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Preventive and therapeutic aspects of selected herbal medicines in diabetes mellitus

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Summary. Diabetes mellitus is an endocrinological metabolic disorder in which patients have elevated blood glucose levels compared to normal healthy individuals. Type 1 and type 2 diabetes mellitus are the two major forms of diabetes. Type 2 diabetes mellitus accounts for more than 95% of the entire diabetic population. Incidence and prevalence of type 2 diabetes mellitus is increasing globally, especially in developing countries. Diabetes mellitus includes various complications associated with deterioration of function in the kidneys, retina, heart, and neurons. Complications associated with type 2 diabetes are risk factors for cardiovascular disease. Taking care of treatment cost, it is necessary to explore and understand the current therapeutic aspects of herbal medicinal plants for the prevention of diabetes. The current review summarizes updated information related to the most widely used medicinal plants used in the treatment and management of type 2 diabetes. Additionally, this review discusses promising results and challenges associated with herbal medicine. Herbal plants are a good alternative for patients with type 2 diabetes and remains unique sources for future drug discovery.

Key words: Herbal medicine, anti-hyperglycemic activity, diabetes mellitus, phytochemicals

Introduction

Diabetes mellitus is derived from the Greek words 'diabaino,' which means 'to go through,' and 'mellitus,' which means 'sweet or sugar'. Diabetes mellitus is considered as a chronic metabolic syndrome characterized by an abnormally high level of glucose in the blood and excretion of sugar in the urine. In other words, diabetes mellitus is a metabolic disorder with multiple etiologies characterized by chronic hyperglycemia, with disturbances in carbohydrate, fat, and protein metabolism, resulting from defects in either insulin secretion, insulin action, or both (1). Diabetes is a major global health problem with an estimated rise in its prevalence from 171 million in 2000 to 366 million in 2030, with a majority still undiagnosed (2). Diabetes mellitus is one of five major causes of death worldwide. Age-adjusted prevalence of diabetes among adult men doubled from 1980 to 2014 (4·3% to 9·0%), and age-adjusted prevalence of diabetes among adult women has increased by 60% (5·0% to 7·9%) (3).

Long-term complications of type 2 diabetes mellitus include retinopathy with potential loss of vision, nephropathy leading to renal failure, peripheral neuropathy with risk of foot ulcers, amputation, and charcoal joints. Patients with diabetes mellitus have higher incidences of cardiovascular, peripheral vascular, and cerebrovascular disease (4). Figure 1 describes the categorization of diabetic complications in the form of a ray diagram. Diabetic complications are chronic in nature affects almost every important organ in the body, and pose a threat to adult and elderly populations. Oxidative stress is mediated mainly by hyperglycemia-induced free radicals, which contributes to the development of diabetes and its complications (5).

According to the American Diabetes Association (ADA), both patients and primary health care have insufficient access to diabetic care since there is no definite cure for diabetes mellitus, and no satisfactory effective drugs are available to cure diabetes. Western medicines such as sulfonylurea and biguanides used for the treatment of diabetes are expensive and

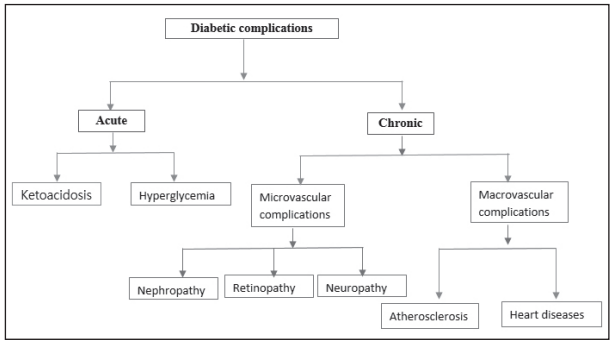

Figure 1. Complications of diabetes mellitus

thus not feasible for every patient due to their undesirable side effects. Sulfonylurea exhibits toxic effects such as heartburn, vomiting, skin rashes, etc. The action of chloropropamide results in water retentions and dilutional hyponatremia. Long-term biguanides (metformin) consumption may initiate gastrointestinal effects, anorexia, vomiting, and B_{12} malabsorption (6). Insulin is the most common therapy for diabetes but does not reinstate permanent glucose homeostasis. Insulin therapy has a profound effect on glucose level but is ineffective with regards to a number of aspects such as its ineffectiveness as an oral drug, short half-life, need for continual refrigeration, and hypoglycemic effect upon high dosage (7).

