effects. A wide number of medicinal plants are described in Ayurveda and traditional medicinal system which are used for the treatment of diabetes from ancient time. The present paper is an attempt to represent the list of the anti-diabetic plants, and their active constituents with a particular mechanism of action. The active principles present in medicinal plants have been reported to possess various activities such as pancreatic beta cell regeneration, stimulating insulin release, showing insulin-like action, fighting the problem of insulin resistance, and reducing the uptake, absorption and utilization of glucose. The recent development of herbal formulations for the treatment of diabetes include using combined extracts of the different plants or different parts of the same plants; development of novel targeted drug delivery systems etc. Perceived effectiveness, fewer side effects, controlled rate of drug release and targeted approaches are the recent areas of herbal technological developments.

Key words: Diabetes mellitus, Hyperglycemia, Insulin, Pancreatic beta cell, Herbal formulation.

INTRODUCTION

In the last few decades there is a great demand for herbal medicines in the developed as well as developing countries because of their wide biological activities, higher safety margin and lesser costs than the synthetic drugs. In a health condition of a body, Pancreas plays an important role to regulate the glucose level in blood. Pancreas mainly consists four types of cells IE; alpha cells (secrets Glucagon), beta cells (secrets Insulin), delta cells (secrets Somatostatin) and Gamma cells also called as PP cells (secrets Pancreatic polypeptide) (Adeghate *et al.*, 2003). The increased level of blood glucose stimulates Insulin secretion from the beta cells of the Pancreas while alpha cells' secrets Glucagon in the condition of low blood glucose level, to maintain the normal blood glucose level in the body (Fig No: 1) (Aronoff et al., 2004).

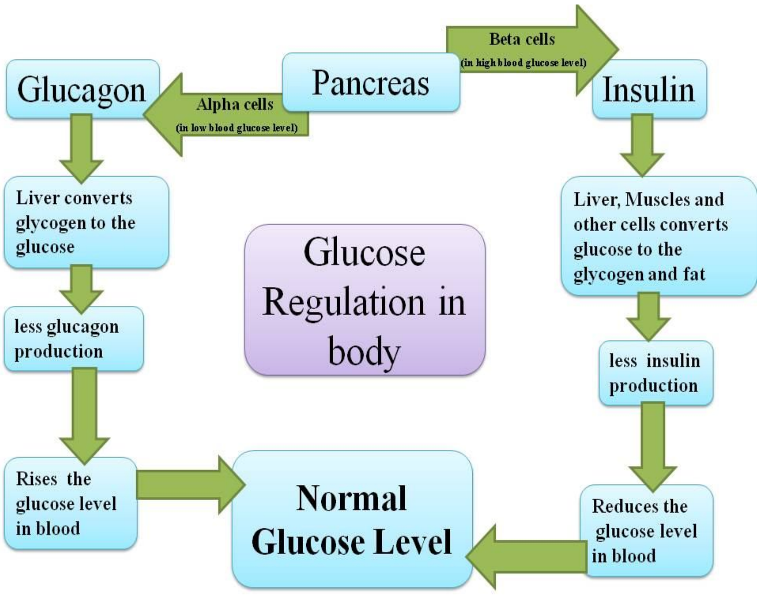

Fig No 1 Regulation of blood glucose level in body

The imbalance between Insulin and Glucagon is one of the great reasons behind the diabetes. Diabetes is known as a group of heterogeneous disorders with the common symptoms of hyperglycemia and glucose intolerance due to insulin deficiency, impaired the effectiveness of insulin action or both. Diabetes mellitus is also defined as a systemic metabolic disorder characterized by hyperglycemia, hyperlipidemia, hyperaminoacidemia, and hypoinsulinaemia which leads to decrease in both insulin secretion and insulin action (Altan 2003). It is often linked with the development of micro and macro vascular diseases which include a long term damage, dysfunction and failure of various organs especially the eye, nerves, kidney, heart and blood vessels (Amreen *et al.*, 2012). Diabetes mellitus is also associated with the complications like retinopathy, nephropathy and neuropathy (both peripheral and autonomic). The risk for atherosclerotic vascular disease also increases in persons with diabetes mellitus. These complications are related to both duration of diabetes and the severity of hyperglycemia (Atsunori 2001).

Diabetes mellitus is most common endocrine disorders, about 2.8% (171 million) of the population suffers from this disease throughout the world and it may rise to 4.4% (366millions) by the year 2030 (Wild et al., 2004). Different approaches have been developed for the treatment of diabetes, like insulin management in type 1 diabetes, and use of a range of oral hypoglycemic agents such as- Sulphonylureas (increases insulin release from pancreas by blocking the ATP-sensitive potassium channels); Biguanides (decreases the insulin resistance); Thizaolidinediones (increases the insulin sensitivity); Metiglinides (act like insulin secretogogues) Alpha-glucodase inhibitors like Acarbose, (decreases glucose absorption from intestine) (Jarald *et al.,* 2008). Treatment of diabetes with these synthetic drugs is costly and has high chances of side effects. For example, long-term use of Sulfonylureas cause abdominal upset, headache and hypersensitivity, while Metformin causes diarrhea, nausea, gas, weakness, indigestion, abdominal discomfort and headache. Thiazolidinediones show side effects like, upper respiratory infections and sinusitis, headache, mild anemia, retention of fluid in the body which may lead to heart failure and muscle pain (DeFronzo, 1999; Dey *et al.,* 2002, Michael *et al*., 2005).

