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A REVIEW ON ANTI-DIABETIC POTENTIAL OF MEDICINAL PLANTS

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ABSTACT

Diabetes mellitus (DM) is a group of metabolic disorders characterized by hyper-glycemia due to insufficient insulin secretion or action (resistance to insulin action by the cells). Contributing factors include genetic predisposition, obesity, family history, inactivity and environmental risks. Type- 2 Diabetes mellitus (T2-DM), the most common form, involves impaired insulin secretion by pancreatic β-cells of islets of Langerhans or resistance to insulin Although synthetic drugs are effective in managing DM, but often they come up with side effects. Consequently, plant-based phytochemicals with antidiabetic properties are gaining attention. Research indicates that around 115 medicinal plants (MP's) have antidiabetic effects, particularly those from the **Fabaceae, Liliaceae and Lamiaceae families**. Bioactive compounds like alkaloids, triterpenoids, flavonoids and phenolics are known to combat DM. Traditional medicinal systems particularly offer effective management of DM. This review highlights the importance of MP's with potential antidiabetic significance, their modes of action together with the methods used for their assessment.

INTRODUCTION

DM is a chronic disorder characterized by a deficiency in insulin production, its action or both that leads to prolonged hyper-glycemia with disturbances in most of the metabolic processes inside the body.[1] Untreated cases show severe tissue and vascular damage leading to serious complications such as retinopathy[2], neuropathy[3], nephropathy[4], cardiovascular complications[5] and ulceration.[6] Moreover, diabetes has an indirect relation with many other

diseases being the most common endocrine disorder.

Both insulin and glucagon, in an adequate level, pancreatic endocrine hormones are responsible for controlling blood-glucose levels based on the body needs. Normally in response to high levels of blood sugar. Insulin is secreted by the β-cells found at the islets of Langerhans. It promotes the ability of muscle, red blood cells and fat cells to absorb sugar out of the blood and consume it in other metabolic processes, which restore the normal sugar levels. On the contrary, glucagon is secreted by α- cells of the pancreas as a result of low blood-glucose level in between meals and during exercise. That stimulates the liver and other cells in muscles to release glucose into the blood.[7]

Classification of Diabetes Mellitus

DM is classified into different categories, based on the etiology of the disease, but it is widely accepted that the two main types are type- 1 and type- 2.[8] Type- 1 IDDM (Insulin Dependent Diabetes Mellitus) occurs in patients with little or no insulin secretory capacity and type- 2 NIDDM (Non-Insulin Dependent Diabetes Mellitus) Consequently, they are in need for a replacement therapy of insulin for survival. The two major forms of type- 1diabetes are type 1a (90% of type- 1) and type- 1b (10% of type 1). Type- 1a results from immunological destruction of pancreatic ß- cells associated with diseases such as Addison's disease, Grave's disease and Hashimoto's thyroiditis.[9,10] However, type- 1b is idiopathic where no etiological basis is identified. Some of these patients have predominant insulin deficiency and are susceptible to ketoacidosis, but no evidence of developing autoimmune diseases.[11]

On the other hand, type- 2 (NIDDM), is the most known form of diabetes, characterized by abnormality in insulin secretion and its resistance.[12] Traditionally, it is predominant among elderly people (over 40 years). Commonly, it occurs in people with obesity, decreased body activity and it may also be inherited.[13] The disease is often controlled through dietary supplements, physical activity along with oral hypoglycemic agents.[14]

Moreover, there is another temporary disease related to diabetes, which is known as gestational diabetes (GD) mellitus. It refers to the occurrence or initial recognition of glucose intolerance during the period of pregnancy.[1]

Drugs Controlling DM and their mechanism of action

The present treatments of DM are usually in the form of oral hypoglycaemic drugs, which are divided into two main groups; sulfonylureas and biguanides. Functionally, sulfonylureas enhance insulin production from β cells in the pancreas and promote other action around the pancreas while biguanides reduce the production of glucose in the liver and increase the use of glucose in the body.

