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An update on natural compounds in the remedy of diabetes mellitus: A systematic review

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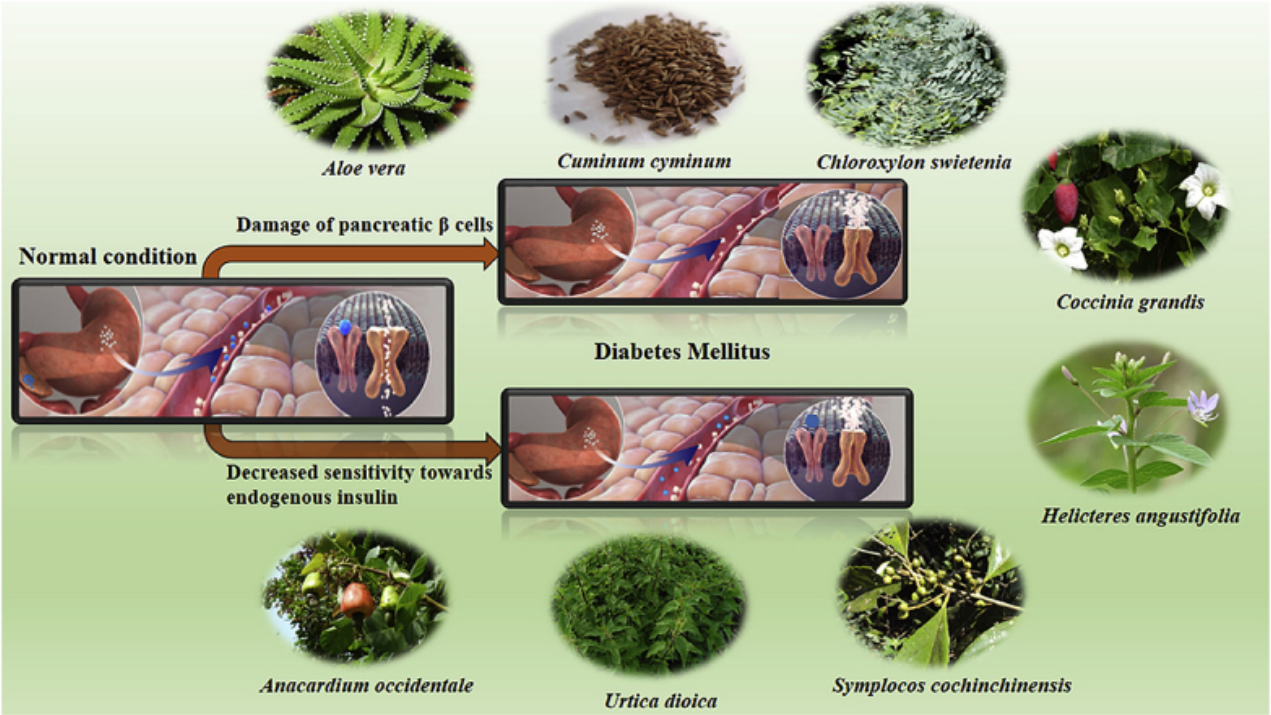
Abstract

Herbal medicine, phytomedicine or botanical medicine are synonymous, utilizes plants intended for medicinal purposes. Medicinal use of herbal medicine in the treatment and prevention of diseases including diabetes has a long history compared to conventional medicine. Diabetes is one of the major public health concerns over the world. Diabetes or hyperglycemia is considered to be one of the common public health hazard; optimal control of which is still not possible. Persistent hyperglycemia or uncontrolled diabetes has the potential to cause serious complications such as kidney disease, vision loss, cardiovascular disease, and lower-limb amputations which contributed towards morbidity and mortality in diabetes. There are various approaches to treat and prevent diabetes as well as its secondary complications, one of it is herbal medicines. However, the selection of herbs might depends on several factors, which include the stage of progression of diabetes, types of comorbidities that the patients are having, availability, affordability as well as the safety profile of the herbs. This review focuses on the herbal and natural remedies that play the role in the treatment or prevention of this morbid disorder – diabetes, including their underlying mechanisms for the blood glucose-lowering property and the herbal products already been marketed for the remedial action of diabetes.

Keywords: Herbal medicine, Insulin secretion, Insulin resistivity, Active component, Diabetes control

Graphical abstract



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1. Introduction

Use of herbal products are not only limited to dietary uses, such as food, nutrition, etc., it has its distinct role in remedy of several diseases. Herbal medicine, sometimes known as phytomedicine or botanical medicine, utilizes different parts of the plants, including its flowers, fruits, seeds, leaves, berries, bark and roots intended for medicinal purposes.[1] The use and delivery of herbal medicine as dosage form in treating and preventing of diseases has a long history started with use in Mesopotamia in 2600 B.C.,[2] although the oldest record on practice of medicinal plants for drug preparation was engraved on a Sumerian clay slab, created over 5,000 years ago.[3] The use of medicinal plants are still continuing in this modern era, and it has been estimated that approximately one fourth of prescription medicines worldwide are derived from plants.[1] World Health Organization has also reported the use of traditional medicine for primary health care needs in most countries.[4] Herbal products in Malaysia have molded an essential component in the medicine system, where the Malaysian market for herbal products stands at approximately RM4.6 billion with a 15–20% annual projected growth rate.[5] Therefore increased interest of Malaysians' for the use herbal medicines lead to tremendous growth of the Malaysian herbal product market.

Herbal medicine is one of the subgroups of complementary and alternative medicinal (CAM) therapies. Many patients consider CAM over conventional therapies due to dissatisfied outcomes from the conventional therapies, higher treatment costs and increased side effects of modern medicines. Therefore, the active ingredients of the medicinal plants are directing towards its particular use in diseased condition, may be applied in complex formulation of one or more plants. The use of traditional herbal medicines is more associated with patient conception and less paternalistic compared to allopathic medicine in general.[6, 7, 8, 9] Moreover, traditional herbal medicines may be used in combination with or as alternative to the conventional allopathic medicines. Thus, there are thousands of medicinal plants for the treatment of a range of diseases. There are several complications which are targeted to treat with herbal medications,

including cancer, memory impaired condition, liver disorder, peptic ulcer and other gastrointestinal disorder, inflammatory disorder, hypertension and other cardiovascular disease, diabetes mellitus, hyperlipidemia, tuberculosis, dermatological infections, along with undefined muscular pains and other diseases related to urinary tract, respiratory tract and central nervous system.[6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19] The worldwide utilization of herbal medicines are summarized in Fig. 1. In this article, we aim to focus the potential herbal medications as an effective and sustainable alternative for the treatment of diabetes. In due course of the study, we have done extensive literature search to provide a summarized database on available herbal treatments in the control and treatment of diabetic condition.

2. Clinical overview of diabetic mellitus

Diabetes is a chronic disease characterized by hyperglycemia, and is categorized into two types: Type I Diabetes Mellitus (T1DM) and Type II Diabetes Mellitus (T2DM). In T1DM, β-cells of the pancreas are damaged, leading to a decreased insulin supply to the circulation. Patients will be fully dependent on exogenous insulin administration for existence. Contrarily, T2DM has been observed in majority of diabetic patients (85%) and results in peripheral insulin resistance, thereby results in decreased insulin sensitivity to the skeletal muscles, adipose tissues and liver (Fig. 2).[20] Another category of diabetes can also be categorized in pregnant women without previously diagnosed diabetes, known as gestational diabetes mellitus. Factors such as aging, obesity, physical inactivity, population growth and urbanization can gradually leads to steady increase in the number of patients with diabetes. In year 2000, prevalence of diabetes worldwide among adults is estimated to be approximately 171 million,[21] whereas the number has been increased to 422 million (approximately 1 in every 11 people) in 2014.[22] The prevalence of diabetes in the world is expected to be doubled to approximately 366 million in year 2030 due to demographic changes in people of more than 65 years old and most importantly, adaptation of sedentary life style by the people in the urban areas of the world.[21] If this disease left untreated it can lead to acute fatal complications including diabetic ketoacidosis and coma due to exceptional increase in blood glucose. Additional dreadful consequences of diabetes include vascular complications due to damage of the vessels for high glucose level, may result in macrovascular and microvascular disorders. Consequences of microvascular complications are retinopathy, neuropathy, etc., whereas, macrovascular complications lead to cardiovascular complications. Other complications for chronic diabetic conditions include dementia, sexual dysfunction, depression and lower-limb amputations.[20]

Different categories of antidiabetic medications are there in the market for the remedial action, which includes insulin analogues, sulphonylureas, biguanides, dipeptidyl peptidase-4 inhibitors, thiazolidiones, α-glucosidase inhibitors, etc, where the mechanism of counteracting this increased glucose level is different for different categories (Fig. 3).[22] However, long term treatment and side effect of the available hypoglycemic medications leading towards huge demand for efficacious, decreased side effects and affordable agents for the treatment of diabetic condition.

3. Herbal remedy in diabetes

Complementary or alternative treatments using herbal medicines draw the attention of many diabetic patients. Numerous common herbs are claimed to reduce blood glucose level, therefore the possibility of having better glycemic control or being less dependent on insulin injections by taking herbal medicines is unquestionably appealing. However, the selection of herbs might depends on several factors, which include the stage of progression of diabetes, types of comorbidities that the patients are having, availability, affordability as well as the safety profile of the herbs. Preclinical studies have crossed the doorstep of laboratories and reached to the bed-side of the patients. Several clinical studies in human patients have been conducted in recent years, reported that medicinal plants such as *Scoparia dulcis*,[23] *Cinnamomum cassia*,[24] *Ficus racemosa* bark[25] and *Portulaca oleracea* L. seeds were shown to have

antidiabetic potential. Subsequent research on laboratory on herbal products has reached to the diabetic patients by the brand name of Diabecon®, Glyoherb® and Diabeta Plus®. Thus, herbal supplements can be used as an adjuvant or as favorable alternative therapy for diabetic condition (Fig. 2).

3.1. The selection of herbs for diabetes

Several medicinal plant have shown to be effective in different stages of diabetes, such as curcumin is proposed to be used as one of interventions in pre-diabetes therapy to prevent the progression of T2DM due to its proven benefits and safety profile,[26] whereas, cinnamon can be a better option for diabetic patients who are having co-existing hypertension,[27] and on the other hand, the extract of *Aloe vera* leaf gel with doses of 300 mg/kg demonstrated increased levels of insulin from regenerated pancreatic beta-cells.[28] Therefore it is important to know the history of the patient and therapeutic benefits of the medicinal plant for proper treatment of the patient. The following sections of this article will institute different activities of medicinal plants to replace the existing therapies of diabetes.

