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Review Article

Natural Remedies for the Treatment of Diabetes Mellitus

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Abstract

Natural remedies have been used for decades to treat a variety of diseases. Diabetes mellitus (DM) is still one of the most common chronic diseases that cause death. Aside from its complex pathophysiology, it has been shown to be widespread in both developed and developing countries. The current pharmacological treatment has contributed to a significant reduction in disease occurrence. However, the economic burden and various pharmacological and non-pharmacological side effects associated with them, have necessitated the development of alternative naturally-derived treatment options. This review focuses on how safer, more effective, and less expensive treatments can help reduce diabetes-linked mortality rates. Furthermore, a wide range of medicinal plants with varying α-glucosidase and α-amylase inhibitory activity and improved IC50 and LD50 values evaluated in-vivo and in-vitro have been discussed. This review can help open new treatment paths for diabetes mellitus through new plant-derived medicines.

Keywords: Diabetes mellitus, medicinal plants, ethnopharmacology, pharmacotherapy

1. Introduction

A chronic metabolic disease known as diabetes mellitus (DM) is defined by persistent hyperglycemia, which may be brought on by decreased insulin production, resistance to the peripheral effects of insulin, or both (Goyal and Jialal 2022). It is a metabolic disorder characterized by an inappropriate rise in blood glucose levels (>110 mg/dL) (Sapra and Bhandari 2022). People with diabetes have a lower life expectancy than the general population due to various complications and comorbidities. Natural remedies have the potential to lower their progression and risks.

The development of diabetes, especially type 2, is mostly attributed to the action of insulin and adipocyte inflammation. It is also reported that insulin resistance in the hypothalamus (central nervous system) attenuates circulating insulin's ability to inhibit glucose production, which may further enhance renal tubular glucose reabsorption, increasing glucose levels in the blood (Solis-Herrera et al. 2000).

The initial classification of diabetes was limited to only two types: juvenile diabetes, now known as type 1 diabetes, and adult diabetes, now known as DM type 2. This has evolved into the recognition of more than 50 subtypes caused by different pathogenic mechanisms or accompanied by other diseases and syndromes (Genuth, Palmer, and Nathan 2018).

Type 1, type 2, maturity-onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes, as well as particular types resulting from various causes, including endocrinopathies, steroid use, etc., are some of the most common types of DM according to the American Diabetes Association (ADA) (Association 2019). While type 2 diabetes is expected to affect middle-aged and

older adults who experience chronically high blood glucose due to lifestyle choices and a typical diet, type 1 diabetes is more likely to affect children or teenagers. The pathogenesis of either type is completely different; thus, each has a different etiology, manifestation, and treatment (Sapra and Bhandari 2022).

Several symptoms of this metabolic disease, including frequent urination, increased thirst, appetite, diabetic ketoacidosis (DKA), and hyperosmolar coma, are common (World Health Organization 2014). Kidney failure, diabetic heart disease, stroke, neuropathies, and vision impairment are examples of long-term complications (Ziqi Tao, Shi, and Zhao 2015b). Patients with prediabetes should expect increased blood glucose levels between 110 mg/dL and 125 mg/dL, while normal blood glucose levels fall between 70 mg/dL and 99 mg/dL (Alvarez, Coffey, and Algotar 2022).

Confirmatory DM is done based on elevated blood glucose with overnight fasting, oral glucose tolerant test (OGTT), and glycated hemoglobin (A1C), which has greatly helped define individuals such as pregnant women with a high fetal risk of gestational diabetes (Genuth, Palmer, and Nathan 2018). A1C ranges from 6.0% to 6.4%, impaired fasting glucose (IFG) ranges from 100 to 125 mg/dL, and impaired glucose tolerance (IGT) ranges of 140 to 199 mg/dL for a 2-hour monitored blood glucose reading is indicative of DM (Genuth, Palmer, and Nathan 2018).

Looking into various natural treatment options for remedies may help reduce associated risks and long-term complications with DM, lower economic burden, especially in underprivileged societies, and decrease the overall morbidity and mortality rates.

2. Epidemiology of DM

Diabetes has developed into one of the most significant endocrine diseases that negatively affect patients' quality of life as a result of complications such as cardiovascular disease, retinopathy, neuropathy, and renal disease (Lu et al. 2022). According to the 2013 global diabetes statistics, there are around 382 million cases of the illness globally, with 90% of cases belonging to type 2 diabetes (Z. Tao, Shi, and Zhao 2015a). It ranks as the sixth most common cause of death in the US, with an estimated 82.4/per 100,000 mortality rate (Glovaci, Fan, and Wong 2019).

With increased economic prosperity in developing countries, the incidence of DM is also on the rise. Well-known associations between diabetes and wealth, physical inactivity, occupation, and high cholesterol levels, mean that there has been an epidemiological shift and increase in the incidence of non-communicable diseases like diabetes in developing countries. Other ethnically related contributing factors, such as food, physical activity levels, age, weight, and genetic susceptibility, may also play some role. Both types of diabetes are more likely to occur in malnourished and obese populations. According to some studies, cultural interventions are necessary to slow down or stop the progression of diabetes in South Asians, who are more prone to developing the disease (Shah and Kanaya 2014).

