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Review

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Herbal Products in Diabetes Management: Therapeutic Potential, Clinical Relevance, and Regulatory Challenges

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Abstract: The rising occurrence of diabetes mellitus is attributed to many factors. Despite the effectiveness of the latest therapeutic agents, long-term use has been affected by their side effects, expense, incompleteness and patient non-compliance. Herbal and plant-derived therapies, which were previously used traditionally, have gained much more interest as complementary or alternative approaches to diabetes mellitus treatment. Herbal medicine represents a complex mixture of numerous phytochemicals; the action of each phytochemical is associated with its potential to produce an antidiabetic effect through multiple methods. These methods include stimulating insulin release, increasing insulin sensitivity, inhibiting carbohydrate digestion, modifying glucose transporters, and decreasing oxidative stress. The purpose of this review is to comprehensively evaluate the use of herbal medicines in controlling diabetes, while also integrating both mechanistic and clinical studies. The pathophysiology of diabetes with the corresponding herbal treatment will also be reviewed, in order to provide an in-depth assessment of the methods of action of herbal medications. Additionally, we consider clinical significance of therapeutic uses for medicinal plants using both evidence-based and clinical data. This helps us to evaluate limitations and inherent problems, such as their inability to produce consistent results and variation in plant composition. We also assess regulatory limitations and restrictions that affect clinical applications and guide future implementation strategies for diabetes mellitus treatment.

Keywords: diabetes mellitus; herbal medicine; clinical relevance; regulatory challenges; insulin resistance

1. Introduction

Diabetes mellitus is characterized by an increased level of blood sugar (hyperglycemia) caused by either a lack of adequate insulin production by the pancreas or by the body not using insulin correctly, or by both of these factors occurring together [1]. In the 10th Edition of the IDF Diabetes Atlas, it is shown that an estimated 537 million adults had diabetes in 2021, with projections for 2045 showing this number rising to 783 million, a 46% increase [2]. The complications of diabetes may range from microvascular diseases such as diabetic nephropathy, retinopathy, and peripheral neuropathy to macrovascular disorders such as coronary artery disease and stroke [3]. Despite the beneficial results obtained through the existing drugs such as metformin, sulfonylureas, GLP-1 receptor agonists, and SGLT-2 inhibitors, these therapies still come with some significant limitations. Metformin, which has been found to cause B12 deficiency due to its interference with absorption at the ileal cubilin receptors [4]. Sulfonylureas can be associated with hypoglycemia and weight gain, whereas SGLT-2 inhibitors are known to cause urinary tract infections, genital mycotic infections, and euglycemic diabetic ketoacidosis [5]. These limitations, taken together contribute to increasing interest in complementary and alternative medicine. Herbal and plant-derived supplements provide an additional form of therapy for people with diabetes because of their multiple

active ingredients and diverse pharmacological targets. For example, the polyphenolic compound curcumin, isolated from the plant species *Curcuma longa*, regulates inflammatory pathways by modifying the function of NF-κB, leading to a reduced oxidative stress environment and increased insulin sensitivity, which decreases diabetic complications [6]. The gymnemic acids obtained from the *Gymnema sylvestre* plant regulate glucose absorption in the intestine and stimulate insulin secretion by the pancreatic cells. [7]. These agents collectively act on insulin signaling, glucose metabolism, oxidative stress, and inflammatory pathways that are central to the pathogenesis of diabetes.

The research findings from the clinical trials demonstrate that the application of certain herbal formulations has already shown some clinically significant improvements in glycemic index and lipid profile and thus, suggest that they have a potential for treatment of diabetes. However, there are several factors that restrict using herbal formulations to treat diabetes within the existing medical community, including differences in the composition of phytoconstituents, lack of quality control, poor quantity of clinical studies and differences between countries in their approaches to regulating their safety, documentation and approval [8]. All of these aforementioned factors also prevent widespread global use of herbal formulations, due to the variation between countries on how they require herbal formulations to be evaluated for safety and their subsequent documentation and approval. For example, while the European Medicines Agency (EMA) evaluates traditional herbal medicines under a well-defined regulatory pathway, many herbal products in the United States are regulated as dietary supplements under the Dietary Supplement Health and Education Act (DSHEA) framework, and India's AYUSH system operates under its own distinct standards [9]. Therefore, it is vital to evaluate the clinical efficacy of herbal formulations for the treatment of diabetes and to examine the regulatory barriers that prevent the use of these innovative treatments.

2. Pathophysiology of Diabetes Mellitus

2.1. Classification of Diabetes

Diabetes mellitus is an ongoing metabolic disease that occurs when the blood glucose levels rise due to either too little insulin being produced by the pancreas or insulin not working properly in controlling blood glucose levels. There are three primary types of diabetes: type 1, type 2, and gestational (diabetes caused by pregnancy). These three forms of diabetes are classified by the reason for developing them and also by the way they present themselves clinically. Type 1 diabetes is characterized by insufficient insulin production and the resulting high blood glucose levels (hyperglycemia). It occurs as a result of autoimmune destruction of the β-cells of the pancreas, resulting in inadequate amounts of insulin within the body [10]. Type 2 diabetes mellitus is the most common type of metabolic disorder, as it makes up over 90 percent of cases and is characterized by both insulin resistance and deficiency due to β-cell dysfunction. There are many risk factors that contribute to an elevated blood glucose level, as well as being clinically obese (over-weight), that increase the risk for Type 2 Diabetes (Figure 1) [3].