As a result, there is an intense need to identify natural resources and study their activities on different targets in order to develop new anti-diabetic therapeutics as effective, easily accessible, and cheap means to prevent diabetes mellitus. An increasing number of people now use dietary and herbal supplements for treatment of diabetes mellitus (8). The impact of alternative medicine has garnered the attention of many researchers worldwide. Even the World Health Organization (WHO) has declared herbal plants as effective therapeutic agents, especially in areas lacking safe modern drugs (9).

In this review, we have selected nine herbal plants, namely *Momordica charantia, Swertia chirayita, Gymnema sylvestre, Trigonella foenum, Eugenia jambolana, Aegle marmelose, Terminalia chebula, Emblica officinalis,* and *Zingiber officinale,* and described their anti-diabetic as well as antioxidant properties with the aim of developing interest in using herbal therapeutics as a preferred therapy for the prevention and treatment of diabetes.

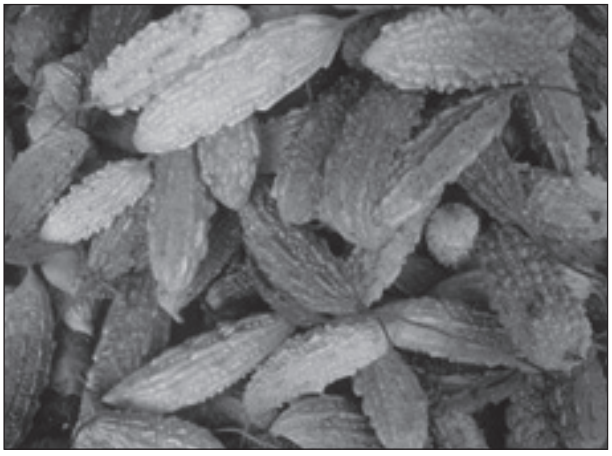

Figure 2. *Momordica charantia* (Bitter Gourd)

Traditional medicinal plants used in the management of type 2 diabetes

Momordica charantia (Fig. 2) is a useful vegetable plant and common traditional remedy for diabetes. This is a potent nutrient-rich plant composed of various advantageous compounds such as bioactive chemical compounds, vitamins, minerals, and antioxidants for the treatment of wide range of ailments (10, 11). Charantin, a bioactive compound, is similar to cucurbitane-type triterpenoid isolated from *Momordica charantia,* which shows promising results for the prevention and management of diabetes (12)**.** Several studies have established the anti-hyperglycemic and hypoglycemic effects of various extracts of *Momordica charantia* in both animal models and human. The effective dose of bitter gourd was reported to be 2000 mg/day in patients with type 2 diabetes and 400-600 mg/kg body weight of diabetic rats (13, 14).

Momordica charantia exhibits anti-diabetic activities mediated by several mechanisms such as stimulation of insulin release from isolated beta cells (15), utilization of peripheral and skeletal muscle glucose (16), and curtailing of gluconeogenic enzymes (17) (Table 1). Sarkar *et al*. (1996) demonstrated the hypoglycemic activity (26%) of alcoholic extract of *Momordica charantia* (18). It has also been reported that *Momordica charantia* with exercise reduces blood glucose levels in KK-Ay hyperinsulinemic mice, an animal model of type 2 diabetes through elevation of glucose transporter type 4 (GLUT4) protein content (19).

Table 1. List of selected anti-hyperglycemic medicinal plants used in the treatment of diabetes mellitus