Sulfonylureas are believed to close potassium channels in pancreatic cells, resulting in an increase of insulin release from β- cells of pancreas. This is confirmed by the reduced fasting plasma glucose.[15]

Meglitinides consist of nateglinide and repaglinide and Nateglinide binds to the same site of sulfonylurea receptor- 1 as those of the sulfonylurea derivatives. Repaglinide binds to a nearby site of the receptor, stimulating the release of insulin from pancreatic β-cells.[16]

Wherein biguanide Metformin lowers the glucose production in the liver and stimulates the transport of glucose into muscle.

Thiazolidinediones (TZDs) stimulate the function of insulin in muscle, fat and other tissues. They are selective and potent agonists for the peroxisome proliferator-activated receptor- □ (PPAR-□) nuclear receptors. When they are activated, these receptors regulate the transcription of insulin responsive genes which are contributed to the control of production, transport and utilization of glucose.

The α-glucosidase inhibitors consist of acarbose and miglitol. Acarbose lowers glycaemic excursions and prevent the development of diabetes and cardiovascular disease. They inactivate the rate of carbohydrate absorption in the small intestine, leading to a reduction in plasma glucose level. Further they inhibit the conversion of dietary starch and sucrose into glucose.[17]

Table 1: Drugs for treatment of diabetes mellitus with their mechanism of action and side effects.[18]

Oral antidiabetics	Mechanism of action	Side effects
Sulfonylureas Glimiperide (Amaryl) Glipiside (Glucotrol) Glipiside-gits (Glucotrol-XL) Glyburide (Diabeta, Micronase) Glyburide micronized (Glynase) Tolbutamide (Orinase) Chlorpropamide (Diabinese) Tolazamide (Tolinase) Acetoheximide (Dymelor)	Stimulate first-phase insulin secretion by blocking K^+ channel in β-cells	Late hyperinsulinemia and hypoglycaemia Weight gain
Meglitinides Repaglinide (Prandin) Nateglinide (Starlix)	Stimulate first-phase insulin secretion by blocking K^+ channel in β-cells	Hypoglycaemia Weight gain
Biguanides Meformin (Glucophage, Riomet) Metformin-XR (Glucophage-XR)	Decrease hepatic glucose production Increase muscle glucose uptake and utilization	Nausea, Diarrhea Anorexia, Lactic acidosis
Thiazolidinediones Rosiglitazone (Avandia) Pioglitazone (Actos)	Increase insulin sensitivity via activation of PPAR-γ receptors	Fluid retention and weight gain
α-Glucoside Inhibitors Acarbose (Precose) Miglitol (Glyset)	Decrease hepatic glucose production Delay glucose absorption	Flatulence Abdominal bloating

Medicinal Plants with Potential Antidiabetic Activity

There are lots of chemical agents available to control and to treat diabetic patients, but total recovery from diabetes has not been reported till this date. In addition most of the oral antidiabetic drugs are costly and have a lot of side-effects. Alternative to these synthetic agents, plants provide a potential source of hypoglycaemic drugs and are widely used in several traditional systems of medicine to prevent diabetes.[19] Further more several medicinal plants, used to control diabetes along with life style management, have been investigated for their beneficial effect in different types of diabetes and are being more desired, owing to lesser side- effects and low cost. In addition, during the past few years, many

phytoconstituents responsible for antidiabetic effects have been isolated from various plants.[20] There are about 200 pure compounds from plant sources reported to show blood glucose lowering activity. The compounds may be flavonoids, terpenoids, alkaloids, carbohydrates, glycosides, steroids, peptides and amino acids, lipids, phenolics, glycopeptides and iridoids.[20] Many antidiabetic products of herbal origin are now available in the market. More than 1200 species of plants have been screened for anti-diabetic activity on the basis of ethnomedicinal uses.[21] The mechanisms of medicinal plants for glucose control in diabetes include the inhibition of glucose absorption, improvement of insulin sensitivity, protection of β-cell damage, increase of insulin release, enhancement of antioxidant defence, attenuation of inflammation, modulation of carbohydrate metabolism pathway and regulation of insulin-dependent and insulin independent signalling pathways.