Gestational Diabetes that occurs during pregnancy typically is a result of hormone-induced insulin resistance in pregnancy and β-cells failing to secrete sufficient amounts of insulin to maintain normal glucose levels. Other range of factors like obesity, family history of diabetes, and maternal age can also trigger this. It can be diagnosed late in the second trimester (13–26 weeks gestation) or early in the third trimester (27–40 weeks) [11].

2.2. Role of Insulin Resistance, Oxidative Stress and β-Cell Dysfunction

Insulin resistance and β-cell dysfunction are the two most common underlying pathological mechanisms that cause diabetes mellitus, including type 2 diabetes. Insulin Resistance can be defined as a decreased biological sensitivity of the target tissues, such as skeletal muscle, fat and liver, to insulin. The main contributing factors to insulin resistance include defects in the insulin action cascade, malnutrition in utero, visceral adiposity, poor physical activity, increased counter insulin hormones, and other pharmacological agents. [11]. In the initial phase of insulin resistance, there is a compensatory hypertrophy and hyperplasia of β-cells, therefore, there is an enhanced β-cell secretion of insulin in an attempt to compensate for the defect in order to maintain glucose levels within normal limits.

Oxidative stress refers to a persistent imbalance between excessive ROS/RNS production and limited antioxidant defence, a situation that occurs in β-cells during the pathogenesis of diabetes. Oxidative stress in β-cells affects secretory capacity and cell viability and both parameters contribute to β-cell failure. Sites of reactive oxygen (ROS)/reactive nitrogen species (RNS) formation in β-cells, as in other cell types, the mitochondrial respiratory chains represent a major source of ROS in β-cells. $O_2^{-}\cdot$ is generated by single electron reduction of molecular oxygen at the inner mitochondrial membrane, mainly by complexes I and III. In islet cells $O_2^{-}\cdot$ production is tightly coupled to mitochondrial metabolism [12]. Chronic hyperglycemia triggers an increased level of ROS synthesis through mitochondrial damage, glucose autoxidation, and advanced glycations, which spills the

antioxidant capability of the body. Prolonged exposure to excessive glucose, higher FFA levels, or both can lead to β-cell dysfunction. Due to the lack of free-radical antioxidant enzymes like catalase, glutathione peroxidase, and superoxide dismutase, β-cells are more vulnerable to ROS. In the peripheral tissues, oxidative stress blunts insulin action by suppressing insulin receptor substrate and PI3K/Akt signalling pathways [13].

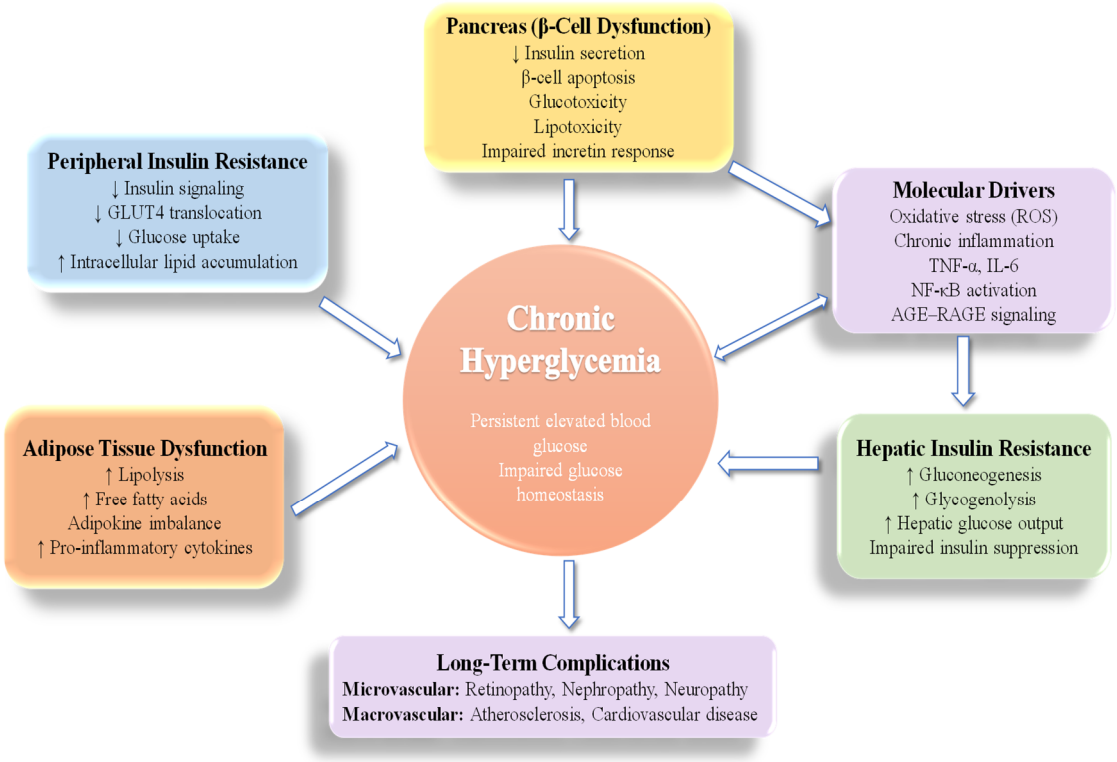

Figure 1. Pathophysiology of Diabetes Mellitus.

