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REVIEW ARTICLE / DERLEME MAKALE

IMPACT OF PLANT METABOLITES IN GLUCOSE METABOLISM FOR REGULATION OF BLOOD GLUCOSE LEVEL IN DIABETES: AN EXCLUSIVE UPDATE

DİYABETTE KAN GLUKOZ SEVİYESİNİN DÜZENLENMESİ İÇİN GLUKOZ METABOLİZMASINDA BİTKİ METABOLİTLERİNİN ETKİSİ: ÖZEL GÜNCELLEME

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ABSTRACT

Objective: *To explore the molecular targets of plant chemicals and their role in regulating hyperglycemia, providing insights into potential strategies for developing new treatment for this condition.*

Result and Discussion: *Understanding the biochemical pathways involved in sugar regulation is crucial for developing treatments for conditions such as hyperglycemia. Phytochemicals derived from plants have shown promise in regulating blood sugar levels through various molecular targets. By targeting specific enzymes and pathways involved in glucose metabolism, these phytochemicals offer potential therapeutic benefits for managing hyperglycemia. Plant chemicals have demonstrated the ability to influence key enzymes and pathways in glucose metabolism. Phytochemicals have been found to modulate glycolysis, the Krebs cycle, and gluconeogenesis, offering the potential for regulating blood sugar levels. Additionally, these plant extracts have shown effects on processes such as cholesterol synthesis, glycogen synthesis and degradation, carbohydrate metabolism and absorption, as well as insulin production and release. The diverse impact of these medicinal plants on multiple physiological processes highlights their potential to address hyperglycemia through a multi-faceted approach. In this review, we will further explore the molecular targets and mechanisms of action of these plant chemicals, which can provide valuable insights for developing novel treatments for hyperglycemia.*

Keywords: *Biochemical pathways, diabetes, medicinal plants, phytochemicals*

ÖZ

Amaç: *Bu makalenin amacı, bitki kimyasallarının moleküler hedeflerini ve hiperglisemiyi düzenlemedeki rollerini araştırmak, bu durum için yeni tedaviler geliştirmeye yönelik potansiyel stratejiler hakkında fikir vermektir.*

Sonuç ve Tartışma: *Şeker regülasyonunda yer alan biyokimyasal yolların anlaşılması, hiperglisemi gibi durumlara yönelik tedavilerin geliştirilmesi açısından çok önemlidir. Bitkilerden elde edilen fitokimyasallar, çeşitli moleküler hedefler aracılığıyla kan şekeri seviyelerinin düzenlenmesinde umut vaat etmektedir. Glikoz metabolizmasında yer alan spesifik enzimleri ve yolakları hedef alan bu fitokimyasallar, hipergliseminin yönetilmesinde potansiyel terapötik faydalar sunar. Bitki kimyasalları, glikoz metabolizmasında yer alan anahtar enzimleri ve yolakları etkileme yeteneğini göstermiştir. Fitokimyasalların glikolizi, Krebs döngüsünü ve glukoneogenezi*

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modüle ettiği ve kan şekeri seviyelerini düzenleme potansiyeli sunduğu bulunmuştur. Ek olarak, bu bitki özlerinin kolesterol sentezi, glikojen sentezi ve bozulması, karbonhidrat metabolizması ve emiliminin yanı sıra insülin üretimi ve salınımı gibi süreçler üzerinde de etkileri olduğu gösterilmiştir. Bu şifalı bitkilerin çoklu fizyolojik süreçler üzerindeki farklı etkisi, bunların hiperglisemiyi çok yönlü bir yaklaşımla ele alma potansiyelini vurgulamaktadır. Bu derlemede, bu bitki kimyasallarının moleküler hedeflerinin ve etki mekanizmalarının daha fazla araştırılması, hiperglisemiye yönelik yeni tedavilerin geliştirilmesi için değerli bilgiler sağlayabilir.
Anahtar Kelimeler: *Biyokimyasal yolaklar, diyabet, fitokimyasallar, tıbbi bitkiler*

INTRODUCTION

In the Indian traditional system Ayurveda, "Madhumeha" or diabetes mellitus, was extensively described in classical literatures such as "*Charaka-Samhita*," "*Sushruta-Samhita*," and "*Bhrigu-Samhita*". Herbal remedies for diabetes are described in the "*Shushruta-Samhita*," along with the distinctions between acquired and inherited types of the disease [1].

Ethnobotanically, more than 1200 plant species have been found to have hypoglycemic properties. Due to their various beneficial medicinal qualities conferred by various plant parts as well as the presence of host of multi-componential compounds, medicinal plants are of great interest to contemporary medicine for the treatment of hypoglycemia and hyperglycemia. All those herbs are enriched with numerous phytochemicals, including alkaloids, glycosides, flavonoids, polysaccharides, hypo glycans, guanidine, steroids, carbohydrates, terpenoids, amino acids, inorganic ions, saponins, etc. All those secondary metabolites play an active role in the regulation of blood sugar levels in diabetic conditions, either directly or indirectly [1].

This overview, aims to pinpoint the metabolic pathways that phytochemicals most likely influence to determine a patient's blood sugar level. A thorough literature search was carried out to find pertinent research publications in the English language. We searched PubMed, Science Direct, and Google Scholar, three electronic databases, for publications published between 2000 and 2024. More or less all published data are likely to have a superficial approach to the mechanism of action of hyperglycemia, but accurate mechanisms still need to be uncovered. Hence, this review will provide a comprehensive idea about the mechanism of medicinal plants in diabetes management.

Influence of Phytochemicals on Glucose Regulation in the Body

Both simple and complex sugars belong to the family of carbohydrates. Simple sugars include glucose and fructose, whereas complex sugars include cellulose, starch, and glycogen. Multi-monosaccharide molecules combine to form complex sugars, also known as polysaccharides. Polysaccharides function as structural elements and energy storage molecules, i.e., starch and glycogen.

Blood glucose levels are regulated by biochemical metabolic processes such as glycolysis, gluconeogenesis, glycogenesis, and glycogenolysis, wherein the glucokinase (GK) enzyme is a key player in maintaining glucose homeostasis. Any element that alters the above-stated metabolic processes is damaging.

Glycolysis and Kreb's Cycle

Glycolysis is the primary biological pathway in the human body where glucose is converted into pyruvic acid by the oxidation process and starts energy production for the cell. The entire process of conversion is catalyzed or regulated by various enzymes like hexokinase, phosphofructokinase, pyruvate kinase, etc. [2]. The central pathway of energy production is known as the Krebs cycle. The pyruvate produced after glycolysis, is further oxidized into carbon dioxide and water via Acetyl-CoA with the production of energy and NADH, which further produces ATP through the electron transport chain. This cycle is catalyzed or regulated by various enzymes, like succinate dehydrogenase and malate synthase [2]. Various herbs have been reported to control glycolysis and the Krebs cycle by regulating various catalysts through their phytochemicals. The descriptions of their targeted sites are indicated in Figure 1 and 2 and the reported plants with this regulatory activity and their indicated dose have been listed in the Table 1 and 2, respectively.