3.1.1. Herbs that regulate insulin secretion Defects in insulin secretion are the one of the main causes that leads to Diabetes Mellitus. Recently, numerous botanical herbs have demonstrated antidiabetic potential through regulation of insulin secretion (Table 1). As the long-term use of conventional secretagogues such as glibenclamide in diabetes patients tend to cause damage of β-cells due to overstimulation of pancreatic islet, treatment can be switched to the use of *Cuminum cyminum* in long-term diabetes treatment since it can help in lowering the blood glucose level and at the same time it carries benefit of beta-cells protection. The study Patil *et al* showed that the diabetic rats treated with the essential oil of cumin, cuminaldehyde and cuminol, at doses of 25 μg/mL for 45 days were demonstrated 3.34 and 3.85 folds increase in insulin secretion, respectively when compared to 11.8 mM-glucose control. Additionally, a dose-dependent inhibitor of insulin secretion was observed and it was said to have potent beta-cell protective action as a result from the comet assay. Besides, the high availability of this common spice and its safety profile with no reported toxicity also make it a better alternative in diabetes treatment.[29] Concurrently, a recent study indicated that the green cumin could effectively control glycemic factors along with inflammatory mediators.[30] Like regulation of insulin by cumin seed, another variety of cumin, black seeds/cumin, *Nigella sativa,* of Ranunculaceae family possessing anti-diabetic and anti-hyperlipidemia properties. Black-colored seeds are bitter in taste and contain different chemicals than cumin seed in it, which include flavonoids, unsaturated fatty acids, nigellone, thymoquinone, p-cymene and carvone. Study results revealed that the blockage of sodium-dependent passage of glucose across isolated rat jejunum was proportional to doses of *N. sativa* aqueous extract ranging between 0.1 pg ml^{-1} and 100 ng ml^{-1}, where maximum inhibition of 80% had been achieved with an IC_{50} = 10 pg ml^{-1}. Oral glucose tolerance test was performed in rats ensuring the first dose as well as after continuous therapy with 2 g/kg body weight/day of *N. sativa* for a period of 6weeks and a comparison was made with 300 mg/kg body weight/day of metformin. The efficiency of long term *N. sativa* treatment in the improvement of glucose tolerance was found to be equivalent to metformin. The *N. sativa* regimen also resulted in a reduction in body weight in a similar manner as metformin without any toxic effects.[31] These results support the use of aqueous extract of *N. sativa* as a traditional remedy for diabetes.

On the other hand, ethanolic extract of *Aloe vera* leaf gel, belongs to family Liliaceae, with doses of 300 mg/kg demonstrated increased levels of insulin from regenerated pancreatic beta-cells. Besides, the plasma lipids, liver cholesterol and kidney triglycerides (TG) levels of the tested diabetic rats also being reduced after the administration of *Aloe vera* extract.[28] The extracts of *Chloroxylon swietenia* bark were also found to have hypoglycemic effects in streptozotocin (STZ)-induced diabetic male albino Wistar rats. The results showed that the blood glucose level was moderately controlled, comparable to glibenclamide, through intragastric intubation for 45 days, as well as increased plasma insulin level, in treatment group as compared to control group.[32] Antidiabetic potential of ethyl acetate extract of *Forshythia suspense* in STZ-

induced diabetic rats also reflected by the dose dependent significant reduction in blood glucose level associated with significant increase in plasma insulin level in the treatment group.[33] Similarly, *Coccinia grandis* leaf was also found to have antidiabetic activity in STZ induced diabetic rats, where oral treatment of ethanolic extract of *C. grandis* leaves at 50, 250 and 500 mg $kg^{-1}.day^{-1}$ for 21 days resulted in significant reduction in plasma glucose level and increase in serum insulin level in a dose-dependent manner. The blood glucose and plasma insulin level were 169.60 ± 0.70 mg dL^{-1} ($p < 0.01$) and 3.10 ± 0.08IU.dL^{-1} ($p < 0.01$) respectively with 500 mg/kg/day extract treated rats, whereas, those levels in control diabetic group were 312.70 ± 2.05 mg dL^{-1} and 1.28 ± 0.05IU.dL^{-1}, respectively.[34] Leaves of the same plant also has promising diabetic control properties by its insulin secretory property which is supported by its antioxidant and antiglycation properties.[35] Thus, medicinal plants have specific role in the improvement of diabetic condition for the healthier quality of life *via* ameliorating the number of pancreatic β-cells in the islets of Langerhans, acting like secretagogues, thus increasing the insulin secretion and at the same time protect the beta-cell from destruction, however, further investigations should be conducted to study the mechanism of actions of these plants on insulin secretion.

3.1.2. Herbs that control insulin resistance Majority of the diabetic patients are suffering from T2DM, due to development of resistance to the endogenous insulin by the cells and tissues of the body. Resistance to the cells can be reverted to sensitivity by the use of medicinal agents. The hydroalcoholic extract of *Urtica dioica* leaves showed hypoglycemic activities in male *Wistar* rats with fructose-induced insulin resistance. After two weeks of intraperitoneal injection of *U. dioica* extract at different dosage to the experimental rats showed significant reduction in plasma glucose level and fasting insulin resistance index (FIRI) than the control group and the effects were dose-dependent.[36] Besides that, serum insulin concentration in rats in treatment group was significantly lower than the control group, thus the results signifies that the sensitivity to the tissues and cells have been increased by the use of leaf extraxt as evidenced by the decreased plasma glucose level.[36] The ethanolic extract of *Anacardium occidentale* leaves also demonstrated antidiabetic activities in neonatal STZ-induced diabetic rats. Oral administration of 100 mg/kg body weight of *A. occidentale* extract for 30 days, showed significant reductions in fasting sugar levels, serum insulin level (11.69 ± 0.93 IU.mL^{-1}) and FIRI.[37] Garlic oil extracted by steam distillation of *Allium sativum* shown to improve insulin and glucose tolerance and improves glycogenesis in skeletal muscle. The hypoglycemic activity of garlic oil has shown to improve GLUT4 expression in STZ induced diabetic rats.[38] The ethanol extract of *Symplocos cochinchinesis* bark has also shown to have effects in regulating insulin resistance. The oral administration of *S. cochinchinesis* extract at 250 and 500 mg $kg^{-1}.day^{-1}$ significantly reduced the plasma glucose level in diabetic induced rats with insulin resistant on day 20.[39] Simultaneously, it was observed that the plasma insulin level and homeostatic model assessment score on insulin resistance (HOM-IR) in treatment group were significantly lower as compared to control group, suggesting improved sensitivity of the cells towards endogenous insulin.[39] Similarly, ethanolic extract of *Helicterus angustifolia* root was also found to have antidiabetic potential. A 200 and 400 mg/kg/day dose for a period of 28 days in STZ-induced diabetic rats resulted in significant reduction in blood glucose, plasma insulin level and HOMA-IR in treatment group as compared to control group.[40] In rats receiving 400 mg/kg/day extract, the blood glucose, plasma insulin level and HOMA-IR were 23.86 ± 0.25mmol.L^{-1}, 6.98 ± 0.22μU.mL^{-1} and 7.41 ± 0.29, respectively whereas, those values in control diabetic group were 31.47 ± 0.30mmol.L^{-1}, 7.24 ± 0.38μU.mL^{-1} and 10.13 ± 0.56, respectively.[40]

On the other hand, aqueous extract of *Pleurotus ostreatus* demonstrated glucose-reducing effects in high-fat diet and STZ induced insulin resistant diabetic rats where 100, 200 and 400 mg $kg^{-1}.day^{-1}$ oral treatment of *P. ostreatus* extract for 4 weeks showed that the fasting blood glucose level in treatment group were significantly lower as compared to control group at day 14, 21 and 28.[41] Besides that, the level of fasting serum insulin level (FINS) and HOM-IR were lower meanwhile the insulin sensitivity index (ISI) and the homeostatic model assessment score for beta cell function (HOM-β) were higher in treatment

group.[41] Likewise, stem bark of *Afzelia africana* and *Uvaria chamae* root have also shown to have hypoglycemic effects in STZ-induced diabetic rats, where *A. africana* controls the diabetic condition in dose dependent contrary,[42] whereas extent of reduction was not directly proportional to the dose of *U. chamae* extract.[43] In explanation to the anti-diabetic research on *U. chamae* extract, the authors showed the tissue histology study where the pancreas of the rats in treatment group showed clusters of regenerated Islet of Langerhans of variety size,[43] however, the plasma insulin level and HOMA-IR were not accessed in this study.

Resveratrol is one of the important herbs proven to exhibit anti-diabetic effects in diabetic animal's model. It stimulates intracellular glucose transport and result to increase glucose uptake by various cells.[44] In absence of insulin, resveratrol showed its stimulatory action on glucose transport.[45] Numerous research findings have shown that resveratrol enhance insulin sensitivity in experimentally induced insulin resistance animal model.[46]

Hence, reviewing these studies it can be concluded that long term diabetic treatment with certain anti-diabetic medicinal plant could result in better control of blood glucose *via* improvement of cellular sensitivity towards endogenous insulin, thus more clearance of the glucose molecules became possible to achieve a healthier lifestyle.

3.1.3. Herbs have impact on glucose absorption The utilization of α-glucosidase inhibitor is one of the remedies for diabetes as it suppresses carbohydrate digestion, thus decelerating the process of glucose assimilation and resulting in significant reduction of postprandial plasma glucose and insulin level with a significant decrease of HbA1c postprandially. There is a wide use of α-glucosidase inhibitor in the control of T2DM, for e.g., acarbose, voglibose, miglitol, etc.[47] Several researches are ongoing in search of potential natural candidates for the effective control of diabetes consequently, several herbs, such as cinnamon, China aster, mistletoe fig and bitter oleander have been found to exhibit inhibitory actions on α-glucosidase. Besides that, inhibition of α-amylase has also been associated with anti-hyperglycemic actions of medicinal herbs like *Camellia sinensis, Aloe vera,* basil, etc.[48] In addition to the inhibitory effect on these two enzymes, polyphenol-rich herbs such as jute and soybean have additional benefit in managing diabetes and hypertension due to inhibitory activities on angiotensin converting enzyme (ACE).[49] Other herbs that showed potential in treating diabetes include olive leaves, which has been shown to reduce digestion and absorption of starch, as well as black seed, where the inhibition of sodium-dependent glucose transport has been demonstrated. Below are examples of herbs that influence glucose absorption *via* their respective mechanism of actions:

Phyllanthus urinaria is a wild plant in Indonesia of Euphorbiaceae family being used traditionally in urinary tract disorders and diabetes. Chromatographic separation of hydro-methanolic extract of *P. urinaria* leaves and subsequent purification of the active fractions using preparative HPLC revealed corilagin, gallic acid and macatannin B constituents, which showed *in vitro* inhibitory effect against pancreatic amylase isolated from swine (21%, 23% and 33%, respectively at 1 m.mol.L^{-1} concentration)[50].