Botanical name	Family	Common name/ or Hindi name	Active compounds	Plant used part	Widely grown	Mode of action
Momordica charantia L.	Cucurbitaceae.	Bitter gourd, Karela.	Polypeptide p, phenols, charantin, flavonoids, isoflavones, terpenes, anthraquinones and glucosinolates.	Extracts of fruit pulp, seed, leaves and the whole plant.	Asia, Africa, and the Caribbean.	Lower blood glucose due to their insulin-like chemical structures (17).
Swertia chirayita L.	Gentianaceae.	Chirayata, Chiraita, Kairata.	Ophelic acid, sawertiamarin, swerchirin, and amarogentin.	Leaves or Whole plant.	India, Nepal, Bhutan, Pakistan, Bangladesh and Tibet. Himalayan Ranges.	Stimulates insulin release from islets (25).
Gymnema sylvestre Schult.	Apocynaceae.	Cowplant, Gudmar Patra, Madhunashini.	Gymnemic acid, triterpenoids, saponins.	Leaves.	Central and western India, tropical Africa and Australia.	Stimulate βcell regeneration (27), stimulation of insulin release (31).
Trigonella foenum graceum L.	Fabaceae.	Fenugreek, Methi dana.	Diosgenin, 4-hydroxyleucine.	Fruit /Grains.	India and Southeastern Europe.	Regeneration of islets cells (42), elevated serum insulin levels (43), insulin sensitivity (37).
Eugenia jambolana Lam.	Myrtaceae.	Jamun, Java plum, black plum Indian blackberry.	Mycaminose extracted from the seeds of Jamun, alkaloid, flavonoid jambosine, and glycoside jambolin or antimellin.	Seed, pulp and bark.	India, Bangladesh, Pakistan, Nepal, Sri Lanka, Malaysia, the Philippines, and Indonesia tropical as well as in Subtropical zones.	Stimulate synthesis of insulin from the residual beta cells (49), unregulated the glucose transporter GLUT-4 and activated the peroxisome proliferator-activated receptor gamma (50).
Aegle marmelos (L.) Corr.	Rutaceae.	Bilva patra, bael tree.	Alkaloids, among which aegline, marmesin, marmin and marmelosin.	Leaves and fruits.	India, Pakistan, Bangladesh, Sri Lanka, Burma, and Thailand.	Leaf and callus extracts possess the ability to stimulate the insulin secreting cells of pancreas (56).
Terminalia chebula Retz.	Combretaceae.	Harad.	Tannins, shikimic acid compounds, triterpenoids, ellagic acid, gallic acids.	Fruit.	South Asia from India and Nepal east to southwest China and Sri Lanka, Malaysia, and Vietnam.	Terminalia chebula extract activates the remnant βcells in the pancreas and increased the level of insulin and C-peptide, exhibits a beneficial effect on glycoproteins (59).
Emblica officinalis Gaertn	Euphorbiaceae.	Indian Gooseberry, Amalika, Amla.	Tannins, apigenin, gallic acid, ellagic acid, chebulinic acid, quercetin), corilagin, isostrictiniin, methyl gallate, and luteolin.	Fruit.	India, tropical and subtropical regions such as Malaysia, China, Sri Lanka, Southeast Asia.	Enriched fraction of its tannoids are effective in delaying development of diabetic cataract in rats(63) , polyphenols, tannins, alkaloids, and phenols. of Emblica officinalis appears to be mediated by direct insulin-like or insulin mimetic effect in diabetic conditions (64).
Zingiber officinale Roscoe	Zingiberaceae.	Ginger, Adrak, Singabera.	Mono, and sesquiterpenoids, zingerone and gingerols.	Rhizome.	India. South and southeast Asia, Sierra Leone and Nigeria, Latin America, the Caribbean and Australia.	Islet cell protection and increased insulin receptor signaling (68).

Figure 3. *Swertia chirayita* (Chiretta)

Figure 4. *Gymnema sylvestre* (Periploca of the woods)

Swertia chirayita (Fig. 3) is a medicinal plant indigenous to India, Nepal, Bhutan, Pakistan, Bangladesh and Tibet. The phytochemical Swertiamarin, an active compound isolated from *Swertia chirayita,* was shown to have anti-diabetic properties *in vitro* (20). Oral administration of the ethanolic extracts (95%) and hexane fraction of *Swertia chirayita* (10, 50 and 100 mg/kg) to normal, glucose-fed, and streptozotocin (STZ) induced diabetic rats significantly lowered blood glucose in all groups of animals (21). Alam *et al* (2011) evaluated the hypoglycemic effect of whole *Swertia chirayita* plants and leaves (22).

In a prior study, swerchirin (a xanthone isolated from hexane fraction of the plant) resulted in significant lowering of blood sugar in fasting, postprandial and tolbutamide pre-treated albino rats (23). Force feeding of swerchirin (35 and 65 mg/kg i.v) to STZ diabetic rats (50 mg/kg) showed a significant anti-hyperglycemic effect at 0, 1, 3, and 7 h after administration in both healthy as well as STZ-induced rats (35 mg/kg) but not in the group treated with STZ (65 mg/kg) (24). Sexana *et al* (1993) demonstrated that crude/impure swerchirin lowers blood glucose by stimulating insulin release from pancreatic β cells. Glucose uptake and glycogen synthesis by muscle (diaphragm) were increased in serum from swerchirin-treated rats *in vitro*. Swerchirin treatment (100, 10, and 1 mM concentration) was shown to greatly enhance glucose (16.7 mM) stimulated insulin release from isolated islets (25).