Chronic hyperglycemia results from the interaction of pancreatic β-cell dysfunction and insulin resistance in the peripheral tissues, including muscle, liver, and adipose tissue. Hyperglycemia results from the impairment of insulin secretion, uptake of glucose, increased hepatic glucose output, and adipose tissue dysfunction. Oxidative stress, inflammation, and AGE-RAGE signaling play a major role in the molecular mechanism leading to hyperglycemia. All these factors result in chronic micro- and macrovascular complications of diabetes mellitus.

2.3. Molecular Targets Relevant to Herbal Therapeutics

Modern and traditional medicine both reduces blood glucose by stimulating the release of insulin from pancreatic islet β-cells, inhibiting hormones that raise blood glucose and increasing insulin receptors activity. They also decrease glycogen release, improve glucose utilization, eliminate free radicals, correct lipid and protein metabolic disorders, and improve microcirculation. Chronic diabetic problems such as peripheral neuropathy, retinopathy, and cataracts have been linked to aldose reductase, a crucial enzyme in the polyol pathway that catalyzes the conversion of glucose to sorbitol [14]. Based on these targets, antidiabetic drugs can be classified into insulin, insulin secretagogues, insulin sensitivity improvement factors, insulin-like growth factor, aldose reductase inhibitors, α-glucosidase inhibitors, and protein glycation inhibitors. Many natural products, including terpenoids, alkaloids, flavonoids, and phenolics, have demonstrated antidiabetic potential and act through these diverse targets [15].

3. Overview of Herbal Products Used in Diabetes Management

3.1. Traditional Systems of Medicine

With strong philosophical, clinical, and experimental foundations, Ayurveda, Traditional Indian Medicine (TIM), and Traditional Chinese Medicine (TCM) continue to be some of the oldest and most active medical systems. Modern medications increased side effects, the absence of effective treatments for a number of chronic illnesses, the high expense of new medications, microbial resistance, and developing illnesses have all contributed to a resurgence of interest in complementary and alternative medicine. Approximately 60% of people worldwide

utilize traditional remedies made from medicinal plants, and several medicinal plants are used to treat diabetes in India. From the 21,000 plants classified by the World Health Organization as being used medicinally worldwide, 2500 species are found in India, and about 150 of these are utilized on a reasonably considerable scale for commercial purposes (Table 1) [16].

The majority of Ayurvedic practitioners prepare and dispense their own herbal remedies. Numerous Indian medicinal plants, such as *Allium sativum, Momordica charantia, Ocimum sanctum, Pterocarpus marsupium, Tinospora cordifolia, Trigonella foenum-graecum,* and *Eugenia jambolana*, have been shown to have antidiabetic and related positive properties. Many of these medicinal plants also have antioxidant qualities, which may add to their therapeutic effects because diabetes is a multifactorial disease and oxidative stress is a major contributor to its complications [17].

Table 1. Major Herbal Products Used in Diabetes Management.

S. No.	Herbal Product (Botanical Name)	Common Name	Major Bioactive Constituents	Primary Antidiabetic Mechanisms	Level of Evidence	References
1.	*Allium sativum*	Garlic	Allicin, sulfur compounds	It improves insulin sensitivity, exhibits antioxidant and lipid-lowering effects	Preclinical, limited clinical	[18]
2.	*Aloe vera*	Aloe	Aloin, polysaccharides	Aloe enhances insulin sensitivity and has antioxidant activity	Preclinical, limited clinical	[19]
3.	*Capsicum annuum*	Cayenne pepper	Capsaicin	Suppresses hepatic gluconeogenesis via AMPK and FOXO1 phosphorylation	Preclinical	[20]
4.	*Cinnamomum verum*	Cinnamon	Cinnamaldehyde, polyphenols	It has antioxidant activity, improves insulin sensitivity and increases glucose uptake	Clinical	[21]
5.	*Curcuma longa*	Turmeric	Curcumin	It possesses anti-inflammatory, antioxidant activity and improves insulin resistance	Preclinical, clinical	[6]
6.	*Gymnema sylvestre*	Gurmar	Gymnemic acids	It reduces intestinal glucose absorption, increases insulin secretion and β-cell protection	Preclinical, clinical	[22]
7.	*Momordica charantia*	Bitter melon	Charantin, polypeptide-p	It has insulin-like activity, inhibits gluconeogenesis and improves glucose uptake	Preclinical, clinical	[23]
8.	*Morus alba*	White mulberry	Flavonoids, polyphenols	It inhibits carbohydrate digestion	Preclinical	[24]
9.	*Nigella sativa*	Black seed	Thymoquinone	It has anti-inflammatory, antioxidant effects and improves insulin sensitivity	Preclinical, clinical	[25]
10.	*Ocimum sanctum*	Holy basil (Tulsi)	Eugenol, ursolic acid	It improves insulin secretion, antioxidant and anti-stress effects	Preclinical	[26]
11.	*Panax ginseng*	Ginseng	Ginsenosides	Stimulates insulin secretion	Preclinical, clinical	[27]
12.	*Pterocarpus marsupium*	Indian kino	Epicatechin	Helps in β-cell regeneration and improves insulin secretion	Preclinical, limited clinical	[28]
13.	*Salacia reticulata*	Salacia	Salacinol, kotalanol	Inhibits α-glucosidase	Preclinical	[27]
14.	*Trigonella foenum-graecum*	Fenugreek	4-hydroxyisoleucine, saponins	It improves insulin sensitivity, delays glucose absorption and stimulates insulin secretion	Clinical	[29]

