A Target Based Therapeutic Approach Towards Diabetes Mellitus Using Medicinal Plants

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Abstract: Diabetes mellitus (DM) is not one disease but is a heterogonous group of syndromes. Contrary to the popular belief DM is a metabolic disorder characterized by increased blood glucose level (hyperglycemia) and this is because of insufficient or inefficient insulin secretary response. Glucose is the main energy source for the body, and in the case of DM, management of glucose becomes irregular. There are around 410 experimentally proven medicinal plants having antidiabetic properties but the complete mechanism of action is available only for about 109. There are several medicinal plants whose extract modulate glycolysis, Krebs cycle, gluconeogenesis, HMP shunt pathway, glycogen synthesis and their degradation, cholesterol synthesis, metabolism and absorption of carbohydrates, and synthesis and release of insulin. This paper provides a comprehensive review of the mode of action of medicinal plants that exhibit anti-diabetic properties.

Keywords: Diabetes mellitus, Hyperglycemia, Ayurveda, Anti-diabetic, Insulin.

1. INTRODUCTION

Diabetes mellitus (DM) is the most common endocrine disorder, which is characterized by a defective or deficient insulin secretary process, glucose underutilization, and increased blood sugar (hyperglycemia). It is a congenital or acquired inability to transport sugar from the bloodstream into the cells. DM is a major health problem, affecting 5% of the total population in the US and 3% of the population worldwide [1]. It causes about 5% of all deaths globally each year. DM can be divided into two major categories- Insulin dependent diabetes mellitus (IDDM) or type 1 (an autoimmune disease of younger patients with a lack of insulin production causing hyperglycemia and a tendency towards ketosis) and noninsulin-dependent diabetes mellitus (NIDDM) or type 2 (a metabolic disorder resulting from the body's inability to produce enough or properly utilize insulin hence patients have hyperglycemia but are ketosis resistant). Over 90% of patients with diabetes have type 2 and the remainder has type 1 diabetes [2]. The complications associated with diabetes are neuropathy, nephropathy, retinopathy, diabetic foot, and ketoacidosis.

All tissues have energy requirement that is usually met by metabolizing glucose. The entry of glucose from the blood into the cells, liver, skeletal muscle, and adipose tissue is promoted by insulin. In the case of diabetics, these tissues cannot normally assimilate glucose, and hence it accumulates within the blood. As the blood glucose concentrations increases, osmotic forces come into play that tends to increase the blood volume and urine output (polyuria). As the blood glucose level exceeds its renal threshold (i.e., 180 mg/dL), glucose appears in the urine (glucouria). This causes an increased loss of water from the body and triggers a compensatory adjustment that leads to an increase in thirst (polydipsia) [3]. The inability of glucose to enter some tissues increases the need for alternate sources of energy, such as ketone bodies (acetoacetate, acetone and 3-beta-hydroxybutyrate) [4].

Humankind has a long history in the use of herbal medicines. Well-known Ayurvedic physicians Maharshi Charaka (600 BC) and Sushruta (400 BC) correctly described almost all the symptoms of this disease [5]. The present review discusses the mechanism of action of medicinal plants to combating diabetes. World ethnobotanical information about medicinal plants reports that about 800 plants are used in the control of diabetes mellitus [6, 7]. There are around 410 experimentally proven medicinal plants having antidiabetic properties but complete mechanism of action is available only for about 109 plants.

2. THERAPEUTIC STRATEGIES

The management of diabetes without any side effect is still a challenge to the medical system. Herbal drugs are prescribed widely because of their effectiveness, fewer side effects and relatively low cost. Wide array of plant derived active principles have demonstrated antidiabetic activity. The main active constituents of these plants include alkaloids, glycosides, galactomannan gum, polysaccharides, peptidoglycan, hypoglycans, guanidine, steroids, carbohydrates, glycopeptides, terpenoids, amino acids and inorganic ions. These affect various metabolic cascades, which directly or indirectly affect the level of glucose in the human body [8]. Previous work, which has been published in non-indexed and obscure journals, may have been missed out in this review as citations for the present article were predominantly taken from Diabetes Medicinal Plant Database "DiaMedBase" (http://www.progenebio.in/DMP/DMP.htm) [9].

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Table 1. Medicinal Plants that Regulate Glycolysis and Krebs Cycle

S. No.	Plant	Constituent	Activity	References
1.	*Aegle marmelose* L. Correa e-xRoxb(Rutaceae)	Aegelin, β & γ-Sitosterol, Marmelosin, Marmesin.	1 gm/kg/day	[11, 43]
2.	*Allium cepa* L. (Liliaceae)	S-methyl cysteine sulfoxide, S-allyl cysteine sulfoxide.	100-200 mg/kg	[27, 28]
3.	*Allium sativum* L. (Alliaceae)	Allicin, Apigenin, Alliin, S-allyl cysteine sulfoxide.	200 mg/kg	[25, 26]
4.	*Casearia esculenta* Roxb. (Flacourtaceae)	Leucopelargonidin, Dulcitol, Beta sitosterole.		[19]
5.	*Coscinium fenestratum Colebr*(Menispermaceae)	Berberine, saponin.		[29]
6.	*Curcuma longa* L. (Zingiberaceae)	Curcumin, Turmerone, β-Sitosterol, Zingiberene.	0.08 g/kg body Wt.	[30, 37, 48, 66]
7.	*Eclipta alba* L. (Asteraceae)	Wedelolactone, Demethyl wedelolactone, Eclipticine.		[20]
8.	*Eugenia jambolana* Lam. (Myrtaceae)	Mallic acid, Gallic acid, Oxalic acid, Tannins.	100 mg/kg	[24, 30, 76]
9.	*Eucommia ulmoides* Oliv. (Eucommiaceae)	Isoquercitrin, Quercetin3-O-**α**-l-arabinopyrano syl -(1, 2)-**β**-d-glucopyranoside, Astragalin.		[14]
10.	*Gongronema latifolium* Benth (Asclepiadaceae)		100 mg/Kg	[15]
11.	*Momordica charantia* L. (Cucurbitaceae)	Charantin, Momordicoside.	200 mg/kg /day	[24, 30, 44, 53, 63, 77]
12.	*Mucuna pruriens* L. (Fabaceae)	Mucunine, Mucunadine, β-Sitosterol, Mucuadinine.	200 mg/kg /day	[77]
13.	*Murraya koenigii* L. Speng (Rutaceae)		80 mg/kg /day	[11, 31]
14.	*Ocimum sanctum* L. (Lamiaceae)	Eugenol, Carvacrol, Linalool, Caryophylline, β-Sitosterol.		[11, 62, 78]
15.	*Panax quinquefolius* L. (Araliaceae)	Quinquenoside L3 & L9, Vina-Ginsenoside R3.		[79]
16.	*Piper betle*L. (Piperaceae)	β-phenol, Chavicol, Cadinene.	75 mg/kg	[21]
17.	*Plumbago zeylanica* Linn. (Plumbaginaceae)			[80]
18.	*Pterocarpus marsupium* Roxb. (Fabaceae)	Pterostilbene, Liquiritigerin, Isoliquiritigerin, Epicatechin.	1g/kg	[8, 30]
19.	*Tinospora cordifolia* Hook. f. & Thomson (Meninspermaceae)	Berberine.		[30, 32, 60, 76]
20.	*Trigonella foenumgraecum* L. (Leguminosae)	Trigonelline, Choline, Galactomannan.	1g/kg	[22, 81]

3. BIOCHEMICAL PATHWAYS, MEDICINAL PLANTS AND THEIR TARGET SITES

Most of the tissues metabolize glucose for their energy requirement and other purposes such as glucosylation of protein. In mammals, glucose is the only fuel that the brain uses under nonstarvation conditions and the fuel that red blood cells use [10]. In the following sections the important biochemical pathways where glucose is involved, either as a substrate or liberated as a product and the medicinal plants that inhibit or activate one of these regulatory steps in the pathways are listed.

3.1. Glycolysis and Krebs Cycle

Glycolysis is the most important metabolic pathway in all the cells of the human body through which the 6-carbon glucose molecule is oxidized to two molecules of pyruvic acid.