This review aims to provide the knowledge and highlight the most widely used anti-diabetic herbs as presented below:

Cinnamomum zeylanicum

It is commonly known as Cinnamon (Lauraceae) and widely used in East Asia and Europe, extensively used in folklore medicine to treat diabetes. It contains volatile oils, mainly cinnamaldehyde. Cinnamon ingestion decreased total plasma sugar level with improvement in insulin sensitivity, also significantly reduced gastric emptying and profoundly decreasing postprandial glycaemic response.[22] In addition, cinnamon aqueous extract exhibited a potent antidiabetic effect through its up regulation of uncoupling protein-1 (UCP-1) and enhancing the translocation of GLUT-4 in the muscle and adipose tissues.[23] Oral administration of cinnamaldehyde, its chief active constituent, resulted in significant reduction in serum glucose, glycosylated haemoglobin , total cholesterol and triglyceride levels accompanied by a marked increase in serum insulin, hepatic glycogen and high-density lipoprotein in a dose-dependent manner.[24]

Eugenia jambolana

It is familiar by Jamun or black plum, belonging to family Myrtaceae, also known as *Syzygium cumini* and is widely being used over many centuries for the treatment of diabetes by the traditional practitioners. Oral administration of the pulp extract of the fruit resulted in the enhancement of insulinemia through stimulation of insulin secretion and insulin activity suppression from liver and kidney.[25] While, administration of the alcohol extract of dried seeds resulted in hypo-glycemia and decreased glycosuria, partially restoring the altered

hepatic and skeletal muscle glycogen content as well as hexokinase, glucose- 6-phosphatase, phosphofructokinase and glucokinase levels.[26]

Moreover, the flavonoid rich extract of its seeds showed a potent antidiabetic activity manifested by a reduction in fasting and peak blood glucose levels, in addition to an improvement in glycogen biosynthesis, glucose homeostatic enzymes activities as well as the *in vitro* insulin release from pancreatic islets. Its mechanism of action is probably due to up-regulation of both PPAR-α and PPAR-γ in addition to its ability to differentiate 3T3-L1 preadipocytes.[27] Besides, seed kernel extracts were found to effective in inhibiting α-glucosidase accounting for the mode by which this herb exerts its anti-diabetic effect.[28]

Psidium guajava

It is known as Guava belonging to family Myrtaceae. It contains a high percentage of vitamins B1, B2, B6, vitamin C, free sugars (glucose, fructose and sucrose) and carotene. Oral administration as well as intraperitoneal injection of aqueous extract of leaves to alloxan-induced hyperglycemic rats has shown beneficial effect not only on blood glucose but also on body weight, glucose and ketone level of urine and tissue of pancreas showing a marked inhibitory activity on protein tyrosine phosphatase1B.[29] While, the methanolic extract showed hypoglycemic effect in type-2 diabetes. Flavonoid glycosides exemplified by pedunculagin, isostrictinin and strictinin are the potent constituents, that have been used in clinical treatment of diabetes to improve insulin sensitivity. Additionally ethanol extract of *P. guajava* stem bark showed a marked hypoglycemic effect, which may not be due to stimulating insulin release from pancreatic β-cells, but may be attributed to extra pancreatic mechanism exemplified by enhancing peripheral glucose metabolism.[30]

Trigonella foenumgraecum

It is commonly known by Fenugreek seeds and is belonging to family Fabacea,. famous for the presence of mucilage, proteins, proteinase inhibitors, steroid saponins and saponin-peptide esters, sterols, flavonoids, nicotinic acid, coumarin, trigonelline and volatile oil.[31] Administration of the defatted seed decreased fasting and postprandial blood levels of glucagon, glucose, insulin, somatostatin, triglycerides, total cholesterol, while increased HDL-cholesterol levels. The intake of seed fibre of *T. foenumgraecum* decreases sugar absorption rate, delaying gastric emptying, thus inhibiting the increase in blood glucose levels after meals. It also stimulates insulin receptor sites to burn cellular glucose at high-fibre diet. Its chemical analysis revealed that galactomannan constituted the major ingredient

that of the seed fibre to which the antidiabetic activity may be attributed.[32,33]

