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Review

Trends in diabetes care with special emphasis to medicinal plants: Advancement and treatment

Bichitrananda Tripathy[a,*], Nityananda Sahoo[a], Sudhir Kumar Sahoo[b]

[a] Centurion University of Technology & Management, Odisha, 752050, India
[b] Royal College of Pharmacy and Health Sciences, Berhampur, Odisha, 759024, India

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ABSTRACT

Diabetic mellitus (DM) is a common metabolic disorder prevailing throughout the world. It may affect a child to an older person depending upon the physiology and the factors influencing the internal metabolic system of the body. Several treatments are available in the market ranges from synthetic drugs, insulin therapy, herbal drugs, and transdermal patches. Interestingly, the development of technologies and digital health have proving very helpful in improving the lifestyle of diabetic patients. All treatment approaches have their own advantages and disadvantages in the form of effectiveness and side effects. Medicinal plants have a long history of traditional application in the treatment of diabetes and even the use of plants are growing day-by-day due to the significant results against diseases and fewer side effects as compared to other treatment therapies. The intention behind writing this review is to gather all information and discussed them exhaustively in an article. The novel Coronavirus 2019 (COVID-19) pandemic has affected my lives including diabetic patients. The antidiabetic treatment strategies during this period has also discussed. In this article, we highlighted the molecular mechanism and herbal phytoconstituents that are responsible for lowering blood glucose level. The factors responsible for the progression of metabolic disorders can be controlled with the use of phytoconstituents present in herbal plants to maintain β-cells performance and restore blood glucose level. It can be concluded that medicinal plants are effective and affordable with lesser side effects for treating DM.

1. Introduction

Diabetes mellitus (DM) has become a serious metabolic disorder and threatening public health all-over-the world. DM is among the top 10 deadly disorder in adults and estimated to cause four million deaths every year globally (Saeedi et al., 2019). According to the results of the International Diabetes Federation 2019, the global diabetes prevalence in 2019 was 463 million people. It is expected to rise up to 578 million by 2030 and 700 million by 2045 (Saeedi et al., 2019). DM is a condition of carbohydrate and lipid metabolism imbalance that increases blood glucose levels. Mechanistically, the body cannot regulate the amount of glucose in the blood during DM. It leads to hyperglycemia due to rise in carbohydrate contents (Peixoto Araujo et al., 2021). The two main types of diabetes are type 1 diabetes mellitus (T1DM), and type 2 diabetes mellitus (T2DM). T1DM is insulin-dependent DM generally occurs in children and youngsters; in this condition pancreas does not produce sufficient insulin. On the other hand, T2DM is non-insulin-dependent DM that occurs when the body cannot effectively use the amiable insulin. T2DM has reached to epidemic proportions due to sedentary lifestyle and over-nutrition. It is very common in adults. It is considered as a complex disease that requires continuous medical care and strategies to reduce blood glucose level. Several biochemical and chemical agents are known that helps in controlling diabetes but no cure is yet available to get complete recover from the disorder (Verma et al., 2018). Education and support are very critical in controlling acute phases of diabetes and reducing risk of long-term complications (ADA, 2021). The treatment of diabetes has been improving day-by-day due to new research and technology that improving the well-being and health of diabetic patients. The field of diabetes care has been changing rapidly due to new research, technology, and treatments. These can improve the health and well-being of people with diabetes. The conventional treatments are no doubt effective but associated with certain complications or side effects. The complications are thus promoting researchers to develop some safe, affordable and efficient treatments against diabetes.

* Corresponding author.
E-mail address: bichitratripathy@gmail.com (B. Tripathy).

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Interestingly, traditional herbal medicines have been found effective against diabetes (Kumar et al., 2017; Rathore et al., 2014). The phytoconstituents from extract have always been a rich source for controlling disorder and other complications arises due to it (Kumar et al., 2016). Medicinal plants have been used in the treatment of diabetes since ancient times (Singh et al., 2016). The World Health Organization (WHO) has found that 21,000 medicinal plants have been used for the treatment of different diseases all over the world, in which 2500 species of plants is found in India. The selection of herbs against diabetes depends on various factors such as stage of diabetes progression, availability, types of co-morbidities in patients, toxicities and safety profile of the herbs (Jain et al., 2014, 2015, 2016; Shrawan et al., 2015, 2016). The objective of the present review was to describe the utility of medicinal plants in the treatment of diabetes mechanistically. Thus, this article may help researchers in conducting future studies for the development of antidiabetic drugs and other therapies in the management of diabetes based on phytoconstituents and extracts from plants.

2. Factors causing diabetes

Diabetes is more prevailing in developing or low-income countries as compared to high-income nations, it is due to lifestyle factors and urbanization (IDF, 2017). The modifiable risk factors are obesity, hyperlipidemia, consumption of alcohol and tobacco (Barik et al., 2016). The vulnerable factors responsible for development of diabetes are biological risk factors including sex, age, marriage status, race, stress, and family history of diabetes; financial factors; severity of disease including poor disease control, complications, and co-morbidities; lack of education or low literacy; distrust of primary health services; occupational restriction; limited daily life behaviors; lifestyle factors including consumption of unhealthy food, lack of exercises and low-quality sleep; and mental condition including lack of friends and family and community environment (Chen et al., 2019; Bosun-Arije et al., 2019). Fig. 1 showing several genetic and environmental factors causing loss of β-cell mass and that leads to hyperglycemia. In this state, insulin do not respond to its demand in the body that causes increase in the level of blood glucose sufficient to diagnose diabetes (Skyler et al., 2017).