As per the International Diabetes Federation published report, Pakistan is No. 10 internationally with 7.5 million cases of diabetes, mostly in metropolitan areas (IDF) (Adnan and Aasim 2020). DM is reported to be 26.3% prevalent in Pakistan, with males having a higher prevalence across different provinces (Meo et al. 2016). Based on a survey conducted across the two major provinces of Sindh and Punjab, increased cigarette use, sedentary lifestyle, dietary choices, and weight gain have all been key contributors to its incidence (Rafique et. al 2016).

3. Pathophysiology of DM

Normal glucose homeostasis requires a healthy and functional mass of pancreatic beta cells, while there is a varying degree of beta-cell dysfunction in DM. A gradual decline of beta-cell mass and function is a major contributor to the emergence of diabetes. In addition to causing many other problems, oxidative stress plays a critical role in

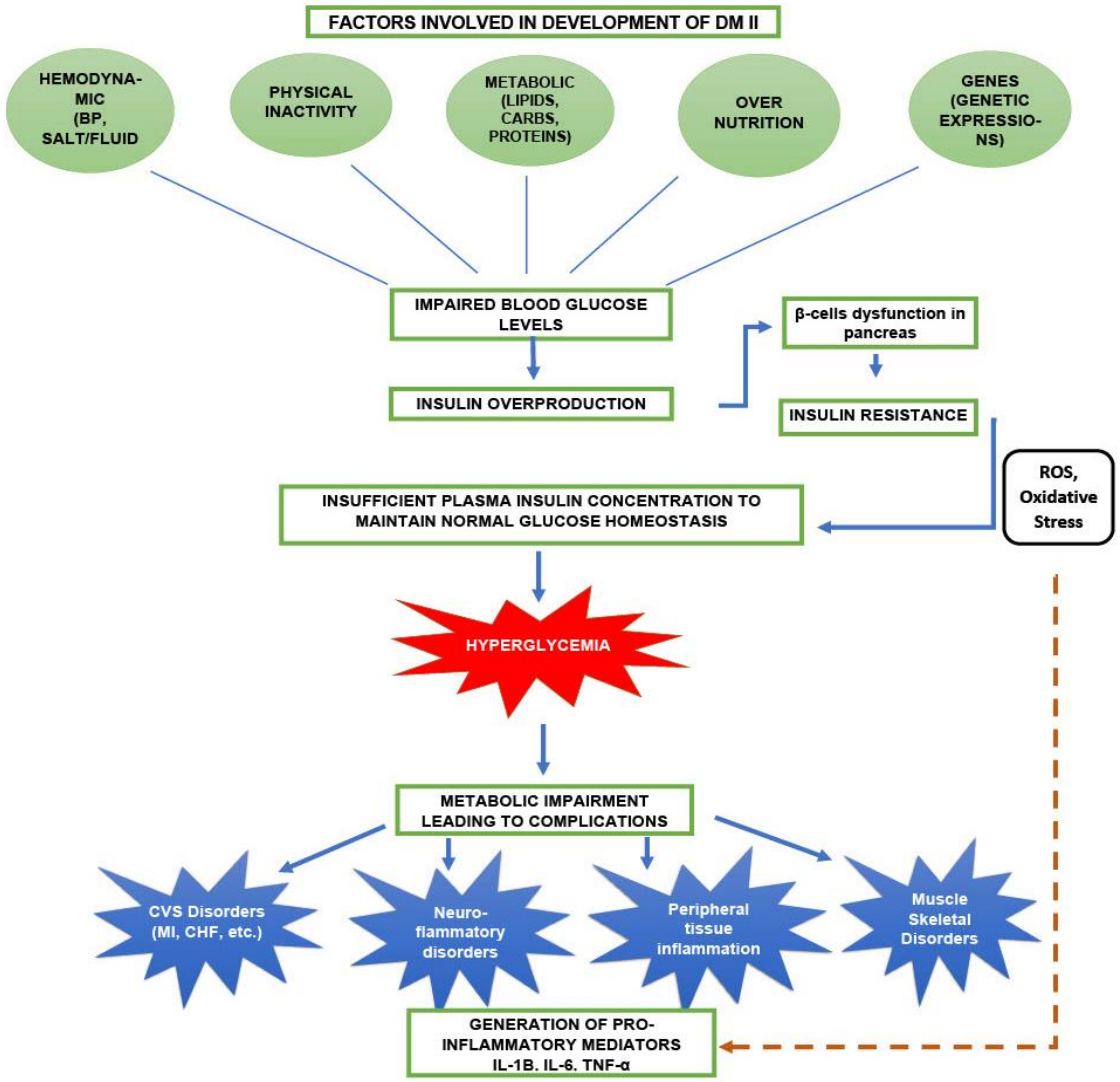

Figure 1. Several factors contribute to β-cell damage/dysfunction through altering insulin and glucose levels. Metabolic damage, as a result, leads to long-term complications. The release of these inflammatory cytokines highly influences oxidative stress.

the pathophysiology of insulin resistance and DM **(Figure 1)**. More and more *in vivo* studies show that higher levels of free radicals significantly impede proper insulin signal transduction and glucose homeostasis in several ways. Oxidative stress in beta cells is common in DM and plays a significant role in the loss of their function in both Type 1 and Type 2 diabetes since beta cells have a poor antioxidant defense system. It significantly lowers the amount of insulin produced, hinders the insertion of proinsulin vesicles into the plasma membrane, and minimizes their exocytosis in response to blood glucose levels.