The underlying mechanism by which fenugreek seeds act as an orally effective hypoglycemic agent may be achieved through enhancing insulin synthesis and its release from the pancreatic β- cells of the islets of Langerhans. The relevant therapeutic role of Trigonella powdered seed in type- 1 diabetes mainly attributed to the reversion of lipid and glucose metabolizing enzyme activities to normal levels, thus stabilizing glucose homeostasis in the liver and kidney.[34]

Aloe vera

A.vera is a medicinal plant belonging to the family Liliaceae, distributed in the hot and dry regions of North Africa, the Middle East of Asia, the Southern Mediterranean and the Canary Islands, and used in the treatment of diabetes in India and in the Arabian Peninsula. The inner leaf gel contains the hypoglycaemic and insulin-sensitising water-soluble fibre glucomannan. Although studies have shown in consistent results, clinical trials have shown that *A. vera* extract provides an improvement, particularly in fasting blood glucose levels. It has also been shown to have a potential effect on glycaemic control, reducing hyperglycaemia and hypercholesterolaemia in people with DM. Aloeresin-A, an active compound of the plant inhibits α-glucosidase activity and reduces α-glucosidase and intestinal glucose absorption.[35]

Zingiber officinale Roscoe

It is commonly known as ginger and is a spice from India, China, Nigeria, Indonesia, Bangladesh, Australia, Jamaica and Nepal. The effects of ginger include anti-inflammatory, immunomodulatory, anti-oxidant, hypolipidaemic, hypoglycaemic, antiemetic, antihypertensive and antidiabetic. Many preclinical and clinical studies have shown that ginger is a promising hypoglycaemic dietary supplement, particularly for the treatment of T2-DM. Ginger regulates insulin, promoting glucose removal from insulin-responsive tissues and helping to maintain blood sugar balance. Specifically, 6-gingerol in its structure has been found to increase glucose uptake in insulin-responsive adipocytes, and insulin-responsive glucose uptake increases and ameliorates DM in cells treated with gingerol.

Ginger rhizomes have been reported to prevent the development of insulin resistance, particularly by regulating “Peroxisome Proliferator Activated Receptors” (PPARs). It was reported that the consumption of 30 g / day of ginger powder for 3 days significantly reduced blood glucose levels in patients with T2-DM. Gingerol has been shown to attenuate sodium

arsenite induced T2-DM. This attenuation protects islet cells and activates insulin receptors.[36]

Allium sativum

It is the commonly known as Garlic, a plant in the Liliaceae family, one of the most fascinating medicinal plants used throughout history. Garlic is known to have antihypertensive, immunomodulatory, cardioprotective, hypolipidaemic, hypoglycaemic anti-inflammatory, antioxidant, antimicrobial and anticancer activities. Research have suggested that garlic may help lower blood glucose level and improve insulin sensitivity, which may be beneficial for diabetes. Clinical studies have shown that garlic supplementation with standard antidiabetic medications effectively reduces insulin resistance, lipid profile and glycaemic parameters, including fasting plasma glucose and HbA1c, particularly for T2-DM. These effects are due to sulphur compounds such as diallyl disulphide and diallyl trisulphide in its structure, act as hydrogen sulphide donors that control T2-DM.[37]

Annona squamosa

It is commonly known as custard apple, cultivated throughout India. The pharmacological active ingredients are present in seeds, leaves and aerial parts of the plant. The research reveals that the plant possesses both hypoglycemic and antidiabetic activity. It acts by enhancing insulin level from the pancreatic islets, increases utilization of glucose in muscle and inhibits the glucose output from liver with a high margin of safety. The extract obtained from leaves of this plant is useful in maintaining healthy blood sugar and cholesterol levels.[38]