3. Pharmacologic therapy for treating diabetes

3.1. Treatment for type 1 diabetes mellitus (T1DM)

T1DM is a condition of serious decrease in the level on endogenous insulin and its release from β-cells of pancreas (Oram et al., 2019). The precise pathological mechanism and etiology are still not clear. It usually develops in child or young ones. People with type 1 diabetes are treated with multiple injection of prandial and basal insulin. The rapid acting insulin analogues are also used for reducing hypoglycemic risk. The rapid-acting prandial analogues i.e. lispro, aspart and glulisine are preferred over regular human insulin. However, aspart as faster-acting insulin is a new option due to advantage of better postprandial glucose coverage (Janež et al., 2020). The diabetic patients are being aware about prandial insulin dose to pre-meal blood glucose, carbohydrate intake and anticipated physical activity. The surgical treatment of type 1 diabetes such as islet and pancreas transplantation can also normalize the glucose levels and mitigate the complication of the disease (Meloche et al., 2007). However, patients availing this treatment need to take life long immunosuppressant drugs to prevent graft rejection of islet and pancreas.

3.2. Treatment for type 2 diabetes mellitus (T2DM)

T2DM is chronic metabolic disorder that develops due to defective insulin secretion and action. The primary cause of fasting hyperglycemia is the excessive production of glucose in the presence of hyperinsulinemia (ADA, 2013). However, after meals the impaired suppression of glucose production by insulin leading to decrease in the uptake of glucose by muscles and tissues. Metformin being the most preferred oral antidiabetic drug for the treatment of type 2 diabetes. It should be continued for life-long and not contraindicated with insulin. The second generation sulfonylureas include glyburide, glipizide and glimepiride; meglitinides include repaglinide, and nateglinide; thiazolidinediones include pioglitazone and rosiglitazone; alpha-glucosidase inhibitors include acarbose and miglitol; depeptidyl peptidase-4 inhibitors include sitagliptin, saxagliptin, linagliptin and alogliptin; colesevelam as bile acid sequestrant; bromocriptin as dopamine-2 agonist;

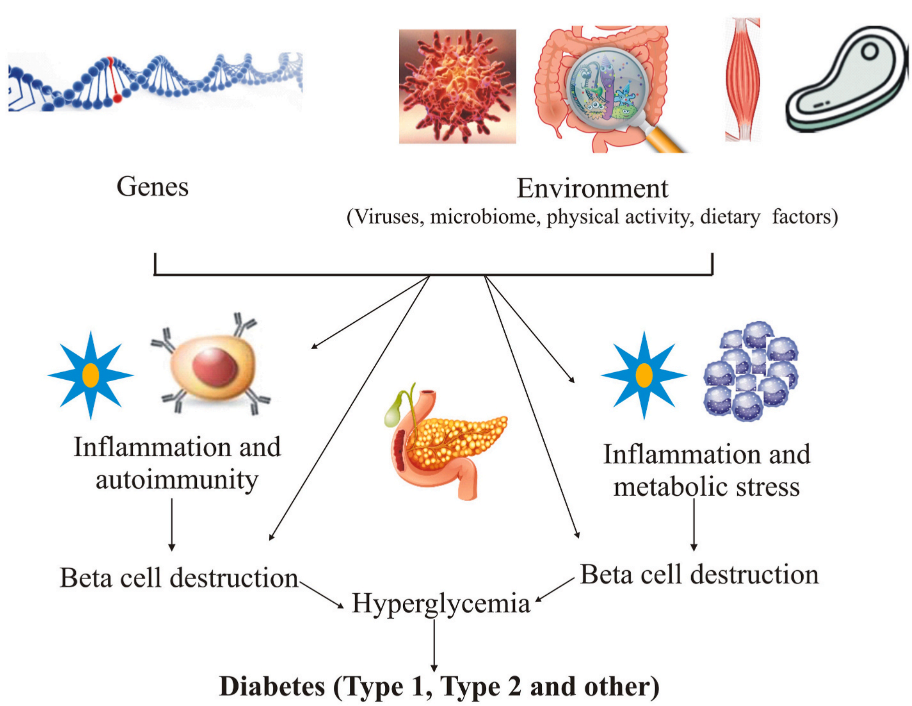

Fig. 1. Genetic and environmental factors causing hyperglycemia.

pramlintide as amylin mimetic; sodium glucose cotransporter - 2 inhibitors include canagliflozin, dapagliflozin, and empaglifozin; and glucagon-like peptide-1 receptor agonists include exenatide, liraglutide albiglutide and dulaglutide (Chamberlain et al., 2017). Table 1 showing the list of antidiabetic drugs with their mechanism and side effects. The injection of insulin is also considered during evidence of ongoing weight loss, symptoms of hyperglycemia (≧ 300 mg/dL). Fig. 2 showing pharmacological treatment for diabetes.

4. Medicinal plants used against diabetes traditionally

Medicinal plants have been used in the treatment of diseases since ancient times (McGaw et al., 2019). The importance of plants as raw material for pharmaceutical industries cannot be overlooked. The use of medical plants is increasing worldwide due to its better long-term results with fewer side effects. They have been used to maintain and augment mental, spiritual and physical health along with treating diseased condition and ailments. Plants possess several active constituents present in their secondary metabolites such as alkaloids, phenol, glycosides, tannins, flavonoids, and terpenoids that are responsible for varieties of biological effects (Akinyemi et al., 2018). Thus, medicinal plants have an immense role to play in sustainable human health. Table 2 showing the list of medicinal plants having reported antidiabetic property.

Table 1
List of existing anti-diabetic drugs with their mechanisms and side effects.