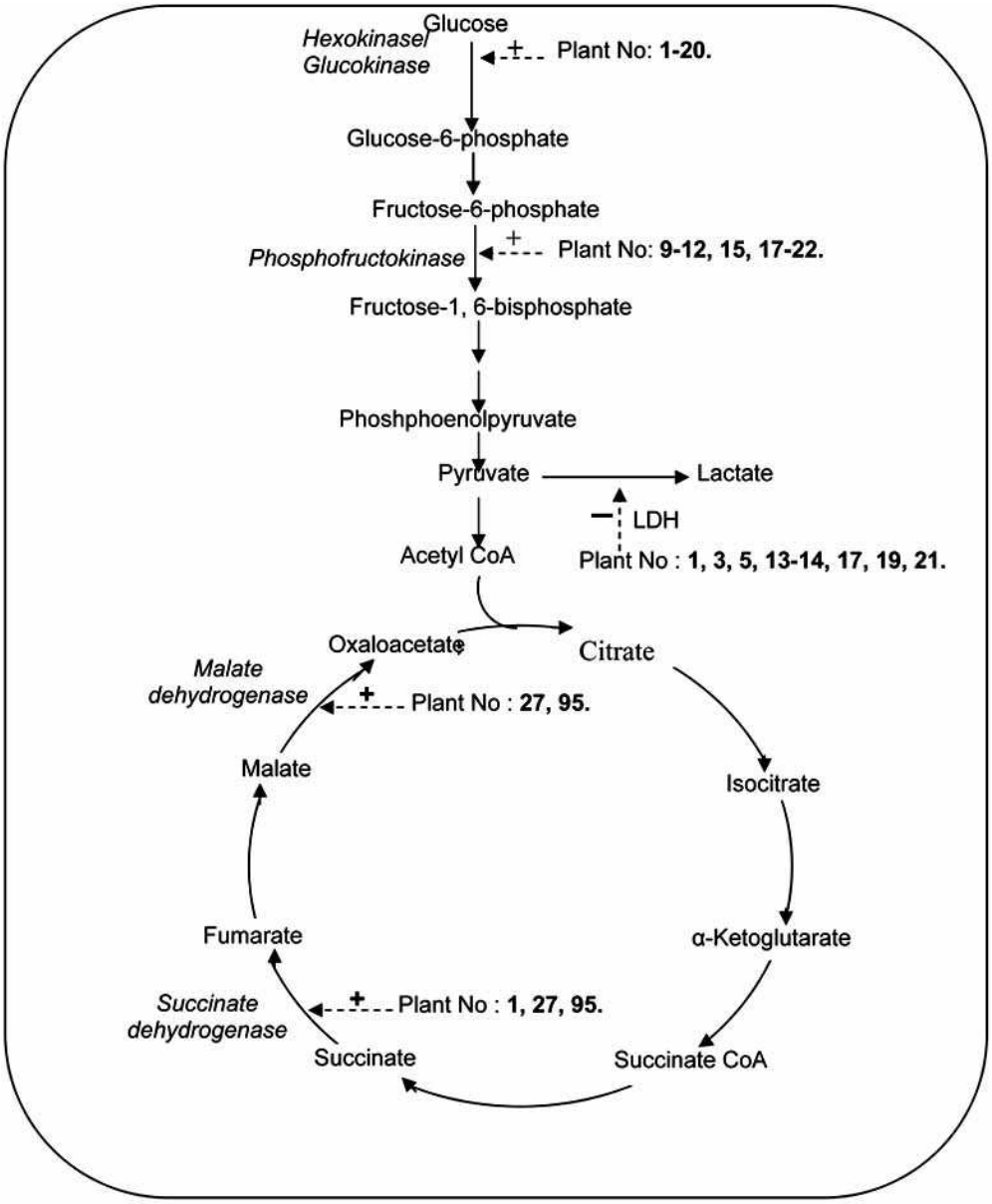


Fig. (1). Medicinal plants which regulate the glycolysis and Krebs cycle (see Table **1**). {Plant No. **95** = *Panax ginseng* C. Meyer [13]}.

Glycolysis is the main energy producing pathway in some specific tissues which lack mitochondria such as mature RBC and cells under low oxygen conditions such as heavily-exercising muscle. In glycolysis, the reactions catalyzed by hexokinase, phosphofructokinase, and pyruvate kinase are irreversible, and hence, these enzymes would be expected to have regulatory as well as catalytic roles [10].

Krebs cycle is the central pathway for energy production in which pyruvate is oxidized to CO_2 and H_2O via acetyl CoA with the synthesis of energy equivalent, NADH. The latter gets oxidized and produces ATP through the electron transport chain. There are seven enzymes involved in this cycle, of which only two enzymes, succinate dehydrogenase and malate synthase are regulated by plants and their respective constituents [10].

Several medicinal plants control the glycolysis and the Krebs cycle (Fig. **1**). The activity and the principal constituents of medicinal plants which regulate the enzyme hexokinase/ glucokinase are listed in Table **1** (Plants No.**1-20**). Plants No: **9-12**, **15** and **17-22** activate phosphofructokinase (Table **1**, Fig. **1**). However, last regulatory step of the glycolytic pathway which is catalysed by pyruvate kinase is not regulated by any medicinal plant. In the case of anaerobic respiration and in tissues which lack mitochondria, pyruvate is converted to lactic acid by the enzyme lactic acid dehydrogenase. The plants that regulate the conversion of pyruvate to lactate by inhibiting lactate dehydrogenase (LDH) in the anaerobic glycolysis step are plants No: **1, 3, 5, 13-14, 17, 19** and **20** respectively (Table **1**, Fig. **1**). Plants such as *Aegle marmelose* L. Correa ex Roxb [11], *Catharanthus roseus* (L.) G. Don. [12] and *Panax ginseng* C. Meyer [13] (Plant No: **1, 27** and **95** respectively) activate succinate dehydrogenase, while *Catharanthus roseus* (L.) G. Don. [12] and *Panax ginseng* C. Meyer [13], activate malate dehydrogenase (Plant No: **27** and **95** respectively) (Table **1**, Fig. **1**).

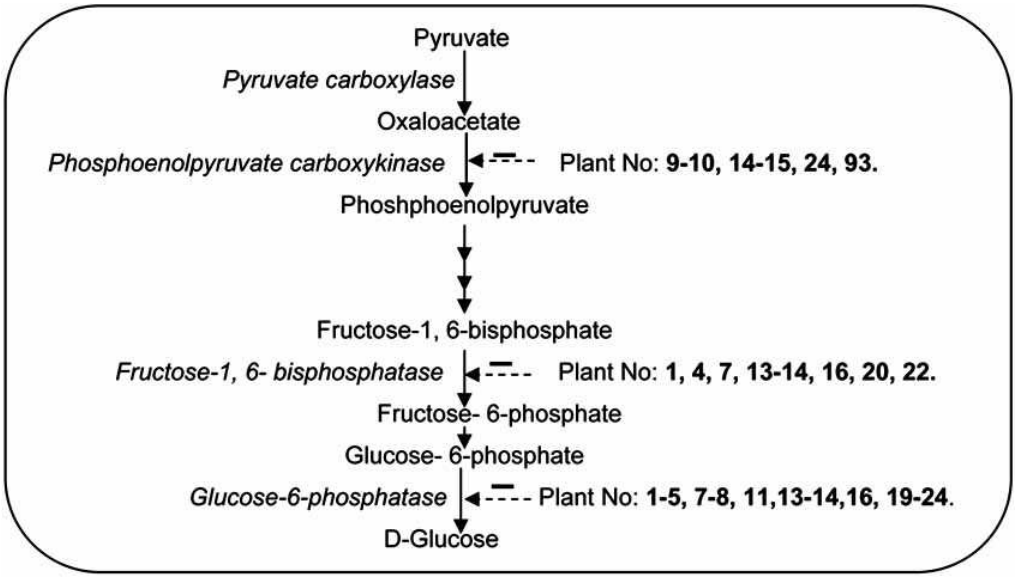


Fig. (2). Medicinal plant that modulate gluconeogenesis pathway (see Table **3**).

Table 2. Medicinal Plants (in Addition to Plant No. 1-5, 7, 9, 11, 13-14, 16, 19-20) that Inhibit Gluconeogenesis (Glucose-6-phosphatase)

S. No.	Plant	Constituent	Activity	References
21.	*Aconitum carmichaeli* Debeaux(Renunculaceae)	Songoramine, Hypaconitine, Karakanine, Songorine		[33]
22.	*Coccinia indica* Weigh & Arn (Cucurbitaceae)	Taraxerone, Taraxerol	2 gm/kg	[23, 24]
23.	*Enicostemma littorale* Blume (Gentianaceae)		2 gm/kg	[30, 34]
24.	*Syzygium aromaticum* (L.) Merr. & Perry (Myrtaceae)	Isoflavones	50 mg/kg	[17, 46, 47]

3.2. Gluconeogenesis

Gluconeogenesis is the pathway that generates glucose from non-sugar carbon substrates like pyruvate, lactate, glycerol, and glucogenic amino acids (primarily alanine and glutamine). Gluconeogenesis cannot be considered to be simply a reverse process of glycolysis, as the three irreversible steps in glycolysis are bypassed here with four irreversible and regulatory steps which are catalyzed by pyruvate carboxylase; PEP carboxykinase; Fructose-1, 6-bisphosphatase and glucose-6-phosphatase. The medicinal plants *Eucommia ulmoides* Oliv [14], *Gongronema latifolium* Benth. [15], *Panax quinofolium* L. [16], *Syzygium aromaticum* (L.) Merr. & Perry [17] and *Camellia sinensis* (L.) Kuntze. [16, 18] inhibit phosphoenol pyruvate carboxykinase (Plant No: **9-10, 14-15, 24** and **93** respectively); and *Aegle marmelose* L. Correa ex Roxb [11], *Casearia esculenta* Roxb. [19], *Eclipta alba* L. [20], *Murraya koenigii* (L.) [11], *Ocimum sanctum* L. [11], *Piper betle* L. [21], *Trigonella foenum-graecum* L. [22] and *Coccinia indica* Weigh & Arn [23, 24] inhibit fructose-1, 6-bisphosphatase (Plant No: **1, 4, 7, 13-14, 16, 20** and **22** respectively). Green tea flavonoid epigallocatechin gallate (I) has glucose lowering effect by decreasing the expression of phosphoenol pyruvate carboxykinase gene (Fig. **2**) [18].