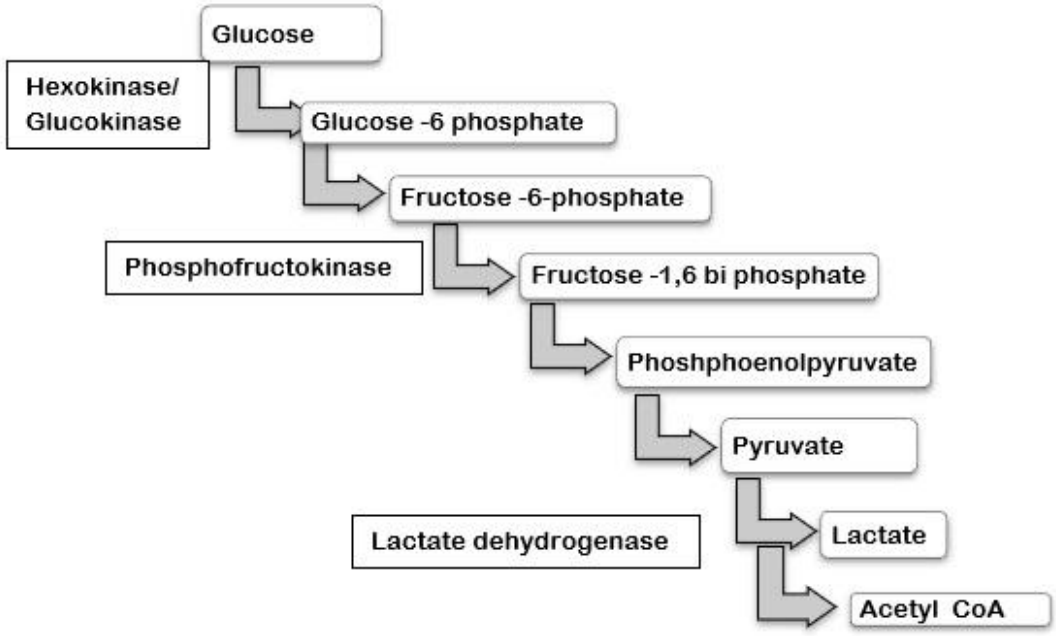

Figure 1. Metabolic pathway of Glycolysis

Table 1. Medicinal plants regulate Glycolysis by activating the enzymes lactate dehydrogenase

Medicinal plant	Family	Major chemical constituents	Dose	Reference
***Aegle marmelos* (L.) Correa**	Rutaceae	Aegelin, β & ϒ-Sitosterol, Marmelosin, Marmesin	1g/kg/day	3,4
Allium cepa L. var. aggregatum Don.	Liliaceae	S-methyl cysteine sulfoxide, S-allyl cysteine sulfoxide.	100-200 mg/kg	5,6
Allium sativum L.	Alliaceae	Allicin, Apigenin, Alliin, S-allyl cysteine sulfoxide.	200 mg/kg	7,8
***Curcuma longa* L.**	Zingiberaceae	Curcumin, Turmerone, β -Sitosterol, Zingiberene.	0.08 g/kg	9,10
***Trigonella foenum-graecum* L.**	Leguminosae	Trigonelline, Choline, Galactomannan	1g/kg	11,12
***Piper betle* L.**	Piperaceae	β-phenol, Chavicol, Cadinene.	75 mg/kg	13
***Mucuna pruriens* (L.) DC.**	Fabaceae	Mucunine, Mucunadine, β-Sitosterol, Mucuadinine.	200 mg/kg /day	14
***Eugenia jambolana* Lam.**	Myrtaceae	Malic acid, Gallic acid, Oxalic acid, Tannins	100 mg/kg	15,16
***Momordica charantia* L.**	Cucurbitaceae	Charantin, Momordicoside	200mg/kg /day	17,18,19, 20
***Panax quinquefolius* L.**	Araliaceae	Quinquenoside L3 & L9, Vina-Ginsenoside R3.	300mg/kg/day	21