Another popular herb, *Ocimum basilicum* (basil) is found to be used in culinary and folk medicine. Phytochemical analysis have shown that aqueous extract of *O. basilicum* leaves contains cardiac glycosides, flavonoids, glycosides, reducing sugars, saponins, steroids and tannins. Leaf extract of the plant exhibited remarkable dose dependently inhibition of intestinal maltase and sucrase of rats and pancreatic α-amylase of swine (IC_{50} = 21.31 mg ml^{-1}, 36.72 mg ml^{-1} & 42.50 mg ml^{-1}, respectively). Greater inhibition of maltase may be attributed to the high total polyphenols and flavonoids contents.[51]

Contrary, the bark of *Cinnamomum zeylanicum* (a species of cinnamon), a spice that has been traditionally consumed to cure diabetes, known to contain flavonoids, glycosides, anthraquinones, terpenoids, coumarins and tannins. Due to its affordable cost, high availability and safety profile, cinnamon is considered as one of the low risk options for diabetic patients.[52] The dose-dependent, competitive and reversible inhibitory effect of cinnamon bark extract on both yeast and mammalian α-glucosidase was evident in *in vitro* studies (IC_{50} = 5.83 μg ml^{-1} & 670 μg ml^{-1}, respectively). The reversible inhibition is desirable as the enzyme remains intact even after the removal of the inhibitor, thus probably could decrease the risk of hypoglycemia due to chronic malabsorption of carbohydrate. Besides that, oral intake of 300 mg kg^{-1} of cinnamon extract exhibited effective suppression of post-meal blood glucose spikes in STZ-induced diabetic rats loaded with maltose and sucrose by 78.2% and 52.0%, respectively compared to normal rats. Alternatively, postprandial hyperglycemia was not effectively suppressed when cinnamon extract was administered to glucose-loaded rats, indicating that the major mechanism involved is through the inhibition of α-glucosidase.[53] On the other hand, another species of cinnamon might be a better option for diabetic patients who is having comorbidity of hypertension. Species of cinnamon, *C. cassia* is having the most established data in TD2M treatment. The details of the study outcomes has been depicted in clinical section.[54] Therefore, cinnamon may be a potential supplement effective in controlling postprandial hyperglycemia and reducing the risk of diabetic vascular complications associated with it.

Similarly, *in vitro* studies have shown significant inhibition of the *α*-glucosidase enzyme (IC_{50} = 8.14 μg ml^{-1}) by hydroalcoholic extract of *Callistephus chinensis* flower. Further testing was carried out on the stepwise polarity fractions of exracts and the ethyl acetate fraction was found to exhibit the greatest inhibiting action on *α*-glucosidase enzyme. Enzyme assay guided fractionation led to the isolation of 8 compounds: apigenin, apigenin-7-O-*β*-D-glucoside, hyperin, kaempferol, kaempferol-7-O-*β*-D-glucoside, luteolin, naringenin and quercetin. Among the compounds isolated, quercetin demonstrated the greatest *α*-glucosidase inhibition (IC_{50} = 2.04 μg ml^{-1}), which is equivalent to that of acarbose (IC_{50} = 2.24 μg ml^{-1}).[55]

Corchorus olitorius (jute) leaves have been used historically as a medicinal plant to treat certain degenerative conditions due to the rich contents of polyphenolic compounds and flavonoids, which have been reported in *in vitro* studies to have α-glucosidase inhibitory activity, making it a potential source of anti-diabetic agent for the management of postprandial hyperglycemia and diabetic complications as a result of oxidative stress. A study demonstrated inhibition of α-amylase and α-glucosidase proportional to doses of *C. olitorius* extracts, results showing substantially greater inhibition against α-amylase and α-glucosidase (IC_{50} = 17.5 μg mL^{-1} & 11.4 μg mL^{-1}, respectively). The major phenolic compounds were found to be chlorogenic acid and isorhamnetin in the free extract and caffeic acid in the bound extract as evidenced *via* reversed phase HPLC analysis.[56] The abundance of these compounds in the leaves of *C. olitorius* may have contributed to the inhibitory activities against important enzymes associated with T2DM and hypertension, hence justifying its traditional use in treating these ailment. Studies also have demonstrated hypoglycemic activity of *Holarrhena antidysenterica* seed extract in STZ-induced diabetic rat.[57, 58] The presence of carbohydrates, flavonoids (quercetin), phenolic compounds (gallic acid), saponins, steroids, and tannins have been shown through phytochemical screening.[58, 59] A recent study has demonstrated inhibitory activity on the α-glucosidase enzyme (IC_{50} = 0.52 mg ml^{-1}), thus result in fall in postprandial glucose level in starch loaded normoglycemic rat.[59] *Glycine max (L.) Merrill* (soybean) is a type of legume and the major dietary protein source all over the world. Soybean is rich in polyphenolic compounds, for example, isoflavones. *In vitro* studies on both the free and bound phenolic extracts of soybean demonstrated a dose-dependent inhibition on two crucial enzymes related to T2DM - α-amylase and α-glucosidase, and another enzyme which plays an important role in hypertension - ACE. Nevertheless, the greater α-glucosidase inhibitory activity shown by free phenolic extract confers an advantage over conventional α-glucosidase inhibitors used in the management of diabetes such as acarbose

because the adverse effects of these pharmaceutical agents are associated with greater inhibition of α-amylase.[60] By inhibiting these enzymes, the breakdown of disaccharides into glucose can be delayed, thus lowering intestinal absorption of glucose. Therefore, normoglycemia and normotension can be achieved through the α-glucosidase and ACE inhibitory effect of soybean extracts.

Another medicinal herb of Moraceae family, *Ficus deltoidea*, has increased popularity as an alternative remedy for diabetes, been experimentally shown to lower elevated blood sugar at various prandial states.[61] The crude extracts and fractions of two fruit varieties of *F. deltoidea* (var. *angustifolia* and var. *kunstleri*) has shown a dose-dependent inhibition on intestinal α-glucosidases of yeast and rats.[62] However, improved basal and insulin-mediated glucose uptake into adipocytes cells for extracts of *F. deltoidea* leaves are due to the insulin-mimetic and/or insulin-sensitizing properties.[61] Furthermore, Choo et al have successfully isolated two bioactive constituents, namely vitexin and isoviten, from *F. deltoidea* leaf extracts *via* bioactivity guided fractionation. Significant reduction in the post-meal blood sugar level was shown in normoglycemic mice loaded with sucrose after receiving 1 mg kg^{-1} of vitexin/isovitexin orally. Oral administration of 200 mg kg^{-1} and 100 mg kg^{-1} of vitexin and isovitexin, respectively in sucrose-loaded STZ-induced diabetic rats showed great reduction (19.7%) of postprandial blood glucose.[63] Such popular *F. deltoidea* is an alternative remedy for diabetes that has led to the rise in commercially available forms as capsules and teas.

From these studies, it is clear that the herbal medicines could potentially be a natural alternative to conventional α-amylase and *α*-glucosidase inhibitors used in the management of diabetes (Table 2) and thus control postprandial hyperglycemia by delaying the intestinal absorption of carbohydrate.

3.1.4. Herbs regulate multiple actions on glucose regulation We have observed that hypoglycemic herbs are widely used traditionally; however, those herbal medicines are projected towards well characterized and demonstrated mechanism of diabetic control. Apart from the described herbs, several herbs investigated to have multiple mechanism in the control of diabetic condition. Few of the medicinal herbs has been described in this section those have multiple mode of action, including regeneration of pancreatic B cells, increases insulin sensitivity, enhance glucose utilization and antioxidant property. Long term elevated blood glucose level in diabetic patients could develop variety of vascular complications due to excessive production of reactive oxygen species (ROS) and the reduction of activities of endogenous antioxidants, such as superoxide dismutase (SOD) and catalase (CAT); hence, by correcting the impaired antioxidant status in diabetic patients will be a benefit in treating diabetes mellitus and also its vascular complications.

Several studies have portrayed blood glucose, cholesterol level and urea lowering effect of garlic extract. Sulphur compounds in garlic are believed as the main biological compound to exhibit hypoglycemic effect. Garlic extract stimulates the secretion of insulin from pancreatic beta cells. It also provides sparing insulin effect by preventing insulin from inactivation by SH group in albumin. Besides, it causes marked reduction of serum glucose by increasing glucose utilization.[64] Reduction of blood cholesterol level also shown in garlic extract may be due to hydroxy methyl glutaryl-CoA reductase inhibition which suppresses the cholesterol producing metabolic pathway. Garlic extract will also decrease serum urea and creatinine level due to reduction activity of xanthine oxidase and lipid peroxidation which participates in oxidative degradation of lipid. Anti-inflammatory effect of garlic extract can be displayed by the reduction of aspartate transaminase (AST) and alanine transaminase (ALT) level.[64] Similarly, *Panax ginseng* is also known to have anticancer and anti-inflammatory effects where the berry and root have been explored for its antidiabetic and hypoglycemic effect, respectively. Ginsenosides are the main biological active components for the antidiabetic effect. Its metabolic activity is not well understood. However, it is believed that the mode of action includes enhancement of insulin sensitivity due to lesser insulin demand. Besides, *Panax ginseng* will stimulate insulin signaling pathway such as protein kinase B and insulin receptor substrate-1 in order to increase secretion from pancreatic β-cells. Its hyperglycemic effect also includes in

enhancing gastrointestinal absorption by intestinal bacteria. Increase of translocation of glucose transporter type 4 (GLUT 4) to cell membrane will also enhance the glucose uptake as well as glucose utilization. Antioxidant effect of the extract is also contributed to the antidiabetic effect. Reduction of oxidative stress can be displayed and therefore preventing endothelial inflammation that may lead to the complication of diabetes [65, 66]. On the other hand, *Aloe vera* leaves are used widely used for the treatment of diabetes now-a-days, where the antidiabetic activity of *A. vera* is due to increasing secretion of insulin from pancreatic β-cells, along with its antioxidant property by reducing the free radical formation, in streptokinin induced diabetic adult female albino rats. This can be further explained by reduction of serum malondialdehyde (MDA) level which is the product of fatty acid peroxidation while there is an increase of antioxidant enzyme such as SOD and glutathione (GSH). Antioxidant potential is directing towards prevention of progression of diabetes mellitus, further, the anti-inflammatory property of *Aloe vera* extract will also provide benefit in lowering blood glucose level. Emodin and mannose-6-phosphate in *Aloe vera* extract are believed as the main active ingredients for the anti-inflammatory properties, where insulin sensitivity will also increase due to prevention of inflammation. Lastly, *Aloe ver*a extracts control hyperglycemia condition by inhibiting pancreatic α-amylase activity which aids in hydrolyses starch and glycogen to simple sugar.[67]