HERBS AS ANTIDIABETICS

Ayurveda and other traditional system of medicine have been described a number of medicinal plants used for the treatment of diabetes. Plant derived active principles represent numerous chemical compounds has established activity constant with their possible use in the treatment of diabetes. Among these are alkaloids, glycosides, gum, polysaccharides, peptidoglycans, hypoglycans, guanidine, steroids, triterpenes, terpenoides, carbohydrates, glycopeptides, amino acids and inorganic ions (Rao *et al.,* 2010). Most often the desired biological response is due to not one but a mixture of bioactive constituents. The relative proportion of active constituents can vary from plant to plant of the same species and also in different parts of plants. The active principles present in medicinal plants have been reported to possess various activities such as pancreatic beta cell regeneration, stimulating insulin release from beta cells, showing insulin-like action, fighting the problem of insulin resistance, and reducing the uptake, absorption and utilization of glucose (Wadkar *et al.,* 2008). Due to the perceived effectiveness, less side effects in clinical experience and relatively low costs, herbal drugs are becoming more popular as an antidiabetic solution (Patel *et al.*, 2012). A list of some antidiabetic herbs with their active constituents and mechanism of action are shown in table no. 1

Table No. 1 List of some antidiabetic herbs and their mode of action:

Sr. No.	Botanical name and Family	Part of plant used	Active constituents	Mode of action
1.	*Acacia arabica* (Indian Gum) Fabaceae	Seed and bark	Polyphenols, tannins	Initiate insulin release from pancreatic beta cells (Patil *et al.*, 2011).
2.	*Aegle marmelos* (Bel, Golden Apple) Rutaceae	Leaf	Again , marmelosin	Increases either the glucose utilization or directly stimulates insulin release from pancreatic beta cells (Arumugama, *et al.*, 2008, Yaheya *et al.*, 2009).
3.	*Allium cepa (onion)* Alliaceae	Bulb	Allyl propyl disulphide, S- methyl cysteine sulphoxide	Stimulates insulin secretion and also increases HMG CoA reductase activity and liver hexokinase activity (Thomson *et al.*, 2007, Tripathi *et al.*, 2012).
4.	*Allium sativum (Garlic)* Alliaceae	Bulb	Allyl propyl disulphide, allicin	Control the blood glucose and lipids in serum as well as in tissues and altered the activities of liver hexokinase, glucose 6-phosphatase and HMG CoA reductase (Ozougwu *et al.*, 2011).
5.	*Aloe barbadensis (Aloe vera)* Liliaceae	Leaf	Alloin and barbaloin	Stimulates synthesis and/or release of insulin from the beta cells of the islets of Langerhans of pancreas and also the action of hepatic gluconeogenesis/ glucogenolysis (Jafri *et al.*, 2011).
6.	*Andrographis paniculata (Kalmegh)* Acanthaceae	Whole plant	Andrographolide, diterpenoid lactone, and kalmeghin	Prevents glucose absorption from the gut wall (Nalamolu *et al.*, 2006).
7.	*Annona squamosa (Custard apple, sugar apple)* Annonaceae	Fruit	Liriodenine, moupinamide	Promotes the insulin release from the pancreatic beta cells, increases the consumption of glucose in the muscles and prevents the glucose output from the liver (Kaleem *et al.*, 2008).
8.	*Artemisia pallens* Asteraceae	Leaf and flower	Germacranolide	Increases the peripheral glucose utilization or inhibits the glucose reabsorption in the proximal