Momordica charantia

A well-known plant (bitter melon) belonging to family Cucurbitaceae that widely used in folklore therapy for the treatment of diabetes. Oral administration of the fruit juice or seed powder resulted in a significant decline in FBG (Fasting Blood Glucose) and pronounced amelioration of glucose tolerance exerting both insulin secretagogue and insulin mimetic activities.[39] This potent antidiabetic activity mainly attributed to the presence of an insulin-like polypeptide known by polypeptide- P, similar in structure to the bovine insulin, which reduces plasma sugar levels when injected subcutaneously into type-I diabetic patients and appears to inhibit gluconeogenesis. In addition, it improves glucose tolerance in type-2 diabetes. It also inhibits hepatic glucose production and enhances the utilization of glucose in peripheral tissues.[40]

Murraya koeingii

The curry leaf tree belonging to family Rutaceae is widely cultivated for its aromatic leaves, which are used as a flavouring agent. It was reported that an oral administration of leaves showed a potent hypoglycemic effect associated with an increase in hepatic glycogen content due to stimulated glycogenesis and suppressed glycogenolysis as well as gluconeogenesis.

Ocimum sanctum

It is commonly known as Holy basil (Labiateae). Oral administration of alcohol extract of its leaves, significantly reduced hyperglycemia and enhanced exogenous insulin action. Administration of leaf powder to healthy and diabetic rats resulted in reduction of FBG after one month.[41] Its pronounced therapeutic potential as antidiabetic agent can be attributed to the presence of eugenol, its chief active constituent, reducing elevated serum sugar, cholesterol triglyceride levels which helps to regulate blood sugar levels by increasing insulin secretion, reducing oxidative stress, and improving glucose metabolism.

Key mechanisms by which medicinal plants exert their anti-diabetic potential

1. Improved Insulin Sensitivity

Some plants enhance the body's response to insulin, thereby improving insulin sensitivity i.e., the cells of the body are better able to absorb glucose from the bloodstream, which helps lower blood sugar levels.

- Example: *Cinnamon* contains compounds like cinnamaldehyde and polyphenols that improve insulin sensitivity by activating insulin receptors. *Ginseng* also helps increase insulin sensitivity by enhancing glucose uptake in cells.[42]

2. Increased Insulin Secretion

Several plants promote the secretion of insulin from the pancreas, either directly or indirectly. This is particularly beneficial for people with type-2 diabetes, where the body’s insulin secretion may be insufficient.

- Example: *Gymnema sylvestre* has gymnemic acids that stimulate insulin release. *Berberine* (found in *Berberis vulgaris*) can also stimulate insulin secretion and improve glucose metabolism by activating AMP-activated protein kinase (AMPK).[43]

3. Inhibition of Carbohydrate Digestion and Absorption

Some plants slow down or inhibit the digestive process, reducing the rate at which carbohydrates are broken down into glucose and absorbed into the bloodstream. This can

prevent spikes in blood sugar levels after meals.

- Example: *Bitter melon* and *Fenugreek* help slow down the absorption of glucose from the digestive tract. *Glucomannan* (*Amorphophallus konjac*) is a water-soluble fibre that slows down carbohydrate absorption and promotes satiety, thus preventing post-meal blood sugar spikes.[44]

4. Antioxidant and Anti-inflammatory Effects

Chronic inflammation and oxidative stress play a significant role in insulin resistance and the development of diabetic complications. Many medicinal plants possess strong antioxidant and anti-inflammatory properties that help to mitigate these processes.

- Example: *Turmeric* (due to its active compound, curcumin) has powerful anti-inflammatory and antioxidant effects, helping to reduce insulin resistance and protect against diabetic complications. *Holy Basil* (Tulsi) has similar properties, reducing oxidative stress and improving glucose metabolism.[45]

5. Inhibition of Hepatic Glucose Production

The liver plays a critical role in regulating blood glucose levels by releasing glucose into the bloodstream. Some plants can inhibit excessive glucose production in the liver, thus helping control blood sugar levels.