Different part of bitter melon, *Momordica charantia* L., has been used widely for antioxidant and antidiabetic activity. Efficacy of *Momordica charantia* L is evaluated with aqueous extracts and its main active ingredient -charantin shows hyperglycemic property in alloxan-induced diabetic mice. The mode of action includes stimulation glucose utilization of adipocytes and skeletal muscle. Besides, bitter melon extract will downregulate MAPKs and NF-κB to lower the impaired insulin signaling as well as provides protection to pancreatic beta cells. Upregulation of peroxisome proliferator-activated receptor gamma (PPAR-γ gene) expression which involve in glucose metabolism also one of the mechanism of *Momordica charantia* L on antidiabetic effect. Modulation of protein-tyrosine phosphatase 1B (PTP1B) acts as negative regulator of the insulin signaling pathway also contribute to the hypoglycemic effect. It stimulates insulin secretion from pancreatic beta cells as well as enhances glucose uptake by translocation of GLUT4 to the cell membrane. The fruits of *Momordica charantia* L stimulate glucose uptake by activating the action of glucose-6-phosphatase dehydrogenase which involve in pentose phosphate pathway.[68, 69] Further, the seed of fenugreek has widely been used for the treatment of diabetes mellitus for multiple benefits. Mechanism of fenugreek alkaloid on glycemic control is believed to prevent the catabolism process, such as proteolysis, glycogenolysis and lipolysis. Improvement of weight of liver and kidney is exerted which indicates the preferable outcome of fenugreek in regulating muscle protein synthesis. Hypoglycemic effect of fenugreek alkaloid also contributed by its antioxidant effect. Antioxidant effect is exhibited by inhibiting reactive oxygen species (ROS) and proinflammatory cytokines that can result in insulin resistance. Dietary fibers in fenugreek seed also aid in its hypoglycemia effect by modulating insulin secretion. Delayed gastric emptying in order to slow down intestinal glucose absorption also contributed to its antidiabetic properties. Regeneration of pancreatic β cell to enhance insulin secretion is also one of the mode of action of fenugreek to control hyperglycemic condition. Besides, fenugreek extract will enhance glucose uptake by adipose and muscle tissue and improve the utilization of glucose through elevation of glucose-6-phosphate dehydrogenase activity.[70, 71] Peel extract of *Punica granatum* has shown to control glucose level in experimental guinea pigs,[71] whereas leaves of the same plant have also displayed to produce beneficial effect in prevention of diabetic as evidenced by effective deterrence of nephropathy, structural and functional abnormality of kidney.[72]

Coptis chinensis is also well known for its antidiabetic effect through regeneration of size of the pancreatic islets of Langerhans in order to enhance the insulin secretion for glycemic control. In due course, *C. chinensis* stimulate AMP-activated protein kinase (AMPK) phosphorylation in skeletal muscle and liver which is important for cellular energy homeostasis. AMPK activation will stimulate skeletal muscle and hepatic fatty acid oxidation, inhibit lipolysis lipogenesis as well as enhance pancreatic β-cell to secrete

insulin. Besides, *C. chinensis* increases glucose uptake in adipose tissue through phosphorylation of insulin receptor substrate 1 (IRS-1). IRS-1 transmit the signal from insulin to intracellular pathways PI3K/Akt and Erk-MAP kinase. Moreover, elevation of expression of GLUT 4 in adipose tissue and skeletal muscle mediates glucose uptake in response to insulin is another mode of action of *C. chinensis* to control hyperglycemic condition. Insulin will increase GLUT 4 translocation to cell membrane of adipocytes and skeletal muscle in order to aid in glucose uptake. Studies have demonstrated that downregulation of expression of hepatic genes which involve in glucogenesis, glucose oxidation and glycogenolysis provide the antidiabetic effect of *C. chinensis*.[73] Alternatively, water decoction of *Catharanthus roseus* is also used in the management of diabetes where vindoline, tetrahydroalstonine and catharanthine are discovered as the main biological ingredients for the hypoglycemic effect. It exerts the activity of antidiabetic effect by enhancing intestinal glucose uptake through activity of glucose-6-phosphate dehydrogenase in pentose phosphate pathway. Several studies have shown that there is an improvement of activity of glucokinase which facilitates Phosphorylation of glucose to glucose-6-phosphate to possess glycemic control. On the other hand, there is an elevation of malate dehydrogenase for catalyzing the oxidation of malate to oxaloacetate and enhancement of succinate dehydrogenase that involves in citric acid cycle and the electron transport chain. The changes of the enzyme indicates that *Catharanthus roseus* provides better utilization of glucose by liver. Besides, level of GSH is observed to be increased in streptokinin induced diabetic rats. Antioxidant is capable to prevent important organ damage by free oxygen radicals. Alternatively, vindoline in *C. roseus* is known as protein tyrosine phosphatase-1B inhibitor which mimics the action of insulin as well as increases the insulin sensitivity by elevating the phosphorylation of insulin receptor. Besides, its direct antidiabetic effect. it is strongly associated with inhibition of α-glucosidase in the gastrointestinal environment that subsequently inhibit hydrolyses of carbohydrates.[74, 75]

Curry leaves, or scientifically *Murrya koenigii* exhibits potent antihyperglycemic and anti-obesity effect that is useful for the glycemic control as well as maintain optimal body weight. Ethanolic extract *Murrya koenigii* is reported to improve glucose intolerance in hyperglycemic condition in high fat diet induced obese and diabetic rats which is associated with insulin resistance and may progress to T2DM. It has also been shown that *Murrya koenigii* exerts insulin sensitizing and antioxidant activities, besides its α-glucosimidase inhibitory activity that can aid in glycemic control.[76, 77] *Ocimun tenuiflorum* leaves are traditionally used in diabetes in Malaysia. Investigation on the hypoglycemic effects of *O. tenuiflorum* extract revealed preventing of hepatic gluconeogenesis as well as activation of glucose uptake in adipose tissues and skeletal muscle. It is also known to enhance the insulin sensitivity attributed by phenolic and flavonoids in the extract, whereas regeneration of beta cells in pancreas may account for its potent antidiabetic effect and glycemic control. Antioxidant property of the plant extract contributes to the glucose homeostasis and α-amylase and α-glucosidase inhibiting activity in the control of hyperglycemic condition.[78] On the other hand, phenolic compound of *Mangifera indica* seeds found to enhance glucose metabolism by inhibition of carbohydrate digesting enzymes, α-amylase and α-glucosidase for the management of T2DM. Preventing the breakdown of starch to simple sugar may lead to enhancement of glucose uptake of circulating glucose, thus lowers the blood glucose level. Besides, inhibition of aldose reductase will prevent degradation of sorbitol for the formation of glucose as well as alleviate the complications of diabetic mellitus. Moreover, inhibition of iron induced lipid peroxidation in pancreas is also one of the modes of action for *Mangifera indica* which will prevent disruption of the fluidity and permeability of cell membrane and thus prevents cell death and damage.[79]

Thus, multimodal mechanisms in the control of diabetes will always be effectively control the diseased condition by lowering the plasma glucose level, increasing the number of β-cells in the islets of Langerhans, preventing absorption of glucose from the gastrointestinal tract, providing antioxidant role against endogenous ROS, etc. This might be possible by the presence of multiple active ingredients within the crude extract (Table 3). Therefore, characterization and validation of the active principles of the herbs will definitely pave the novel path for the effective control of this dreadful disease.

3.2. Polyherbal for diabetes

It has been observed that multiple mechanisms in the treatment of diabetes will effectively control the progress as well as modify the deteriorating condition of the patients. Similar to the previous section, to obtain multimodal activities in control of diabetes, certain purposeful mixtures of herb have been comprehensively evaluated for their effective uses in patients with diabetes. Such polyherbals are usually target the different pathological events throughout instigation and development of diabetes from different mechanistic approaches, to abolish the symptoms to improve the quality of life of the patient (Table 4). In this context we will come up with different polyherbals in the treatment of diabetes. A study conducted by Awasthi et al to assess the efficacy of standardized ayurvedic polyherbal formulation in the treatment of T2DM which consists of *Cyperus rotundus, Cedrus deodara, Berberis aristata, Emblica officinalis, Terminalia bellirica and Terminalia chebula,* showed no significant difference in the reduction of postprandial blood glucose level as compared with metformin after 24 weeks of study period. Besides, the HbA1c of polyherbal formulation-treated group showed a decrease from 7.38 ± 0.77 to 6.07 ± 0.64 whereas the metformin-treated group showed similar degree of decrease from 7.73 ± 0.92 to 6.43 ± 1.06. The polyherbal formulation-treated group also demonstrated greater reduction in serum cholesterol, TG and low density lipoprotein (LDL) after 6 months of study. Since the polyherbal formulation are able to reduce the postprandial blood glucose and Hb1Ac levels almost as effectively as metformin; and it seems to show more significant effect in high cholesterol management compared to metformin; hence, the use of this preparation maybe more useful for T2DM patients with hyperlipidemia since it has no side effects compared to metformin.[80]

Treatment with ‘GSPF kwath’ has shown to have similar anti-hyperglycemic effect as glibenclamide. Due course of treatment with GSPF kwath resulted in significant decline in HbA1c, both postprandial and fasting glucose level in T2DM patients after 6 months. Other than hypoglycemic effect, GSPF kwath also found to produce antihyperlipidemic and antioxidant effects.[81] The levels of total cholesterol, TG, LDL, and very low density lipoprotein (VLDL) were significantly decreased following 6 months of GSPF kwath therapy.