The last regulatory enzyme in this pathway is glucose-6-phosphatase, which is inhibited by *Aegle marmelose* L. Correa ex Roxb [11], *Allium sativum* L. [25, 26], *Allium cepa* L. [27, 28], *Casearia esculenta* Roxb. [19], *Coscinium fenestratum* Colebr. [29], *Eclipta alba* L [20], *Eugenia jambolana* L. [24, 30], *Eucommia ulmoides* Oliv [14], *Momordica charantia* L. [24, 30], *Murraya koenigii* (L.) [11,31], *Ocimum sanctum* L. [11], *Piper betle* L. [21], *Pterocarpus marsupium* Roxb. [8], *Tinospora cordifolia* (Willd.) Hook. f. & Thomson [32], *Aconitum carmichaeli* Debeaux. [33], *Coccinia indica* Weigh & Arn [23, 24], *Enicostemma littorale* Blume [34] and *Syzygium aromaticum* (L.) Merr. & Perry [17] (Plant No: **1-5, 7-9, 11, 13-14, 16, 18-19** and **21-24** respectively) (Table **2**, Fig. **2**).

3.3. Hexose Monophosphate (HMP) Shunt

HMP Shunt is an alternative pathway to glycolysis and Krebs cycle for the oxidation of glucose. It generates two important products namely pentoses (ribose-5-phosphate) and NADPH. It is an anabolic pathway that utilizes the six

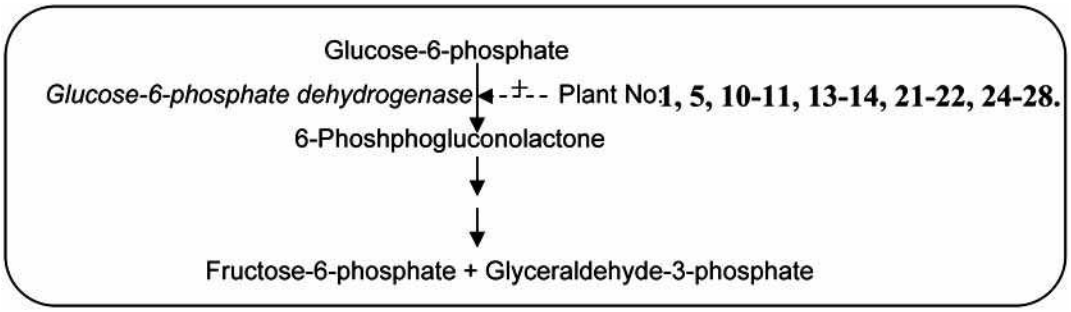


Fig. (3). Medicinal plants affecting HMP shunt.

Table 3. Medicinal Plants (in Addition to Plant No. 1, 5, 10-11, 13-14, 21-22, 24) that Regulate HMP Shunt (Glucose-6-phosphate dehydrogenase)

S. No.	Plant	Constituent	Activity	References
25.	*Balanites roxburghii* (Balanitaceae)	Sapogenin, Diosgenin, Yamogenin, β-sitosterol.	1.5 g/kg	[82]
26.	*Casearia esculenta* Roxb. (Flacourtaceae)	Resin, Sterol, Flavonoid.	300 mg/kg	[19]
27.	*Catharanthus roseus* (L.) G.Don (Apocynaceae)	Vinblastine, Vineristine, Vinine, Vincamine, Alstonine.	500 mg/kg	[12, 61]
28.	*Dioscorea cayenensis* Lam. (Dioscoreaceae)			[35, 36]

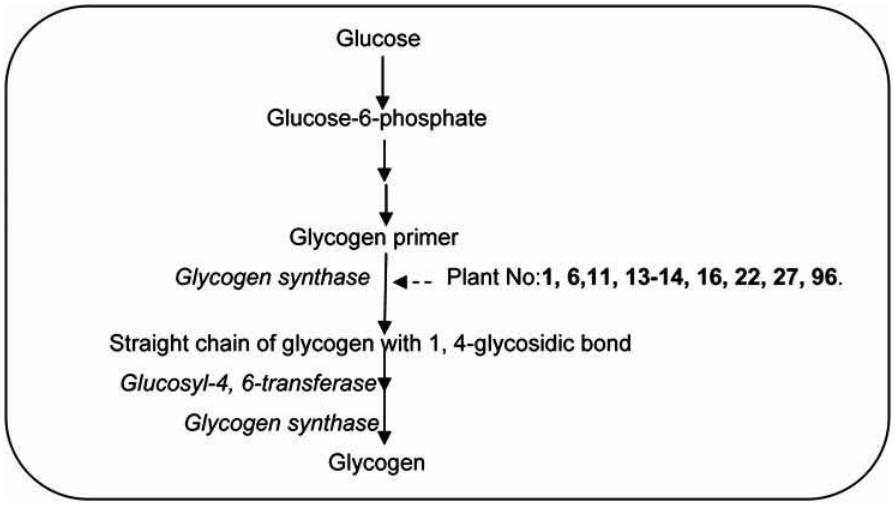


Fig. (4). Glycogen synthesis and medicinal plants involved in its regulation. Plant No. **96** = *Brassica juncea* (L.) Czem. [31].

carbons of glucose to generate five carbon sugars (Fig. **3**). The regulatory and irreversible step in HMP shunt pathway is catalyzed by enzyme glucose-6-phosphate dehydrogenase. Hence, regulation of enzyme glucose-6-phosphate dehydrogenase in the case of diabetes is a very important issue. There are several plants which regulates this enzyme. *Aegle marmelose* L. [11], *Coscinium fenestratum* Colebr. [29], *Gongronema latifolium* Benth [15], *Momordica charantia* L. [24, 30], *Murraya koenigii* (L.) [11, 31], *Ocimum sanctum* L. [11], *Aconitum carmichaeli* Debeaux. [33], *Coccinia indica* Weigh & Arn [23, 24], *Colocassia esculenta* (L.) Schott [35], *Catharanthus roseus* (L.) G.Don [12] and *Dioscorea cayenensis* Lam. [36], affect the enzyme glucose-6-phosphate dehydrogenase in the HMP shunt pathway (Plant No: **1**, **5**, **10-11**, **13-14**, **21-22** and **24-28** respectively) (Table **3**, Fig. **3**).

3.4. Glycogen Synthesis

Synthesis of glycogen from unused glucose is a multistep process carried out by the enzyme glycogen synthase in the liver. This enzyme utilizes UDP-glucose and the non-reducing end of glycogen as another substrate and progressively lengthens the glycogen chain. The activation of glucose to be used for glycogen synthesis is carried out by the enzyme UDP-glucose pyrophosphorylase (Fig. **4**). In the case of diabetes the glucose is not properly converted to glycogen and as a result of which blood glucose level increases. Several plants affect the enzyme glycogen synthase action and they are *Aegle marmelose* L. [11], *Curcuma longa* L.[30, 37], *Dioscorea esculenta* (Lour.) Burk. [37], *Momordica charantia* L [24, 30], *Murraya koenigii* (L.) [11, 31] *Ocimum sanctum* L. [11], *Piper betle* L. [21], *Coccinia indica* Weigh

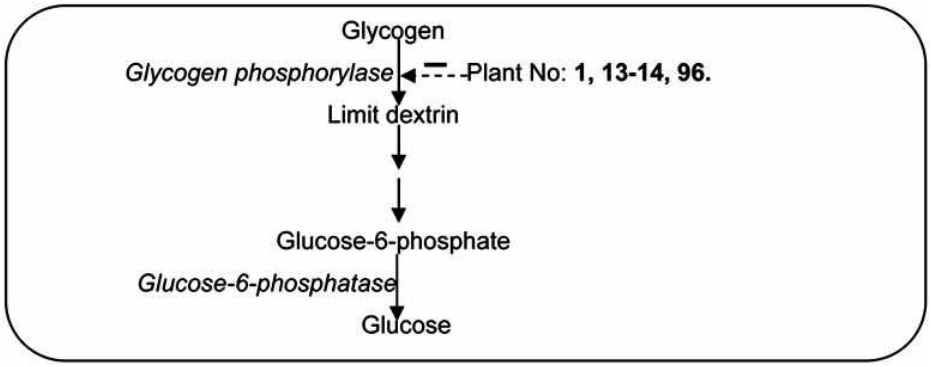


Fig. (5). Medicinal plants which repress the glycogenolysis process.