S. No.	Class	Mechanism of action	Side effects	Complication/Toxicities
1	Biguanide (Metformin)	Increases the effect of insulin	Reduced vitamin B12 absorption, weight loss, lactic acidosis, diar rhea, abdominal cramps	Liver failure, chronic kidney disease
2	Sulfonylureas (glyburid e, glimepiride)	Enhances insulin secr etion from pancreatic beta-cel ls	Hemolysis, agranulo cytosis, weight gain	Obesity, cardiovascular comorbidities, allergy
3	Meglitinides (nateglinide, rep aglinide)	Increase insulin secr etion from pancreatic beta-cel ls	Weight gain, risk of hypoglycemia	Liver and renal failure
4	DPP-4 inhibitors (saxagliptin, sitagli ptin)	Inhibit glucagon-like peptide-1 degra dation and promotes glucose-de pendent insulin secretion	Pancreatitis, headache, gastrointestinal complaints, arthralgia, dizziness	Liver and renal failure
5	GLP-1 agonists (exenatide, liraglutide, albiglutide)	Direct stimulation of glucagon-like peptide-1 receptor	Pancreatitis, pancreati c cancer, nausea	Gastrointestinal motility disorders
6	SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin)	Increased glucosuria by inhibiting SGLT-2 in the kidney	Urinary tract infections, polyuria, dehydration, yeast infections, diabetic ketoacidosis	Urinary tract infections, chronic kidney disease
7	Alpha-glucosidase inhibitors (acarbose)	Reduce intestinal glucose absorption	Flatulence, diarrhea	Renal failure, inflammatory bowel disease
8	Thiazolidinediones (pioglitazone)	Reduce insulin resistance through the stimulation of PPARs	Cardiac failure, weight gain, osteoporosis, edema	Liver disease, congestive heart failure
9	Amylin analogues (pramlintide)	Reduce glucagon release	Risk of hypoglycemia, nausea	Gastroparesis

DPP-4, Dipeptidyl peptidase-4; SGLT-2, Sodium-glucose co-transporter-2; GLP-1, Glucagon-like peptide-1; PPARs, Peroxisome proliferator-activated receptors.

4.1. *Acacia arabica*

Acacia arabica has been used traditionally in the treatment of diabetes, kidney and liver problems, healing wounds, and preventing of microbial attack. The mechanism of its antidiabetic action is due to presence of polyphenols in its bark. Its gives hypoglycemic effect by improving insulin sensitivity and reduction of fatty acid synthesis. Fisetinidol and robinetinidol are the two phytoconstituents responsible for antidiabetic action (Ikarashi et al., 2011).

4.2. *Bambusa arundinasia*

Bambusa arundinasia has been used traditionally for the treatment of diabetes, dysentery, peptic ulcer and aphthous. Mechanistically, it shows, α-glucosidase and α-amylase enzyme inhibitor action. Additionally, showing regeneration of pancreatic tissue and improvement in serum insulin level. It has also shown reduction of HbA1c (glycated hemoglobin), fructose-1-6-biphophatase, glucose-6-phosphatase, triglycerides and total cholesterol. Stigmasterol and β-sitosterol are the two major compounds responsible for antidiabetic activity (Nazreen et al., 2011).

4.3. *Boswellia carterii*

Boswellia carterii is helpful in diabetes due to presence of oleo-gum resin. It shows antidiabetic activity by increasing liver glycogen, serum insulin and prevents degenerative change in β-cells of pancreas. *Boswellia carterii* shows hypoglycemic activity due to suppression of proinflammatory cytokine, apoptosis of cells, and lymphocytes penetration into pancreatic islets. The boswellic acid is the major activity phytoconstituent that showing inhibitor activity on diabetic complication following polyol aldose reductase pathway (Rao et al., 2013).

4.4. *Chrysanthemum indicum*

Chrysanthemum indicum has been used since a long term ago in the treatment of hypertension, inflammation and respiratory disorders in various countries. The phytoconstituents present in plant are luteolin and linarin that are responsible for anti-inflammatory effect on prostatitis and chronic pelvic inflammation. It is due to reduced activation of tissue necrosis factor - alpha (TNF-α) and interleukin-1beta (IL-1β) (Dasgupta, 2019). *Chrysanthemum morifolium* Ramat. a species of *Chrysanthemum* used for antidiabetic activity (Yamamoto et al., 2015). It is a leading flowering plant with applied value worldwide (Su et al., 2019).

4.5. *Coriandrum sativum*

Coriandrum sativum is mainly used for its carminative property. However, its fruits have shown antidiabetic effect via enhancement of insulin release from β-cells along with increasing glucose uptake, glycogenesis and glucose oxidation. *C. sativum* improves cardioprotective indices and atherosclerotic index (Parsaeyan, 2012).

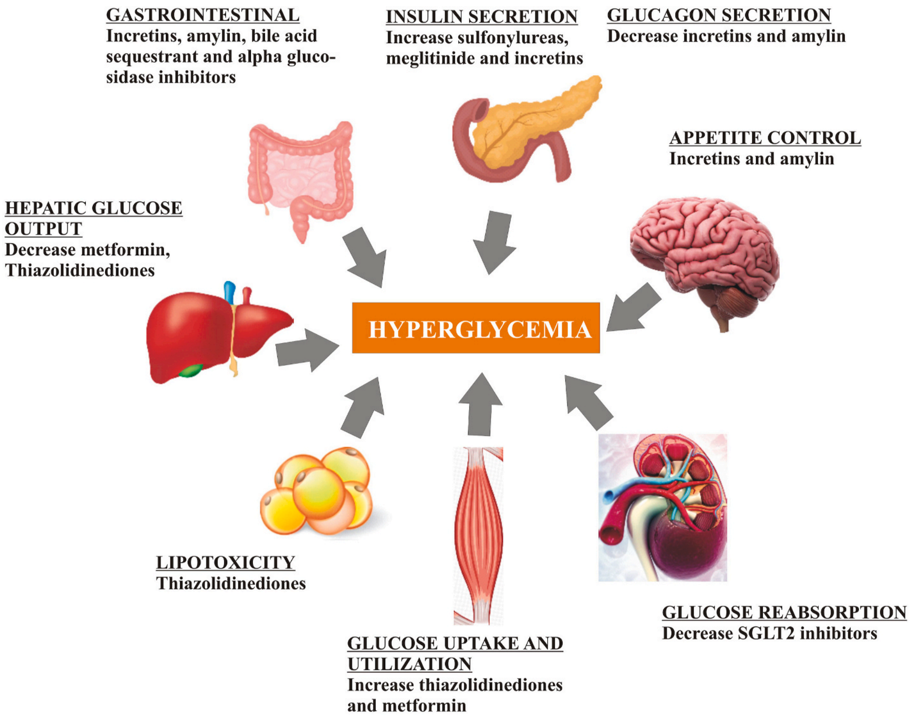

Fig. 2. Pharmacological treatment approaches for T1DM
SGLT-2, Sodium-glucose co-transporter-2.