3.2. Polyherbal Formulations and Their Therapeutic Rationale

Ayurvedic drug formulation is founded on two concepts: single drug use and multi-drug use; the latter is referred to as polyherbal formulations. Also referred to as polypharmacy or polyherbalism, this important traditional therapeutic herbal technique employs the use of a combination of multiple medicinal herbs to obtain additional therapeutic effectiveness [15]. The antidiabetic effects of individual plant parts are scientifically proven; yet, phytotherapeutic medicines prepared from different medicinal herbs may demonstrate augmented pharmacological effects. The bioactive compounds contained in medicinal herbs, which may include alkaloids, flavonoids, and saponins, play an essential role in conferring the desired therapeutic effects in the treatment of diabetes mellitus. An individual plant may contain more than one phytochemical constituent; hence, combining different medicinal herbs may demonstrate a symbiotic effect in conferring the desired pharmacological effects. The pharmacological therapy of antidiabetic drugs should not only be targeted at controlling the levels of glucose in the body but also aimed at preventing the associated complications of diabetes. According to the results of the meta-analysis, the pharmacological effects of polyherbal formulations resulted in a significant reduction in fasting blood sugar, postprandial blood sugar, and glycated haemoglobin levels in the treatment of diabetes, as compared to control subjects. In addition, the results of the clinical drug evaluation of polyherbal formulations revealed significant effects in lowering blood glucose levels to normal levels in type 2 diabetic subjects. This indicates that polyherbal formulations demonstrate significant effects in managing type 2 diabetes mellitus in humans [30,31].

3.3. Nutraceuticals and Functional Foods with Antidiabetic Potential

Nutraceuticals and functional foods of plant origin have shown promise in the prevention and management of diabetes. Ingestion of diets containing phenolic compounds in large amounts may play a protective role against the development of type 2 diabetes. These secondary plant metabolites are broadly distributed in naturally occurring foods in humans, such as in fruits, vegetables, cereals, chocolate, coffee, tea, beer, cider, and wine, which show improved glucose levels and insulin sensitivity. Polyphenolic compounds play a significant role in inhibiting α-amylase and α-glucosidase, thus slowing down carbohydrate breakdown, which in turn delays the rise in plasma glucose levels. Berry fruits, like blueberry and blackcurrant, have shown strong inhibitory effects towards α-glucosidase, whereas strawberry and raspberry are good α-amylase inhibitors. Although current pharmacological therapy is effective in inducing significant improvement in glucose levels, the associated side effects of pharmacological agents have made scientists explore potential hypoglycaemic compounds of plant origin [32,33].

4. Mechanisms of Antidiabetic Action of Herbal Products

4.1. Enhancement of Insulin Secretion and β-Cell Protection

Natural products exert antidiabetic effects through enhancement of insulin secretion and restoration of pancreatic β-cell function. Insulin secretion from β-cells follows the glucose entry through GLUT2, phosphorylation via glucokinase, increased ATP/ADP ratio, closure of ATP-gated potassium channels, membrane depolarization, activation of voltage-gated calcium channels, and thereafter exocytosis of insulin granules [34]. Dysfunction and apoptosis of β-cells are characteristic features in diabetes pathogenesis due to glucotoxicity, lipotoxicity, oxidative stress, inflammation, and cytokine-induced injury. Various natural molecules such as berberine, mangiferin, and quercetin, and other phytoconstituents have been reported to provide regenerative and anti-apoptotic effect on β-cells, enhancing insulin secretion and restoring islet architecture in experimental models [35]. Herbal drugs also increase β-cell mass by anti-apoptotic action, neogenesis and proliferation of β-cells, enhanced glucose-stimulated insulin secretion pathway, along with a reduction of oxidative stress and inflammation. Further, plant polyphenols protect β-cells against oxidative insult, stimulate insulin release via modifications within ATP-sensitive K^+ channels and intracellular Ca^{2+} signalling, and inhibit pathways leading to β-cell apoptosis [36,37].

4.2. Improvement of Insulin Sensitivity

Insulin resistance is the inability of a person's target tissues, mainly skeletal muscles, the liver, and adipose tissue, to properly respond to the stimulus of insulin. It affects the biological responses of the cells to the insulin hormone. The binding of insulin to the cell membrane causes the activation of the insulin receptor, which in turn activates the insulin receptor substrates (IRS-1 and IRS-2), leading to the activation of the downstream signal cascade including the phosphatidylinositol kinase and the Akt enzyme. In contrast, disorders of the insulin receptor cause reduced concentration and reduced kinase activity. Reduced activity of the phosphatidylinositol kinase, reduced activity of the IRS proteins, and reduced translocation of the glucose transporter are associated with insulin

resistance [38]. Several medicinal plants have shown their ability to enhance insulin sensitivity through the modulation of the activity of insulin signalling molecules, including the insulin receptor substrates, phosphatidylinositol kinase, AMP-activated protein kinase, peroxisome proliferator-activated receptor-γ, and the glucose transporter molecules including GLUT4 and GLUT2. Some plants have also been found to possess anti-protein tyrosine phosphatase 1B (PTP1B) activity, decrease hepatic glucose production, inhibit gluconeogenesis, reduce tumor necrosis factor-alpha (TNF-α) levels, and increase adiponectin levels, among other properties. Clinical, as well as experimental, studies reviewed indicate that these herbal medications produce multi-target effects, supporting their potential use in treating insulin resistance-related diabetes mellitus (Figure 2) [39].