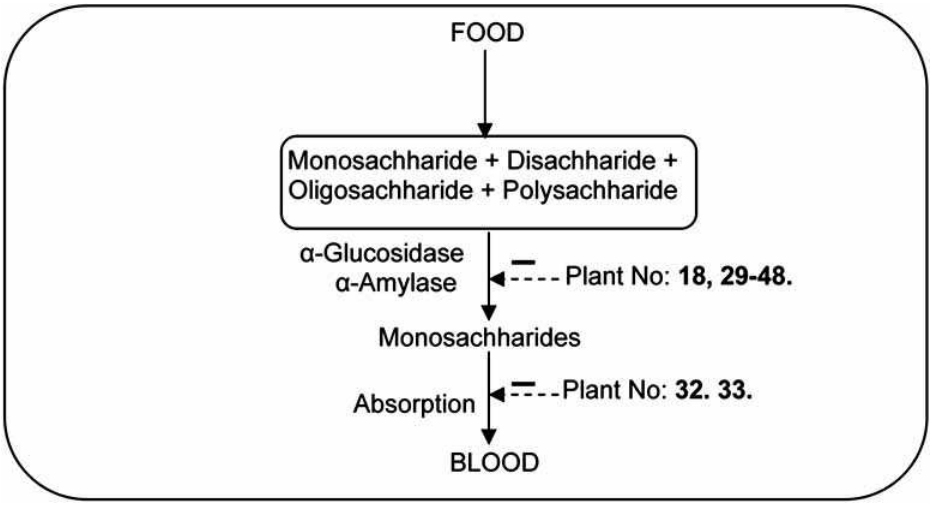


Fig. (6). Mechanism of action of medicinal plant in the digestion and absorption of carbohydrate (see Table **4**).

& Arn [23, 24], *Catharanthus roseus* (L.) G. Don [12] and *Brassica juncea* (L.) Czem [31] (Plant No: **1**, **6**, **11**, **13-14**, **16**, **22**, **27** and **96** respectively) (Fig. **4**).

3.5. Glycogenolysis

Glycogenolysis is the degradation of glycogen to glucose which leads to increase in glucose level in the blood. Glycogen phosphorylase (GP) is the primary enzyme involved in the glycogen breakdown. Plants like *Aegle marmelose L* [11], *Murraya koenigii* (L.) [11, 31], *Ocimum sanctum* L. [11] and *Brassica juncea* (L.) Czem [31], inhibit the enzyme GP, thereby regulating the gluconeogenolysis pathway and hence decrease the glucose level in the blood (Plant No: **1**, **13-14** and **96** respectively) (Fig. **5**). It is reported that leaf extract of *Azadirachta indica* is able to block the reduction in the peripheral utilization of glucose and glycogenolysis in diabetic rabbits [38].

3.6. Digestion and Absorption of Carbohydrates

Carbohydrates are the major energy producing components of the normal diet, supplying more than 80% of the quick requirement of the body. The main constituents of carbohydrates are starch and sucrose. Starch is first decomposed into oligosaccharides by the enzyme α-amylase present in saliva and various pancreatic juices. α-Glucisidase (EC 3.2.1.20), which is a membrane-bound enzyme located at the epithelium of the small intestine, catalyzes the cleavage of glucose from disaccharides and oligosaccharides. Digestion of starch and sugar produces glucose, which is absorbed in the blood stream through the walls of the intestine, and finally carried to the liver (Fig. **6**). This process maintains the glucose level in the blood. Several enzymes take part during the carbohydrate digestion process, which primarily include α-Glucosidase, maltase, sucrase, amylase, lactase, isomaltase etc of which α-glucosidase is the most important. Hence, inhibition of α-glucosidase can be the effective treatments of DM. There are a number of medicinal plants known to suppress this activity (Plant No: **18** and **29-48** respectively) (Table **4**) and some of the plants decrease the absorption of carbohydrates *via* the brush border cell of the intestine. The two active components, (-)-3-O-galloylepicatechin and (-)-3-O-galloylcatechin, from *Bergenia ciliata* Haw have demonstrated inhibition of inhibit rat intestinal α-glucosidase and porcine pancreatic α-amylase [39]. *Alstonia scholaris* (L.) R. Br. containing quercetin 3-O-b-D-xylopyranosyl (1’’’→2’’)-b-D-galactopyranoside and (-)-lyoniresinol 3-O-b-D-glucopyranoside [40], also inhibits α-glucosidase. These inhibitors are known as "diabetes pills" however they are not technically hypoglycemic agents because they do not have a direct effect on insulin secretion or its sensitivity, but they slow the digestion of starch in the small intestine. The glucose comesfrom the starch present in daily intake food enter the bloodstream slowly and can be matched to an impaired insulin response or low production. Miglitol and Acarbose are two commercially available synthetic drugs which inhibits the activity of α-glucosidase.

Table 4. Medicinal Plants (in Addition to Plant No. 18) that Inhibit α-Glucosidase Activity and Glucose Absorption

S. No.	Plant	Constituent	Activity	References
29.	*Anemarrhena asphodeloides* Bunge. (Asphodelaceae)	Sarsasapogenin, mangiferin, neomangifrin.		[83]
30.	*Alstonia scholaris* (Apocynaceae)	Chlorogenic Acid.		[40]
31.	*Angylocalyx pynaertii* de Wild (Leguminosae)	1,4-dideoxy-1,4-imino-D-ribitol, 2,5-dideoxy-2, 5-imino-D-fucitol.		[84]
32.	*Artemisia pallens Wall* ex. DC. (Compositae)	T-Cadinol, α-urunene, β-Eudesmol, β-Ubebene.	100 mg/kg	[85]
33.	*Bauhinia candicans* Link. (Leguminosae)	Astragalin, Kaempferitrin, Astragalin, Bauhinoside.		[86, 87]
34.	*Bergenia ciliata* Haw (Saxifragaceae)	(−)-3-*O*-galloylepicatechin, (−)-3-*O*-galloylcatechin.		[12]
35.	*Cassia auriculata* L. (Leguminoceae)	Di-(2-ethyl) hexyl phthalate.	IC_{50} =0.023 mg/mL	[30, 88]
36.	*Hydnocarpus wightiana* Blume. (Flacourtaceae)	Hydnowightin, Hydnocarpin, Neohydnocarpin.		[89]
37.	*Morus insignis* Bur. (Moraceae)	β-Sitosterol, Ursolic acid, Moracin M,MulberrofuranU.		[90]
38.	*Myrtus communis* L. (Myrtaceae)	Mulberrofuran U, Moracin M3-O-β-D-glucopyranoside.		[91]
39.	*Morus alba* L. (Moraceae)	Isoquercitrin, Astragalin, Scopolin, Roseoside II.	200 mg/kg	[92]
40.	*Morus bombycis* Koide. (Moraceae)	3-Epifagomine, Fagomine, Castanospermine.	IC_{50} = 0.1 mg/ml	[92]
41.	*Myrcia multiflora* DC. (Myrtaceae)	Myrciaphenones A & B, Myrciacitrins I-V, Kotalanol.		[93]
42.	*Phylanthus embelica* L. (Euphorbiaceae)	Pterostilbene, Epicatechin, Liquiritigerin.		[88]
43.	*Salacia reticulata* Wight. (Celastraceae)	Mangiferin, Salacinol, Kotalanol, Epigallocatechin.	1 ml/day/rat	[94]
44.	*Salacia oblonga* (Celastraceae)	Mangiferin, Salacinol, Kotalanol, Epigallocatechin.	250 mg/kg	[94]
45.	*Taraxacum officinale* Weber. (Compositae)	Taraxacin, Acrystalline, Inulin,Taraxacerin, Laevulin.	IC_{50} = 38 μg/mL	[91, 90]
46.	*Urtica dioica* L. (Urticaceae)	Quercetin, Kaempferol, Glucoquinone.		[91]
47.	*Viscum album* L. (Loranthaceae)	Lectins, Misteloe lectin I, II, III, Viscotoxins, Cyclitols.		[91]

4. INSULIN MIMETIC NATURAL DRUGS

Insulin is the most important peptide hormone in the human body. It not only regulates the carbohydrate metabolism, but also stimulates lipogenesis, diminishes lipolysis, and increases amino acid transport into the cells. This is secreted from the β-cells of the islets of Langerhans in response to hyperglycemia. Presently, all focus is targeted to increase the expression of insulin genes, increase secretion of insulin from secretary granules, and inhibit their degradation.