4.6. *Glycyrrhiza glabra*

The antidiabetic activity of *G. glabra* is due to presence of glycyrrhizic acid present in roots of the plant. It increases expression of lipoprotein lipase in body tissues and improves sensitivity of insulin. It reduces total cholesterol, fatty acids in serum, and lipid deposition (Eu et al., 2010).

4.7. *Lactuca sativa*

The seeds of *L. sativa* has been used for its antidiabetic property by Persians since ancient times. It possesses alpha-glucosidase and alpha-amylase enzyme inhibitory activity. The mechanism of glucose lowering activity is based on elevation of serum insulin level, reduction of fructose-1-6- biphophatase and glucose-6-phosphatase (Ahmed et al., 2013).

4.8. *Myrtus communis*

The leaves of *M. communis* possesses antidiabetic action by enhancing antioxidant function in liver of animals. The alpha-glucosidase enzyme inhibitory activity is the mechanism of its antidiabetic activity (Sepici-Dincel et al., 2007).

4.9. *Portulaca oleracea*

The seeds of *P. oleracea* shows hypoglycemic activity by reducing fating and post-prandial blood glucose level. The mechanism of its antidiabetic activity is based on inhibition of alpha-glucosidase and alpha-amylase enzymes (Heidarzadeh et al., 2013).

4.10. *Punica granatum*

The flowers of *P. granatum* has been used for antidiabetic action, it is due to its alpha-glucosidase enzyme inhibitory activity and improvement of insulin sensitivity. It also enhances GLUT4 (Glucose Transporter 4) and PPAR-γ (Peroxisome Proliferator-Activated Receptor–γ) (Huang et al., 2005).

4.11. *Rosa damascena*

The fruits and flowers of *R. damascena* possess glucose lowering and alpha-glucosidase enzyme inhibitory activity.

4.12. *Vitis vinifera*

V. vinifera shows antidiabetic activity due to presence of procyanidins in seeds. It also shows insulinomimetic activity via stimulation of insulin pathway mediator and upgrading glucose uptake. The pharmacological mechanism of plant against chronic diabetes include suppression of oxidative stress, reduction in advanced end glycation products (Li et al., 2008).

5. Highly valuable drug therapies and medicinal plants in 2020–21 for treating diabetes

The coronavirus disease 2019 (COVID-19) has imposed a global economy loss at various levels. During coronavirus disease 2019 (COVID-19) pandemic the diabetic patients were at increased risk of complication like Adult Respiratory Distress Syndrome and multi-organ failure. The following drugs were found more effective and having metabolically interfering effects against COVID-19 patients with diabetes: Metformin; Sodium-glucose-co-transporter-2 inhibitor including dapagliflozin, canagliflozin, and empagliflozin; Glucagon-like peptide-1 receptor agonists including dulaglutide, albiglutide, liraglutide, semaglutide, and lixisenatide; Dipeptidyl peptidase-4-inhibitors including linagliptin, alogliptin, sitagliptin, and saxagliptin; and Insulin (Bornstein et al., 2020). Vaccination should be prioritized in these patients. However, routine vaccination against Hepatitis B, influenza and pneumococcal pneumonia is recommended in diabetic patients (Pal et al., 2021). The current trends prevailing in the market under numerous segments as alternatives to injectable diabetes care. Based on product

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Table 2
List of medicinal plants with reported antidiabetic activity.