4.3. Inhibition of Carbohydrate-Digesting Enzymes (α-Amylase, α-Glucosidase)

Polyphenol-containing plant extracts have been found to inhibit intestinal α-glucosidase activity with Ki values similar to those of acarbose and voglibose, in addition to α-amylase inhibition, which can help manage postprandial blood glucose concentrations. α-Glucosidase is a carbohydrate-digesting enzyme in the small intestine that catalyzes the final stage of carbohydrate digestion in the small intestine, a process regarded as a therapeutic target in postprandial hyperglycaemia management. Anthocyanin-enriched fractions were found to be potent α-glucosidase inhibitors, while the tannin-enriched fractions were found to exhibit more potent α-amylase inhibition than the others. The inhibition of α-amylase in carbohydrates can help reduce blood glucose concentrations in postprandial states. Polyphenolic compounds can interfere with enzymes in the intestinal brush border, slowing down carbohydrate digestion, hence reducing postprandial blood glucose concentrations [40,41].

4.4. Modulation of Glucose Transporters and Hepatic Glucose Output

Hepatic glucose output (HGO) is a critical factor contributing to fasting and postprandial hyperglycaemia associated with type 2 diabetes. HGO occurs as a consequence of defective insulin signalling. Impaired insulin sensitivity leads to defective inhibition of hepatic gluconeogenesis and glycogenolysis. This finally causes increased glucose production [42]. Ethnobotanically selected medicinal plants of Mexico have been found to reduce HGO through reduced production of glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK), associated with reduced activity of the enzyme glucose-6-phosphatase complex. In addition, they have been found to inhibit protein tyrosine phosphatase-1B (PTP-1B), a negative regulator of the enzyme insulin receptor. Traditional Mexican medicinal plant extracts reduced glucose production significantly and reduced the enzyme activity of the glucose-6-phosphatase complex. In addition, plant extracts were found to improve glucose metabolism by reducing protein tyrosine phosphatase-1B activity, promoting the phosphorylation of insulin receptor substrates, and increasing Akt signaling through the regulation of glucose transporter 2 and glucokinase [43].

4.5. Antioxidant, Anti-Inflammatory, and Lipid-Lowering Effects

Oxidative stress due to high levels of reactive oxidative species has been implicated in the pathogenesis of hyperglycemia, dyslipidaemia, endothelial dysfunction, and low-grade chronic inflammation that is seen in persons with diabetes. Natural antioxidant compounds possess anti-oxidative effects, prevent the production of advanced glycosylation end-products, and exert anti-inflammatory effects. Some medicinal herbs can up-regulate lipid-associated genes, stimulate bile production, lower triglycerides, lower total cholesterol, lower LDL, and raise HDL [44]. Polyphenolic compounds can exhibit antidiabetic effects by inhibiting hepatic gluconeogenesis, improving insulin sensitivity, and affecting inflammatory pathways. Metabolic syndrome is characterized by dyslipidaemia, hyperglycaemia, and low-grade chronic inflammation, which makes it a condition that could be targeted simultaneously using a combination of antioxidative compounds [45,46].

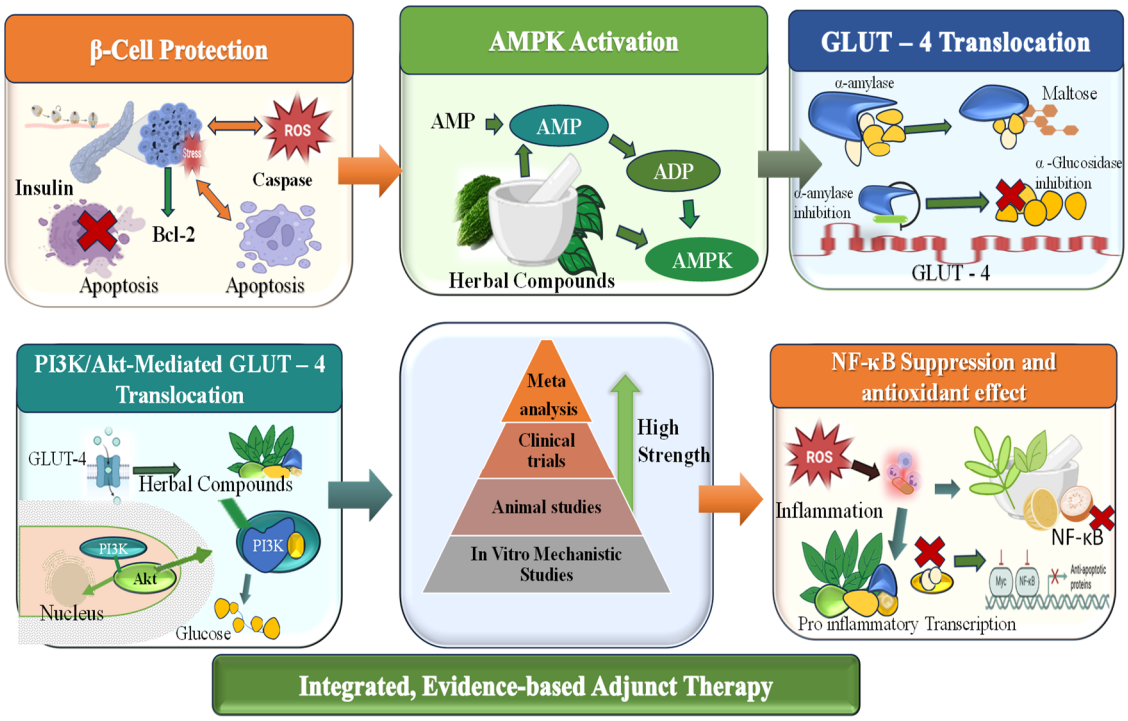

Figure 2. Mechanisms of action of herbal antidiabetic agents and levels of evidence.