Gymnema sylvestre (Fig. 4) a woody climber of the Asclepiadaceae family, has well known therapeutic potential and plays a key role in Ayurvedic medicine for diabetic patients. Srivastava, *et al.* reported that treatment with *Gymnema sylvestre* leaf extract corrected the hyperglycemia and enhances the survivability in moderately diabetic rats (26).

Leaf extracts of *Gymnema sylvestre* consisting of the active compound gymnemic acid were shown to stimulate β-cell regeneration and anti-diabetic activity in treated Wister rats (27). Another study demonstrated the treatment of leaf extract of *Gymnema sylvestre* (400 mg/day) to 27 type 1 diabetic patients and observed enhanced endogenous insulin presumably via regeneration of residual β cells (28). Mechanisms by which *Gymnema sylvestre* produces its anti-diabetic effects include recovery of β cells (29), suppress the elevation of glucose level (30), and stimulation of insulin release (31). In Brazil, capsules containing dried powdered leaves of *Gymnema sylvestre* are highly commercialized in pharmacies and stores and are by far the most popular commercial herbal product for treatment of diabetes. However, another study suggested that dried powdered leaves or any other form of *Gymnema sylvestre* require further study before being recommended for commercialization to treat diabetes and hyperlipidemia (32). Tiwari *et al* (2014) in a recent review updated information related to the phytochemistry and pharmacological activities of *Gymnema sylvestre* and reported modern medications made from this herb (33).

Fenugreek (*Trigonella foenum-graecum* L.) (Fig. 5), one of the oldest medicinal plants, mainly originated from the Middle East, China, Southeastern Europe, and India. The hypoglycemic effect of fenugreek

Figure 5. *Trigonella foenum graceum* (Fenugreek)

Figure 6. *Eugenia jambolana* (Blackberry)

seeds has been reported in experimentally-induced diabetic rats, mice, and healthy volunteers (both type1 and type 2 diabetes) (34, 35). Aqueous extracts of fenugreek seeds and leaves have been shown to possess hypoglycemic activity and are non-toxic (36), but there has been no detailed study elucidating the mechanisms of action of these extracts at the cellular and molecular level. However, extensive *in vitro* activity of fenugreek was evaluated in 3T3 L1 adipocytes. It was found that lyophilized fenugreek powder dissolved in phosphate- buffered saline (PBS) had a marked effect on glucose uptake in 3T3 L1 adipocytes by GLUT4, insulin receptor substrate-1, insulin receptor β subunit, and phosphatidylinositol 3-kinase (PI3- kinase) (37). Diosgenin ($C_{27}H_{42}O_3$), a naturally occurring aglycone obtained from fenugreek, exhibited anti-diabetic potential in animals as well as in humans (38, 39).

Recent studies are described here to explore the anti-diabetic nature of fenugreek. Neelkantan *et al.* (2014) reported a meta-analysis of clinical trials based on the effects of fenugreek on human subjects. This recent clinical trial on fenugreek evaluated the beneficial role of fenugreek seeds on glycemic control in participants with diabetes (40). Fenugreek is easily available for little cost in countries such as India and China where large populations have type 2 diabetes. Kumar *et al* (2012) reported that fenugreek seed powder can reverse hyperglycemia in diabetic rat brains. Fenugreek also was shown to reduce lipid peroxidation and enhances antioxidant activity in diabetic rats (41). Premanath *et al* (2012) evaluated the role of fenugreek leaf extract in STZ-induced diabetic rats and observed reduction of blood glucose, elevation of antioxidant enzyme production, and regeneration of islets cells in diabetic rats (42). Abdelatif *et al* (2012) demonstrated the anti-diabetic effect of fenugreek leaf extract in a diabetic rabbit model. Supplementation with fenugreek elevated serum insulin levels in diabetic rabbits, establishing the insulin-mimetic effect of fenugreek seeds (43).

The therapeutic value of *Eugenia jambolana* Lam. (Fig. 6) commonly known as 'Blackberry' has been traditionally recognized for the treatment of different diseases and ailments. *Eugenia jambolana* is widely distributed in Southeast Asia and India and contains several phytoconstituents such as alkaloids, glycosides, flavonoids, and volatile oil. Several studies using modern techniques have proven its therapeutic efficacy in diabetes and its related complications (nephropathy, cataract, and neuropathy) as an anti-bacterial, analgesic, anti-inflammatory, antioxidant, as well as gastroprotective agents. Several reports have shown the clinical uses of *Eugenia jambolana* in diabetes. French scientists have demonstrated that constituents isolated from ethanolic extract of *Eugenia jambolana* had hypoglycemic effects on alloxan-induced diabetic rats (44).