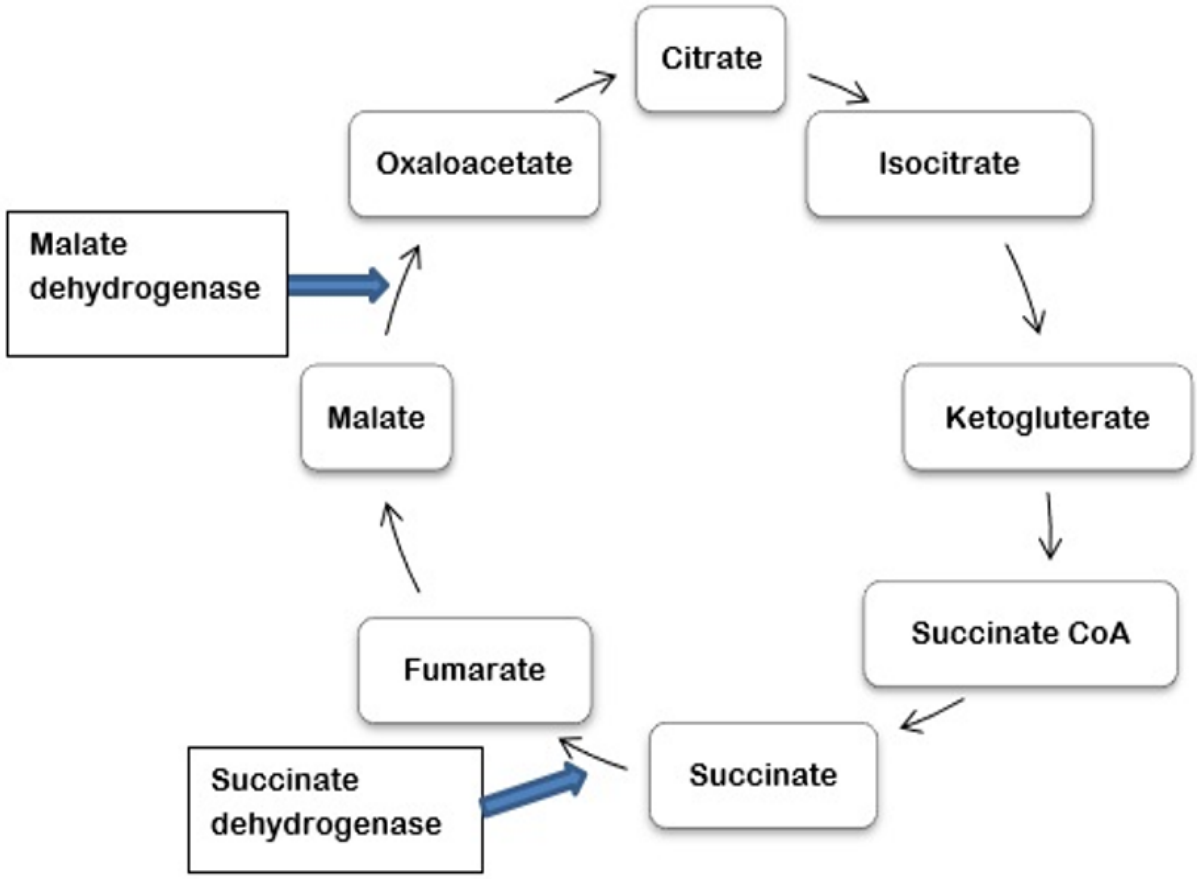

Figure 2. Metabolic pathway of Kreb's cycle

Table 2. Medicinal Plants regulate Kreb's cycle by activating the enzymes Malate dehydrogenase and Succinate dehydrogenase

Medicinal plant	Family	Major chemical constituents	Reported dose	Reference
***Aegle marmelos.* (L.) Corrêa**	Rutaceae	Aegelin, β & ϒ-Sitosterol, Marmelosin, Marmesin	1 g/kg/day	3,4
***Catharanthus roseus* (L.) G. Don**	Apocyanaceae	Vinblastine, Vineristine, Vinine, Vincamine, Alstonine.	500 mg/kg	22,23
***Panax quinquefolius* L.**	Araliaceae	Ginsenosides, peptides, polyacetylenic alcohols, fatty acids	15mg/kg	24

Gluconeogenesis

The generation of glucose from non-sugar carbonated substrates, i.e., pyruvate, lactate, glycerol, and glucogenic amino acids, etc., by the biological pathway known as gluconeogenesis (Figure 3). In this process, the four enzymes catalyze the entire process, i.e., pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose-1, 6-bisphosphatase and glucose-6-phosphatase. Those catalysts are inhibited by various plant phytochemicals, and as a result, glucose formation is altered. Table 3 has a list of medicinal plants that influence or regulate gluconeogenesis.