S.No.	Plant	Family	Chemical constituents	Antidiabetic action	References
1	*Abies pindrow*	Pinaceae	Globulol, maltol, borneol, linalool	Stimulation of insulin secretion	Sinha et al., 2019
2	*Acacia arabica*	Fabaceae	Mallic acid, chlorogenic acid, catechin, epicatechin, chiorogenic acid, ellagic acid, corosolic acid,	Increasing the release of insulin	Hegazy et al. (2013), Bharti et al. (2018)
3	*Achyranthes rubrofusca*	Amaranthaceae	Betulinic acid, momordin Ib, zingibroside R1, Achyranthoside IV	Reduction of blood glucose level and restore pancreatic enzymatic activity	Geetha et al. (2011); He et al. (2017)
4	*Agrimony eupatoria*	Rosaceae	4-caffeoylquinic acid, 3,5-dicaffeoyl quinic acid and luteolin-7-O-glucoside	Insulin-like and insulin releasing activity	Kuczmannová et al. (2016)
5	*Albizzia lebbeck*	Fabaceae	Albizziahexoside, lupeol, docosanoic acid, oleanolic acid, beta-sitosterol	α-amylase and α-glucosidase inhibitor activity	Verma et al. (2013); Ahmed et al. (2014)
6	*Aloe vera*	Asphodelaceae	lophenol, and cycloartanol	Inhibition of α-amylase and α-glucosidase enzymes	Tanaka et al. (2006); Muñiz-Ramirez et al. (2020)
7	*Amaranthus tricolor*	Amaranthaceae	Betacyanins, betaxanthins, rutin, isoquercetin, ferulic,ellagic, p-coumaric	Anti-α-amylase and anti-α-glucosidase activity	Yang et al. (2020); Peter and Gandhi (2017)
8	*Anacardium occidentale*	Anacardiaceae	Anacardic acid, cardanol, cardol	α-glucosidase inhibitor	Jaiswal et al. (2016); Palheta and Ferreira (2018)
9	*Annona squamosa*	Annonaceae	Acetogenin, annonacin, annonastatin samaquasine, squamone, acetogenin	Increase level of plasma insulin	Shirwaikar et al. (2004); Zahid et al. (2018)
10	*Averrhoa bilimbi*	Oxalidaceae	Cyanidin-3-o-h-glucoside, citric acids, amino acids	Increase level of plasma insulin	Kurup and S, 2017; Mathew et al. (2017)
11	*Azadirachta indica*	Meliaceae	Nimbidin	Normalizing altered insulin signaling molecules	Satyanarayana et al. (2015)
12	*Barleria prionitis*	Acanthaceae	Balarenone, pipataline, prioniside B, lupeol	Decrease blood glucose and increase serum insulin level	Dheer and Bhatnagar (2010); Shukla and Gunjegaonkar (2018); Banerjee et al. (2012)
13	*Bauhinia thoningii*	Fabaceae	Alepterolic acid, methyl-ent-3β-hydroxylabd-8(17)-en-15-oate, 2β-methoxyclovan-9α-ol (1)	Insulin mimetic activity	Salehi et al. (2019)
14	*Bixa orellana*	Bixaceae	Cryptoxanthin, phytoene, lutein, zeaxanthin	Promote binding of insulin on receptor and increase plasm insulin level	Vilar et al. (2014)
15	*Boerhaavia diffusa*	Nyctaginaceae	β-Sitosterol, arachidic acid, Ecdysone, urosilic acid, palmitic acid, hexacosonoic, β-triacontanol, hentriacontane	Increase level of plasma insulin	Alam et al. (2018)
16	*Caesalpinia ferrea*	Fabaceae	Galactomannan, kaempferol, galloylorientin, heptacosan	α-Amylase enzyme inhibitory action	Hassan et al. (2015); Macêdo et al. (2020)
17	*Camellia sinensis*	Theaceae	Catechins, theaflavins, and caffeine	α-Amylase and α-Glucosidase inhibitory activity	Fu et al. (2017); Ardiana et al. (2017)
18	*Capsicum frutescens*	Solanaceae	Octadecadienal (Z), tetracosane, 3-carene, 5-eicosene, docosane	Stimulation of insulin secretion	Dougnon and Gbeassor (2016); Gurnani et al. (2016)
19	*Casearia esculenta*	Flacourtiaceae	3-hydroxymethyl xylitol	Insulin mimetic action	Govindasamy et al. (2011); Prakasam et al. (2005)
20	*Cassia fistula*	Fabaceae	β-sitosterol, lupeol, kaempferol, fistulin, rhein, leucopelargonidin	Increase insulin-stimulated glucose uptake	Einstein et al. (2013); Rahmani et al., 2015
21	*Cassia grandis*	Fabaceae	Linalool	α-glycosidase inhibitory activity	Lodha et al. (2010); Prada et al. (2018)
22	*Catharanthus roseus*	Apocynaceae	Limonene, dotriacontane, geraniol, citral, phytol	Increased secretion of insulin from β-cells pancreas	Rasineni et al. (2010); Lawal et al. (2015)
23	*Cecropia pachystachya*	Urticaceae	*C*-glycosyl flavonoids, proanthocyanidins	Increase secretion of insulin	Rivera-Mondragón et al. (2017); Costa, 2011
24	*Ceriops decandra*	Rhizophoraceae	Ceriopsin, lupeol, oleanolic acid, α-amyrin, ursolic acid, and catechin	Regeneration of β cells	Mahmud et al. (2018); Nabeel et al., 2010; Arora et al. (2014)
25	*Chiliadenus iphionoides*	Asteraceae	1,8-cineole, camphor, α-terpineol, terpin-4-ol, and bornyl formate	Increase secretion of insulin	Salehi et al. (2019); Abdelhalim et al., 2020
26	*Cinnamomum cassia*	Lauraceae	Cinnamaldehyde	Insulin mimetic action	Elumalai et al. (2011); Yan et al. (2015)
27	*Citrullus colocynthis*	Cucurbitaceae	Cucurbitacin L, isovitexin, khekadaengoside E	Restoration of pancreatic β-cells	Zheng et al. (2020); Dhakad et al. (2017); Shi et al. (2014)
28	*Clausena anisata*	Rutaceae	β-pinene, germacrene-D, sabinene, linalool, estragole	Stimulation of insulin secretion	Yakoob et al. (2016); Govindarajan, 2010
30	*Coscinium fenestratum*	Menispermaceae	Hentriacontan, palmitic acid, β-sitosterol, oleic acid	Decrease gluconeogenesis and increase enzymatic activity	Nayak et al. (2012); Malarvili et al. (2011)
31	*Eucalyptus citriodora*	Myrtaceae	Citronellol acetate, *cis*-geraniol, dihydrocarveol acetate, β-bisabolene, 3-hexen-1-ol, and pregn-5-en-20-one,3,17-dihydroxy-3-acetate	Increase glucose transporter 4 (GLUT-4) translocation	Wang et al. (2014); Dey and Mitra (2013)
32	*Eucalyptus globulus*	Myrtaceae	1,8-cineol, α-pinene	Enhance release of insulin from clonal pancreatic beta line	Chakraborty et al. (2018); Sebei et al. (2015)
33	*Ficus religiosa*	Moraceae	n-octacosanol, β-sitosteryl-D-glucoside, stigmasterol, lanosterol, methyl oleanolate, lupen-3-one	Stimulation of insulin secretion	Pandit et al. (2010); Chandrasekar et al. (2010)
34	*Gymnema sylvestre*	Apocynaceae	Gymnemic acid, gurmarin, tartaric acid, glucose, calcium oxalate, betaine, stigmasterol, and choline	Prevents absorption of glucose by the intestine to reduce blood sugar level	Kanetkar et al. (2007); Khan et al. (2019); Tiwari et al. (2014)