				tubule (Donga *et al.*, 2011).
9.	*Azadirachta indica (Neem)* Meliaceae	Leaf, flower & seed	Azadirachtin and Nimbin	Regenerate the pancreas beta cells (Khosla *et al.*, 2000).
10.	*Bauhinia candicans* Leguminosae	Leaf	Astragalin, kaempferitrin	Increases peripheral metabolism of glucose (Fuentes *et al.*, 2004).
11.	*Beta vulgaris (Beet root)* Amaranthaceae	Root	Phenolics, betacyanins	Decreases the nonenzymatic glycosylation of skin proteins and blood glucose (Yoshikawa *et al.*, 1996).
12.	*Biophytum sensitivum (Sikerpud)* Oxalidaceae	Entire plant	Unknown	Stimulates the synthesis/release of insulin from the beta cells (Ananda *et al.*, 2012).
13.	*Boerhavia diffusa* Nyctaginaceae	Whole plant	Punarnavine and ursolic acid	Improves the glucose tolerance (Patel *et al*, 2012).
14.	*Brassica nigra* (Mustard) Brassicaceae	Whole plant	Isorhamnetin diglucoside. Isothiocynate, Sinigrin	Increases the activity of glycogen synthetase, decreases the glycogenolysis and gluconeogenesis by decreasing the activity of glycogen phosphorylase and gluconeogenic enzymes (Anand *et al.*, 2009).
15.	*Bumelia storm* Sapotaceae	Root bark	Triterpenoids and steroids	Shows insulin secretaguogue effect in pancreatic cells (Naik *et al.*, 1991, Almeida *et al.*, 1985).
16.	*Camellia sinensis (Black tea)* Theaceae	Leaf	Caffeine and catechins	Shows insulinotropic activity and curative effects of oxidative damage (Islam *et al.*, 2007).
17.	*Cassia auriculata (Senna)* Leguminaceae	Flower	Sennoside A and Sennosede B	It elicits the no. of islets and beta-cells in the pancreas, it also enhances the activity of hepatic hexokinase, and phosphofructokinase enzymes, and suppresses glucose-6-phosphatase and fructose-l, 6-bisphosphatase enzymes (Parietal., 2002, Murugan *et al.*, 2007).
18.	*Caesalpinia bonducella* Cesalpinaceae	Seed	Caesalpins, amorphous glycoside bonducin	Increases the insulin secretion from pancreatic beta–cells (aide *et al.*, 2010).
19.	*Carum carvi (Caraway seed)* Umbelliferae	Seed	Carvone, limonene, dihydrocarvone	Significantly decreases blood glucose levels (Prakasam *et al.*, 2005).
20.	*Casearia esculenta* Hippocratiaceae	Root	Flabetanin, dulcitol, tanin	Reduces the blood glucose level and the activities of glucose-6-phosphatase and fructose-1,6-bisphosphatase and also increases

				the activity of liver hexokinase (Ahmed *et al.*, 2010).
21.	*Catharanthus roseus (Vinca, Red periwinkle)* Apocynaceae	Leaf and twing	Vincristein and veinblastin	Stimulates the insulin release from beta-cells and also found to be useful in the damage caused by oxygen free radicals (Parildar *et al.*, 2010).
22.	*Citrullus colocynthis* Cucurbitaceae	Seed	Myristic , palmitic, stearic, oleic, linoleic and Linolenic acid	Increases insulin release and reduces the plasma glucose level (Dallak *et al.*, 2009, Bashir *et al.*, 2009).
23.	*Coccinia indica (Ivy guard kundru)* Cucurbitaceae	Leaf	Resins, starch, glucose, fatty acid and carbonic acid	Inhibits the key gluconeogenic enzyme glucose-6-phosphatase (Jose *et al.*, 2010, Deokate *et al.*, 2011).
24.	*Cocos nucifera (Coconut)* Cucurbitaceae	Fruit	Neutral detergent fiber, fatty acids, tannins, alkaloids	Increase intake of neutral detergent fiber which cause a significant reduction in glycemic and serum insulin level (Sindurani *et al.*, 2000).
25.	*Coffea Arabica (Coffee)* Rubiaceae	Seed	Caffeine, tannin	Increases the no. of pancreatic beta-cells and stimulates the release of insulin (Park *et al.*, 2007).
26.	*Coriandrum sativam (Coriander fruits)* Umbellifereae	Seed	Coriandrol, coriendryl acetate, geraniol and pinene	Significantly increases the activity of the beta cells and insulin release and also decreases the serum glucose level (Eidi *et al.*, 2009, Gray *et al.*, 1999).
27.	*Cuminum cyminum (Jira)* Umbellifereae	Seed	Cuminaldehyde, phellandrene, hydrocumine	Causes a reduction in blood glucose, glycosylated hemoglobin, creatinine, blood urea nitrogen and improved serum insulin and glycogen (liver and skeletal muscle) content (Jagtap *et al.*, 2010).
28.	*Eclipta alba (Bhringraj)* Asteraceae	Leaf and root	stigmasterol, a-terthienylmethanol, wedelolactone, demethylwedelo-lactone	Decreases the activities of glucose-6- phosphatase and fructose-1,6-bisphosphatase, and potentiate the activity of liver hexokinase (Ananthi *et al.*, 2003).
29.	*Enicostemma littorale* Gentianaceae	Flower	Gentianin , tannins	Induces insulin release through K^+-ATP channel dependent pathway (Rajamani *et al.*, 2012, Vishwakarma *et al.*, 2010).
30.	*Eucalyptus globulas (Nilgiri, Dinkum oil)* Myrtaceae	Leaf	Cineole, pinene, camphene, citronella, geranyl acetate	Enhance peripheral glucose uptake (Gray *et al.*, 1998).
31.	*Ficus bengalensis*	Bark	Leucodelphinidin and	Shows antihyperglycemic,