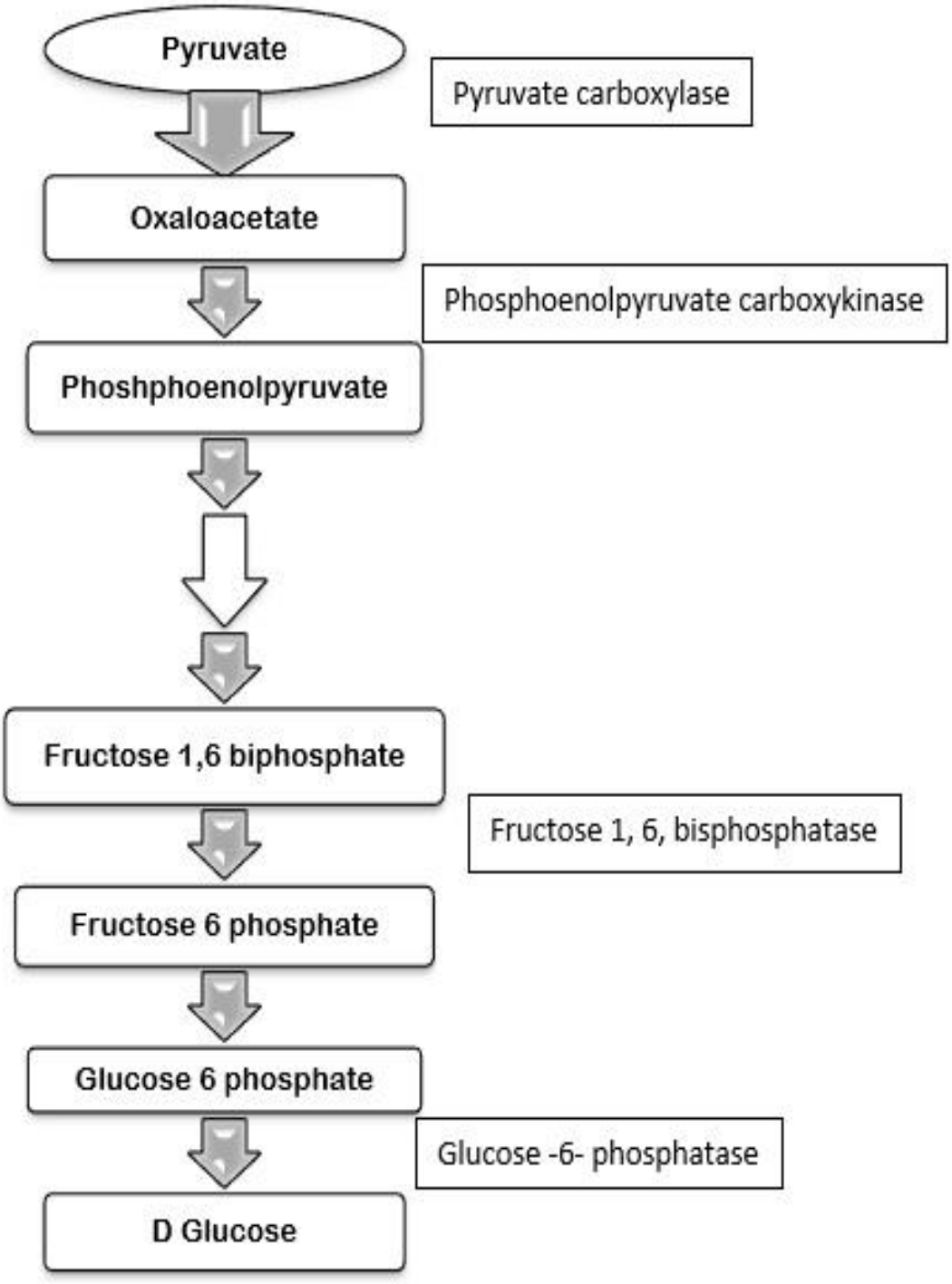

Figure 3. Metabolic pathway of gluconeogenesis

Table 3. Medicinal plants that gegulate gluconeogenesis

Medicinal plant	Family	Major chemical constituents	Reported dose	Reference
Inhibits phosphoenol pyruvate carboxykinase enzyme				
Eucommia ulmoides var.	Eucommiaceae	Isoquercitrin, Quercetin3-O-α-l arabinopyranosyl -(1, 2)-β-d glucopyranoside, Astragalin.	0.187g/ 100g std. diet	25
***Gongronema latifolium* Benth.**	Asclepiadaceae	Phytate, anthranoids, anthraquinones, cyanogenic glycoside, glycides, phblobatannins, hydroxymethyl anthraquinones, polyphenols.	100 mg/Kg	26
***Ocimum sanctum* Linn.**	Lamiaceae	Eugenol, Carvacrol, Linalool, Caryophylline, β-Sitosterol.		27,28
***Panax quinquefolius* L.**	Araliaceae	Quinquenoside L3 & L9, Vina-Ginsenoside R3.	200 mg/kg/day	29
Syzygium aromaticum (L.) Merr. & L.M.Perry	Myrtaceae	Isoflavones	50 mg/kg	30,31
***Hericium erinaceus (*Persoon). (Fungi)**	Hericiaceae	hericenones, erinacines, hericerins, erinarols, 2,6-diethylpyrazine, 2-methyl-3-furanthiol, corallocin	100 mg/kg	32
Inhibits fructose-1, 6-bisphosphatase				
***Aegle marmelos.* (L.) Corrêa**	Rutaceae	Aegelin, β & ϒ-Sitosterol, Marmelosin, Marmesin	1 g/kg/day	3,4
***Casearia esculenta* Roxb.**	Flacourtaceae	Leucopelargonidin, Dulcitol, Beta sitosterole.	250 mg/kg	33
***Eclipta alba* (L.) Hassk.**	Asteraceae	Wedelolactone, Demethyl wedelolactone, Eclipticine.	250 mg/ kg	34
***Murraya koenigii* (L.) Spreng.**	Rutaceae	3-carene, caryophyllene, thujene, allyl(methoxy)dimethyl silane, myrcene, terpinene	80 mg/kg /day	35,36
***Ocimum sanctum* Linn.**	Lamiaceae	Eugenol, Carvacrol, Linalool, Caryophylline, β-Sitosterol.		37,38
***Piper betle* L.**	Piperaceae	β-phenol, Chavicol, Cadinene	75 mg/kg	39
***Trigonella foenum-graecum* L.**	Leguminosae	Trigonelline, Choline, Galactomannan	1g/kg	40,41
***Coccinia grandis* (L.) Voigt**	Cucurbitaceae)	Taraxerone, Taraxerol	2 gm/kg	42,43
Inhibits glucose-6- phosphatase				
***Aegle marmelos.* (L.) Corrêa**	Rutaceae	Aegelin, β & ϒ-Sitosterol, Marmelosin, Marmesin	1g/kg/day	3,4
***Allium sativum* L.**	Alliaceae	Allicin, Apigenin, Alliin, S-allyl cysteine sulfoxide.	200 mg/kg	7,8
***Piper betle* L.**	Piperaceae	β-phenol, Chavicol, Cadinene.	75 mg/kg	13
***Eugenia jambolana* Lam.**	Myrtaceae	Malic acid, Gallic acid, Oxalic acid, Tannins	100 mg/kg	15,16
***Momordica charantia* L.**	Cucurbitaceae	Charantin, Momordicoside	200mg/kg /day	17,18,19,20
***Panax quinquefolius* L.**	Araliaceae	Quinquenoside L3 & L9, Vina-Ginsenoside R3.		44
Coccinia indica	Cucurbitaceae	Taraxerone, Taraxerol	2g/kg	45

Hexose Monophosphate (HMP) Shunt

The glucose is oxidized by alternative pathways called HMP Shunt or Hexose Monophosphate Shunt other than glycolysis and Krebs cycle. In this pathway, with six Carbone structures, glucose produces five-carbon sugars. This entire process is catalyzed by an enzyme called glucose-6-phosphate dehydrogenase. The regulation of this enzyme is one of the vital parts of diabetic control. Numerous plants are found to be potent in this context of enzyme regulation (Table 3) with their secondary chemicals.

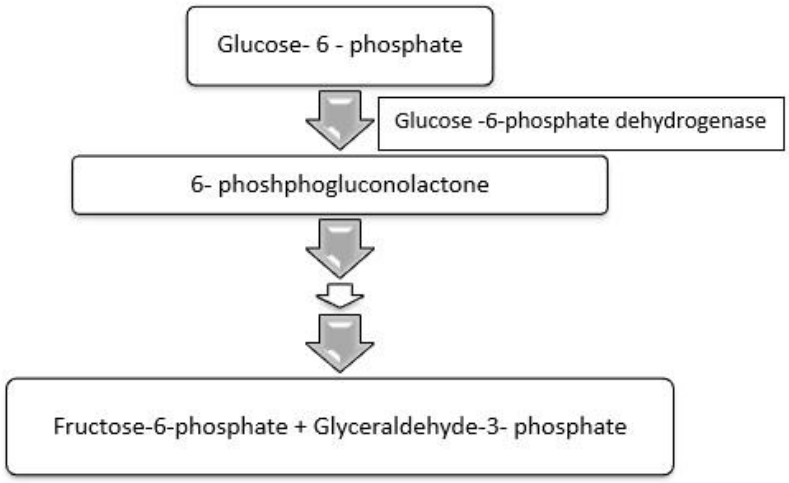

Figure 4. Metabolic pathway HMG shunt

Table 4. Medicinal plants that regulate HMG shunt

Medicinal plant	Family	Major chemical constituents	Reported dose	Reference
***Balanites roxburghii* Planch**	Balanitaceae	Sapogenin, Diosgenin, Yamogenin, β-sitosterol.	1.5g/kg	46
***Casearia esculenta* Roxb.**	Flacourtaceae	Resin, Sterol, Flavonoid.	300mg/kg	47
***Catharanthus roseus* (L.) G. Don**	Apocyanaceae	Vinblastine, Vineristine, Vinine, Vincamine, Alstonine.	500 mg/kg	48,49
***Dioscorea cayenensis* Lam.**	Dioscoreaceae	Hydro-Q chromene, tocopherol-9, 1-feruloylglycerol, dioscorin, cyanidine-3-glucoside, peonidin3-gentiobioside	200mg/kg	50,51
***Aconitum carmichaelii* Debx.**	Ranunculaceae	Songoramine, Hypaconitine, Karakanine, Songorine	12.5 - 50 mg/kg	33,34
Coccinia indica	Cucurbitaceae	Taraxerone, Taraxerol	2 g/kg	42,43
***Curcuma longa* L.**	Zingiberaceae	Curcumin, Turmerone, β-Sitosterol, Zingiberene.	0.08 g/kg	52,53
***Ocimum sanctum* L.**	Lamiaceae	Eugenol, Carvacrol, Linalool, Caryophylline, β-Sitosterol		54,55

Glycogen Synthesis

The role of glycogen synthase is to synthesize glycogen from unused glucose, which involves multiple steps in the liver.