The multiherbal of different composition (mixture 1, 2, 3, 4, 5) results in better restoration of glycemic level to the near normal in comparison to individual herbals. The effect is due to the flavonoids, alkaloids, tannins, and terpenes which act as bioactive antidiabetic principles. Although, among all the mixtures, Mixture 4 showed the highest antihyperglycemic activity.[82] In another study, the polyherbal treatment showed to reduce in blood glucose levels due to property of *Salacia* and tannins present in *Lagerstroemia* species. In addition, mangiferin, a major active compound of *Salacia* can delay the onset or progression of diabetic complications. Besides, the formulation also showed antihyperlipidemic activity due to the presence of hydroxycitric acid. Preclinical studies of polyherbal formulation in diabetic rats resulted in a significant decrease in the activities of fructose-1,6-bisphophatase and glucose-6-phosphatase which lead to decreased gluconeogenesis and thereby reducing the endogenous production of glucose.[83] Further, SMK001 (also known as Dang-Nyp-Ko in Korea) contains both coptidis rhizome and trichosanthis radix and used as Chinese medicine to treat diabetes. Experimental outcomes revealed significant decrease of glucose in urine and plasma of diabetic rats succeeding the treatment of SMK001 for 28 days. SMK001 acts by increasing the pancreatic islets insulin-producing cells and decreasing the glucagon-producing cells.[84] Hypoglycemic effect of SMK001 is dose-dependent, although the mechanism of SMK001 is unclear, but SMK001 has favorable effect in changing body weight as well as the blood and urine glucose levels.[84]

On the other hand, STZ-induced diabetic rats are evaluated with polyherbal formulation Diasol which contains extracts of *Gymnema sylvestre*, *Eugenia jambolana*, *Foenum graecum*, *Taraxacum officinale*, *Terminalia chebula*, *Quercus infectoria*, *Cuminum cyminum*, *Emblica officinalis*, *Phyllanthrus nerui* and *Enicostemma littorale*. Subsequent 14 days treatment of 250 mg kg^{-1} Diasol to diabetic rats showed

63.4% decrease in blood sugar level, whereas 125 mg kg^{-1} glibenclamide showed 50.25% reduction of plasma glucose level.[85] Similarly, the effect of glibenclamide was also comparable with polyherbal formulation containing *Mangifera indica, Tridax procumbens and Glycosmis pentaphylla* in a ratio of 2:2:1 [86]. Diabetic rats treated with 500 mg kg^{-1} and 250 mg kg^{-1} polyherbal preparation showed decreased fasting blood serum glucose level as compared to diabetic control group due to activation of β-cells to release insulin that activates the glycogen synthase system and prevent glycogen depletion in the liver tissue. The polyherbal composition also brought back the hemoglobin and Hb1Ac levels with no observed adverse effects to liver glycogen and protein levels in blood, rather reversed the effect of STZ and nicotimanide on the liver and renal markers. Other than that, the treatment groups showed significant improvement in body weight, which indicates that polyherbal formulation and glibenclamide prevent the hyperglycemia-induced muscle wastage.[86]

It has been established that oxidative stress to the individual may lead to development of metabolic disorders, including diabetes.[87] Thus antioxidant plays role in reduction of diabetes. The ESF/AY polyherbal formulation exhibited significant antioxidant activity by showing increased levels of GSH peroxidase (GPx), GSH, SOD, CAT and thus resulted in decreased level of lipid peroxidation.[88] GSH, SOD and CAT functions as free radical scavenger to repair the radical that causes biological damage and inhibits free radical mediated lipid peroxidation, whereas GPx plays a role in detoxification of endogenous metabolic peroxides and hydroperoxides which catalyses GSH.[88]

Similarly, DiaKure's a mixture of some potent antidiabetic herbal drugs,[89] effect of 27 days treatment on serum sugar levels of STZ-induced diabetic rats has been evaluated by the same group. It has been observed that 200 and 300 mg kg^{-1} of DiaKure showed a 13% and 16.5% reduction in blood sugar at second hour, respectively whereas, glibenclamide treatment showed only 3.4% decreased blood sugar in the rats. In continuation to the study, result of diabetic rats treated with DiaKure 300 mg kg^{-1} showed reduction in serum sugar level by 12.3%, 33.3%, 49.5%, 59.7% on 7th, 14th, 21st, and 28th day of the study. Besides, significant increase in body weight was also reported at the end of the study which may be attributed to increased insulin secretion after polyherbal formulation treatment.[90] Recent toxicological evaluation have implicated that DiaKure will be safe for clinical use below the dose of 500 mg kg^{-1} as evident from the preclinical evaluations of hematological and biochemical parameters.[89]

A combination of *Memordica charantia, Gymnema sylvestre, Withania somnifera, Syzygium cumini, Asphaltum, Trigonella foenum-graceum, Phyllanthus emblica, Terminalia bellirica, Terminalia chebula, Cinnamimum zeylanicum, Pterocarpus marsupium* in a commercial product in India was evaluated for its diabetic potential by Singhal and team[91]. The authors have extensively studied the effects on different parameters on administration of this polyherbal. The antidiabetic control of this polyherbal was comparable to the commercial metformin with additional antioxidant, antilipidemic effects without causing any toxicities towards liver and/or kidney.[91]

Another polyherbal, ADJ6, a combination of six herbs, *Memordica charantia, Psidium guajava, Phyllanthus emblica, Trigonella foenum-graecum, Syzygium cumini and Gymnema sylvestre,* has shown a synergistic effect to inhibit α-amylase and α-glucosidase, whereas they suggested to evaluate further in diabetic animal models.[92]

On the other hand, polyherbal 5EPHF, consists of extracts of five medicinal plant, viz. *Aegel marmelos, Pongamia pinnata, Murraya koenigii, Aloe vera* and *Elaeodendron glaucum,* showed potential blood glucose lowering activity in normoglycemic rats and antidiabetic effect in alloxan-induced rat model. Most importantly, 200 mg kg^{-1} of 5EPHF to diabetic rats resulted in significant reduction of serum sugar, glycosylated hemoglobin, total cholesterol, TG, LDL, creatinine, urea whereas significant increased insulin level. Additionally, lipid peroxidation was also inhibited and antioxidant enzymes level were elevated in alloxanized rats.[93] Pretreatment of DRF/AY/5001 showed significant inhibition of epinephrine

induced hyperglycemia in rat model. No comparable differences observed in hypoglycemic control between 300 and 600 mg kg^{-1} for a period of 15 days, whereas the formulation showed to increase the liver glycogen content by increasing glycogenesis or decreasing glycogenolysis. Besides, DRF/AY/5001 also showed antioxidant effect by inhibiting lipid peroxidation and elevating the antioxidants enzyme in pancreatic tissue. According to the histopathological studies, the inhibitory effects on histological and biochemical parameters were comparable with glibenclamide.[94]

From the studies on polyherbal products, it is clear that polyherbal treatments are composed of several potential herbs, such combination of herbs produce hypoglycemic activity in diabetic animals, along with their antioxidant activities to improve their potential by improving endogenous antioxidants, thus prevents lipid peroxidation. Consequently, further studies need to be carried out to find out the active principles of the drug and particular mechanism of action in the prevention of diabetes.

4. Advanced herbs in clinical trial for the treatment of diabetes

Different active principles of herbal medications possess their individual pharmacological actions to the biological system and are in use since many centuries. Due to their positive role in medicinal field, they have an extensive and worldwide recognition along with their application as herbal medicines. However, lack of safety and efficacy profile of the herbs imposed to insufficient pharmacological, pharmacokinetic and clinical status on the majority of herbal medicinal products. This widespread gap in gathering the regulatory necessities in research on herbal medications further adds to the dilemma of regulation of herbal drugs.[95] In this section of the manuscript a brief description was made of the herbs for diabetic control for which clinical studies has been performed.

In continuation to our previous discussion on cinnamon, that consists of type-A procyanidin polyphenols which are responsible in preventing and treating oxidative stress and insulin resistance as well as improving cognitive function and reducing cardiovascular disease.[54, 96, 97] Tangvarasittichai et al investigated the effect of cinnamon supplementation for 60 days on insulin sensitivity, insulin resistance, level of MDA, high sensitive-C-reactive protein and total antioxidant capacity (TAC) in diabetic patients. The results showed that there was a marked reduction in insulin resistance, oxidative stress and inflammation while insulin sensitivity and TAC were markedly increased.[98] Another study by Anderson et al reported that the administration of cinnamon extract (*C. cassia*) in people with elevated serum glucose reduced 2-hour blood postprandial glucose, fasting insulin, and homeostasis model assessment for insulin resistance (HOMA-IR). Apart from that, total cholesterol level also decreased with cinnamon treatment.[24] In addition, the effects cinnamon and Caucasian whortleberry (*Vaccinium arctostaphylos* L.) were studied by Mirfeizi et al, where they reported the fasting blood glucose, 2-hour postprandial glucose and HOMA-IR scores were reduced markedly in the whortleberry group while a significant difference in body mass index (BMI) was observed in cinnamon group. However, a significant decrease of glucose control in both treatment groups was observed.[99] Another study was carried out by Gul-E-Rana et al, to investigate the effect of *Ficus racemosa* in a group of diabetic patients who were under the treatment of oral hypoglycemics. Twenty five diabetic patients were treated with 5mL of the extract of *Ficus racemosa* bark twice daily for 15 days. At the end of the study, results showed that the blood glucose level (fasting and after breakfast) after taking the herb in conjunction with oral hypoglycemic drug was significantly decreased in both female and male after 1.5 h after breakfast.[25] Antidiabetic activity of twice daily 5 g *Portulaca oleracea* L. seeds on T2DM subjects were compared with 1500mg metformin daily for 2months. They reported a significant decrease in fasting and post-prandial blood glucose, insulin, serum LDL cholesterol, TG, total cholesterol, liver enzymes (ALT, AST, and Gamma-Glutamyl Transferase), bilirubin, body weight and BMI while a significant increase in high density lipoprotein cholesterol (HDL-C) and albumin but non-significant change of alkaline phosphatase in herbal treatment group, whereas metformin group did not show any difference.[100]