- Example: *Berberine* has been shown to reduce hepatic glucose production, which contributes to its blood sugar-lowering effects. *Turmeric* also has a similar mechanism, reducing liver glucose output by inhibiting enzymes involved in gluconeogenesis.[46]

6. Regeneration of Insulin-Producing Cells

Some plants promote the regeneration of pancreatic β-cells, which are responsible for insulin production. This can be particularly helpful for individuals with type-1- diabetes or advanced stages of type- 2 diabetes.

- Example: *Gymnema sylvestre* has shown potential in regenerating insulin-producing β-cells in the pancreas, which can help restore normal insulin secretion. *Neem (Azadirachta indica*) has similar effects by promoting β -cell regeneration.[47]

7. Weight Management

Maintaining a healthy weight is crucial for diabetes management, especially in type- 2 diabetes. Many medicinal plants have properties that can aid in weight loss, reduce fat accumulation, and prevent obesity- related insulin resistance.

- Example: *Fenugreek* is high in soluble fibre, which helps with weight management by promoting satiety and controlling appetite. *Glucomannan* also aids in weight management by absorbing water in the digestive tract and promoting a feeling of fullness.[48]

8. Reduction of Blood Lipid Levels

Diabetes is often accompanied by dyslipidemia, or imbalances in blood lipid levels. Many medicinal plants help to reduce elevated cholesterol and triglyceride levels, which is important for preventing cardiovascular diseases associated with diabetes.

- Example: *Aloe vera* has been shown to improve lipid profiles, lowering total cholesterol and triglycerides. *Black cumin* (*Nigella sativa*) may also reduce cholesterol and triglyceride levels while improving overall metabolic health.[49]

9. Regulation of Blood Pressure

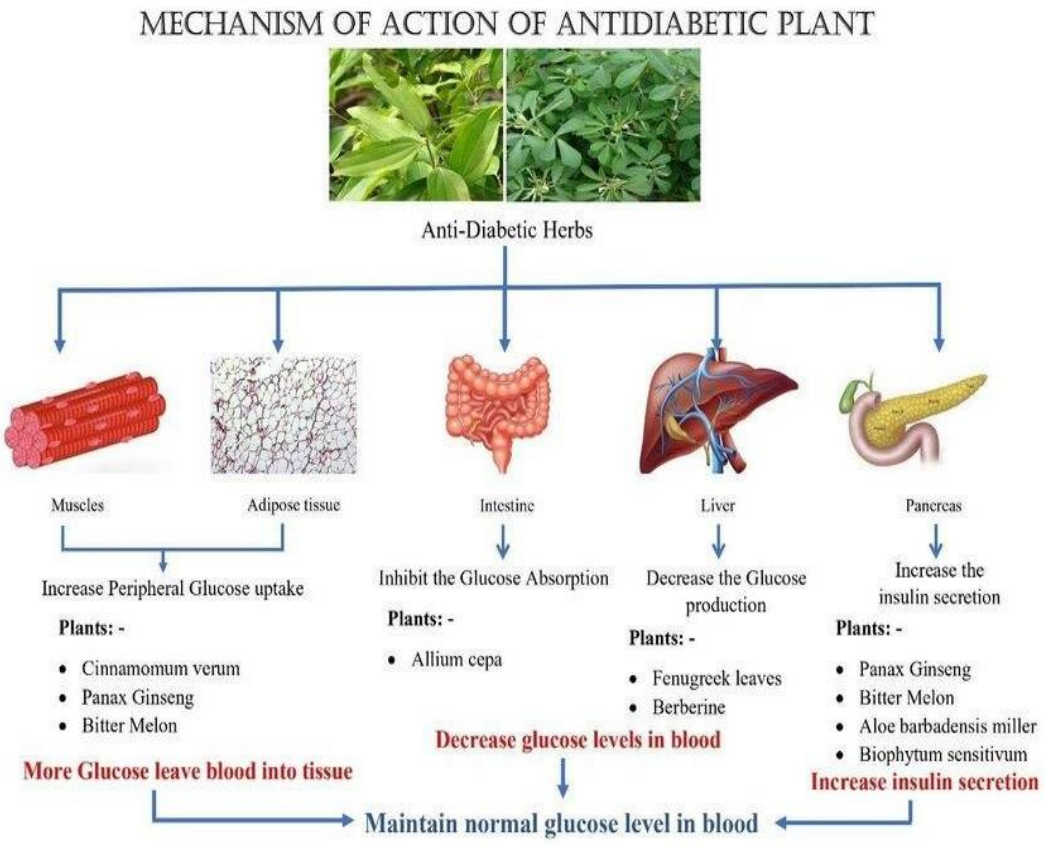
High blood pressure is common in diabetic individuals, and many medicinal plants help manage blood pressure, further reducing the risk of diabetic complications like heart disease and kidney damage.