The enzyme UDP-glucose pyrophosphorylase acts to activate glucose, which further undergoes the synthesis of glycogen (Figure 5). The improper conversion of glucose to glycogen leads to a rise in sugar levels in the blood in diabetic conditions. There are several plants that act on the enzyme glycogen synthase to regulate the blood sugar level in elevated conditions. Some reported findings are listed in Table 5.

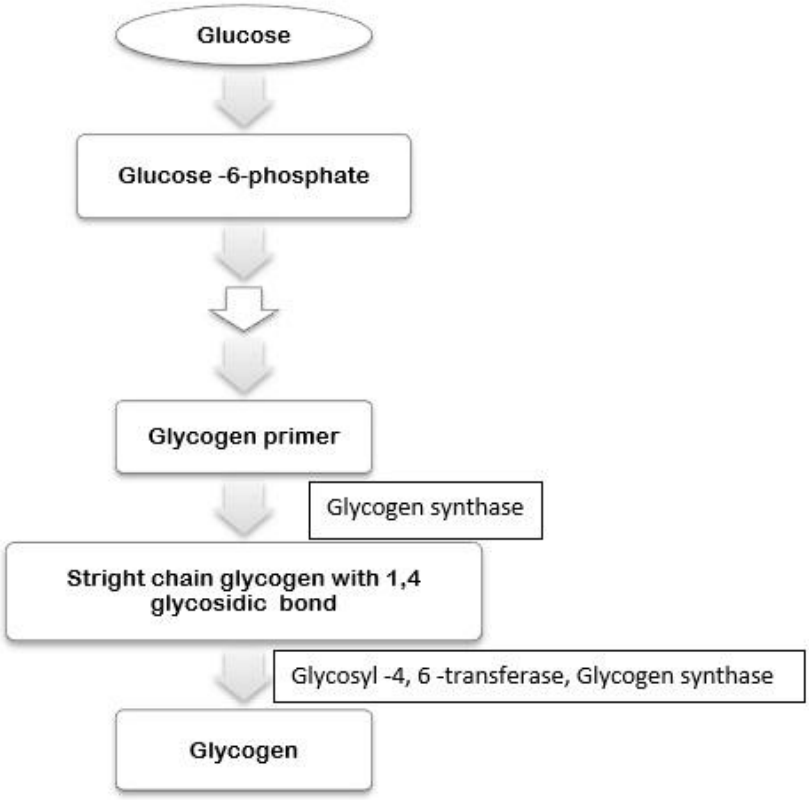

Figure 5. Metabolic pathway of glycogen synthesis

Table 5. Medicinal plants that regulate glycogen synthesis

Medicinal plant	Family	Major chemical constituents	Reported dose	Reference
Coccinia indica	Cucurbitaceae	Taraxerone, Taraxerol	2 g/kg	56,57
***Catharanthus roseus* (L.) G. Don**	Apocyanaceae	Vinblastine, Vineristine, Vinine, Vincamine, Alstonine.	500 mg/kg	22,58
***Ocimum sanctum* L.**	Lamiaceae	Eugenol, Carvacrol, Linalool, Caryophylline, β-Sitosterol.	-	27,28,59
***Piper betle* L.**	Piperaceae	β-phenol, Chavicol, Cadinene	75 mg/kg	39,60
***Curcuma longa* L.**	Zingiberaceae	Curcumin, Turmerone, β-Sitosterol, Zingiberene.	0.08 g/kg	9,10,61,62
***Momordica charantia* L.**	Cucurbitaceae	Charantin, Momordicoside.	200 mg/kg /day	18,19,63

Glycogenolysis

The process of glycogen degradation into glucose is known as glycogenolysis, which results in an increase in blood glucose levels in the body. The primary enzyme called Glycogen phosphorylase is responsible for the breakdown of glycogen in the body (Figure 6). Various plants have been reported

like *Aegle marmelos.* (L.) Corrêa, *Murraya koenigii* (L.) Spreng., *Ocimum sanctum* L., *Brassica juncea* L. etc. that can exhibit the regulation of glycogen degradation by inhibiting the enzyme Glycogen phosphorylase. Hence, the glucose levels decrease in the blood (Table 6). Even in some special cases where it was observed that the peripheral utilization of glucose or the process of glycogenolysis has been blocked by the plant extract like *Azadirachta indica* A. Juss [64].

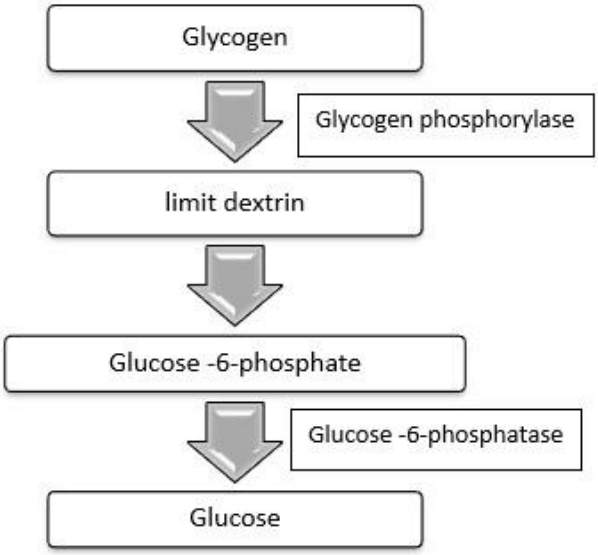

Figure 6. Metabolic pathway of glycogenolysis

Table 6. Medicinal plants that regulate glycogenolysis

Medicinal plant	Family	Major chemical constituents	Reported dose	Reference
***Murraya koenigii* (L.) Spreng.**	Rutaceae	Polyphenols and flavonoids	80 mg/kg /day	36,65,66
***Ocimum sanctum* L.**	Lamiaceae	Eugenol, Carvacrol, Linalool, Caryophylline, β-Sitosterol	-	27,28,67
***Aegle marmelos.* (L.) Corrêa**	Rutaceae	Aegelin, β & ϒ-Sitosterol, Marmelosin, Marmesin.	1g/kg/day	3,4,68