Eugenia jambolana is often used for the treatment of diabetes in India as well as other parts of the world. Blackberry seeds are a crucial part of polyherbal anti-diabetic formulations in Ayurvedic medicine (45). Blackberry seeds have been shown to be effective in various models of type 1 and type 2 diabetes induced by alloxan, STZ, and fructose-induced type 2 diabetes models (46-48). Fractions from aqueous and ethanolic

Figure 7. *Aegle marmelose* (Stone apple or bael)

Figure 8. *Terminalia chebula* (Chebulic Myrobalan)

fruit-pulp extracts are known to stimulate synthesis of insulin from residual β cells (49). *Eugenia jambolana* extract has been shown to up-regulate glucose transporter GLUT4 and activate peroxisome proliferator-activated receptor gamma (50). It has been reported that ethanolic extract of seeds of *Eugenia jambolana* had shown significant anti-diabetic activity and potential protective effect in diabetic nephropathy (51).

Aegle marmelos (Fig. 7), commonly known as stone apple or bael, belongs to the family of Rutaceae, which is widely used in Ayurvedic medicine for treatment of diabetes mellitus. Several research groups in India and other South Asian countries have examined the hypoglycemic activities of its plant extracts. The plant is rich in alkaloids, among which marmesin, marmin, aegline, and marmelosin are the most important chemical compounds with hypoglycemic properties (52). Aqueous extract of *Aegle marmelos* leaves (1 gm/kg for 30 days) was shown to significantly restrain blood glucose, urea, body weight, liver glycogen and serum cholesterol levels in alloxanized (60 mg/kg i.v) rats as compared to controls, and this effect was similar to insulin treatment (53). Aqueous leaf extract administered orally for 28 days also normalized STZ (45mg/kg body weight)-induced histopathological alterations in pancreatic and kidney tissues of rats (54). Aqueous leaf extract (1 gm/kg/day) fed to STZ (45 mg/kg i.v) diabetic rats for 2 weeks resulted in reduction of malate dehydrogenase levels (an enzyme elevated in diabetes) in comparison to diabetic controls. The extract was similarly effective as insulin in restoring blood glucose and body weight to normal levels (55) . Methanolic extract of leaf and callus powder of *Aegle marmelos* was shown to significantly reduce the blood sugar level of STZ-induced diabetic rabbits (56). *Aegle marmelos* acts similar to insulin in the restoration of blood sugar and body weight to normal levels in rats and has therefore been recommended as a potential hypoglycemic agent (55).

Terminalia chebula (Fig. 8) has been reported to exhibit a variety of biological activities, including anti-diabetic, anti-cancer, anti-mutagenic, and anti-viral activities. It was found that the ethanolic extract of *Terminalia chebula* exhibits anti-diabetic activity in rats (57) . Chloroform extract has been investigated for its anti-diabetic and renoprotective effects in STZ-induced diabetic rats (58). It was reported earlier that oral administration of *Terminalia chebula* fruit extract (200 mg/kg body weight) for 30 days significantly reduced glucose levels, glycosylated hemoglobin, urea, and creatinine along with fucose, hexose, hexosamine and sialic acid in diabetic rats (59). Additionally, this study showed histological evidences that established the beneficial effect of *Terminalia chebula* fruit extract in pancreatic tissue from treated diabetic rats. Diabetic rats administered *Terminalia chebula* elevated the levels of liver glycogen, glycogen synthase, while decrease in the activity glycogen phosphorylase was observed (57). Furthermore, activities of hepatic hexokinase, lactate dehydrogenase, glucose-6-phosphatases, and fructose-1,6-bisphosphatase were restored to near normal ranges. Electron microscopy studies reported a significant morphological change in the mitochondria and endoplasmic reticulum of pancreatic β cells from STZ-induced diabetic rats after treatment of *Terminalia chebula* fruits (57).

Figure 9. *Emblica officinalis* (Indian Gooseberry)

A recent review was published by Rathinamoorthy *et al* (2014) on the pharmacological and biochemical effects of *Terminalia chebula* such as fruit, leaf, and bark extracts (60). Bag *et al.* (2013) reported information related to the phytochemical and various medicinal properties of *Terminalia chebula* against human diseases (61). Major ingredients of *Terminalia chebula* are ellagic and gallic acids which are potent antioxidants.