	(Banyan tree) Moraceae		Leucopelargonidin	insulin-releasing and insulin-like activity (Nikhil *et al.*, 2009).
32.	*Glycin max (Soya)* Fabaceae	Bark	3-O-methyl-D-chiro-inositol (D-pinitol), genestein, daidzein	Directly acts on pancreatic beta cells, and lead to the activation of the cAMP/PKA signaling cascade for insulin release (Liu *et al.*, 2006).
33.	*Gymnema sylvestre (Sugar destroyer)* Asclepiadaceae	Leaf	Gymnemic acid and Gymnema saponins	Stimulates pancreatic beta-cell function, increases the number of beta-cells and insulin release by increasing cell permeability of insulin (Shanmugasundaram *et al.*, 1981).
34.	*Helicteres isora* Sterculaceae	Stem bark, root and seed	phytosterol, a hydroxycarboxylic acid, an orange-yellow colouring matter, saponins, sugars, phlobatannins and lignin α-amyrin, β-amyrin, lupeol	Shows insulin-sensitizing activity (Kumar *et al.*, 2009).
35.	*Hibiscus rosa sinensis* Malvaceae	Whole plant	Flavanoids, apigenidine, palargonidine, cianidine, quercitine, crisantemin, antocyanine, kaempherol	Increases insulin release by stimulating pancreatic beta cells or an increase of the glycogen deposition in liver (Soni *et al.*, 2011).
36.	*Ipomoea batatas (Sweet potato)* convolvulaceae	Root	Beta-carotene, fiber	Produces a regranulation of pancreatic islet of beta -cells (Li *et al.*, 2009, Miyazaki *et al.*, 2005).
37.	*Lantana camara* Verbenaceae	Leaf	Lantanoside, lantanone	Increases the insulin and glycogen concentration in dose-dependent manner (Kalita *et al.*, 2012).
38.	*Mangifera indica (Mango)* Anacardiaceae	Leaf	Mangiferin	Reduces the intestinal absorption of glucose (Aderibigbe *et al.*, 1999, Martinez *et al.*, 2000).
39.	*Medicago sativa (alpha-alpha)* Fabaceae	Flower	Phytoestrogen, spinosterol	Stimulates insulin release from pancreatic beta-cells (Tripathi *et al.*, 2011).
40.	*Momordica charantia (karela)* Cucurbitaceae	Leaf	Charantin, sterol	Increases the beta cells production in the pancreas or may permit the recovery of partially destroyed cells and also stimulates the insulin secretion from the beta cells (Savula *et al.*, 2012, Garau *et al.*, 2003).

41.	*Morus alba (white mulberry)* Moraceae	Leaf	Mulberoside , vitamins, fibers	Increases the glucose uptake by stimulating the insulin release and also decreases the lipid peroxidase enzyme (Sadako *et al.*, 2011).
42.	*Murraya koenigii* (Curry leaves) Rutaceae	Leaf	Carbazole alkaloids	Shows hypoglycemic effect coupled with increased hepatic glycogen content due to increased glycogenesis and decreased glycogenolysis and gluconeogenesis (Goel *et al.*, Vinuthan *et al.*, 2004).
43.	*Mucuna prureins (velvet bean)* Leguminosea	Shrub, flower, and seed	l-dopa, dopamine	Shows a direct insulin-like action due to the presence of trace elements like Magnese, zinc etc (Eze *et al.*, 2012, Akhtar *et al.*, 1990).
44.	*Musa sapientum* (Banana) Musaceae	Flower	Flavonoids, steroid and glycoside	Shows insulin-like action (Pari *et al.*, 2000).
45.	*Ocimum sanctum* Labiatae	Whole plant	eugenol	Reduces the uronic acid, total amino acid, total cholesterol, triglyceride and total lipid which indicate its hypoglycemic and hypolipidemic effects (Agrawal *et al.*, 1996, Rai *et al.*, 1997).
46.	*Oleo europoea (Olive oil)* Oleaceae	Fruit	Olein, palmmitin, and linolein	Potentiate glucose-induced insulin release, and increases peripheral uptake of glucose (Gonzalez *et al.*, 1992).
47.	*Panax ginseng* Araliaceae	Root	Ginsenosides, panaxosides	Stimulates insulin release and decreases the liver glycogen level (Vladimir *et al.*, 2005, Kim *et al.*, 2008).
48.	*Picrorrhiza kurrao* Scrophulariaceae	Rhizome	Picroside I and II	Reduces serum glucose level along with Anti-oxidant activity (Joy *et al.*, 1999).
49.	*Punica granum* Lythraceae	Fruit	Punicalagin, punicalin	Reduces blood glucose, lipid parameters and oxidative stress (Jafri *et al.*, 2000).
50.	*Pterocarpus marsupium* Leguminosae	Whole plant	Kenotannic acid, pyrocatechin	Shows protective and regenerating effects on beta cells and may produce insulin like action (Bhoyar *et al.*, 2011, Subhedar *et al.*, 2011).
51.	*Ricinus communis (Castor oil)* Euphorbiaceae	Seed	Ricinolic acid	Increases the insulin level and lipid profile (Rao *et al.*, 2010).
52.	*Salacia reticulata* Celastaceae	Root bark	salacinol	Shows potent inhibitory activity against sucrose and decreases the elevation of the plasma glucose