(*continued on next page*)

Table 2 (*continued*)

S.No.	Plant	Family	Chemical constituents	Antidiabetic action	References
35	*Heinsia crinata*	Rubiaceae	Sapogenin, neochlorogenin and diosgenin	Insulin level elevating effect	Okokon et al. (2009); Yobe et al. (2017)
36	*Helicteres isora*	Sterculiaceae	Kaempferol 7-O-coumaroylhexoside,rosmarinic acid and kaempferol 7-O-rhamnosylhexosides	Increase uptake of glucose	Olivas-Quintero et al. (2017)
37	*Hibiscus rosa*	Malvaceae	Beta-carotene, anthocyanin, Beta-sitosterol, arabinogalactans, gossypetin, L-ascorbic acid, citric acid	Stimulation of insulin secretion from beta pancreatic cells	Moqbel et al. (2011)
38	*Ipomoea batata*	Convolvulaceae	Caffeic acid, chlorogenic acid, rutin, quercetin	Decrease insulin resistance	Akhtar et al. (2018); Zengin et al. (2017)
39	*Juniperus communis*	Pinaceae	Longifolene, totarol, transcommunic acid	Stimulation of insulin secretion and increase glucose consumption	Raina et al. (2019)
40	*Momordica charantia*	Cucurbitaceae	Charantin, cucurbitacins, karounidiols, multiflorenol and nerolidol	Regulate glucose absorption by the gut and stimulate its uptake into muscles	Joseph and Jini (2013); Singh et al. (2011)
41	*Moringa oleifera*	Moringaceae	Oleic acid, ascorbic acid, 9-octadecenoic acid and 9-octadecenamide	α-glucosidase and pancreatic lipase inhibitory activity	Chen et al. (2020); Aja et al. (2014)
42	*Murraya koenigii*	Rutaceae	Linalool, geranyl acetate, elemol, allo-ocimene, myrcene, α-terpinene and neryl acetate	Increased the secretion of insulin and glycogenesis process	Rajendran et al. (2014); Sk et al. (2017)
43	*Olea europia*	Oleaceae	Oleuropeoside	Increase uptake of glucose and release of insulin	Paramanick and Sharma (2017)
44	*Opuntia ficus-indica*	Cactaceae	Phytol, palmitate palmitic acid, and vitamin E	Increases glucose uptake through activation of AMPK/p38 MAPK pathway	Halmi et al. (2012); Luo et al. (2010); Leem et al. (2016)
45	*Origanum vulgare*	Lamiaceae	Amburoside A, apigenin 7-O-glucuronide, luteolin 7-O-glucuronide, lithospermic acid, rosmarinic acid, and demethylbenzolignanoid	α-glucosidase inhibitory activity	Yu et al. (2021);
46	*Passiflora nitida*	Passifloraceae	Luteolin, apigenin, kaempferol and quercetin	α-glucosidase inhibitory activity	Casierra-Posada and Jarma-Orozco (2016)
47	*Paspalum scrobiculatum*	Poaceae	Vanillic acid, syringic acid, *cis-* ferulic acid, p-hydroxy benzoic acid and melilotic acid	Increase glycogen synthesis and decrease in glycated haemoglobin levels	Kiran et al. (2014); Jain et al. (2009)
48	*Persea americana*	Lauraceae	Peptone, glycosylated abscisic acid, cellulose, b-galactoside, polyuronoids, and polygalacto urease	Inhibition of insulinase activity	Yasir et al. (2010); Ezejiofor et al. (2013)
49	*Phoenix dactylifera*	Arecaceae	β-carotene, ascorbic acid, α-tocopherols, selenium	Glucose lowering effect	Abdelaziz et al. (2015)
50	*Phyllanthus niruri*	Euphorbiaceae	Phyllanthin, coumarins, chlorogenic acids, and anthocyanins	Inhibition of glucose absorption and enhancement of glucose storage	Sibiya et al. (2020);
51	*Phyllanthus simplex*	Euphorbiaceae	Corilagin, gallic acid, phyllanthin, geraniin and niranthin	Glucose lowering effect	Mao et al. (2016)
52	*Picralima nitida*	Magnoliopsida	Akuammine, akuammidine, akuammicine, pseudo-akuammigine	Regeneration of β cells	Teugwa et al. (2013);
53	*Piper longum*	Piperaceae	Piplartine and piperine	Glucose lowering effect	Singh and Navneet, 2018; Nabi et al. (2013)
54	*Scoparia dulcis*	Scrophulariaceae	scoparic acid D	Secretagogue activity of insulin	Latha et al. (2009)
55	*Sonchus oleraceus*	Asteraceae	Apigenin, luteolin, 1-cerotol, germanicyl acetate, and oleanolic acid	α-amylase and α-glucosidase inhibitory activity	Xu and Liang (2005); Li and Yang (2018)
56	*Swertia chirayata*	Gentianaceae	Amarogentin, gentianine, ursolic acid, isobellidifolin, sweroside, magniferin	Stimulation of insulin secretion from pancreatic islets	Dey et al. (2020)
57	*Syzygium jambolana*	Myrtaceae	Glucoside, anthocyanins, isoquercetin, kaemferol, ellagic acid and myrecetin	Stimulates insulin secretion	Ayyanar and Subash-Babu (2012)
58	*Tamarindus indica*	Fabaceae	Citric acid, tartaric acid, malic acid, acetic acid, formic acid, and succinic acid	α-amylase and α-glucosidase inhibitory activity	Bhadoriya et al. (2011); Krishna et al. (2020)
59	*Terminalia chebula*	Combretaceae	Chebulic acid, neo-chebulic acid mannitol, chebulagic acid, corilagin	Insulin mimetic action	Senthilkumar et al. (2006); Chang and Lin (2012)
60	*Terminalia catappa*	Combretaceae	Asiatic acid, vitexin, ursolic acid, isovitexin, gallic acid, tergallagin, tercatain, punicalagin, chebulagic acid, punicalin, terflavins A and B, and geranin	α-glucosidase and α-amylase inhibitory activity	Mininel et al. (2014); Behl and Kotwani (2017)
61	*Tinospora crispa*	Menispermaceae	apeginin, diosmetin, genkwanin, cycloeucalenol, cycloeucalenone	Stimulation of insulin secretion from pancreatic islets	Klangjareonchai et al. (2012)
62	*Trigonella foenum-graecum*	Fabaceae	Diosgenin, trigonelline, gentianine, carpaine, butanoic acid, and isovaleric acid	Restoration of pancreatic β-cells	Wani and Kumar, 2018; Geberemeskel et al. (2019)
63	*Urtifca dioica*	Urticaceae	Histamine, acetylcholine, 5-hydroxytryptamine	Stimulation of insulin secretion	El Haouari et al. (2019); Joshi et al. (2019)
64	*Vaccinium arctostaphylos*	Ericaceae	Linalool, α-Pinene, Safranal and Sandaracopimaradiene	Insulin level elevating effect	Salehi et al. (2019); Teimouri et al. (2015); Kianbakht and Hajiaghaee (2013)
65	*Vernonia amygdalina*	Asteraceae	Vernomygdin, Vernoniosides Vernodalol Vernodalin, Epivernodalol	Suppression of gluconeogenesis	Atangwho et al. (2009); Atangwho et al. (2014)
66	*Vinca rosea*	Apocynaceae	Vincristine, vinblastine	Regeneration and rejuvenation of beta cells	Ahmed et al. (2010)