Signaling proteins such as Insulin Receptor Substrate (IRS) can be phosphorylated **(Figure 2)** and activated by the enzymes AMP-activated protein kinase and glycogen synthase kinase 3 (GSK-3). Phosphoinositide 3-kinase (PI3K) and AKT/PKB (Protein Kinase B) are both activated by the binding of activated IRS-1. Phosphatidylinositol 3,4,5-trisphosphate (PIP3), a potent PKB activator, facilitates glucose entry into

cells by targeting Glucose Transporter Type 4 (GLUT-4) and inhibiting glycogen synthase kinase, resulting in enhanced glycogen synthesis (Yaribeygi et al. 2020). The finding that oxidative stress plays a vital role in the initiation of apoptosis in pancreatic islets also made it possible to pinpoint the fundamental cause of pancreatic-cell malfunction during Type 2 Diabetes, which was oxidative stress-induced load and apoptosis. Any interruption in these pathways has the potential to disrupt normal insulin secretion.

4. Treatment options for DM

According to various medical practitioners, most patients request beginning therapy with an oral drug rather than an injectable (such as insulin). Therefore, the oral treatment choices for Type 2 DM have changed over several years from a single alternative to at least 9 different classes of medications. However, with multiple adverse effects seen with oral hypoglycemia, measures are being taken to develop new entities with better therapeutic outcomes and fewer adverse effects in patients with diabetes.

4.1. Metformin

Metformin, a biguanide, is the first-line treatment for many Type 2 DM patients. Metformin's main action is to inhibit hepatic glucose production and thus inhibit gluconeogenesis (Brietzke 2015). However, several serious side effects are associated with its use; a 52-month study evidences a vitamin B12 insufficiency. In addition, the study found that metformin reduces the intestinal absorption ability of Vitamin B12 by 90%. Tolerance is another side effect of metformin, but that can be managed by taking the drug with food and by using extended-release formulations. However, such changes may not be appropriate for certain groups like the elderly. GI issues and anorexia are two other metformin side effects that have frequently also been reported. Additionally, it has to be administered carefully in patients with chronic kidney disease and congestive heart failure, both of which have a significant risk of developing lactic acidosis.

4.2. Sulfonylureas

Due to their function in glycemic control in Type 2 Diabetes in its early stages, sulfonylureas are one of the most commonly administered classes of oral hypoglycemics. It is also one of the least expensive. It accomplishes this by depolarizing the membrane by blocking the potassium channel (K ATP), allowing calcium to enter the cell, and then inducing the release of insulin from storage vesicles. As a first- or second-line therapy for Type 2 DM, it is used extensively and well-adopted. In the first month, hypoglycemia—which occurs more frequently in glimepiride users than in glyburide users and may be related to acute coronary presentations—is its most frequent adverse event. Sulfonylureas are also contraindicated in patients with elevated creatinine levels and in various other drug-drug interactions involving cytochrome p450.

4.3. Thiazolidinediones

As with insulin secretagogues, PPAR receptors are the site of action for several thiozolidinediones, including rosiglitazone and pioglitazone. These may be indicated as a monotherapy or dual therapy with either sulfonylureas or metformin in Type 2 DM. This leads to the activation of several genes, which improves insulin secretion and inhibits nuclear signaling pathways like those involving NF-KB. In addition, this class of medications, which functions by increasing insulin action and secretion due to decreased lipids in multiple cells, is linked to an increase in fatty acid uptake. However, adverse effects have mostly been associated with reported bone loss, which may eventually lead to a 50% greater risk of fracture.

4.4. Alpha-Glucosidase Inhibitors

By slowing the absorption and digestion of carbohydrates, alpha-glucosidase inhibitors such as acarbose are associated with a decrease in postprandial hyperglycemia. However, when used with insulin or an insulin secretagogue, it appears to produce hypoglycemia and has extra adverse effects like flatulence and discomfort in