				level and intestinal α-glucosidase activities in type 1 diabeties (Vasi *et al.*, 2009).
53.	*Salvia lavandifolia* Lamiaceae	Leaf	Monoterpene , 1,8 ceniol, a-pinene	Potentiate glucose induced insulin release, increases the peripheral uptake of glucose; decreases intestinal absorption of glucose; and hyperplasia of the pancreatic islet beta cells (Zarzuelo *et al.*, 1990, Jimenez *et al.*, 1995).
54.	*Scoparia dulcis* Scrophulariaceae	Whole plant	Scoperinol scoparic acid, scopadulcic acid, scopadulciol, and scopadulin	Suppress glucose influx into the polyol pathway and increases activities of antioxidant enzymes and plasma insulin and also decreases the activity of sorbitol dehydrogenase (Abu *et al.*, 2010, Okhal *et al.*, 2010).
55.	*Stevia rebaudiana* Asteraceae	Whole plant	Rebaudioside and stevioside	It stimulates the insulin secretion *via* direct the action on beta-cells of pancreatic islets (Jeppesen *et al.*, 2000, Jeppesen *et al.*, 2002,).
56.	*Swertia chirata* Gentianaceae	Whole plant	Methyl swertianin and bellidifolin	Stimulates insulin release from the islets of Langerhans (Singh *et al.*, 2010).
57.	*Syzygium cumini (Jamun)* Myrtaceae	Fruit and leaf	Ellagic acid, polyphenols	Shows insulin stimulatory activity (Nahar *et al.*, 2010).
58.	*Tinospora cordifolia* Menispermaceae	Root	Tinosporone, tinosporic acid	Inhibits the alpha-glycosidase activity (Gupta *et al.*, 2012).
59.	*Tribulus terrestris (Gokharu)* Zygophyllaceae	Fruit	Harman, harmine, diosgenin, gitogenin	Increases serum insulin level (Raghavendra *et al.*, 2010).
60.	*Trigonella foenum Graecum (Fenugreek)* Fabaceae	Leaf and seed	4-hydroxy isoleucine	Causes the glucose induced insulin release from pancreatic beta cells (Ali *et al.*, 1995, Abdel-Barry *et al.*, 1997, Bawadi *et al.*, 2012).

Herbal medicines are often considered to be less toxic and free from side-effects than synthetic ones (Hui et al., 2009) The attributed antihyperglycemic effects of these herbs is may be their ability to –

1) Increase in insulin output or
2) Inhibit the intestinal absorption of glucose or
3) To the facilitation of metabolites in insulin dependent processes.

Hence, herbal drugs are able to protect beta-cells and control the variation in glucose levels.

Fig No. 2 shows the mode of action of different herbs for their antidiabetic activity.

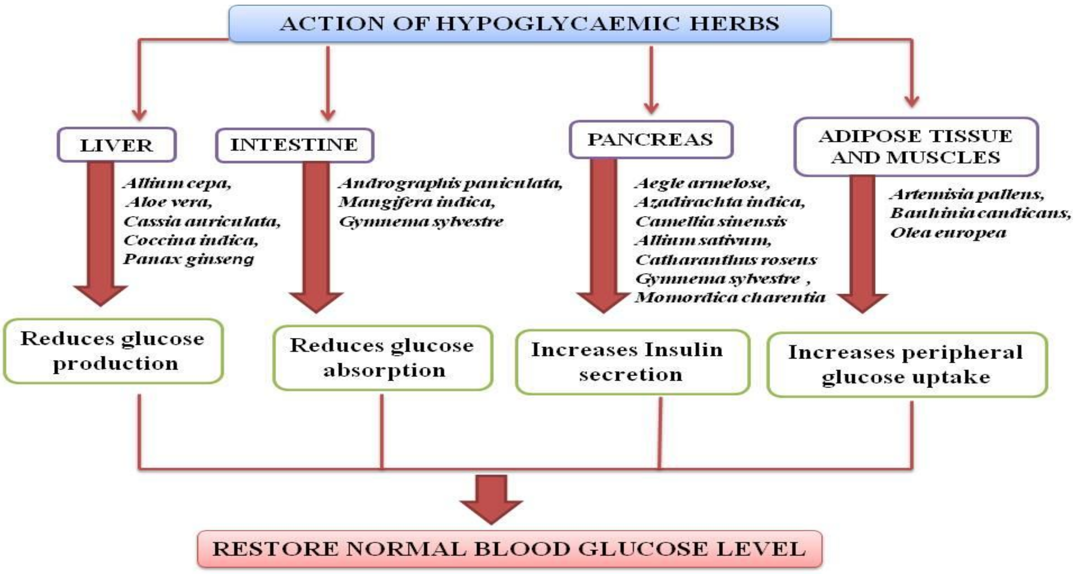

Fig No. 2 Mode of action of antidiabetic herbs

In the traditional system of Indian medicinal plant formulation and in several cases, the combined extracts of plants are used as drug of choice rather than individual. Some of the examples of developed herbal anti diabetic formulations consisting single as well as combination of herbs is listed in the **table no. 2** and also the Patents on some of antidiabetic herbs and herbal formulations are listed in **table no. 3**.