Emblica officinalis (Fig. 9) is used both as a medicine and tonic for vitality and strength. According to the two main classic texts on Ayurveda, *Charaka Samhita,* and *Sushruta Samhita*, *Emblica officinalis* is considered as "the best among rejuvenation herbs" and "the best among the sour fruits" for relieving cough and skin diseases. All parts of the plant are used for medicinal purposes. The fruit pulp is used in several indigenous medical preparations for treatment of diabetes. 'Triphala' a mixture consisting of three components (equal proportion of *Terminalia chebula, Terminalia belerica*, *Emblica officinalis*) (100 mg/kg body weight) were administered orally in normal and alloxan-induced diabetic rats significantly reduced glucose levels within 4 hours. (62). In Unani medicine, *Emblica officinalis* is described as a tonic for the heart and brain. Indian gooseberry is the richest source of vitamin C and has been shown to lower glycosylated hemoglobin levels in diabetic patients. Aqueous extract of *Emblica officinalis* consisting of hydrolysable tannoids was shown to inhibit aldose reductase (enzyme responsible for the reduction of glucose to sorbitol) in a rat model of cataract and may explore the usefulness in the management of diabetic complications (63). It has been reported that the polyphenols, tannins, alkaloids, and phenols of *Emblica officinalis* appears to be mediated by direct insulin-like or insulin mimetic effect in diabetic conditions (64).

Figure 10. *Zingiber officinale* Roscoe (Ginger)

Jain *et al.* recently reviewed information related to *Emblica officinalis* as a versatile medicinal plant. The various properties of *Emblica officinalis,* including immunomodulatory, anti-pyretic, anti-inflammatory, and antioxidant activities, have been explored *in vivo* and *in vitro* (65).

Fresh and dried rhizome of *Zingiber officinale* (Fig. 10) is widely used as a traditional medicine in India, South and Southeast Asia, Sierra Leone and Nigeria, Latin America, the Caribbean, and Australia. Several studies have been carried out on this exotic plant. In an oral glucose tolerance test, treatment with *Zingiber officinale* was found to significantly alleviate the area under the curve of glucose as well as increase the area under the curve of insulin in STZ-induced diabetic rats. Treatment with *Zingiber officinale* also caused reduction of serum cholesterol, serum triacylglycerol and blood pressure levels in diabetic rats (66). Ethanolic extracts of *Zingiber officinale* reduced levels of blood glucose in a dose-dependent manner (50-800 mg/kg) in both normal and STZ-induced diabetic rats (67). The bioactive compounds 6-, 8-, and 10- gingerols obtained from *Zingiber officinale* previously elevated glucose uptake in muscle cell possibly due to expression of GLUT4 (68).

This review provides an illustration of the anti-diabetic potential of herbal plants with medicinal values for management of diabetes mellitus. The review also summarizes the important bioactive compounds and anti-diabetic mechanisms of action of several phytochemicals present in the nine herbs shown in Table 1. The present data will provide support for the clinical development of selected medicinal herbs as additive therapeutics. There

is a global increase in research to identify and evaluate alternative medicines, especially those derived from naturally available plants to fight against diabetes. Much interest has focused on exploring herbal preparations, which include screening of natural bioactive compounds with the potential to cure and/or delay progression of diabetes through various unknown mechanisms.

Limitations and challenges using herbal medicines

Limitations of herbal medicines include lack of scientific evidence and insufficient clinical trials using human and animal models. Usage of polyherbal preparations or individual herbs requires considerations, such as the conditions of the herbal plants at the developmental stage, toxicity, processing and collection, and quality control. Finally, a clinical trial and randomized studies are important to evaluate these aspects, which are essential to effectively translate the active potential of herbal plants.

Important issues with herbal medicines are the isolation and evaluation of active components, elucidation of their interactions in tissues, their cellular targets, and mechanisms of action, which are important to understand the efficacy and efficiency of herbal preparation.

Conclusion

This study highlights the importance of anti-diabetic plants used in the treatment of diabetes and their complications. More clinical research based on herbal plants is needed to determine efficiency. There is still a requirement to monitor the effectiveness of herbal medicines due to safety concerns. Despite the presence of known anti-diabetic medicines on the pharmaceutical market, remedies derived from medicinal plants can be used since they are less toxic, lack undesirable side effects, easy available, affordable compared to synthetic ones.

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