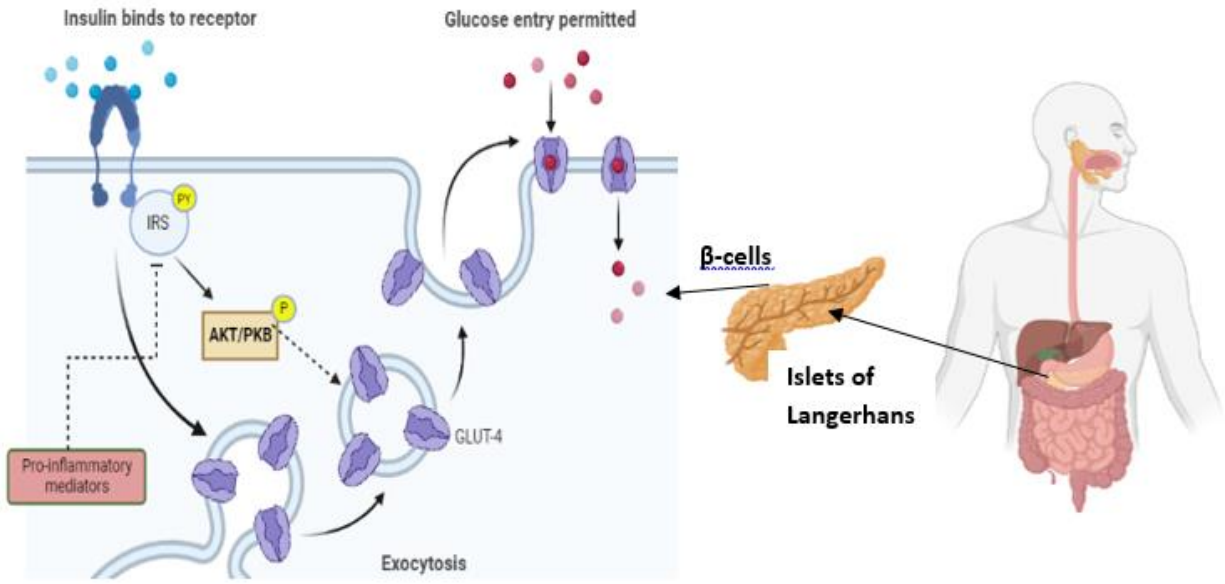

Figure 2. Cascade of pro-inflammatory markers affecting β-cells of pancreas altering insulin signal transduction (IRS) by AKT/PKB phosphorylating IRS. GLUT4 undergoes exocytosis on insulin sensitivity allowing intracellular uptake of glucose molecules that may otherwise cause the release of pro-inflammatory cytokines and disrupt the cycle.

the abdomen, especially when taken with metformin.

4.5. Dipeptidyl peptidase-4 inhibitors

DPP-4 inhibitors are expected to enhance islet function and glycemic management in Type 2 diabetes. This is accomplished by raising incretin levels, which the enzyme dipeptidyl peptidase-4 would otherwise block, promoting insulin release and decreasing glucagon in response to dietary intake.

In addition to causing various adverse effects like headaches and respiratory tract infections, vildagliptin and alogliptin have been shown to result in hepatic impairment that requires enzymatic monitoring. As a result, nausea, nasopharyngitis, and upper respiratory tract infection are among the most frequently reported adverse reactions.

4.6. Insulin

Patients with all kinds of diabetes are treated with insulin. When human insulin-like NPH failed to mimic endogenous insulin, insulin analogs, including aspart, lispro, gluisine, detemir, and glargine were developed to do so. For pre-meal coverage, rapid-acting insulins with both faster and shorter durations of action have been developed, while long-acting insulin remains compliant, requiring only once-daily dosing. However, severe hypoglycemia is one of the most serious side effects of parenteral insulin, with complications such as hypovolemic shock leading to death. It has been a great challenge to develop new and improved insulin with a broad safety therapeutic window.

5. Challenges with Current Treatment Options

The widespread adoption of existing diabetic mellitus treatment alternatives has, to date, also had many challenges. As mentioned earlier, incretin analogs frequently cause gastrointestinal adverse effects. In addition, the use of insulin has been associated with undesirable side effects in many patients, which include hypoglycemia and weight gain (Heise 2022). The long-term adverse effects have not been maintained since individual