Table No. 2 List of Some Herbal Formulations and Their Composition

S. No.	Herbal Formulations	Herbal Composition
1	*Alangium salvifolium* tablet	*Alangium salvifolium, Gycin max* (Kaushik *et al.*, 2011)
2	D-400 tablet	*Gymnema sylvestre, Eugenia jambolana, Tinospora cordifolia, Pterocarpus marsupium, Momordica charantia,* *Ocimum sanctum (* Anturlikar *et al.*, 1995)
3	*Ipomea digitata* tablet	*Ipomea digitata* (Chandira *et al.*, 2010)
4	Bitter gourd tablets	*Momordica charantia* (Hasan *et al.*, 2012 *)*
5	Diabet capsule	*Curcuma longa, Coscinium fenestratum, Strychnos potatorum, Tamarindus indica, Tribulus terrestris, Phyllanthus reticulates* (Umamaheswari *et al.*, 2010)
6	Diamed powder	*Azardirachta indica, Cassia auriculata, Momordica charantia* (Pari *et al.*, 2001)
7	Dihar powder	*Syzygium cumini, Momordica charantia, Emblica officinalis, Gymnema sylvestre, Enicostemma littorale, Azadirachta indica, Tinospora cordifolia, Curcuma longa* (Patel *et al.*, 2009)

8	Pan five powder	*Toddalia asiatica, Terminalia chebula, Terminalia bellirica, Eclipta elba, Enicostemma littorale* (Hemlatha *et al.*, 2006)
9	Diasulin powder	*Cassia auriculata , Syzigium cumini, Scoparia dulcis, Coccinia indica, Tinospora cordifolia, Emblica officinalis, Trigonella foenum graecum (*Ramalingam *et al.*, 2005*)*
10	Dianex powder	*Gymnema sylvestre, Eugenia jambolana, Momordica charantia Azadirachta indica, Cassia auriculata, Aegle marmelose, Withania somnifera* and *Curcuma longa* (Mutalik *et al.*, 2005)
11	Hyponidd powder	*Momordica charantia, Melia azadirachta, Pterocarpus marsupium, Tinospora cordifolia, Gymnema sylvestre, Enicostemma littorale, Emblica officinalis, Eugenia jambolana, Cassia auriculata, Curcuma longa* (Pandurangan *et al.*, 2004)
12	DRF/AY/5001	*Gymnema sylvestre, Syzigium Cumini, Emblica officinalis, Terminalia chebula, Terminalia bellirica, Pterocarpus marsupium, Momordica charantia* (*Naik et al.*, 2008)
13	Madurisht churna	*Syzigium Cumini, Emblica officinalis, Momordica charantia Ocimum sanctum, Azadirachta indica, Trigonella foenum graecum, Tinospora cordifolia, Aegel marmelos* (Agrawal *et al.*, 2012)
14	MTEC powder	*Musa paradisiacal, Tamarindus indica, Eugenia jambolana, Coccinia indica* (Chatterjee *et al.*, 2009*)*
15	Polyherbal formulation (powder)	*Tribulus terrestris, Piper nigrum, Ricinus communis (*Baldi *et al.*, 2011)
16	Polyherbal formulation ((powder)	*Syzgium cumini, Mangifera indica, Ficus bengalensis, Ficus religiosa, Lawsonia inermis, Juglans nigra, Terminalia bellirica and Hibiscusrosa sinensis (*Agarwal *et al.*, 2012 *)*
17	Polyherbal formulation - 5EPHF powder	*Aegel marmelos, Murraya koenigii, Aloe vera, Pongamia pinnata, Elaeodendron glaucum* (Lanjhiyana *et al.*, 2011)
18	Diashis powder	*Syzygium cumuni, Gymnema sylvestre, Holarrhena antidysenterica, Tinospora cordifolia, Pongamia pinnata, Asphultum, Psoralea corylifolia, Momordica charantia* (Bera *et al.*, 2010)
19	Pancreas tonic or antibetic	*Aegle marmelose, Pterocarpus marsupium, Syzigium cumini Momordica charantia, Gymnema sylvestre, Trigonella foenum graecum, Azadirachta indica, Ficus racemosa, Tinospora cordifolia, Cinnamum tamala (*Shojaii *et al.*, 2011*)*
20	Stevioside-PLA-nanoparticles	*Stevia rebaudiana*, Pluronic-F-68 copolymer (Barwal *et al.*, 2012)

Various approaches have been developed to fight against the diabetes and the research is continuously going ahead. Patent search is an important area of the literature search. The following table (**Table No.3)** enlists some of the patents available on antidiabetic herbs and herbal formulations.