Many herbal bioactive compounds are effective at treating diabetes by a variety of mechanisms, such as protecting β-cells from oxidative stress and apoptosis, activating AMPK, and facilitating glucose uptake through GLUT-4 translocation via PI3K/Akt activation. Many of these compounds have also been shown to inhibit α-amylase and α-glucosidase activity, which leads to lower postprandial glucose levels, and suppress NF-κB-mediated inflammation. The Evidence Pyramid provides a graphical representation of the hierarchies of information compiled from various sources, such as *in vitro* studies, human trials, and meta-analyses, based on quality and strength of evidence. It indicates that there is stronger support for adjunctive use than there is for monotherapy.

5. Preclinical Evidence Supporting Herbal Antidiabetic Agents

5.1. In Vitro Screening Models and Biomarkers

Plant extracts and natural products are frequently screened for antidiabetic activity using *in vitro* models, which include enzyme inhibition assays, cell-based bioassays, and molecular approaches. The most commonly used enzymatic assays involve the inhibition of carbohydrate-hydrolysing enzymes, including α-amylase and α-glucosidase, therapeutic targets for the reduction of postprandial hyperglycaemia. Assays of α-amylase utilise starch as substrate and its activity is measured spectrophotometrically following reaction with dinitrosalicylic acid, while α-glucosidase inhibition is measured with *p*-nitrophenyl glucopyranoside as substrate by measuring the release of p-nitrophenol. Insulin secretagogue and insulin-mimetic activities have been investigated with the use of cell-based assays using murine and human β-cell lines, pancreatic islets, adipocytes, and muscle cells. These *in vitro* techniques provide mechanistic information on glucose uptake, insulin secretion, and enzyme inhibition and constitute necessary preliminary screening tools prior to *in vivo* validation [47,48].

5.2. In Vivo Animal Models of Diabetes

In animals, experimental diabetes is induced by pharmacologic, surgical, or genetic methods. Rodents are the animals most widely used because of ease of handling and the ready availability of well-characterized strains. Streptozotocin (STZ) and Alloxan (ALX) are two widely used chemical agents that cause selective destruction of pancreatic β-cells. STZ enters β-cells via the GLUT2 transporter and causes DNA alkylation, whereas alloxan induces β-cell necrosis through reactive oxygen species generation. Depending on the administered dose, models resembling type 1 or type 2 diabetes, as well as glucose intolerance, can be produced. Surgical pancreatectomy models and spontaneous or genetically derived models such as ob/ob mice, db/db mice, Goto–Kakizaki rats, NOD mice, and BB rats are also used to investigate insulin resistance, β-cell dysfunction, and diabetic complications [49,50].

5.3. Toxicological and Safety Evaluation Studies

The preclinical safety studies conducted on herbal antidiabetic formulations have included acute oral toxicity studies, repeated dose toxicity studies in two species, Ames' bacterial reverse mutation assay studies, and *in vivo* micronucleus tests. The standardized polyherbal formulation Synacinn did not exhibit any mutagenic activity in the Ames' bacterial reverse mutation assay tests in *Salmonella typhimurium* strains and exhibited no clastogenic effects up to a dose of 2000 mg/kg in bone marrow micronucleus tests. Safety pharmacology studies on the formulation indicated no significant inhibitory effects on hERG potassium channels and no abnormalities in neurobehavioral tests conducted on rats [51]. The standardized fenugreek extract Fenfuro showed no mortality and no treatment-related toxicity in acute and 28-day repeated dose studies up to 5000 mg/kg dose levels and caused no adverse effects on haematological and biochemical profiles and histopathology in 28-day studies. Ames' assay also indicated no mutagenic potential with this formulation. Hence, the standardized herbal antidiabetic formulations have passed preclinical safety tests under the conditions of the study [52].

5.4. Limitations of Preclinical Findings

Preclinical studies evaluating herbal antidiabetic agents have largely been based on *in vitro* enzyme assays and animal models, such as STZ-induced diabetic rats, and may not fully extrapolate to human clinical outcomes. While significant reductions in fasting blood glucose, lipid parameters, and histopathological improvements are reported in experimental models, translation to clinical practice is complicated by potential herb-drug interactions mediated through cytochrome P450 enzymes and transport proteins. Many herbal extracts demonstrate CYP inhibition or induction *in vitro;* however, precise clinical correlation and dose standardization remain inadequately defined, phytochemical composition varies widely, and proper interaction studies, preceding coadministration, are lacking. Moreover, while animal studies document pharmacokinetic and pharmacodynamic alterations, comprehensive human studies are limited, and further quality research is needed to evaluate safety and efficacy before widespread therapeutic application [53,54].