Dilatory Carbohydrate Digestion and Absorption

A lion's share of the energy supply in the body directly comes from the diet, especially from carbohydrate- enriched foods, through its metabolism. Generally, starch and sugar, i.e., sucrose, are the major chemical constituents in carbohydrates. In preliminarily, starch decomposition in the presence of a digestive enzyme called α-amylase, the starch is converted to oligosaccharides. This enzyme, α-amylase, is commonly found in the salivary glands and also in pancreatic juice. On the other hand, another membrane-bound enzyme, i.e., α-Glucosidase, is located in the small intestinal epithelial region. This enzyme actively catalyzed the process of converting glucose from disaccharides and oligosaccharides. Such converted glucose is absorbed through the walls of the intestine, reaching into the bloodstream and ultimately reaching the hepatic system (Figure 7). Eventually, various digestive enzymes will actively participate in the process of carbohydrate digestion. It includes α -Glucosidase, maltase, sucrase, α-amylase, lactase and isomaltase etc. Among all, α-amylase and α -Glucosidase play the most crucial role in carbohydrate metabolism. That is why herbs with these enzyme-inhibitory actions become the indirect choice for diabetes treatment. There are several medicinal plants reported to suppress this enzymatic activity during carbohydrate metabolism, even several plants are also been found (Table 7) which can decrease the absorption of carbohydrates through the deactivation of the

intestinal brush border cells. Currently, Miglitol and Acarbose are two commercially available synthetic drugs which inhibit the activity of these digestive enzymes in the body.

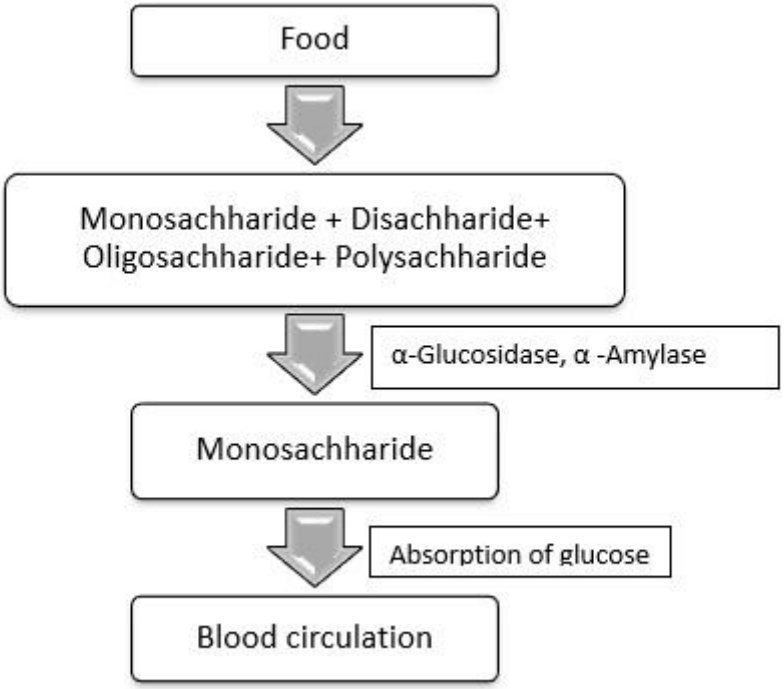

Figure 7. Metabolic pathway of carbohydrate

Table 7. Medicinal plants that regulate the inhibition of digestive enzyme and absorption of carbohydrate

Medicinal plant	Family	Major chemical constituents	Reported dose	Reference
Inhibition of α-glucosidase, α -amylase enzyme action				
***Artemisia pallens* Wall. ex-DC**	Compositae	T-Cadinol, α-urunene, β-Eudesmol, β - Ubebene.	100 mg/kg	69
***Morus alba* L.**	Moraceae	Isoquercitrin, Astragalin, Scopolin, Roseoside II.	200 mg/kg	70
***Salacia reticulata* Wight**	Celastraceae	Mangiferin, Salacinol, Kotalanol, Epigallocatechin	1 ml/day/rat	71
***Salacia oblonga* Wall. ex Wight & Arn.**	Celastraceae	Mangiferin, Salacinol, Kotalanol, Epigallocatechin	250 mg/kg	72
***Urtica dioica* L.**	Urticaceae	Quercetin, Kaempferol, Glucoquinone.	-	73
***Morus bombycis* Koidz.**	Moraceae	3-Epifagomine, Fagomine, Castanospermine	IC50 = 0.1 mg/ml	74
Decrease the absorption of glucose				
***Artemisia pallens* Well.**	Compositae	T-Cadinol, α-urunene, β-Eudesmol, β - Ubebene.	100 mg/kg	75
***Bauhinia variegata* L.**	Leguminosae	Astragalin, Kaempferitrin, Astragalin, Bauhinoside.	400 mg/kg	76,77

Natural Herbs with Insulin Mimetic Action

Typically, Insulin is a peptide hormone produced due to the sensitization of the islet of Langerhans of pancreatic beta cells for the regulation of glucose levels in the bloodstream by regulating the carbohydrate metabolism in the body. It is the main anabolic hormone in the body for the promotion of glucose uptake, stimulation of lipogenesis, diminished lipolysis, and increasing amino acid transport into the cells.

The mechanism of insulin release is a complex process (Figure 8). It involves the process of ATP-gated potassium channels closer and voltage-gated calcium channels activation for the release of insulin from cellular granules. A vast number of medicinal plants are reported for their action to alter insulin expression along with its synthesis and degradation (Table 8). Some plants also reported their action on Sulphonylurea binding site 1 (SUR1). Due to the cellular membrane depolarization, the Ca^{2+}influx takes place which leads to the close down of the ATP-sensitive potassium channel [78]. The medicinal plants directly act on the Ca^{2+} channels for insulin secretion and also those plants decrease the degradation by inhibiting insulinase enzyme are listed in Table 8**.**

There is a group of nuclear receptor transcription factors responsible for the Peroxisome proliferators and cellular metabolism of carbohydrates along with protein and lipids known as Peroxisome proliferator-activated receptors or (PPARs) [78]. There are three types of PPAR (Figure 8).