Table No. 3 List of some Patent on antidiabetic herbs and herbal formulations

PATENT NO.	DATE OF PATENT	APPLICATION NO.	TITLE	INVENTORS
US 4,761,286	Jan 27, 1987	07/008,081	Intestinal Absorption Inhibiting Agent	Hiji; Yasutake (Nishi-machi, Yonago-shi, Tottori-ken, JP)
US 4,912,089	Nov 6, 1987	07/117,587	Cariostatic Materials And Foods, And Method For Preventing Dental Caries	Hiji; Yasutake (Nishi-machi, Yonago-shi, Tottori-ken, JP)
US 5,612,039	Apr 21, 1995	08/426,677	Dietary Supplement	Policappelli; Nini E. (Los Angeles, CA), Garzone; Rafaele (Bari, IT), Russo; Claudio (Bari, IT), JP)
US 5,730,988	Mar 24, 1997	08/822,483	Nutritional Supplements For Improving Glucose Metabolism	Womack; Rick W. (Houston, TX)
US 5,980,902	Mar 26, 1998	09/048,966	Compositions For Treating And Preventing Diabetes, Impaired Glucose Tolerance And Related Symptoms, And Methods For Preparing And Using Such Compositions	Shanmugasundaram; Edayatimangalam Raja Bhavani (Chennai, IN), Shanmugasundaram; Kalathinkal Radha (Chennai, IN), Hebert; Rolland (Seattle, WA), Malik; Sohail (Seattle, WA), Baker; Michael (Seattle, WA).
US 5, 900,240	May 4, 1999	09/036,317	Herbal Composition And Their Use As Hypoglycemic Agents	Onkar S.Tomer, Watchung; Peter Glomaski, South Amboy; Kripanath

				Borah, Moris Plains, All of N. J.
US 5,916,567	Jun 29, 1999	08/984,253	Herbal Antidiabetic Therapeutic Product Containing Powdered *Dolichos Biflorus* Seeds	Kameswaran Neelakantan, T. Nagar Chennai, India
US 5,997,877	Dec 7, 1999	09/199,649	Method Of Extraction Of Commercially Valuable Fractions Of *Fenugreek*	Peter Chang, Saskatoon Kanada;
US 2002/0025349 A1	Feb 28, 2002	09/845,723	Novel Herbal Composition For Diabetes Patients And A Process For Producing The Same	Narasimha Baba Brindhavanam, Ghaziabad (In); Chandrakant Katiyar Ghaziabad (In); Yadlapalli Vanketeshwara Rao, Ghaziabad (In);
US 20050048144 A1	Mar 3, 2005	10/651,194	Herbal Extract Based Cosmoceutical Cream For Controlling The Blood Sugar Level Of Diabetes And Method For Making It.	Xiao-Qing Han, Naperville, IL (Us); MingXia Liu, Naperville, IL (Us);
EP 1589983 A1	Nov 2, 2005	A61K 36/185	A Process Of Preparing An Extract Of *Annona Squamosa* For The Treatment Of Diabetes	Ramesh Dr. B.R. Ambedkar Cen. for Bio.Res Chandra
US 2007042062 (A1)	Feb 22, 2007	-	Novel Anti-Diabetic Herbal Formulation	Pushpangadan Palpu [IN]; Rao Chandana V [IN]; Rawat Ajay K S [IN]; Kumar Dadala V, (IN)
US 7,014, 872 B2	Mar 21, 2006	10/108,095	Herbal Neutreceutical Formulation For Diabetes And Process For Preparing The Same	Palpu Pushpangadan, Lakhnow (IN); Dhan Prakash, Lakhnow (IN);
US 2008/0199543A1	Mar 3, 2008	12/065,599	Pharmaceutically Active Extract Of *Vitex Leukoxylon*, A Process Of Extracting The Same And Method Of Treating	Ganga Raju Gokaraju, Andhra Pradesh (IN); Rama Raju Gokaraju Andhra Pradesh (IN);