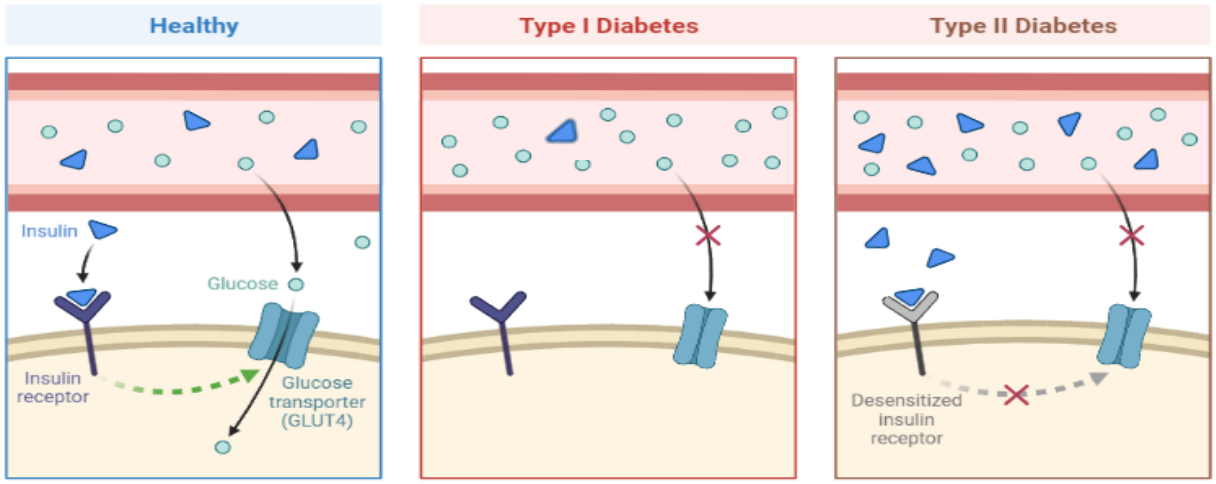

Figure 3. Figure indicating insulin release in Healthy, Type I DM, and Type II DM states.
a) Healthy cells with normal insulin secretion and sensitivity maintain optimum homeostatic intracellular glucose uptake through GLUT4 transporters. b) Type I Diabetes: Reduced insulin secretions allowing minimal glucose uptake through the membrane. GLUT4 transports are not activated due to insulin insufficiency. c) Type II Diabetes: Reduced insulin sensitivity also resisting the sensitization of insulin receptors preventing insulin uptake and further leading to hyperglycemia indicative of higher blood concentrations of glucose.

response heterogeneity has also been found to play a crucial role in drug response.

Pharmacokinetic considerations have strongly influenced orally administered medications in terms of absorption and metabolism. This could further be influenced by the microbial enzymes in the gut interfering with the drug's active or inactive metabolites, increasing its ability to remain inactive or pharmacologically toxic. Metformin's adverse effects associated with gastrointestinal disorders, for example, could be attributed to its impairing effect on E. coli's folate metabolism. The presence of these complex microbiome interactions may also influence drug effects in diabetes management. Sulfonylureas, on the other hand, with a prolonged half-life, have been demonstrated to increase the risk of hypoglycemia in patients with renal disorders by around five times. Biguanide inhibition of gluconeogenesis in the liver may also contribute to its adverse effect associated with lactic acidosis in hepatically impaired patients, resulting in hepatotoxicity, henceforth contradicting its use in patients with impaired liver. A study on the usage of sulfonylureas and insulin in elderly patients came to the conclusion that both medications are risky since they can cause life-threatening hypoglycemia (Inamdar and Kulkarni 2017).

With the aid of pharmacogenomics analysis of a link between nucleotide variants and drug resistance, genetic causes appear to play a significant role alongside numerous non-genetic variables such as intestinal, renal, and hepatic abnormalities.

Drug responsiveness has been explored in relation to polymorphism in genes related to drug metabolisms, such as CYP2C9, and insulin signalings, such as ABCC8, PPARG, and KCNJ11 (Pollastro et al. 2015). Furthermore, DM and its management have resulted in an overburdened healthcare budget in both the developed and developing worlds, with an estimated cost of USD 548 billion in 2013 (Kokil et al. 2015).

Considering various natural remedies with a relatively low cost may be a way forward in undeveloped and developing countries to overcome the drawbacks associated with cost, pharmacokinetics, receptor-specific pharmaceutical choices, and several physiological aspects. This approach might also benefit

developed countries by providing a uniform treatment, which can help overcome other pharmacological and non-pharmacological factors associated with them.

6. Remedies From the Plants

There is a great need for effective, safe, and economical treatments for diabetes owing to the long-term use and adverse effects of the present hypoglycemic drugs.

Although using herbal medications as an alternative therapy to conventional medications is not a new strategy to overcome dissatisfied outcomes from oral hypoglycemics, higher treatment costs of insulin therapy, and increasing overall side effects of anti-diabetes, there has been a revival of interest in herbal medicine recently. The phytocompounds from medicinal plants are being exploited for use in specific diseased conditions and can be combined with other plants/phytocompounds to create complex formulations, particularly for DM, hence improving glycemic control and becoming less insulin-dependent (Choudhury et al. 2018).

6.1. *Momordica charantia*

Momordica charantia L. (Cucurbitaceae), sometimes known as bitter gourd or melon, is widely planted in many tropical areas. Its extensive historical use in the management of DM and various in vitro and in vivo investigations have documented its beneficial effects on blood glucose and lipid concentrations (Çiçek 2022). In metabolic disorders such as diabetes, in-vivo studies, including alloxan-induced diabetic rat models, have confirmed the α-glucosidase inhibitory activity of the methanolic extract of M. charantia. It showed improved insulin and glucose levels and thus may be used as a therapeutic adjunct in diabetic patients (Hussain et al. 2022). Studies on its toxicology profile have not revealed any significant negative effects in humans. The fruit of M. charantia did not exhibit lethality at doses up to 200 µg/ml. However, the LD50 of the seed extract was found to be 50 µg/ml.

6.2. *Limonium axillare*

The bark and root of *Limonium axillare* have been used as an antidiabetic remedy in various parts of East Africa. Its antidiabetic activity may be attributed to a mechanism involving α-glucosidase and α-amylase inhibition, resulting in greater glucose uptake via enhanced GLUT2 and GLUT4 expression, increased insulin secretions, and antioxidant potential. This antidiabetic mechanism has been confirmed in both in-vivo and in-vitro studies.

In a separate investigation, the ethanol extract of *L. axillare* root (REE), at a dose of 500 mg/kg, reduced blood glucose levels in the streptozotocin-induced diabetic animal model by boosting the expression of GLUT2 and GLUT4. At the same time, diabetic rats' pancreatic tissue damage was greatly diminished. Further, in-vitro studies of REE at IC50 revealed its radical scavenging activity as well as inhibitory α-glucosidase and α-amylase activity (Abdel-Sattar et al. 2021).