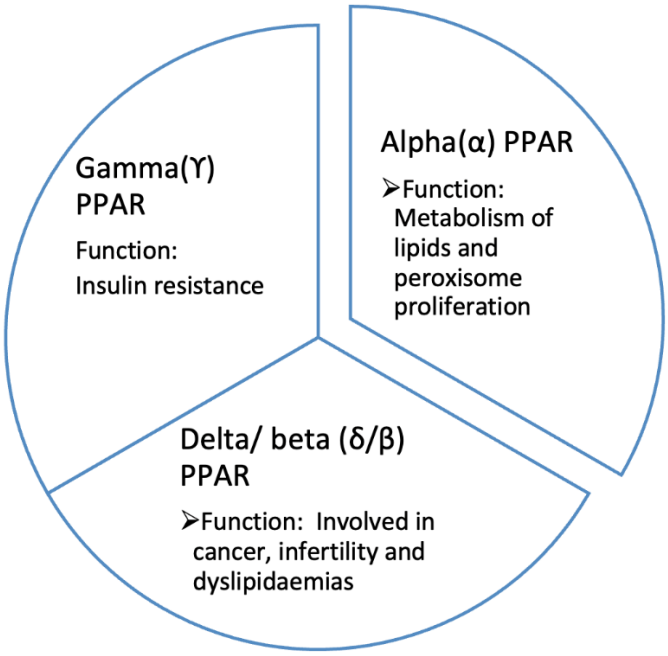

Figure 8. Types and functions of PPARs

Many medicinal herbs are reported for their elevated expression of PPAR gamma and decreased insulin resistance. For example, the phytoconstituents Curcumin from *Curcuma longa* L. and 6-gingerol from *Zingiber officinale* Roscoe are likely to target PPAR gamma. Even synthetic antidiabetic molecules like the Thiazolidinedione class of drugs, including roziglitazone, troglitazone and pioglitazone also target PPAR gamma.

The alteration of cellular signaling and metabolic process is also triggered by a messenger called cyclic AMP which naturally mediates the cellular network of signaling. It leads to suppress the intensity of insulin by decreasing the action of cAMP phosphodiesterase. Several medicinal plants which include *Betula alnoides* Buch.-Ham. ex D. Don, *Hiptage benghalensis* (L.) Kurz, *Leea indica* (Burm. f.) Merr.

and *Senna surattensis* (Burm. f.) H.S. Irwin & Barneby [79] possess cAMP phosphodiesterase inhibitory activity, as a result of which the action of insulin is retained**.**

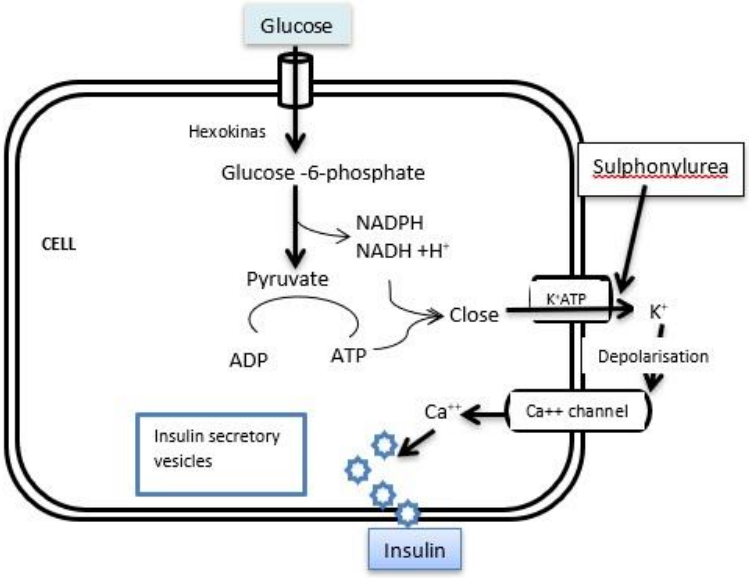

Figure 9. Exocytosis mechanism of insulin and sulfonylurea

Table 8. Medicinal plants used to increase insulin secretion

Medicinal plant	Family	Major chemical constituents	Reported dose	Reference
***Aloe barbadensis* miller.**	Aloaceae	Isobarbalin, Aloe-emodin, Aloetic acid, Barbaloin	500 mg/kg	80
***Caesalpinia bonduc* (L.) Roxb.**	Caesalpiniaceae	Bargenin, Caeselpinine A, α & β-Amyrin, Lupeol.	30 mg/kg	81
***Agaricus campestris* L.**	Agaricaceae	α -Terpineol, Hexanol, Furfural, Captylic acid	1 mg/mL	82
***Acacia arabica* Willd. var. indica Benth.**	Mimosaceae	m-Digallic acid, Chlorogenic acid, (+)- Catechin	4 g/kg	83,84
***Abelmoschus moschatus* Medik.**	Malvaceae	β -Sitosterol, Ambrettelide, Myricetin-3-glucoside.	1.0 mg/kg	85
***Helicteres isora* L.**	Sterculiaceae	Cucurbitacin B, Isocucurbitacin B.	100 mg/kg	86
***Musa sapientum* L.**	Musaceae	2-heptyl acetate, 2-methylbutyl acetate	150 mg/kg	87
***Swertia chirayita* (Roxb.) H. Karst.**	Gentianaceae	Amarogentin, Swerchirin, Chirantin, Gentiopicrin	100 mg/kg	88
***Catharanthus roseus* (L.) G. Don**	Apocyanaceae	Vinblastine, Vincristine, Reserpine, Vinceine	500 mg/kg	89,90
***Xanthocercis zambesiaca* (Baker) Dumaz-le-Grand.**	Leguminoceae	Castanospermine, Fagomine, Epifagomine, α-Homono jirimycin, Deoxynojirimycin	50 mg/ml	91
Potentiates insulin action by inactivating insulinase enzyme				
***Arctostaphylos uva-ursi* (L.) Spreng.**	Ericaceae	Arbutin, Ericolin, Ellagic acid, Myricetin,Ursone.	6.25% by weight	92
***Ocimum canum* Sims**	Lamiaceae	Camphor, Eugenol, Juvocimene I & II, Trans ß-ocimene, Linalool.	0.03 mg/ml	93

Herbs Helps in the Effective Transportation of Glucose Transporters Glut (GLUT)

The cytoplasmic vesicles include glucose transporters (GLUT), which aid in the movement of glucose into and out of cells. GLUT travels to the membrane in response to glucose stimulation and carries out its necessary activity. In the instance of DM, GLUT is not transported to the plasma membrane (Figure 9). GLUT is effectively transported to the plasma membrane by a group of medicinal plants, including *Syzygium cumini* L. Skeels, *Aegle marmelos.* (L.) Corrêa, *Allium sativum* L. [94-96], *Canna indica* L. [97], *Lagerstroemia speciosa* (L.) Pers. [98], and *Cornus officinalis* Siebold. & Zucc. [99]. This allows glucose to be transported into the cells and its concentration in the blood decreases (Table 9).