- **Example:** *Holy Basil* and *Neem* have hypotensive effects, which help in controlling high blood pressure. *Ginseng* also has cardiovascular benefits, supporting healthy blood pressure levels.[50]

10. Reduction of Glycation

Glycation is the process where sugar molecules bind to proteins, leading to the formation of advanced glycation end products (AGEs), which contribute to diabetic complications like neuropathy, retinopathy and nephropathy. Some medicinal plants can reduce or inhibit this process.

- Example: Mango leaves contain anthocyanins, which help inhibit glycation, thereby protecting against complications like nerve and kidney damage. *Cinnamon* also reduces the formation of AGE's, protecting tissues from damage.



DISCUSSION

The increasing prevalence of diabetes, particularly type- 2 diabetes, has led to a growing interest in alternative and complementary therapies, including the use of medicinal plants. While pharmacological treatments for diabetes, such as insulin and oral hypoglycemic agents, are widely available, many individuals seek natural remedies that offer fewer side effects and additional health benefits. This review of the antidiabetic potential of medicinal plants highlights the complex mechanisms through which these plants exert their effects, as well as the scientific evidence supporting their use.

Despite the promising results from studies on the antidiabetic potential of medicinal plants, there are several challenges and considerations that must be addressed before these plants can be recommended for widespread clinical use:

- **Quality Control and Standardization**: One of the major challenges with medicinal plants is the inconsistency in their active ingredient content. The bioactive compounds in plants can vary widely depending on factors such as the plant's source, harvesting time and method of preparation. Without proper standardization, it is difficult to ensure the efficacy and safety of these plants in the management of diabetes.

- **Clinical Evidence**: Although many *in-vitro* (lab) and animal studies support the antidiabetic effects of medicinal plants, human clinical trials are often limited, small, or of variable quality. More large- scale, well-designed clinical trials are needed to confirm the safety and efficacy of these plants in diabetic populations, especially in combination with conventional treatments.
- **Toxicity and Side Effects**: Although many medicinal plants are considered safe when used properly, some can cause side effects, especially if used in excessive amounts or over extended periods. Turmeric, for example, may cause gastrointestinal discomfort in some individuals, while Ginseng can lead to insomnia or headache when consumed in high doses. Toxicity and side effects need to be better understood, particularly in long-term use.

CONCLUSION

Natural resources are still considered as potent candidates for drug discovery and are playing a pivotal role in drug development programmes. Moreover, many medicinal herbs provide a rich mine for bioactive chemicals that are markedly free from undesirable side effects and of powerful pharmacological actions. The present review has presented comprehensive details of antidiabetic plants used in the treatment of diabetes mellitus and their potential mechanism of action. Various plants have demonstrated the ability to regulate blood glucose levels through multiple mechanisms. Additionally, many of these plants possess antioxidant and anti-inflammatory properties that can help mitigate the chronic complications of diabetes, such as cardiovascular disease, neuropathy and kidney damage. However, for these plants to be incorporated into mainstream diabetes care, there is a need for more robust clinical evidence, careful standardization and awareness of potential herb-drug interactions.

Consequently for the discovery of new natural herbal antidiabetic drugs much effort should be afforded to optimize a procedure for screening of different plant extracts as well as isolated bioactive compounds that can be used as an alternatives to synthetic oral hypo-glycemic drugs with less or even no prominent side effects.

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