6.3. *Taraxacum officinale* & *Momordica charantia*

Combination therapies of extracts may also be used as a treatment of Type 2 DM. The improved antidiabetic activity was found in the chemical quantification of diabetes-linked enzymes such as DPP-4, α-amylase, and α -glucosidase that were inhibited by the polyherbal combination of *T. officinale* and *M. charantria* when analyzed through liquid chromatography-mass spectroscopy (LCMS). Furthermore, in an in-vivo study on diabetic rats with glibenclamide and metformin as standards, the combination of extracts showed blood glucose-lowering activity concluding it to be a potential treatment source in diabetes (Perumal et al. 2022).

6.4. *Centaurea species*

The antidiabetic properties of *Centaurea* species leaf extracts have been studied using in-vivo and in-vitro techniques. *Centaurea* species have been found to be effective in lowering blood sugar, secreting insulin, and promoting hepatic glycogenolysis, particularly *C. papposa* dichloromethane extract, which has the strongest α -glucosidase inhibitory activity, and *C.*

centaurium n-hexane root extract, which has the strongest α -amylase inhibitory activity.

When given in an STZ-induced diabetic mouse for two months, methanolic extracts of *C. alexanderina* roots at different concentrations where 600 mg/kg dose resulted in reductions of 9.4% and 10.5% in blood glucose at 1 and 2 hours and 300 mg/kg dose resulted in a reduction of 2.8% in 2.5 hours, respectively (Fattaheian-Dehkordi et al. 2021).

6.5. Aloe pulcherrima

The leaf latex of *Aloe pulcherrima* has shown anti—hyperglycemic and diabetic dyslipidemic activity when administered for two weeks in high-fat fed diabetic-mice due to the presence of various phytochemicals such as flavonoids, alkaloids, glycosides, and terpenoids. This was found by investigating the latex's antioxidant activity that was concentration-dependent, with 800 g/ml showing the highest inhibition. Sucrase, maltase, and -amylase enzymes were all inhibited by A. *pulcherrima* leaf latex (IC50 = 2.92 g/ml, 11.81 g/ml, and 14.92 g/ml, respectively) (Amare, Meharie, and Belayneh 2020). This discovery points to the possible development of a safe and effective herbal treatment for DM.

6.6. Rhazya stricta

R. stricta belonging to the Apocynaeceae family has a central stem with dense semi-erect branches mostly found in parts of Asia and Pakistan, and has been investigated in various pharmacological and toxicological studies. *R. stricta* at doses of 8 g/kg produced significant decreases in plasma glucose concentration at 0.5 and 1 h after treatment in streptozotocin-diabetic rats loaded orally with glucose (1 g/kg), reducing plasma glucose to 24.32 mM within 30 mins on an oral glucose tolerance test as compared to the untreated diabetic group with plasma glucose at 35.82 mM. (Tanira et al. 1996).The majority of extracts of the plant demonstrated remarkable antidiabetic effects, with IC50 values of 169 g/ml for β-secretase inhibition and an increase in GLP1 secretion. When extract-treated mice were compared to control mice, in vivo studies revealed a substantial reduction in blood glucose and HbA1c levels, as well as a positive impact on other variables, including lipid levels, liver functions, and glomerular functions (Mahmood et al. 2020).

6.7. Chenopodium ambrosioides

Chenopodium ambrosioides leaves are frequently used in Moroccan traditional medicine to address diabetes and other ailments. (Assaidi et al. 2014).

In a study to determine the antidiabetic potential and toxicity of *C. ambrosioides* in comparison to control, its aqueous and methanolic extracts lowered blood glucose levels at 60th minute when checked at intervals of 30, 60, 90, and 120 minutes. In another study, glibenclamide at 5 mg/kg reduced blood glucose by 46.91%, while aqueous extract of plant reduced it by 16.72% compared to control and other treatment groups. With an LD50 of 2000 mg/kg, single oral administration of aqueous and methanolic extracts may help reduce rats' blood glucose levels (Kasali et al. 2022).

6.8. Gynura procumbens Merr. extract

Gynura procumbens Merr. (GP) is found in Malaysia and other countries in Southeast Asia. Due to the herb's anti-inflammatory properties in disorders like diabetes, it is used as a treatment for a variety of inflammatory-associated conditions (J.N. Tan et al. 2022). *Gynura procumbens* extract's potential has been examined utilizing a variety of qualitative and quantitative data, including in-vitro procedures employing HPLC. Through various analytical techniques, including western blot and enzyme-linked immunosorbent assay, the expression of several inflammatory cytokines, such as TNF-α and NfkB phosphorylation, was decreased. These findings support the extract's ability to treat inflammation-related diseases and as a potential source for treating inflammatory conditions such as DM (J.N. Tan et al. 2022).