			Diabetes And Inflammatory Disease	Venkata Subbaraju Gottumukkala Andhra Pradesh (IN); Venkateshwarlu Somepalli Andhra Pradesh (IN);
US 7, 429,395 B2	Sep 30, 2008	11/ 260, 504	Anti-Diabetec Extract Isolated From *Rauvolfia Vomitoria* And *Citrus Aurantium* And Method Of Using Same	Joan Compbell-Tofte, Adolphsvej 10, DK-2820 Gentofte (DK)
EP2054070 A2	May 6, 2009	A61K 36/37	A Novel Herbal Drug And A Process For Preparation Thereof For The Prevention And Management Of Endothellal Dysfunction Among Type-II Diabetes Mellitus Cases	Dubey G. P, Banaras (IN); Rajamanickam, Victor G. Thanjavur, (IN); Singh R. G. Banaras (IN); Agrawal, Aruna, Varanasi (IN); Vyas, Neera, Delhi(IN);
US 2011/0045108A1	Feb 24, 2011	12/531,028	Anti-Diabetic Extraction Of *Honeybush*	Peter Mose Larsen, Odense (DK); Stephen John Fey, Blommenslyst (DK); Johan Louw, Tygerberg (ZA); Lizette Joubert, Pretoria (ZA)
EP2411033 A1	Feb 1, 2012	A23L 1/30B	Anti-Diabetic Nutraceutical Composition From *Palm* Leaf Extract	Suhaila. MOHAMED Tan Rosalina Roslan Tan
US 2012/0071427 A1	Mar 22, 2012	13/322,460	Novel Antidiabetic Furostanolic Saponin Rich (FSR) Fraction From *Fenugreek* Seeds	Pawan Kumar Goel, Panchkula (IN);
US 8,163,312 B2	Apr 24, 2012	13/063,804	Herbal Formulation For Prevention And Treatment Of Diabetes Associated Complications	G. Geetha Krishanan, Patparganj (IN);
US 2012/0148692 A1	Jun 14, 2012	13/162, 778	Novel Herbal Formulation For The	Govind Prasad Dubey, Varanasi

			Prevention And Management Of Type II Diabetes Mellitus And Vascular Complications Associated With Diabetes	(IN); Aruna Agrawal, Varanasi (IN); Nirupama Dubey, Kattankulathur (IN); Shipra Dubey, Kattankulathur (IN); Rajesh Dubey Kattankulathur (IN); Samathanam Merey Deborah, Varanasi (IN);

NOVEL HERBAL DELIVERY SYSTEMS

Novel drug delivery systems have entered in the area of antidiabetics to prevent the ingredients from degradation within the gastrointestinal (GI) tract or undergo first-pass metabolism in the liver; to control the rate and period of drug delivery and target specific areas of the body for treatment. Recent advances in nanotechnology are very useful for poorly soluble, poorly absorbed, and labile herbal extracts and phytochemicals (Chanchal and Saraf, 2008; Saraf and Kaur, 2010). Different approaches to deliver insulin, including transdermal, transmucosal, pulmonary route using dry aerosols and inhalers, smart hydrogels, nasal delivery, oral delivery, and treatment of diabetes with synthetic beta cells, has resulted in recent developments in treatment of diabetes (Varshosaz, 2007). Liposomes,microemulsions, nanocibicles etc have been developed to prevent insulin from degradation and release in the intestinal area (Kinesh et al, 2010). This approach could be utilized for development of novel delivery systems with herbal antidiabetic phytoconstituents and produce maximum therapeutic effect.

The oral antidiabetics had the problem of patient non compliance, which was trying to overcome by developing transdermal drug delivery systems which bypassed the first-pass metabolism associated with gastrointestinal administration of drugs, maintained a constant drug level in blood (Mutalik, et al, 2006). Transdermal films were formulated for diabetes through modern pharmaceutical formulation techniques incorporating diethyl ether fraction of ethanolic extract of *Momordica charantia* fruits (Bhujbal et al, 2011). *Gymnema sylvestre* extract-loaded niosomes were prepared using nonionic surfactants, and evaluated their antihyperglycemic efficacy in comparison with the parent extract. The niosome formulation demonstrated significant blood glucose level reduction in an oral glucose tolerance test, and increased antihyperglycemic activity compared with the parent extract in an alloxan-induced diabetic model (Kamble et al, 2012).

CONCLUSION

Diabetes mellitus is a metabolic disorder characterized by inappropriate hyperglycemia caused by a relative or absolute deficiency of insulin or by a resistance to the action of insulin. Different approaches are there for the treatment of diabetes, like insulin treatment and use of various oral hypoglycemic agents such as Sulphonylureas, Biguanides, Thizaolidinediones, alpha-glucosidase inhibitors, repaglimide and nateglamide. But use of these synthetic drugs is costly and possesses high chances of side effects. On the other hand, traditional medicinal plants with various active principles has discussed in this article have been used since ancient times by physicians and practitioners to treat diabetes. Plant materials which are being used as traditional medicine for the treatment of diabetes are considered as one of the best sources for a new drug or a lead to make a new drug for the treatment of diabetes. *Trigonella foenumgraecum, Momordica charantia, Tinospora cordifolia, Enicostema littorale, Gymnema sylvestre, Azadirachta indica, Syziygium cumini etc.* are some of the most effective and the most commonly studied Indian plants in relation to diabetes. Various types of mechanisms are associated with phytoconstituents like causing a change in carbohydrate metabolism, preventing and restoring the function of beta-cells, insulin-releasing activity, improving glucose uptake and utilization and also the antioxidant properties which offer an exciting opportunity to develop them into novel therapeutics. Therefore, a proper scientific evaluation, a screening of plant by pharmacological tests followed by chemical investigations is necessary.

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