The mechanism of insulin release from β-cells in response to changes in blood glucose concentration is a complex process (Fig. **7**). The release of insulin from insulin stored granules involves closure of ATP-gated potassium channels and activation of voltage-gated calcium channels [41].

Many medicinal plants modulate this expression, synthesis and degradation of insulin (Table **5a**). There are a few plants which act on the Sulfonylurea binding site 1 (SUR1) and close the ATP-sensitive potassium channel (K_{ATP}), due

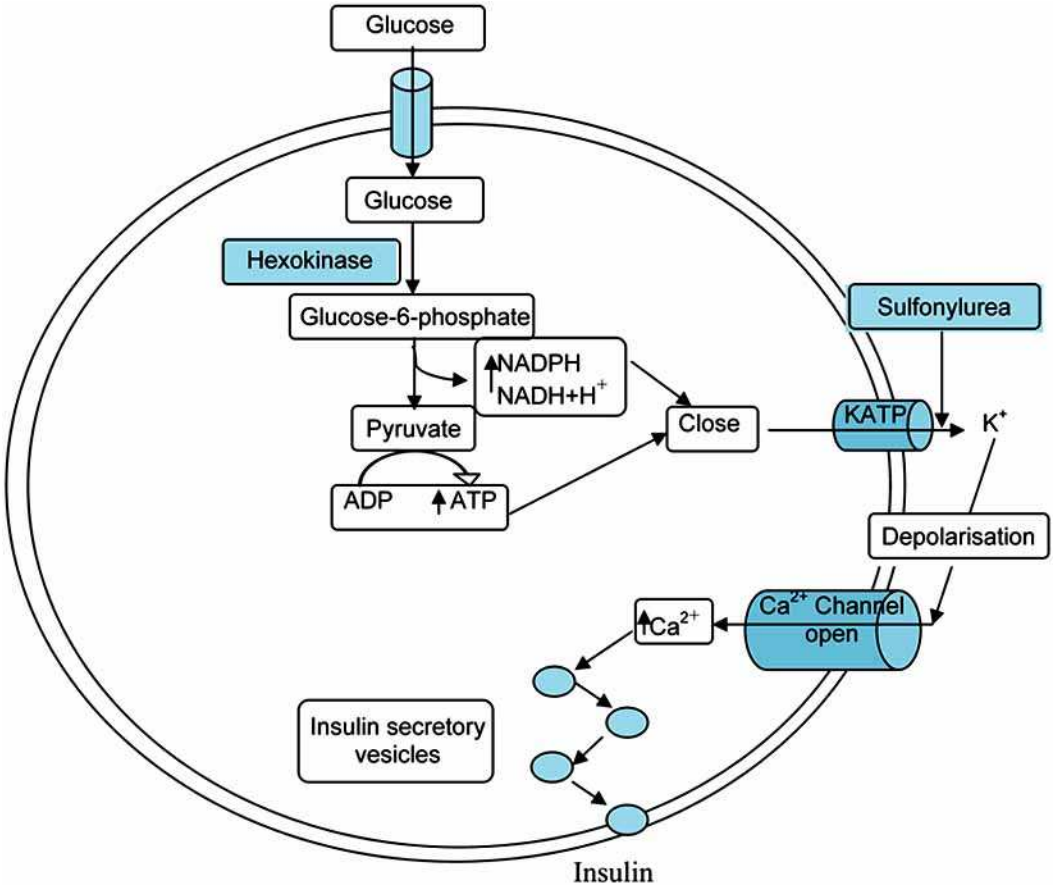


Fig. (7). Mechanism of action of exocytosis of insulin and of sulfonylurea (Table **5a**).

to which the cell membrane gets depolarized leading to the influx of Ca^{2+} [41]. Plants which directly act on the Ca^{2+} channels affecting insulin secretion are listed in Table **5a** (Plant No: **12**, **14-15**, **18**, **40** and **49-89**) and those which increase the activity of insulin and decrease their degradation by inhibiting insulinase are listed in Table **5b** (Plant No: **14**, **51** and **90-92**).

Peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptor transcription factors that induce the proliferation of peroxisomes in the cells, which are also involved in the cellular metabolism of carbohydrates, protein and lipids [41]. There are three types of PPAR, namely, alpha, delta/ beta and gamma. Among these, alpha participates in the metabolism of lipids and peroxisome proliferation, beta has been implicated to be involved in some disorder such as cancer, infertility and dislipidemis whereas gamma participates in the insulin resistance [42]. Medicinal plants such as *Aegle marmelose* (L.) Correa ex Roxb (Rutaceae) [43], *Momordica charantia* L. [44], *Helicteres isora* L. (Sterculiaceae) [45], and S*yzyzium cumini* (L.) Skeel [43], increase the expression of PPAR gamma and decrease the insulin resistance (Plant No: **1**, **11**, **72** and **94** respectively). Thiazolidinedione class of drugs which include roziglitazone, troglitazone and piaglitazome also target PPAR gamma. DehydroglyasperinC (II), dehydroglyasperinD (III), glyasperinB (IV), glycycoumarine (V), glycyrin (VI), and glyasperinD (VII), isolated from *Glycyrrhiza uralensis* and neolgnan dehydroeugenol (VIII) isolated from *Syzygium aromaticum* exhibit significant PPAR-gamma ligand-binding activity [46, 47]. PPAR gamma is one of the most important targets for Curcumin (IX), extracted from *curcuma longa* and 6-gingerol (X), a natural analog of curcumin derived from the root of ginger (*Zingiber officinale* Roscoe.). The latter compound exhibits biological activity profile similar to that of curcumin [48].

Cyclic AMP is one of the second messengers that mediate intracellular signaling networks triggered by membrane receptor stimulation, eventually leading to alteration of cell functions including metabolic activities. The synthesis of cAMP is catalyzed by adenylate cyclase, which has a short half life as the enzyme cAMP phosphodiesterase cleaves it. This eventually leads to a decrease in the intensity of insulin [49]. Several medicinal plants which include *Orthosiphon aristatus* Blume.[50], *Passiflora edulis* Sims. f [51], *Hylocereus undatus* (Haworth) Britton & Rose [52], *Luffa cylindrical* (L.) Roem [53], *Momordica charantia* L. [53] and *Panax ginseng* L. [13] possess cAMP phosphodiesterase inhibitory activity, as a result of which the action of insulin is retained**.**

Glucose transporters (GLUT) which are present on the vesicles in the cytoplasm help in transporting glucose in and out of the cells. On excitation by glucose, GLUT comes to the membrane and performs its required function. In the case of DM the transportation of GLUT to the plasma membrane does not takes place (Fig. **8**). A group of medicinal plants, such as *Aegle marmelose* (L.) Correa ex Roxb [11, 43], *Allium sativum* L. [25, 26], *Canna indica* L. [54], *Lagerstro-*

Table 5a. Medicinal Plants (in Addition to Plant No. 12, 14-15, 18, 40) that Increase Insulin Secretion and Potentiates its Action