Table 9. Phytochemicals and their glucose uptake inhibition potentials

Phytochemicals	Mechanisms of action	References
Cyanidin	↓ glucose uptake in monoblast U937 cell lines	100
Genistein	↓ glucose uptake monoblast U937 cell lines and binds on GLUT1 surface.	101
Apigenin	↓ glucose uptake monoblast U937 cell lines and MC3T3-G2/PA6 cells and inhibits activation of GLUT4.	102
Daidzein	↓ glucose uptake in U937 cell lines.	103
Fisetin	↓ glucose uptake in U937 and MC3T3-G2/PA6 cells	104
Catechin	↓ glucose uptake in monoblast U937 cell lines.	105
Hesperetin	↓ glucose uptake in human myelocytic cell lines.	106
(−)-Epigallocatechin gallate	↓ insulin-stimulated glucose uptake in MC3T3-G2/PA6 cell lines (mouse).	107
Kaempferol	↓ insulin-stimulated glucose uptake in mouse MC3T3-G2/PA6 cells and inhibits activation of Akt and translocation of GLUT4	108
Naringenin	↓ glucose uptake in human U937 cells	109,110
Silybin	↓ insulin-stimulated glucose uptake in mouse MC3T3-G2/PA6 cells	111,112
Myricetin	↓ glucose uptake in human U937 cell line.	113
Quercetin	↓ glucose uptake in U937 and MC3T3-G2/PA6 cell lines and GLUT4.	114,104
Luteolin	↓ insulin-stimulated phosphorylation of IR-*β*, and translocation of GLUT4.	115

Various classes of phytochemicals also been reported as potent glucose uptake inhibitors such as hesperetin **(***Citrus aurantium* L.), catechin (*Camellia sinensis* (L.) Kuntze), cyanidin (*Viburnum rafinesquianum* J.A. Schultes**)**, myricetin (tomatoes, oranges**)**, genistein (*Genista tinctoria* L.), quercetin, apigenin, daidzein (soy phytoestrogens) etc. few phytochemicals name and their effect are listed in Table 9.

RESULT AND DISCUSSION

Many plants are known to decrease the synthesis of glucose, increase its consumption, and address subsequent problems. Merely 1% of the approximately 25 billion plants have undergone pharmacological screening, with a small portion of those screenings being evaluated for diabetes [116]. As such, it makes sense to investigate herbal medication a choice of treatment for diabetes. Therefore, it is established that medicinal plants have the potential to be helpful in the treatment of diabetes and that phytochemicals play a significant role in diabetes management. The Presence of phytochemicals such as flavonoids and phenolic compounds in biological systems makes them strong antioxidants and scavengers. According to the research, diabetes mellitus causes free radicals to increase and may even lower the antioxidant capacity of cells, which can result in oxidative stress in both insulin-dependent and independent forms of the disease. For instance, the *Cassia auriculata L., Cinnamomum tamala* (Buch. -Ham.) T. Nees & Eberm. *Ficus benghalensis* L, *Mangifera indica* L., *Trichosanthes dioica*

Roxb. are the well-versed hypoglycemic plants acting on various pathways to control the blood sugar levels with their high antioxidant potentials [117].

Kinsenoside (*Anoectochilus roxburghii* (Wall.) Lindl) functions against oxidative stress and NO factor, as well as regulating antioxidant enzymes that scavenge free radicals and aid in the regeneration of injured β cells in the pancreas [118]. In addition to protecting against oxidative damage, bacosine (*Bacopa monnieri* (L.) Wettst.) functions similarly to insulin and may affect peripheral glucose consumption due to its antihyperglycemic action [119]. Several mechanisms are known to be involved in the action of berberine (*Berberis aristata* DC.), including insulin-mimetic activity, AMPK (5′ adenosine monophosphate-activated protein kinase)-induced improvement of insulin action, AMPK-dependent up-regulation of insulin receptor expression in reducing insulin resistance, and glycolysis [120]. Even though, both piceatannol and scirpusin B (*Callistemon rigidus*) exhibit significant repressive effects on α-amylase-related activities. Moreover, scirpusin B has antidiabetic activity via controlling α-amylase [121]. The most notable isolated antidiabetic compound chamaemeloside, 3-hydroxy-3-methylglutaric acid (*Chamaemelum nobile* (L.) All.) revealed hypoglycemic activity by slowing down digestion and lowering the rate of absorption of carbohydrates [122]. Most of the scientific reports, stated plants for their antidiabetic properties but the responsible phytoconstituent or constituents need to be better reported in broader pharmaceutical management of diabetes. To achieve greater success in this arena of diabetes, we need more focus on the area of identification and isolation of biomolecules in specified targets of glucose regulation such as 1.5-dideoxy-1.5-imino-D-sorbitol (DNJ) in *Morus alba* L. [123], shogaol, gingerol in *Zingiber officinale* Roscoe [124], ginsenoside in *Panax ginseng* Meyer [125], galactomannans, 4-hydroxyisoleucine in *Trigonella foenum-graecum* L. [126,127] etc. are been highlighted with great specifications for the purpose.

Targeting cellular and molecular pathways involved in carbohydrate metabolism has been demonstrated by plant metabolites such as alkaloids (broussonetine, radicamine, catharanthine, vindoline and vindolinine etc.), flavonoids (Rutin, Silymarin, Kaempferol, puerarin etc.), and saponins (Arjunolic Acid, Christinin-A, Senegasaponins A, B and C, Gymnemic Acid, and Platyconic Acid etc.). These substances have the ability to lessen oxidative stress, restore insulin signalling, shield pancreatic beta cells, and prevent the breakdown and absorption of carbohydrates [128]. Finding safe, natural, and effective antidiabetic drugs to supplement or improve existing diabetes treatment is the goal of this review, which aims to comprehend these processes.

This comprehensive study may lead the researchers to get equipped with the basic molecular mechanism of various plant chemicals towards the regulation of blood glucose level in blood. Further research is required to meet the demand for the development of pharmaceuticals and nutraceuticals derived from natural plant resources. To fully understand the pharmacological actions of herbal treatments used to treat diabetes mellitus, more study is obligatory.

Furthermore, few studies have looked at combination therapy, including prescription and naturally occurring plant-based medicines [129]. Without the proper identification of constituent/constituents acting on elevated blood sugar levels and knowledge upon their specific mechanistic pathways, the further advances in the field of diabetes management are quite inadequate. It is advisable to increase the number of clinical studies by using bigger populations in the diabetes segment for better therapeutic outcome. Overall, this review contributes in understanding how natural plant-based compounds can be incorporated in to nutraceuticals that can have significant effect on countering oxidative stress and subsequently into diabetes management strategies, alongside, supporting the development of new therapies that leverage the health benefits of plant metabolites.

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CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

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