6.9. Seriphidium stenocephalum

A plant-derivative Stenophocol was structurally described and demonstrated to show antidiabetic action after being obtained from *Seriphidium stenocephalum*, an Asteraceae family plant. Due to its therapeutic characteristics, this substance, which has a botanical origin, has been widely used for various ailments in Pakistan and Afghanistan

Table 1. Tabulated Herbal Remedies used in the treatment of Diabetes Mellitus

Plant Name	Family	Part Used	Extract/Isolated Compound	Reference
Limonium axillare	Plumbaginaceae	Root and Bark	Ethanolic extract of axillary root (REE)	(Abdel-Sattar et al. 2021)
Momordica charantia	Cucurbitaceae	Fruit	Methanolic extract of fruit	(Çiçek 2022)
Taraxacum officinale	Asteraceae	Flower	Aqueous dandelion extract	(Lis and Olas 2019)
Centaurea species	Asteraceae	Roots, Leaves	Dichloromethane extract of *C. papposa* n-hexane extract of *C. centaurium* roots Methanolic extract of *C. alexanderina* roots	(Fattaheian-Dehkordi et al. 2021)
Aloe pulcherrima	Asphodelaceae	Latex of leaf	Methanolic extract of latex	(Amare, Meharie, and Belayneh 2020)
Rhazya stricta	Apocynaceae	Root	Root extract	(Mahmood et al. 2020)
Chenopodium ambrosioides	Amaranthaceae	Leaves	Aquesous and methanolic extracts of leaves	(Kasali et al. 2022)
Gynura procumbens Merr	Asteraceae	Root	Ethanolic and Methanolic extract from the root	(H.L. Tan et al. 2016)
Seriphidium stenocephalum	Asteraceae	Leaf	Methanolic extract	(Nusrat Shafiq et al. 2014)
Caffeic acid phenolic derivative	Lamiaceae	-	n-octyl caffeamide	(Gou et al. 2016)
Caralluma edulis	Apocynaceae	Root	Methanolic extract of the root	(M. Khan et al. 2022a)
Corchorus olitorius	Malvaceae	Leaves, Seeds	Methanolic extract from leaves	(Egua et al. 2013), (Nakaziba et al. 2022)
Leptadenia hastata	Asclepiadaceae	Leaves	Ethanolic and methanolic extract from leaves	(Attah et al. 2019), (Chukwuma et al. 2022)
Calotropis species	Apocynaceae	Latex, Leaves	***C. procera:*** Hydroalcoholic extract of leaves ***C.gigantea:*** Chloroform extract from the leaf	(Kumar and Padhy 2011)
Caralluma europaea	Apocynaceae	Flowers, leaves, fruit	Methanolic extract	(Dra et al. 2019; Ouassou et al. 2021)

in the form of pastes and nutraceuticals (Nusrat Shafiq et al. 2020). This hydroquinine derivative demonstrated inhibitory activity against glycogen synthesis with an IC50 of 8.794 μM vitro investigations. The inhibition of glycogen phosphorylase would significantly improve the management of DM, particularly type II (N. Shafiq et al. 2022). Based on these results, stephonocol may be considered a promising plant-derived chemical that offers type II diabetics a suitable means of managing their blood glucose levels.

6.10. Caralluma edulis

Caralluma edulis is a plant-derived species of perennial herbs in the genus *Caralluma* that belongs to the Apocynaceae family and is found in Pakistan's mountainous regions. This plant has been known to have hypoglycemic and anti-inflammatory potential (M. Khan et al. 2022a). In a study, methanolic extracts of *Caralluma edulis* roots demonstrated the highest bioactive compounds isolated, with significant anti-inflammatory and antidiabetic activity in a subacute diabetic animal model with minimal adverse effects at a dose of 200 mg/kg. In-vivo studies in alloxan-induced diabetic models revealed that the extract's ability to increase insulin was comparable to Glibenclamide, a synthetically available line of oral hypoglycemic therapy. Different phytochemicals (such as alkaloids) in the extract may lower blood sugar levels via processes that either entail inhibiting α-glucosidase or involve increased secretion from pancreatic islet cells. Damage to β-cells, which frequently happens in DM patients, may also benefit from its anti-inflammatory effect (Maria Khan et al. 2022b), making it a possible natural agent for delaying or preventing diabetes progression.

6.11. Corchorus olitorius

The leaves and seed extracts of the plant *Corchrus olitorius* have been shown to have potential antihyperglycemic effects (Egua et al. 2013). Methanolic extracts of *C. olitorius* were administered in alloxan-treated rats that confirmed antihyperglycemic activity and antidiabetic activity. When the antidiabetic activity was studied for methanolic leaf extracts of *Corchorus olitorius*, antihyperglycemic activity was observed in comparison with the control (Nakaziba et al. 2022) hence making it an antidiabetic remedial option of the herbal source.

6.12. Leptadenia hastata

According to a recent report, the roots and leaves of *Leptadenia hasata*, a member of the Asclepiadaceae family, have demonstrated pharmacological actions in conditions like DM (Attah et al. 2019). *L. hastata* ethanolic extracts contained phytochemical constituents that were confirmed in-vitro as inhibiting α-glucosidase and α-amylase with 1C50 values of 14.14 and 4.22 g/mL, respectively. (Chukwuma et al. 2022). Another study found that *L. hasata* leaf extract had significant antihyperglycemic effects in streptozotocin (STZ)-induced diabetic rats. It was later confirmed that ethanolic and methanolic extracts of the leaf also regulate blood glucose in alloxan-induced hyperglycemic rats (Kabir et al. 2021). In a different investigation, phytochemical analysis of the plant product's n-hexane extract revealed the presence of terpenoid, which has antidiabetic potential (Attah et al. 2019). These results suggest that different *L. hasata* extracts have hyperglycemia-lowering pharmacological activities, indicating their antidiabetic significance as a potential practical treatment for DM.