6. Clinical Relevance of Herbal Products in Diabetes Management

6.1. Evidence from Clinical Trials and Observational Studies

Randomized clinical trials offer the gold standard when it comes to assessing safety and efficacy in diabetes management, though it can be argued that there are some limitations when it comes to restrictions. Evidence gathered from the real world, which offered information on the effectiveness of diabetes management, offered additional data [55]. Studies published in a systematic review of the use of medicinal plants in managing diabetes through clinical trials showed evidence that fasting levels of blood glucose, HbA1c, and insulin resistance showed favorable outcomes for type 2 diabetes. Randomized clinical trials on herbal remedies, including cinnamon, ginger, and turmeric, demonstrated favorable data concerning their use in improving glycemic indices, as well as levels of triglycerides, total cholesterol, and LDL levels. Assessments on randomized trials on natural products showed some limitations, including the failure to randomize, which allowed errors in blinding, reporting, and baseline characteristics [56,57].

6.2. Efficacy in Glycemic Control and Metabolic Parameters

A clinically randomized evaluation of a conventional herbal combination on type 2 diabetes mellitus patients showed that the randomized herbal combination resulted in significant improvement on glycemic parameters after three months of treatment. Measures of glycemic parameters such as fasting plasma glucose and HbA1c concentrations were significantly reduced compared with baseline concentrations and placebo. Approximately 25% and 15% of baseline concentrations were reduced compared with placebo controls [58]. Moreover, the randomized herbal combination was comparable with metformin in the management of reductions of FPG and HbA1c concentrations. Total cholesterol resulted in significant reductions compared with placebo controls. Pharmacotherapeutic evaluation of antidiabetic agents underscores that glycemic management should include a multifactorial approach to the management of diabetes mellitus. Pharmacotherapeutic evaluations underscored that glycemic management should be integrated with a multifactorial pharmacotherapeutic management plan that includes management of lipid fractions and potential drug interactions. This underlines the herbal combination potential management of glycemic parameters among type 2 diabetes mellitus patients conventionally treated [59].

6.3. Role as Monotherapy Versus Adjunct Therapy

However, herbal medicine is being increasingly viewed as a complementary form of treatment, rather than a replacement for conventional pharmacotherapy. Evidence also suggests that the concomitant use of herbal medicines with the conventional antidiabetic agents like metformin, sulfonylureas, and insulin can show better glycemic control and improved insulin levels compared to the use of the herbal medicine formula by itself. A study of the effect of a combination of a herbal formula with conventional anti-hyperglycemic drugs given in combination with the same drugs showed a positive effect in reducing fasting plasma and HbA1c levels, without the dosage of conventional drugs being affected [60]. Another study with Jinlida given in combination with metformin monotherapy showed better HbA1c, fasting, and 2-h postprandial glucose levels being lowered compared to metformin monotherapy. Complementary and Alternative Medicine is defined as the use of therapies in conjunction with the conventional treatment, rather than in place of conventional treatment. Thus, there is evidence to say that herbal medicines can be used as adjunctive therapy to increase the treatment effect [61,62].

6.4. Patient Adherence, Acceptability, and Quality-of-Life Outcomes

Adherence to therapy, which is defined as the degree to which an individual's behavior conforms to accepted guidelines for management, is critical to the optimal management of diabetes mellitus. Non-adherence to treatment regimens is a universal problem, as a result, almost 50% of the population in developed countries is not adherent to prescribed regimens. The acceptance of the illness has been established as an independent predictor for adherence to the prescribed regimens; hence, acceptance of the illness is to be encouraged as a method for enhancing non-adherence to regimens in type 2 diabetic patients [63]. Results from quality-of-life assessment instruments, including the SF-36 and QOLID showed improved satisfaction with therapy as well as an enhanced perception of general health for patients on herbal therapy as opposed to synthetic preparations. With the QOLID instrument, there was an improved vitality as well as an enhanced level of irritability for the patients receiving the herbal therapy. Adherence to regimens has been associated with improved outcomes and quality of life for diabetic patients [64].

6.5. Herb–Drug Interactions and Clinical Safety Concerns

Herbal medicinal products are intricate combinations of bioactive compounds that may affect drug metabolizing enzymes such as cytochrome P450 isoenzymes and interact with conventional antidiabetic drugs via pharmacokinetics [65]. Herb-drug interactions may exhibit pharmacokinetic or pharmacodynamic effects such as an impact on absorption, distribution, metabolism, excretion of the active pharmaceutical ingredient of the co-administered medication, or effects on the therapeutic response without significant effects on plasma concentrations. Antidiabetic medicines are known to be metabolized by cytochrome P450 isoenzymes and transporters such as P-glycoprotein. There is an increased potential risk due to this. Herbal and conventional antidiabetic drug therapies can evoke additive or synergistic effects of hypoglycemia, diminishing effects of the medication, and increased risks of adverse effects such as hypoglycemia. Since herbal therapies are often under disclosed and because of inadequate data on their effect on patients with diabetes mellitus, there appears to be considerable doubt regarding the potential risks [59,66].