(*continued on next page*)

Table 2 (*continued*)

S.No.	Plant	Family	Chemical constituents	Antidiabetic action	References
67	*Zaleya decandra*	Aizoaceae	6-octadecenoic acid, n-hexadecanoic acid	Stimulation of insulin secretion	Meenakshi et al. (2010)
68	*Zingiber officinale*	Zingiberaceae	Gingerols, paradols, shogaols, gingerdiones, zingerones, gingerdiols	Stimulation of insulin secretion and decrease glucose level	Obih et al. (2017)
69	*Zizyphus mauritiana*	Rhamnaceae	Palmitic acid, ethyl stearate and α-linolenic acid	Restoration of blood glucose level	Ashraf et al. (2015); Niamat et al. (2012)

GLUT-4, Glucose transporter-4; AMPK, AMP-activated protein kinase; MAPK, Mitogen-activated protein kinase.

types, it include insulin pumps, smart glucose meter, tethered insulin pumps, implantable insulin pumps, insulin patches and artificial pancreas. Based on device types include wearable and hand held.

Several plants have been used for treating diabetes and counting is continue to get most beneficial agents with lesser side effects. Interestingly, few plants are very common in different countries that are frequently used in diabetes due to their effectiveness, economic profile and easy availability. The passed year was very difficult due to COVID pandemic throughout the world; peoples stayed at their homes and protecting themselves. However, medicines were accessible to patients even though the diabetic patients have been consuming herbs to remain healthy and maintain normal blood glucose levels. Famous medicinal plants used for antidiabetic purposes in the year 2020–21 are as follows:

5.1. Aloe vera

Aloe vera L. has been used traditionally in the treatment of various diseases in many countries since a long term ago. The major chemical constituents present in the plant are anthraquinones, phytosterols, lignins, salicylic acid and polysaccharides. It is very efficient in reducing blood glucose level of diabetic patients by improving the body response towards insulin. *A. vera* is also effective in reducing lipid level in the body due to presence of phytosterols such as lupeol, campesterol and sitosterol that are structurally similar to cholesterol and reduce its absorption by competition with it (Joseph et al., 2018; Choudhary et al., 2014).

5.2. Cinnamon

Cinnamomum cassia is commonly known as cinnamon. The bark of cinnamon is sweet in taste and most widely used as flavoring agents in the food and beverages. It is well recognized due to its medicinal properties and traditionally used in menstrual irregularities, diarrhea and arthritis. Cinnamon is a well known plant, its bark is used for antidiabetic action. Around 250 species of Cinnamon has reported in which *C. cassia* and *C. zeylanicum* are popular ones (Medagama, 2015).

5.3. Ginger

Ginger (*Zingiber officinale*) is a safe and non-toxic spice with lesser side effects as considered by the food and drug administration (Huang et al., 2019). Its origin is from Southeast Asia and has a long traditional use due to its medicinal properties. Ginger is used as an antidiabetic herb due to its action on inhibiting the enzymes α-glucosidase and α-amylase. It is due to the presence of shagol and gingerol as phytoconstituents (Lindstedt, 2018).

5.4. Garlic

Garlic (*Allium sativum*) belongs to family Liliaceae. *A. sativum* is used exhaustively due to its medicinal and nutritional properties. It is native to central Asia and being used for culinary purposes due to its health benefits since ancient times. The phytoconstituents present in plant parts are Diallyl disulfide, Allicin, S-allyl cysteine, Allyl mercaptan and Alliin. *A sativum* is effective in reducing blood glucose level and insulin resistance in the body. The other well established uses of garlic include anticoagulant, antiatherosclerotic, anticancer, antimicrobial, immunomodulatory, antidote and hypolipidemic activities (Shabani et al., 2019).

5.5. Bitter gourd

Bitter gourd is *Momordica charantia* Linn. belongs to family Cucurbitaceae. It is also known as karela and balsam pear. The fruits of *M. charantia* has been used for several decades to treat diabetes to the indigenous people of Asia, East Africa and South America. The hypoglycemic mechanism of *M. charantia* is due to presence of phytoconstituents that possess AMP-activated protein kinase activity. The phytoconstituents present in the plant are charantin, cucurbitins, karounidiols, momordicinin, stigmasterol, zeaxanthin and pipecolic acid (Joseph and Jini, 2013; Mahmoud et al., 2017).