S. No.	Plant	Constituent	Activity	References
48.	*Abelmoschus moschatus* L. (Malvaceae)	β-Sitosterol, Ambrettelide, Myricetin-3-glucoside.	1.0 mg/kg	[95]
49.	*Abies pindrow* Royle. (Pinaceae)	β-Sitosteral, Terpenoids, Flavonoids.	10 µg/ml	[96]
50.	*Acacia arabica* (Lam.) Muhl. ex Willd. (Mimosaceae)	m-Digallic acid, Chlorogenic acid, (+)-Catechin.	4 gm/kg	[97, 98]
51.	*Achyranthes aspera* L. (Amaranthaceae)	Betaine, Achyranthine, Aschyranthes α-aponins (B3).	4 mg/kg	[99]
52.	*Agaricus campestris L.*. (Agaricaceae)	α-Terpineol, Hexanol, Furfural, Captylic acid.	1 mg/mL	[100]
53.	*Artemisia roxburghiana* Besser. (Compositae)	1,8-Cineole, Camphor, α-Thujone.	1 µg/mL	[66, 85, 96]
54.	*Aloe barbadensis* L. (Aloaceae)	Isobarbalin, Aloe-emodin, Aloetic acid, Barbaloin.	500 mg/kg	[62]
55.	*Asparagus adscendens* Roxb.(Asparagaceae)	3-Hepatadecanone, Steroidal glycosides.		[101]
56.	*Azorella compacta* Lam. (Umbelliferae)	Mulinol, Azorellanol, Mulinolic acid.		[102]
57.	*Bauhinia forficata* Link. (Leguminosae)	Astragalin, Kaempferitrin, Bauhinoside, β-sitosterol.	25.9% decrease	[103]
58.	*Biophytum sensitivum* auct. (Oxalidaceae)	Shamimin (flavonol glucoside).		[104]
59.	*Bauhinia variegata* L. (Caesalpiniaceae)	Quercetin, Quercetrin, Apigenin, Rutin.	20 µg/ml	[105]
60.	*Bergenia himalaica* Boriss. (Saxifloriaceae)	Bergenin.	20 µg/ml	[96]
61.	*Caesalpinia bonducella* L. Roxb. (Cesalpinaceae)	Bargenin, Caeselpinine A, α & β-Amyrin, Lupeol.	30 mg/kg	[106]
62.	*Centaurea iberica* Trev. ex Spreng (Asteraceae)		10 µg/mL	[96]
63.	*Cinnamomum cassia* Lour. (Lauraceae)	Melilotic acid, Cinnamaldehyde	0.1 mg/ml	[107]
64.	*Cinnamomum zeylanicum* Blume. (Lauraceae)	L-arabino-D-xylan, D-glucan, Cinnzeylanin, Cinnzeylanol,		[107]
65.	*Citrullus colocynthis* L. Schrad. (Cucurbitaceae)	Citrullol, Elaterin, Elatericin B, Colosynthetin.		[108]
66.	*Coriandrum sativum* L. (Umbelliferae)	Linalool, Geraniol, α-Pinene, p-Cymene, Limonene.		[109]
67.	*Eugenia uniflora* Lam. (Myrtaceae)			[110]
68.	*Euphorbia helioscopia*L. (Euphorbiaceae)		10 µg/mL	[96]
69.	*Ficus religiosa* L.(Moraceae)	Leucopelargonidin, Pelargonidine.		[111]
70.	*Gynostemma pentaphyllum* Thumb. (Cucurbitaceae)			[112]
71.	*Gymnema sylvestre* Retz. (Asclepiadaceae)	Gymnemosides, Gymnemic acid I-IV.		[30, 65]
72.	*Helicteres isora* L. (Sterculiaceae)	Cucurbitacin B, Isocucurbitacin B.	100 mg/kg	[45]
73.	*Hylocereus undatus* Britton & Rose. (Cactaceae)	B-Sitosterol, Vit-B1, B2, B3, C, Stigmasterol, Ca, P, Fe.		[52]

Table 5a. contd…

S. No.	Plant	Constituent	Activity	References
74.	*Luffa cylindrica* (L.) Roem (Cucurbitaceae)	Momordin-a, Luffin-a.		[53]
75.	*Musa sapientum* L. (Musaceae)	2-heptyl acetate, 2-methylbutyl acetate.	150 mg/kg	[113]
76.	*Marrubium vulgare* L. (Lamiaceae)			[114]
77.	*Monstera deliciosa* Liebm. (Areceae)		1 μg/mL	[96]
78.	*Orthosiphon aristatus* Blume. (Lamiaceae)	Neoorthosiphols A & B, 3-hydroxy-2methyl-4-pyrone		[50]
79.	*Panax notoginseng* (Burk.) F.H.Chem (Araliaceae)	Saponin, Dencichine, Flavonoid, Polysaccharide.		[115]
80.	*Panax quinquefolium* L. (Araliaceae)	Quinquenoside L3 & L9, Vina-Ginsenoside R3.		[79, 116]
81.	*Salvia coccinia* Salmon & Red. (Lamiaceae)		1 μg/mL	[96]
82.	*Scoparia dulcis* L. (Scrophulariaceae)			[117]
83.	*Swertia chirayita* Roxb. ex Fleming.(Gentinaceae)	Amarogentin, Swerchirin, Chirantin, Gentiopicrin.	100 mg/kg	[118]
84.	*Stevia rebaudiana* Bertoni (Compositae)	Sstevioside.		[119]
85.	*Teucrium polium* L. Labiaceae)			[120]
86.	*Tinospora crispa* L. (Menispermaceae)	Cordifole, Cordifolide, β-Sitosterol, Tinosporine.		[121]
87.	*Vinca rosea* (L.) G. Don (Apocyanaceae)	Vinblastine, Vincristine, Reserpine, Vinceine.	500 mg/kg	[12, 61]
88.	*Viburnum foetens* Decne (Caprifoliaceae)		40 μg/mL	[96]
89.	*Xanthocercis zambesiaca* (Baker) Harms (Leguminoceae)	Castanospermine, Fagomine, Epifagomine, α-Homono jirimycin, Deoxynojirimycin.	50 mg/ml	[122]

Table 5b. Medicinal Plants (in Addition to Plant No. 14 and 51) that Potentiates Insulin Action by Inactivating Insulinase Enzyme

S. No.	Plant	Constituent	Activity	References
90.	*Arctostaphylos uva-ursi* (L.) Spreng.(Ericaceae)	Arbutin, Ericolin, Ellagic acid, Myricetin, Ursone.	6.25% by weight	[123]
91.	*Ocimum canum* L. (Lamiaceae)	Camphor, Eugenol, Juvocimene I & II, Trans-ß-ocimene, Linalool.	0.03 mg/ml	[124]

emia speciosa (L.) Pers. [55], S*yzyzium cumini* (L.) Skeel. [43], and *Cornus officinalis* Siebold. & Zucc. [56] help in the effective transportation of GLUT to the plasma membrane, as a result of which glucose gets transported into the cells and its concentration in the blood decreases.

Insulin modulates several metabolic pathways through a cascade of steps by activating PI3 Kinase (Fig. **8**) [57]. However, when its action is insufficient then these steps do not take place. Plants, such as *Aegle marmelose* (L.) Correa ex Roxb [11, 43], *Helicteres isora* L. [45], *catharanthus roseus* (L.) G. Don [12], *Camellia sinensis* (L.) Kuntze. [16, 18] and *Hericium erinaceus* Persoon. (Fungi) [58] have PI3 kinase activating capacity thereby affecting all the metabolic pathways inspite of inefiicient insulin (Table **5c**, and Plant No: **1**, **72**, **86-87** and **92-94** respectively). Epigallocatechin gallate (I), a green tea flavonoid, mimics insulin by increasing the PI3 Kinase activity [18].

5. PHYTOCOSTITUENTS HAVING HYPOGLYCEMIC POTENTIAL

Several phytochemicals including alkaloids, flavonoids, glycosides, glycolipid, polysaccharides, peptidoglycans, carbohydrates, amino acids and saponin obtained from plant sources have been reported to posses hypoglycemic activity (Fig. **9**) [8]. Many of them may be found in a single plant and their combined synergistic action may be giving the observed behaviors. First three groups of phytochemical, which are explained below, can be considered as insulin mimetic natural drugs. They either increase the serum insulin level or increase the activity of insulin. The remaining groups either suppress glucose production or enhance glucose metabolism.

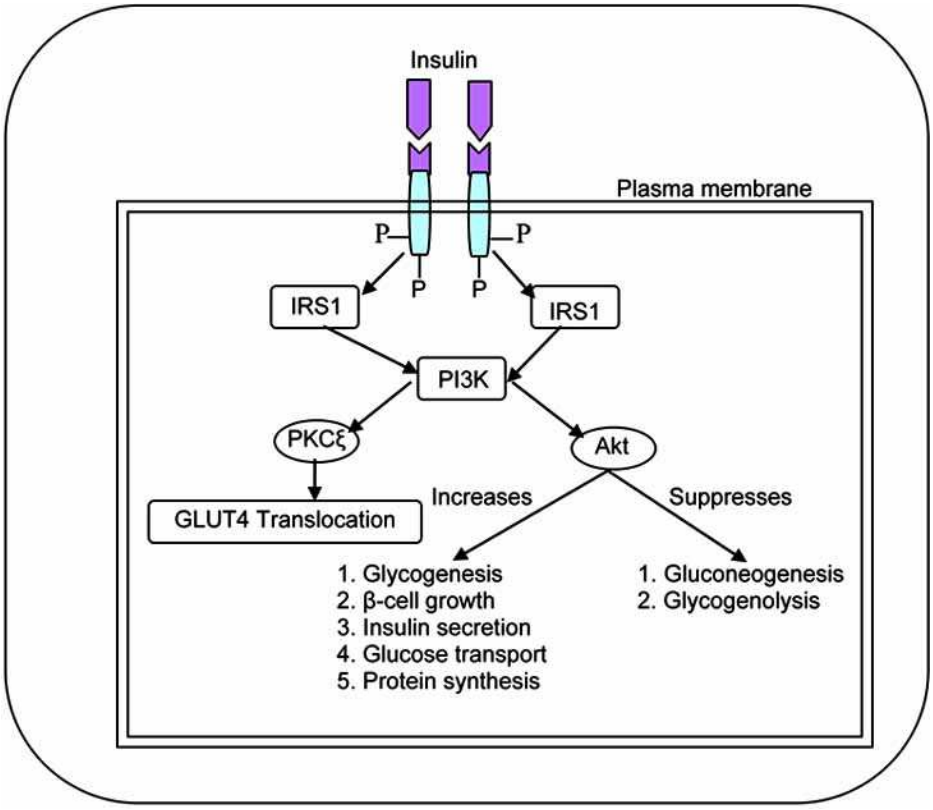


Fig. (8). Mechanism of action of insulin (Tables **5b** and **5c**).