6.13. Calotropis species

Calotropis species, belonging to the Apocynaceae family, is reported to have latex-secreting plants with a diverse range of medicinal properties. The latex part of *C. gigantea* is traditionally used for the management of DM. *C. procera*, another of its similar subtypes, has shown reno-protective effects confirmed by reduced glycemic levels through hepatic glycogen restoration and oxidative stress as well as histopathological parameters in in-vivo studies against alloxan-induced diabetic renal damage in rats (Kumar and Padhy 2011). Non-competitive α-amylase and α-glucosidase activity of *C. procera* leaves with IC_{50} of 7.80 and 3.25 mg/mL, respectively, was also

observed that validated its antidiabetic activity due to its phytochemicals (Kazeem et al. 2016).

6.14. Caralluma europaea

The aerial part of *Caralluma europea*, a member of the Apocynaceae family, has demonstrated significant pharmacological activities in treating various diseases, particularly DM, especially in resource-poor developing countries, while also being cost-effective and having fewer side effects (Dra et al. 2019; Ouassou et al. 2021). In a recent study on its antidiabetic potential, *Caralluma europaea*, showed promising *in-vivo* results in an alloxan-induced diabetes animal model that confirmed its antihyperglycemic effects. The plant also displayed protection against pancreatic Langerhans, as observed through morphometric analysis on administering its methanolic extract. - *In-vitro* studies showed an antioxidants effect (Dra et al. 2019). In another study, morphometric analysis on the administration of *Caralluma europaea* methanolic extract has shown its hypoglycemic effects along with the pancreatic protective activity. It was revealed in vitro that ferulic acid, having the highest extract concentration and an LD50 of more than 2000 mg/kg, might be responsible (Ouassou et al. 2018). These studies demonstrate how herbal sources like these could be a successful diabetic care strategy in nations experiencing economic hardship.

6.15. Caffeic acid phenolic derivative (N-octyl caffeamide)

N-octyl caffeamide is a polyphenol derivative obtained from honeybee propolis, related to caffeic acid phethyl ester (CAPE) (Gou et al. 2016). In order to assess its antidiabetic potential, in vitro and in vivo studies were conducted. In a recent study, the antidiabetic effects of n-octyl caffeamide were noted via its involvement in AMP-activated protein kinase (AMPK) activation and Protein tyrosine phosphatase 1B (PTP1B) inhibition, both of which had shown excellent glucose-lowering activity. In-vivo studies in high-fat-induced obese animal models also evaluated the compound's involvement in slowing diabetes progression via AMPK regulation. This compound indirectly reduces insulin resistance, improves GLUT4 transport, and may work as a potential treatment for Type 2 DM (Wu et al. 2022). Numerous CAPE derivatives studied for their cytotoxicity showed a 3–16% drop in viable cells while simultaneously improving glucose absorption by about 70% (Eid et al. 2010). One or more of these polyphenolic derivatives may be a potential candidate in slowing the development of diabetes and become a cheaper and safer option to currently available oral hypoglycemics.

7. Conclusions and Future Directions

Since diabetes mellitus is one of the most complex pathological conditions, its treatment may not be simple. Moreover, the challenge of lowering disease prevalence, particularly in less developed nations, has been exacerbated by a number of linked factors that continue to exist despite the current therapeutic approaches. These factors include associated economic burden, genetic polymorphism, uncertainty regarding the efficacy of current medications, adverse effects associated with pharmacological treatment and various drug interactions, and changes in pharmacokinetics and physiological functions.

Given these findings, it may be necessary to develop natural diabetes management treatments. This could be a promising step toward enhancing positive treatment outcomes. Numerous herbal treatments have been investigated through experimental studies, which showed favorable antihyperglycemic characteristics against diabetes, such as the ability to reduce oxidative stress in pancreatic cells or inhibit the enzymes α-glucosidase or α-amylase, along with showing relatively lower toxic effects as discussed in the review.

Moreover, there are no well-organized and conducted clinical trials to authenticate the use of natural remedies. To gain a thorough understanding of patient response to herbal treatments, overcoming obstacles like lack of funding, dearth of skilled and trained personnel,

poor data quality, and volunteer education may be necessary. These challenges must be met to conduct well-controlled trials to evaluate the safe and effective use of natural remedies in DM as an alternative to current pharmacological treatment, ultimately minimizing disease progression, decreasing prevalence, and improving lifestyle.

Conflict of Interest

The authors declare that they have no competing interests.

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Study Approval

NA

Consent Forms

NA.

Authors Contribution

MA conceptualized the study and wrote the final manuscript, AZ helped in the analysis and writing the first draft, did the review analysis.

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