Further, in a 12-week study by Pnina et al depicted the safety and efficacy of DBCare®, a traditional Indian herbal food supplement, on patients with inadequately controlled T2DM despite oral hypoglycemic treatment. The study designed to provide DBCare® or placebo tablets to the patients whose HbA1c>7.0% and were also on oral hypoglycemic drug. At the end of the study, HbA1C reduced to 0.4 ± 0.7% in the DBCare® group and 0.2% ± 0.8% in the placebo group.[101] On the other hands, there were no significant changes observed in fasting blood glucose, lipid profile, or homeostasis model assessment throughout the study or in BMI, waist circumference, or blood pressure values. However, there were more frequent hypoglycemic episodes has been observed in the DBCare group.[101] Another study has been conducted on nutritional supplement, Delphinol®, in people with moderate glucose intolerance to identify the physiologic mechanism. Delphinol® is an extract of maqui berries (*Aristotelia chilensis*), which contains anthocyanins and delphinidins. They reported that there was a significant decrease in postprandial glucose and insulin as compared to placebo following consumption of Delphinol®, suggesting improvement of insulin sensitivity of the cells towards endogenous hormone.[102]

Curcumin is proposed to be used as one of the interventions in pre-diabetes therapy to prevent the progression of T2DM due to its proven benefits and safety profile.[103] In the randomized, double-blinded, placebo-controlled human clinical trial study conducted by Chuengsamarn et al, none of the subjects who treated with curcumin for a period of 9 months developed T2DM; whereas 16.4% of subjects from placebo group were found to develop T2DM. Furthermore, in the last visit (9 months), the subjects treated with curcumin were demonstrating better overall beta-cells function by having lower values of C-peptide and higher values of HOMA-β compared to placebo subjects. Additionally, the curcumin-treated subjects also produced significant higher level anti-inflammatory cytokine, adiponectin as compared to the placebo subjects, where increased level of adiponectin might play a positive role in reducing the beta-cells inflammation and hence protect the beta-cells from degradation.[26] Furthermore, a randomized controlled trial has been conducted on Sajabalssuk (*Artemisia princeps* Pampanini) to a group of subjects with pre-diabetes for 9 weeks. Sajabalssuk has positive effect on lowering their fasting blood glucose (−16.51± 2.78%, $p < 0.05$) and HbA1c (−7.81± 3.39%, $p < 0.05$) significantly compared to placebo and positive-control group (Pinitol, 1140 mg/day). Additionally, Sajabalssuk treatment also showed reduction in insulin resistance and improvement on plasma non-HDL as well as HDL cholesterol levels in pre-diabetes patients significantly as the secondary outcomesn.[104] A recent randomized double-blind placebo-controlled clinical study with green cumin capsule for a 8 week long study suggested significant reduction of serum insulin level together with increased insulin sensitivity, The authors has also observed that cumin supplement could also control inflammatory mediators, TNF-α and hsCRP.[30]

To support the antihyperglycemic effect of cinnamon in pre-clinical studies, clinical study has been conducted in diabetic patients. The study was designed to give 2 g of cassia cinnamon daily for 84days. The results demonstrated a statistically significant reduction in mean HbA1c (-0.36%, $p < 0.005$) as compared to the placebo group. Another additional outcome in this study showing decreased values of systolic (-4 mmHg, $p < 0.001$) and diastolic (-4 mmHg, $p < 0.001$) blood pressure in patients.[105] However, by consuming large amounts of cassia cinnamon (suggested dosage range is 1–6 g per day) might possibly unsafe since cinnamon contains certain amount of coumarin, which might cause reversible hepatotoxicity.[106] In short, cinnamon should be used in caution for those who are at risk of having liver disease.[27] Similarly, to support the antidiabetic and antihyperlipidemic properties of *Aloe vera* in human subjects, Yagi et al, displayed results of decreased fasting blood glucose and TG levels in diabetic patients after oral administration of high molecular weight *A. vera* fractions consisting verectin and acemannan in a design with TID dosing for 12 weeks. *A. vera* fraction showed its ability in limiting the absorption of water in intestine and bowel movement stimulation which supports the previous reports of *A. vera*.[107, 108] The laxative effect of *Aloe vera* might due to its active metabolites which inhibit Na^+/K^+-ATPase activity in

water reabsorption mechanism that takes place in large intestine. In short, *Aloe vera* can be safely considered as an alternative in treating diabetic patients with comorbidity of hyperlipidemia as well as with constipation problem.[28]

The leaves of *Olea europaea* L (olive) is a prevalent botanical medicine in Europe and Mediterranean regions to combat diabetes, where the traditional people chewing it and/or consume as tea. The presence of antioxidant and phenolic compounds, hydroxytyrosol, oleuropein, oleuropein aglycone, and tyrosol, appeared to have contributed to the biological effects of olive tree extracts. In a controlled randomized clinical trial, HbA1c and fasting plasma insulin levels were significantly lowered in diabetic patients (8.0%–1.5% & 11.3–4.5, respectively) treated with once daily oral doses of 500 mg olive leaf extract tablet as compared to the placebo group (8.9%–2.25% & 13.7–4.1 respectively) after 14 weeks. STZ-induced diabetic animal models receiving olive leaf extract has shown substantial decrement in the digestion and absorption of starch as compared to untreated intestine, suggesting that the possible hyperglycemic mechanism may be by inhibition of disaccharide digestion at the intestinal mucosa.[109] The randomized controlled trial of *Cornus officinalis* extracts and its active compounds – morroniside, ursolic acid and loganin suggested improvement of diabetes-induced damages and complications *via* different mechanisms. Ursolic acid plays its main role in ROS scavenging activity and α-glucosidase inhibitory activity whereas loganin achieved its hypoglycemic effects mainly by stimulating glucose uptake. Interestingly, the diabetic mice in this study showed the least weight loss by using dual-regimen of ursolic acid and loganin.[110]

Other clinical studies with resveratrol has been proven to its potential diabetic control property in human patients. Administration of resveratrol as dietary supplement (150 mg dL^{-1}) in obese patients for 30 days, showed suppression on effective postprandial glucagon responses.[111] In another clinical study in sixty-two T2DM patients, where one group was treated with oral hypoglycemic agent whereas another group received commercial oral hypoglycemic agent along with resveratrol at a dose of 250 mg.day^{-1} for three months. Oral hypoglycemic along with resveratrol group showed an improvement in HbA1c suggesting an enhancement of glycemic control in T2DM patients.[112] Furthermore, a separate clinical study with resveratrol 2 × 5 mg for four weeks in T2DM patients showed a reduction in insulin resistance through amelioration of oxidative stress.[44, 113]

Lastly, the availability of herbal porridge of *Scoparia dulcis* leaf extract has remedial action in T2DM due to its anti-hyperglycemic effects by lowering the fasting blood glucose and HbA1c levels. The anti-hyperglycemic effect was supported by previous study of the authors, where the STZ-induced diabetic Wistar rats showed decreased level of Hb1Ac, significant improvement in body weight ($p < 0.05$) following administration of *Scoparia dulcis* porridge with dried leaf of 200 mg kg^{-1} body weight per day for 3 months.[114] Additionally, in the recent randomized cross-over clinical trial in mild and moderate T2DM patients also showed decreased levels of fasting blood glucose and HbA1c both study periods. Hence, *S. dulcis* leaf porridge can be suggested as better breakfast option for diabetic patients due to its blood glucose-lowering effect, medium glycemic index (GI) and its rice-based fulfilling effect compared to tablets.[23]

As a conclusion, treating pre-diabetes or diabetic patients with herbals might be an alternative choice of oral hypoglycaemic effects since it is not only showing benefit in lowering the blood glucose but also helps in improving the lipid profile, antioxidant role, control of hypertension, etc. Although thorough toxicological studies need to be carried out before the extracts are incorporated as an adjunctive agent in the management of diabetes.

5. Marketed herbal medications for diabetic treatment

Enormous research of herbal products for the remedy of diabetes has developed several antidiabetic products in the market worldwide. Few of them include, Diabecon®, Glyoherb, Diabeta Plus, etc. Diabecon® is a product by Himalaya Herbal Healthcare, is one of the well marketed polyherbal formulation in diabetes care.[115] Composion of the formulation has been depicted in Table 5. Aside from promoting β-cell repair and regeneration, it also protects the β-cells from oxidative stress and increases C-peptide levels. It mimics insulin actions by reducing HbA1c level, normalizing microalbuminuria and regulating the lipid profile. Diabecon® also possess antioxidant properties and claims to minimize complications in diabetic patients.[115] Diabecon was compared to Hyponidd, Inolter and Cogent DB based on their effectiveness in reducing HbA1c,[116] where Diabecon® showed an increased fasting insulin and C peptide levels compared to the other agents.[116] Similarly, Glyoherb is also a polyherbal antihyperglyceamic formulation that has additional properties of antihyperlipidemic and antioxidant properties. It is marketed to prevent, delay or improve complications such as retinopathy, neuropathy and retinopathy.[115] Results in animal testing suggested that it increases glucose tolerance and lowers blood glucose levels in STZ-induced type 1 diabetic rats.[117] Additionally, treatment with Glyoherb has shown to reduce serum cholesterol, TGs, VLDL, LDL levels compared to control groups but is not as effective as glibenclamide. It had also shown to increase HDL levels[117] Glyoherb did not exert any toxic effects in STZ-induced impaired kidney and liver functions rather it improved the kidney and liver functions.[117] On the other hand, Diabeta Plus is also an antidiabetic polyherbal formulation that has additional properties of potent immunomodulator, antihyperlipidemic, anti-stress and is hepatoprotective.[115] Monotherapy of Diabeta works by attacking various factors that can precipitate diabetic condition thus preventing or delaying the complications in pre-diabetics.[115] It helps to decrease resistance when used in conjunction with oral hypoglycaemic agents, claims to relief complaints of pruritus, pain and polyuria caused by diabetes mellitus.[115]

6. Conclusion and future trends

The use of plants is one of the ancient traditions, being imposed to current society in the urge to evaluate the mechanism of their underlying pharmacological action and their associated benefits and adverse effects. Thus, use of herbal medicines is still continued in modern society for the prevention, wellbeing and treatment of diabetes. Commercially produced drugs are largely derived from plants and form the mainstream of today's modern medicine. Therefore, many herbs have shown to have antidiabetic activity by regulating insulin secretion, insulin sensitivity to the cells, glucose abruption, etc. in order to improve the glycemic control of the patients. Addition to the glycemic control, some of the herbs depicted effectiveness in the control of cardiovascular complications by reducing TG, cholesterol levels, and BMI. Herbal medicine are always preferred treatment options by patients or as adjunctive to conventional treatment for diabetes due to the belief on the soil and affordability, thus laboratory research has reached to the bedside of the patients though clinical trials and marketed formulations. However, the fast growth of the ethnopharmaceutical field in the control of diabetes urgently requires validated testing protocols in order to evaluate the quantity and quality of active pharmaceuticals present in the final products, which will finally need to be tested in human subjects *via* well designed clinical trials, confirmed and certified by the concerned regulatory authorities of the country to build confidence of the consumers for the safety and efficacy of the herbal formulations.