Table 5c. Medicinal Plants (in Addition to Plant 1, 72, 86-87) that Activate PI3K

S. No.	Plant	Constituent	Activity	References
92.	*Camellia sinensis* (L.) Kuntze. (Theaceae)	Epicatechin Epigallocatechin gallate, Epigallo-catechin.		[16, 18]
93.	*Hericium erinaceus* Persoon. (Fungi)(Hericiaceae)			[58]
94.	*Syzyzium cumini* (L.) Skeel.		200 mg/kg	[43]

5.1. Alkaloids

Alkaloids are naturally occurring amines and they have pharmacological effects on human and animals. Resveratrol is a phytoalexin, a class of antibiotic compounds produced as part of a plant's defense system against disease. It increases glucose uptake in STZ-induced type 1 diabetic rat mediated through nitric oxide [59]. Berberine (XI) is known to have potent hypoglycemic activity and it is found in *Tinospora cordifolia* (Willd.) Hook. f. & Thomson [60]. Alkaloids such as Catharanthine (XII.), vindoline (XIII) and vindolinine (XIV) isolated from *Catharanthus roseus* (L.) G. Don have been reported to lower blood sugar level [61].

5.2. Polysaccharides

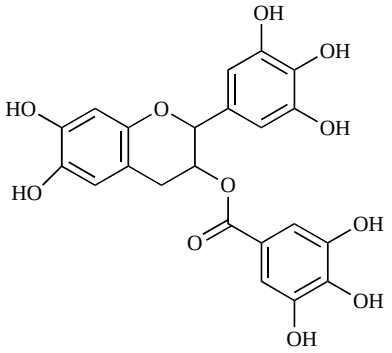
Medicinal plants which include *Aloe vera* L., *Ocimum sanctum* L., and *Alpinia galanga* (L.) Willd. contain polysachharides which increases the insulin level and showing hypoglycemic properties [62]. A protein-bound polysaccharide isolated from pumpkin is shown to increase the levels of serum insulin, reduce blood glucose level and improve tolerance of glucose [62].

5.3. Saponins

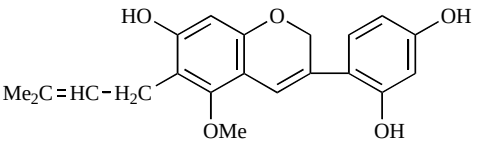
Saponins are glycosides of steroids, steroid alkaloids (steroids with a nitrogen function) or triterpinoids found in plants. Charantin (XV), a steroidal saponin, isolated from *Momordica charantia* L. is reported to posses an insulin-like activity [63], by enhancing the release of insulin and slowing down the glucogenesis. β-Sitosterol (XVI), a steroid found in *Azadirachta indica* A.Juss. andrographolide (XVII), a diterpenoid lactone, isolated from *Andrographis paniculata* Nees.[64] and saponin gymnemic acid IV (XVIII) isolated from *Gymnema sylvestre* R, exhibit potent hypoglycemic activity in animal models [65].

5.4. Ferulic Acids

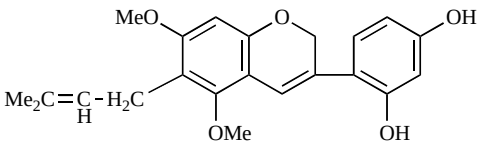
Ferulic acid (4-hydroxy-3-methoxycinnamic acid) (XIX) is a flavonoid which is a highly abundant phenolic photochemical present in cell walls of many plants that include



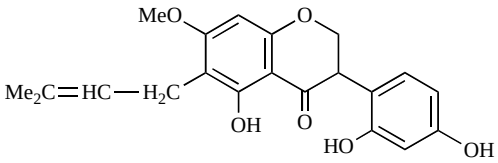
Epigallocatechin gallate [I]



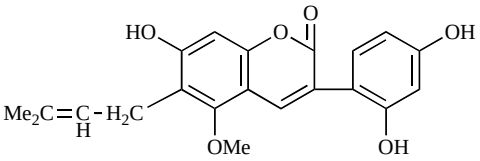
Dehydroglyasperin C [II]



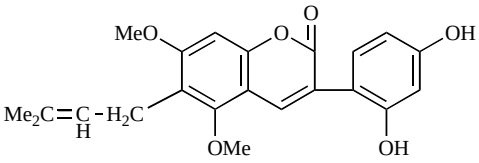
Dehydroglyasperin D [III]



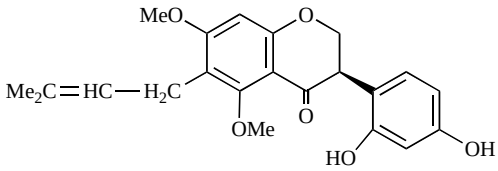
Glyasperin B[IV]



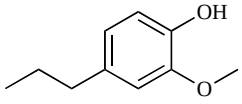
Glycycoumarin [V]



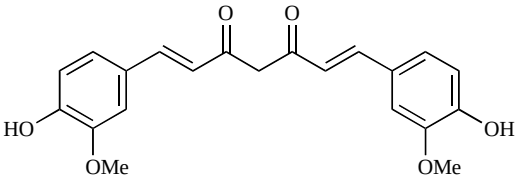
Glycyrin [VI]



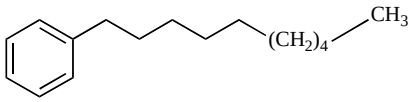
Glyasperin D [VII]



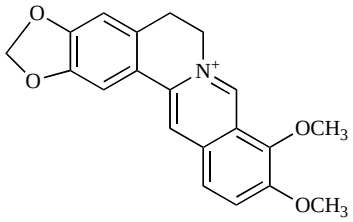
Dihydroeugenol [VIII]



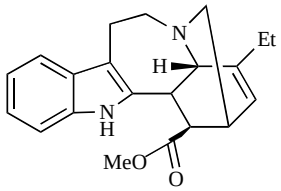
Curcumin [IX]



6-Gingerol [X]



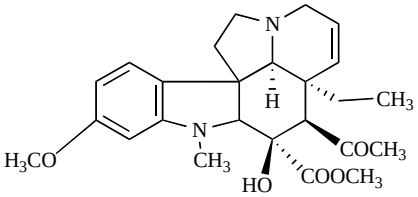
Berberine [XI]



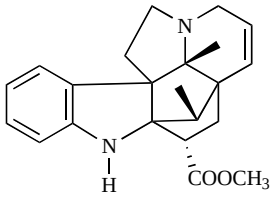
Catharanthine [XII]

Fig (9). Hypoglycemic phytochemicals. (Contd…)

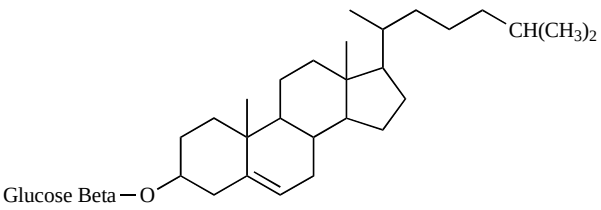
Fig (9). Contd.…



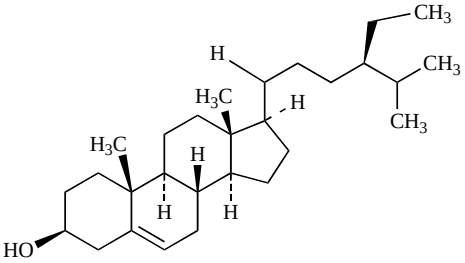
Vindoline [XIII]



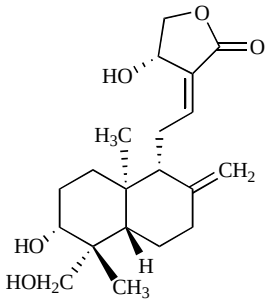
Vindolinine [XIV]



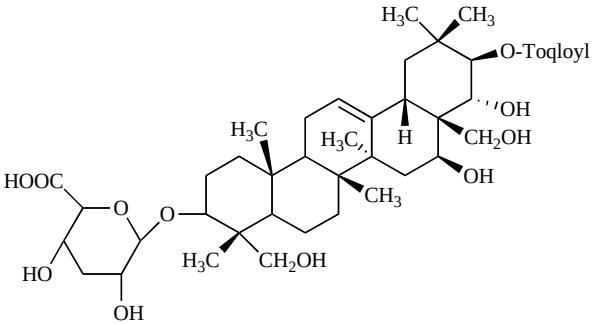
Charantin [XV]