5.6. Sweet potato

Sweet potato *(Ipomoea batatas*) is used as an edible product in various countries including India, Tanzania, Japan, Peru and New Zealand. The shoots and leaves have been employed traditionally as medicine in the treatment of diabetes. It belongs to the family Convolvulaceae. The roots of *I. batatas* are rich in mineral salts and vitamin C. It is used to alleviate vitamin A deficiency in Eastern India and East Africa due to high quantity of beta-carotene in roots (Gunn et al., 2013; Kusano and Abe, 2000).

5.7. Black seed

Black seed (*Nigella sativa*) or black cumin is dicotyledon plant belongs to family Ranunculaceae. It has been used as an important culinary herb containing medicinal properties. The phytoconstituents present in the seeds are p-cymene, nigellone, flavonoids, carvone and thymoquinone in which thymoquinone is considered the chief active compound. The seeds are used as good antidiabetic agents that can lower increased glucose level of the body and also restore lipid profile. It is also used for neuroprotective, nephroprotective, anticonvulsant, anticancer and antimutagenic properties (Heshmati and Namazi, 2015; Bamosa et al., 2010; Gunn et al., 2013).

5.8. Chirayita

Chirayita (*Swertia chirayita*) is a popular indigenous herb of Himalayas belongs to family Gentianaceae. It has been traditionally used in the treatment of several ailment including diabetes, malaria and liver disorders. It is a rich sources of flavonoids, xanthones, terpenoids, irridoid and alkaloids. *S. chirayita* is known for its bitter taste, it is due to the presence of phytoconstituents such as amarogentin, swertiamarin, and swerchirin (Alam et al., 2011; Kumar and Van Staden, 2016; Dey et al., 2020).

6. Advancement in the treatment of diabetes

- An artificial pancreatic system is a big addition in the treatment of diabetes. It is critical to quantify blood glucose level non-enzymatically, accurately and in stable manner (Wang et al., 2019).
- Teplizumab, an immune stimulant drug is under phase 3 trial that delayed type 1 diabetes. Anti-thymocyte globulin (ATG) is good alternative for people with newly diagnosed type 1 diabetes. It can preserve the function of beta cells and decreases blood sugar levels.
- A new protein, Hybrid Insulin Peptides (HIPs) has found on beta-cells of pancreas with type 1 diabetes and this are recognized as foreign body by the immune cells of patients (Baker et al., 2019). Thus, HIPs can be an important target for type 1 diabetic patients.
- Bisphenol A (BPA), a synthetic chemical present in our food has identified recently its association with increased risk for developing type 2 diabetes. Therefore, it should be administered in a controlled manner to humans due to its direct effect on glucose and insulin levels (Hagobian et al., 2019).
- The digital diabetes care market has gone beyond the earlier diabetes management. The digital solutions for diabetes such as applications, connected devices and services along with healthcare professionals and payers have change the earlier scenario of the disease (Deepa et al., 2020). Digital health is proving very helpful in improving the lifestyle of diabetic patients (Kaufman and Khurana, 2016). It is a complementary tool in diabetes-intervention studies.

7. Scope and prospects

Diabetes is a common metabolic disorder that can affect people of any group in developed as well as developing countries (Zaid et al., 2016). The rise in global diabetic patients has been linked with several factors like poor diet, obesity and sedentary lifestyles. However, older people have share a significant portion of diabetic patient worldwide. Several conventional and pharmacological treatments are available to restore normal blood glucose level. However, the conventional therapies and drugs treatments are associated with certain side effects. The advancement in the technologies like mobile phones and personal digital assistants are very helpful to tell the current status of health of an individual. The most frequently used digital services for healthcare wellness including mobile telemedicine, health call centers and emergency toll-free telephone services according to the second global survey on electronic health (WHO, 2011). However, a long-term study is desired to determine their sustainability, efficacy, cost-effectiveness and patient satisfaction. The traditional herbal medicines have been used in the treatment of several disorders (Jain et al., 2015; Rao et al., 2014, 2015; Rathore et al., 2014). The bioactive compounds are very effective in controlling bacteria, pathogens, viruses, and other foreigns agents (Jain et al., 2019 a; Jain et al., 2018; Jain et al., 2020 a; Jain et al., 2020 b; Jain et al., 2020 c; Rao et al., 2016; Jain et al., 2020 d; Jain et al., 2020 e). The medicinal plants have been used in the treatment of diabetes and they are getting recognition after their standardization and proper clinical trials (Jain et al., 2019 b). The herbs have several modes of antidiabetic action including insulin mimetic, alteration of glucose metabolizing enzymes, inhibition of intestinal absorption of glucose, increase uptake of glucose peripherally, regeneration of pancreatic cells, promotes insulin release and ameliorating oxidative stress (Mwiti and Jide, 2015). Several herbs have been used traditionally in the treatment of diabetes since ancient times in many countries. It is due to their effective role in medicinal field. The herbal drugs are recognizing worldwide because of their safety profile improved pharmacokinetic, pharmacological and clinical status (Choudhury et al., 2017).

8. Conclusion

Medicinal plants have been used in the treatment of several disorders. They can lower the blood glucose level through combination of more than one mechanism. These plants have similar mode of action and mechanism as conventional drugs for treating diabetes but advantageously they have lesser side effects. There is a need to standardize all the traditional herbs used for medicinal purposes and determine their molecular mechanism for alleviating diabetes. The standardized, validated and characterized herbal drugs with their identified phytoconstituents can enter the world of clinical trials and further reach to their ultimate market. Thus, traditional knowledge for the use of medicinal herbs against diabetes with molecular mechanism may be a useful tool for new drug development.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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