Disclosures

There is no conflict of interest and disclosures associated with the manuscript.

Conflict of interest

The authors declare no conflict of interest.

Declare of interest

We are declaring that all the listed authors have read and approved the submitted manuscript. This manuscript/data, or parts thereof, has not been submitted for possible publication to another journal or that the work has previously been published elsewhere.

Footnotes

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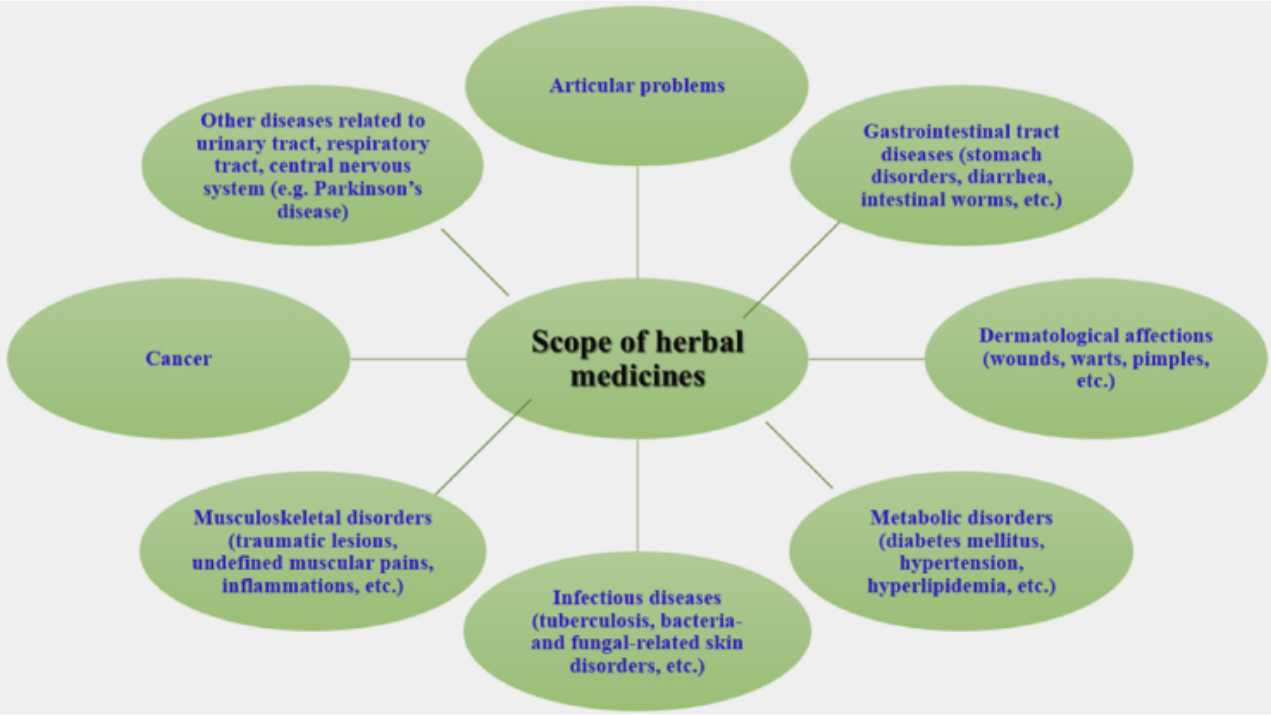
Figures and Tables

Fig. 1



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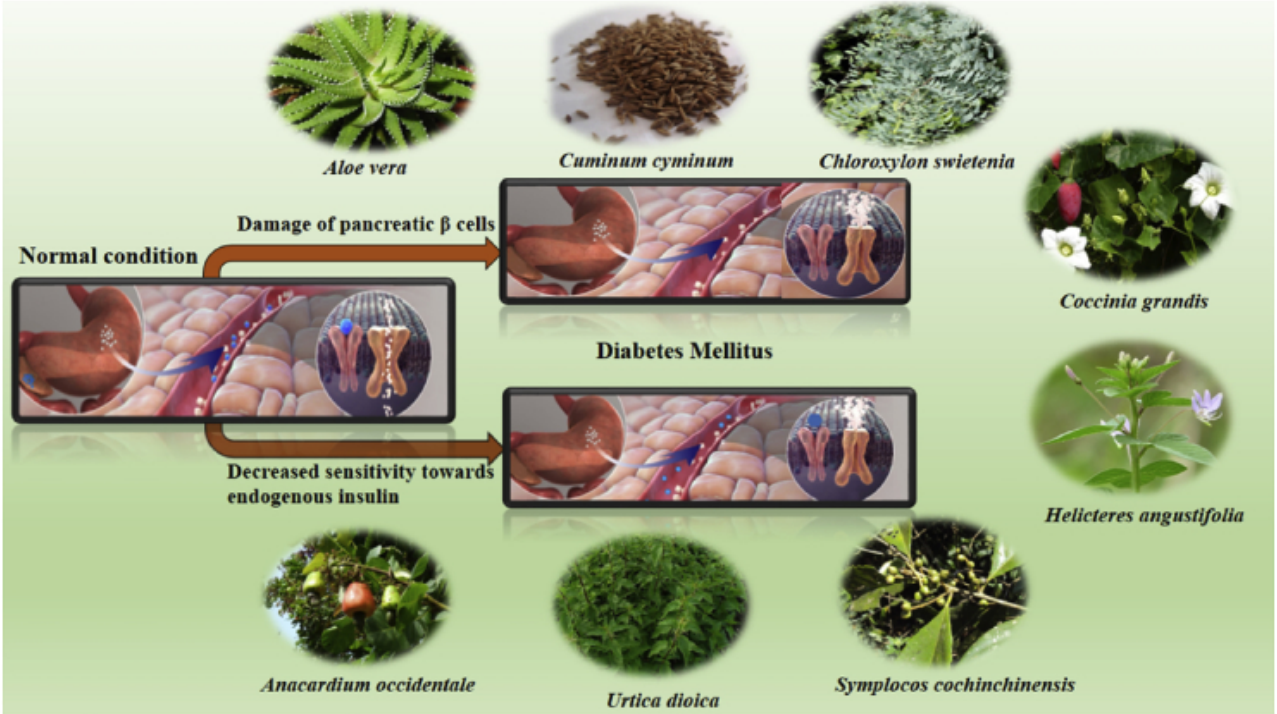
The traditional utilization of herbal medicines in different field of medical field.

Fig. 2



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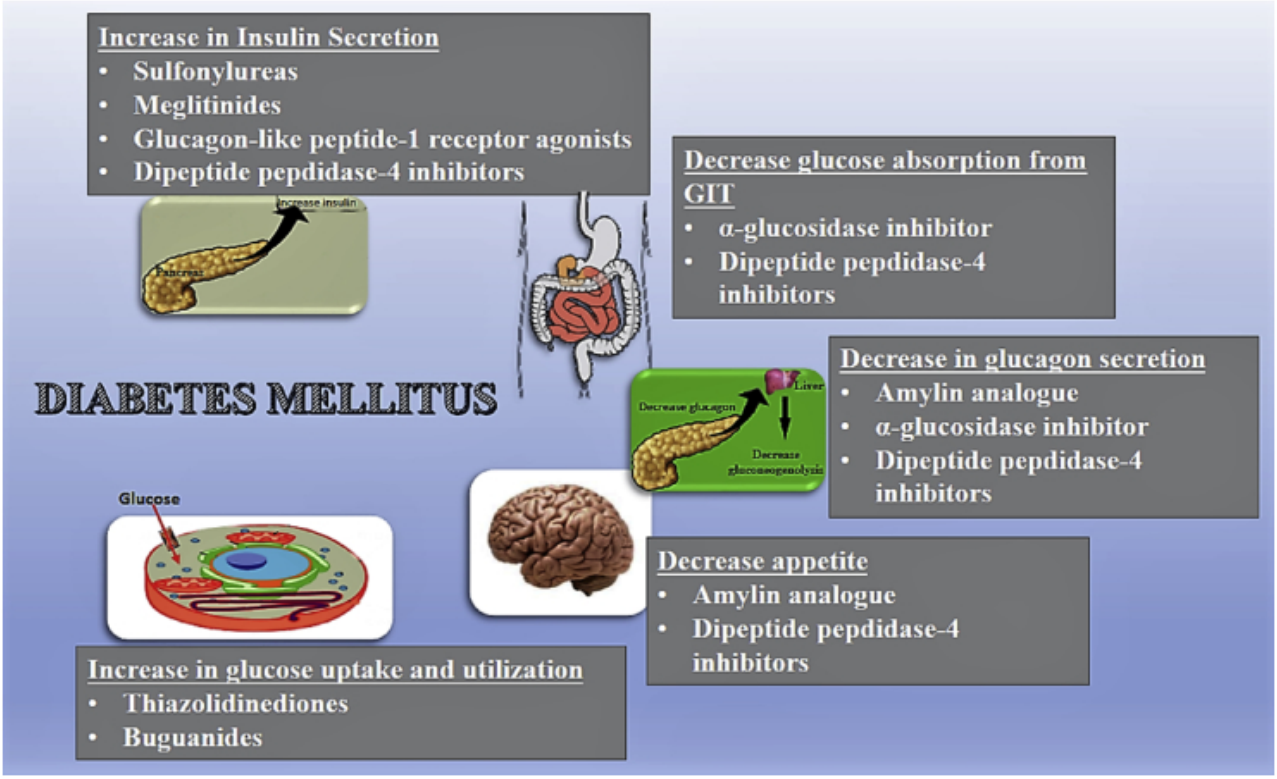
Condition to develop diabetic mellitus disease and herbal approaches in the improvement of insulin secretion or improvement in insulin resistivity of the body cells.

Fig. 3



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Mechanism of actions of different anti-diabetic agents in the treatment of high glucose level in the circulation.

Table 1

Herbals in the management of plasma glucose level, acting through secretogogues mechanism or by improvement of insulin sensitivity to the cells.