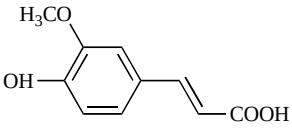
B-Sitosterol[XVI]



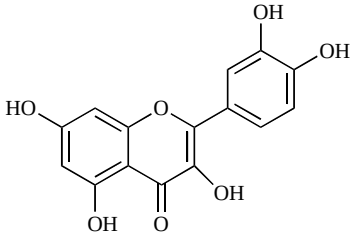
Andrographolide [XVII]



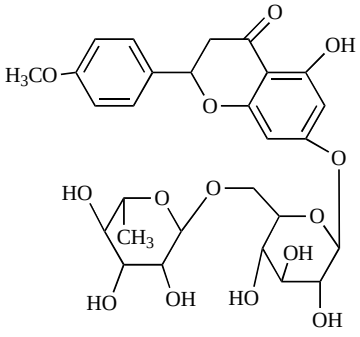
Gymnemic acid [XVIII]



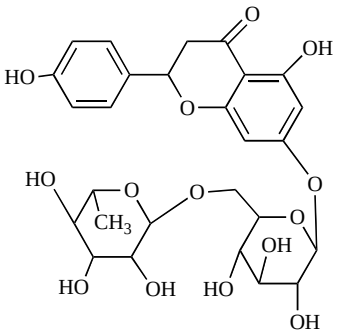
Ferulic acid [XIX]



Quercetin [XX]



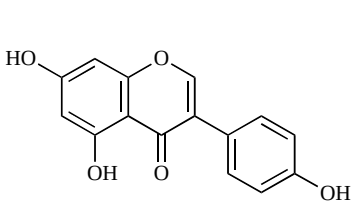
Hespiridin [XXI]



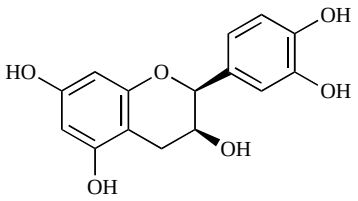
Naringin [XXII]

Fig (9). Hypoglycemic phytochemicals. (Contd…)

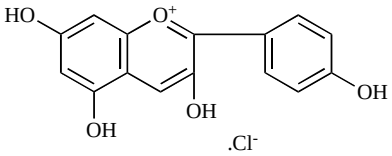
Fig (9). Contd.…



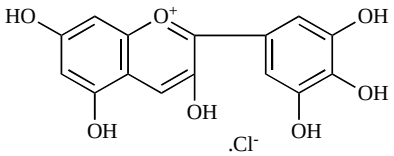
Genistein [XXIII]



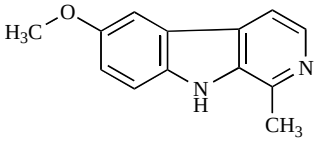
(-) Epicatechin [XXIV]



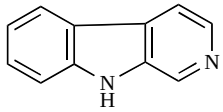
Pelargonidin [XXV]



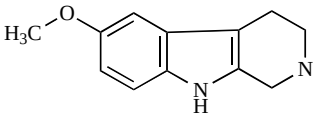
Delphinidin [XXVI]



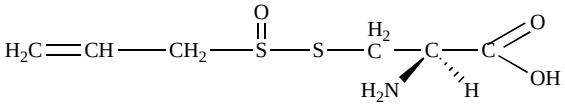
Harmane [XXVII]



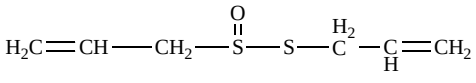
Norharmane [XXVIII]



Pinoline [XIX]



S-allyl cysteine sulfoxide [XXX]



Allicin(Diallyl thiosulfinate) [XXXI]

Fig (9). Hypoglycemic phytochemicals.

C*urcuma longa* L, *Artemisia arborescens* L (Compositeae), *A. herba habla* L (Compositeae) and it may have significant health benefits through its antioxidant, anti-cancer properties and blood glucose lowering activity [66].

5.5. Flavonoids

Flavonoides is a group of naturally occurring compounds which possess hypoglycemic as well as antioxidant properties. They are also a class of plant secondary metabolites. Flavonoids can be widely classified into flavanols, flavones, catechins, flavanones, etc. Some flavonoids have hypoglycemic properties because they improve altered glucose and oxidative metabolisms of the diabetic states [67]. Quercetin (XX) is an important flavonoid known to increase hepatic glucokinase activity, probably by enhancing the insulin release from pancreatic islets [68]. It also exerts stimulatory effect on insulin secretion by changing Ca^{2+} concentration [69]. Supplimentation of (0.2 g/kg) citrus bioflavonoids, namely hesperidin (XXI) and naringin (XXII), in the diet of the male C57BL7KsJ-db/db mice (Type II diabetes model) lead to reduction in the blood glucose levels, increase in hepatic glucokinase activity and glycogen concentration. Naringin lowers the activity of hepatic glucose-6-phosphatase and phosphoenolpyruvate carboxykinase and the plasma insulin, C-peptide. Genistein (XXIII) and soy isoflavonoids when tested on obese Zucker rats (type II diabetes model) significantly improved lipid and glucose metabolism by acting as a hypoglycemic on PPAR [70]. Green tea flavonoid, epigallocatechin gallate (I) has a glucose-lowering effect in animals [18]. It is reported to decrease hepatic glucose production and increase tyrosine phosphorylation of the insulin receptor and insulin receptor substrate-1 (IRS-1), similar to insulin. It also reduces phosphoenolpyruvate carboxykinase gene expression in a phosphoinositide 3-kinase-dependent manner and mimics insulin by increasing PI3K, MAP kinase [18]. Another flavonoid, (−)-epicatechin (XXIV), has been reported to possess insulin-like activity [71] which acts on erythrocyte membrane-bound acetylcholinesterase in Type II diabetic patients [72]. Pelargonidin (XXV) and delphinidin (XXVI) have also shown good hypoglycemic activity [73].

5.6. Imidazoline Compounds

Pancreatic beta cells have imidazoline-I binding sites on them and imizoline derivatives found in some of the plants have stimulatory action on insulin secretion by activating this binding site [74]. β-carbolines which include harmane (XXVII), norharmane (XXVIII) and pinoline (XXIX), obtained from *Tribulus terrestris* L. have found to increase insulin secretion two- to three-folds in isolated human islets of Langerhans [75].

5.7. Sulfur Containing Compounds

Administration of sulfur containing amino acids namely S-methyl cysteine sulfoxide (XXX) and Diallyl thiosulfinate isolated from the plants *Allium sativum* L. [25, 26] and *Allium cepa* L. [27, 28], to alloxan induced diabetic rats activate the enzymes hexokinase, glucose-6-phosphatase, HMG Co-A reductase, and LCAT.

6. CONCLUSION

Traditionally herbal treatments for diabetes have been used in patients with insulin-dependent and non-insulin-dependant diabetes, diabetic retinopathy, diabetic peripheral neuropathy, etc. There are a number of plants which have the capacity to reduce the glucose production, induce the utilization of glucose and combat with secondary complications. Out of an estimated 250 000 plants, less than 1% have been screened pharmacologically and only a fraction of these for DM [8]. The most commonly used drugs of modern medicine such as aspirin, anti-malarials, anti-cancers, digitalis etc. have originated from plant sources. Therefore, it is prudent to look for options in herbal medicine for diabetes. Hence it is proven that medicinal plants have potential effectiveness against diabetes and the photochemical play a major role in the management of diabetes, which needs further exploration for necessary development of drugs and nutraceuticals from natural plant resources. This aspect also gains importance in the light of the fact that many herbal therapies have not undergone proper scientific assessment for their potential to cause serious toxic effects and major drug-to-drug interaction. Continued research is necessary to elucidate the pharmacological activities of herbal remedies being used to treat diabetes mellitus.

ABBREVIATIONS

ADP	=	Adenosine diphosphate
ATP	=	Adenosine triphosphate
cAMP	=	Cyclic AMP
DM	=	Diabetes mellitus
GLUT	=	Glucose transporter
HMP	=	Hexose monophosphate
IRS	=	Insulin receptor substrate
IDDM	=	Insulin dependent diabetes mellitus
NIDDM	=	Non-Insulin dependent diabetes mellitus
KATP	=	ATP dependent K channel
LDH	=	Lactate dehydrogenase
NADH	=	Reduced nicotinamide adenosine dinucleotide
NADPH	=	Reduced nicotinamide adenosine dinucleotide phosphate
PI3K	=	Phosphatidylinositol-3-kinase
PKC	=	Protein kinase C
RNA	=	Ribose nucleic acid
TZD	=	Thiazolidinedione
PPAR	=	Peroxisome proliferator-activated receptors
SUR	=	Sulfonylurea binding site 1

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