Botanical name	Part used	Type of extract	Cases	Animal model	Outcome (effects)
Afzelia africana	Stem bark	Aqueous extract	STZ-induced diabetes	Wistar rats	The blood glucose level was significantly reduced in a dose-dependent manner with the best result obtained at 200 mg kg^{-1} body weight per day,
Urtica dioica	Leaf	Hydroalcoholic extract	Fructose-induced insulin resistance	Wistar rats	The blood glucose and FIRI in hyperglycemic rats were reduced in a dose-dependent manner with the best result obtained at 200 mg kg^{-1} body weight/day. The plasma insulin level was also found to be reduced in treatment group.
Chloroxylon swietenia	Bark	Methanolic and aqueous extract	STZ-induced diabetes	Male albino Wistar rats	Diabetic rats in treatment group showed moderate reduction in blood glucose and glycosylated haemoglobin levels, in addition, plasma insulin were elevated. The outcomes of methanolic extract were comparable to glibenclamide.
Anacardium occidentale	Leaf	Ethanol extract	STZ-induced diabetes	Female albino Wistar mice	Blood glucose was decreased 147.67 ± 6.09 mg dL^{-1} to 123.83 ± 2.87 mg dL^{-1} after 30 days treatment with plant extract. At the same time, glycosylated haemoglobin level, FIRI and serum insulin level were decreased in treatment group.
Forsythia suspensa	Fruit	Ethyl acetate fraction of methanol extract	STZ-induced diabetes	Male Kunming mice	Blood glucose was significantly decreased; insulin secretion and glucose tolerance were significantly increased.
Symplocos cochinchinesis	Bark	Ethanol extract	High fructose and saturated fat induced insulin resistance	Male albino Sprague Dawley rats	Blood glucose level was significantly reduced at day 20.
Pleurotus ostreatus	–	Aqueous extract	High fat diet and	Male Wistar	Treatment group showed significant reduction in fasting blood glucose level, FINS and HOM-IR

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Table 2

List of medicinal herbs affecting the absorption of carbohydrates from the gastrointestinal environment by inhibiting α-glucosidase and α-amylase.

Herb	Botanical name	Part used	Type of extract	Chemical constituent	Animal model	Outcome (effects)
Leafflower	*Phyllanthus urinaria*	Leaves	50% aqueous methanolic extract	Corilagin, gallic acid and macatannin B	–	Corilagin, gallic acid and macatannin B demonstrated low inhibitory activity against amylase (21%, 23% and 33% respectively in 1 mmol.L^{-1} concentration)
Cinnamon	*Cinnamomum zeylanicum*	Bark	Methanol extract	Tannins, flavonoids, glycosides, terpenoids, coumarins and anthraquinones	STZ-induced diabetic rats	*In vitro*: Inhibition of yeast and mammalian α-glucosidase (IC_{50} = 5.83 μg ml^{-1} & 670 μg ml^{-1} respectively) *In vivo*: Decreased postprandial hyperglycemia by 78.2% and 52.0% compared to normal rats
Black seed	*Nigella sativa*	Seeds	Aqueous extract	Flavonoids, unsaturated fatty acids, nigellone, thymoquinone (TQ), p-cymene and carvone	–	*In vitro*: Inhibition of sodium-dependent glucose transport *In vivo*: Chronic treatment improved glucose tolerance and reduced body weight similarly as metformin
China aster	*Callistephus chinensis*	Flower	70 % ethanol extract	Apigenin, apigenin-7-O-*β*-D- glucoside, hyperin, kaempferol, kaempferol-7-O-*β*-D- glucoside	–	Inhibition of *α*-glucosidase by quercetin (IC_{50} = 2.04 μg ml^{-1}) comparable to that of acarbose (IC_{50} = 2.24 μg ml^{-1})

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Table 3

Multimodal activities of listed herbs in the effective control of diabetic symptoms.

Herb	Botanical name	Part used	Type of extract	Cases	Outcome (effects)
Garlic	*Allium sativum* L	Garlic	Ethanol	Streptokinin induced diabetic rats	Stimulate the secretion of insulin from pancreatic B cells, sparing insulin effect, increasing glucose utilization, hydroxy methyl glutaryl CoA reductase inhibitor, antioxidant, anti-inflammatory
Ginseng	*Panax Ginseng*	Berry	Methanol	Streptokinin induced diabetic rats	Enhancement of insulin sensitivity, stimulate insulin signaling, increase translocation of GLUT4, antioxidant
Aloe vera	*Aloe Barbadensis Miller*	Leaves	Methanol	Streptokinin induced diabetic rats	Increase secretion of insulin from pancreatic beta cells., antioxidant, anti-inflammatory, inhibiting pancreatic α-amylase activity, increase insulin sensitivity
Bitter Melon	*Momordica charantia*	Fruit	Aqueous extract	Alloxan-induced diabetic mice	Stimulate glucose utilization, protection of B cell, downregulate MAPKs and NF-κB, upregulate PPAR, modulation of PTP1B, enhance glucose uptake, stimulate insulin secretion
Fenugreek	*Trigonella foenum-graecum*	Seed	Methanol	STZ-induced diabetic guinea pigs	Prevent catabolism, antioxidant, modulating insulin secretion, regeneration of pancreatic B cell, improve glucose utilization, and slow down glucose absorption.
Huanglian	*Coptis chinensis*	Rhizome	Ethyl acetate	High fat diet induced diabetic mice	Regeneration of pancreatic cell, stimulate fatty acid oxidation, inhibit lipogenesis, increase glucose uptake
Madagascar periwinkle	*Catharanthus roseus*	Seed	Methanol	Streptokinin induced diabetic rats	Increase glucose uptake and glucose utilization, antioxidant, increases the insulin sensitivity, inhibit alpha glucosidase
Curry tree	*Murraya koenigii*	Leaves	Methanol	High fat diet induced obesity and diabetic rats	Antioxidant, antiobesity, increase insulin sensitivity, alpha glucosidase inhibitor
Holy basil	*Ocimun tenuiflorum*	Leaves	Methanol	Streptokinin induced	Increase glucose uptake, antioxidant, increase insulin sensitivity, regeneration of pancreatic

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Table 4

Composition of polyherbal formulations in the treatment of diabetes mellitus.

Polyherbals	Botanical composition (part used)
GSPF kwath[81]	*Gymnema sylvestre (Retz.) R.Br.* (leaves), *Syzygium cumini (L.) Skeels* (seeds), *Phyllanthus emblica* L. (fruit), *Curcuma longa* L. (rhizome), *Pterocarpus marsupium Roxb.* (Heart-wood), *Terminalia chebula Retz.* (fruit), *Cassia fistula* L. (fruit), *Picrorhiza kurroa Royle ex Benth.* (rhizome), *Swertia chirata* (seeds), *Terminalia bellirica* (fruit)
Polyherbal formulation[82]	*Ferula assafoetida*, *Annona squamosal*, *Zingiber officinale* (juice), *Gymnema sylvestre* (leaves), *Tamarindus indica* (seeds), *Azadirachta indica*, *Trigonella foenumgraecum* (seeds), *Moringa oleifera* (roots), *Aegle marmelos* (seeds), *Cajanus cajan* (leaves)
Polyherbal formulation[118]	*Salacia roxburghii* (root and fruits), *Salacia oblonga* (root and fruits), *Garcinia indica* (fruits and seeds), *Lagerstroemia parviflora* (bark)
SMK001[84]	*Coptis chinensis, Trichosanthes kirilowii*
DIASOL[85]	*Eugenia jambolana, Foenum graecum, Terminalia chebula, Quercus infectoria, Cuminum cyminum, Taraxacum officinale, Emblica officinalis, Gymnema sylvestre, Phyllanthrus nerui, Enicostemma littorale*
DiaKure[89], [90]	*Vetiveria zizanioides* (root), *Hemidesmus indicus* (rhizome), *Strychnos potatorum* (seed), *Salacia reticulata* (bark), *Holarhena antidysenterica* (seed), *Cassia auriculata* (bark), *Trigonella graecum* (seed), *Acacia catechu* (bark)
ESF/AY[88]	*Aegle marmelos* (leaves), *Bambusa arundinacee* (leaves), *Eruca sativa* (leaves), *Aerva lanata* (aerial), *Catharanthus roseus* (aerial), *Ficus benghalensis* (bark), *Salacia reticulate* (bark), *Syzygium cumini* (bark)
DRF/AY/5001[94]	*Gymnema sylvestre* (leaves), *Syzygium cuimini* (seed), *Pterocarpus marsupium* (stem), *Momordica charantia* (seed), *Emblica officinalis* (fruit), *Terminalia belirica* (fruit), *Terminalia chebula* (fruit), *Shudh Shilajit*

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Table 5

Composition of marketed polyherbal formulations used in the treatment of diabetes.

Polyherbal Formulations	Ingredients
Diabecon[119]	*Sphaeranthus indicus, Tribulus terrestris, Tinospora cordifolia, Triphala, Curcuma longa, Rumex maritimus, Aloe vera, Swertia chirata, Ocimum sanctum, Gymnema sylvestre, Sphaeranthus indicus, Glycyrrhiza glabra, Commiphora wightii, Phyllanthus amarus, Boerhavia diffusa, Piper nigrum, Tribulus terrestris, Pterocarpus marsupium, Syzygium cumini, Tinospora cordifolia, Berberis aristata, Gmelina arborea, Asparagus racemosus, Abutilon indicum, Casearia esculenta, Berberis aristata, Gossypium herbaceum.*
Glyoherb[115]	Gudmar (*Gymnema sylvestre*), Mahamejva, Katuki (*Picrorhiza kurrooa*), Chirayata (*Swertia chirata*), Karela (*Momordica charantia*), Indrajav (*Holarrhena pubescens*), Amala (*Phyllanthus emblica*), Gokshur (*Tribulus terretris*), Haritaki (*Terminalia chebula*), Jambu bij (*Eugenia Jambolana*), Methi (*Trigonella foenum-graecum*), Neem, Chandraprabha, Arogyavardhini, Haridra (*Curcuma longa*), Bang Bhasma, Devdar, Daruhaldi (*Berberis aristata*), Nagarmotha (*Cyperus scariosus*), Shuddha Shilajit, Galo
Diabeta Plus[120]	Vijayasar (*Pterocarpus marsupium*), Gurmar (*Gymnema sylves*), Jamun (*Syzygium cumini*), Karela (*Momordica charantia*), Shilajit (Asphaltum), Madagascar periwinkle (*Catharanthus roseus*)