7. Standardization and Quality Control of Herbal Antidiabetic Products

7.1. Challenges in Phytochemical Variability

Herbal formulations contain a number of bioactive constituents. Their qualitative or quantitative variations may occur due to variations in the source material, geographical location, climate, time of harvest, processing during the manufacturing stage, transportation, and storage conditions. Polyherbal formulations are complex multicomponent products containing scores to even hundreds of bioactive constituents. A polyherbal formulation may not be as easy to standardize compared to synthetic drugs containing a smaller number of bioactive compounds with well-defined qualitative and quantitative characteristics mentioned in classical texts. Variations in the quality of herbal drugs or materials used for the manufacturing process may lead to a number of problems with polyherbal formulations [67]. In addition to this, the problem of contamination with microbes, aflatoxins, pesticides, and heavy metals has also been stated as one of the significant problems limiting the reliability of herbal antidiabetic formulations [68].

7.2. Marker-Based Standardization Approaches

Selection of chemical markers suited to the purpose is the foundation for the quality control of herbal medicines, including authentication of the material, examination of the crude and prepared materials, and recognition of noxious constituents present in the compound. Chemical markers can be therapeutically active, bioactive, characteristic, major, synergistic, correlative, toxic, and general constituents together with the spectra obtained in the fingerprint technique. When the therapeutically active chemical constituents are unknown or unclear, the use of bioactive or characteristic chemical markers is done for qualitative and quantitative testing. Analytical markers, as per the European Medicines Agency, include active chemical markers, which can be used for testing, notwithstanding the active constituents being unknown, and the other class being utilized for quality testing only [69].

7.3. Good Agricultural and Collection Practices (GACP)

WHO guidelines lay emphasis on GACP for medicinal plants to ensure that herbal raw materials are of good quality, safe, and authentic. GACP covers all aspects related to sustainable cultivation, genetic authenticity of the planting material, appropriate harvesting techniques, and the avoidance of environmental contaminants. It is advisable that suitable planting sites should be selected, plant material should be authentic, and proper agricultural practice should be followed with minimal use of pesticides to maintain the integrity of raw materials. Traceability systems are necessary to be implemented for documentation of origin, cultivation, harvesting, and handling at every stage of the supply chain. Adherence to GACP contributes to reducing variability, preventing adulteration, and ensuring the consistent quality of herbal medicinal products [70].

7.4. Good Manufacturing Practices (GMP) for Herbal Products

Good Manufacturing Practices (GMP) are important for sustaining the quality, safety, and consistency of herbal medicines. GMP for herbal medicines include raw material sourcing and identification, facility and equipment design, development of standard operating procedures, batch records and documentation, quality control, product testing and release, stability studies, and recall. In reporting GMP practices by the WHO, there are several steps and requirements that are noted. In detailing these requirements, attention is given to important practices such as proper documentation, training of staff, hygienic practices, and validation of processes and analytical methods. In addition to that, quality assessment and standards are noted as this impacts the safe usage, efficacy, and general acceptability of herbal medicines. This indicates that GMP plays a critical role in preventing and managing issues of contamination, adulteration, and variability [70,71].

7.5. Analytical Techniques for Quality Assurance

The intricate nature of the herbal medicines and extracts available in the market dictates the requirement for suitable analysis, as the outcomes will invariably help in the identification, standardization, and detection of adulterants present in the medicines. The choice of the method is also influenced by the analysis objective, which includes methods like microscopy, spectrometry, spectroscopy, chromatography, and hyphenated techniques like GC/MS, HPLC/MS, or MS/MS. Chromatography-based and spectroscopy-based methods are commonly used for the detection of undeclared synthetic drugs and chemical adulteration in herbal medicines. UPLC-QTOF-MS/MS, LC/MS/MS, TLC-SERS, densitometry, and infrared spectrophotometry, along with multivariate calibration, have emerged as efficient tools to expand the spectrum of available methods to achieve quality assurance [72].

8. Regulatory Framework for Herbal Antidiabetic Products

8.1. Global Regulatory Perspectives (WHO, FDA, EMA)

Oversight of the regulatory process differs around the world and can range from the U.S. FDA and EMA to national agencies, each with structured processes for approval. The U.S. FDA holds new drugs through the IND and NDA processes; similarly, botanical products fall within these processes, facilitated by the establishment of a Botanical Review Team focused on pharmacognostic evaluation [9]. The European Medicines Agency (EMA) utilizes centralized authorization procedures and publishes assessment reports for approved medicines publicly. WHO reports highlight that herbal medicines are used by large numbers of people worldwide, recommending national quality specifications, monitoring safety, and regulation to assure their efficacy and protection of consumers. Furthermore, differences in regulatory requirements-such as the size of clinical trials, safety assessment, and post-marketing surveillance-have regional consequences on drug development strategies. These

collectively aim at ensuring quality, safety, and effectiveness, while responding to the increasing global burden of diabetes [73].

8.2. Regulatory Status in India (AYUSH, CDSCO)

India monitors the regulation of herbal medicines through the Drugs and Cosmetics Act of 1940, along with the Drugs and Cosmetics Rules of 1945. These guidelines cover the quality, safety, and efficacy of AYUSH system medicine. The regulating body is the Department of AYUSH, which is the governing body responsible for the regulation, promotion, and standardization of the sale of Ayurvedic, Siddha, Unani, and Homoeopathic medicines. India specifies the standards of identity, purity, and strength of these drugs through the Ayurvedic, Siddha, Unani, and Homoeopathic Pharmacopoeias of India. Permit for manufacturing is a requirement, and Schedule T, under Chapter IV-A of the Act, specifies the Good Manufacturing Practices to be incorporated by herbal drug companies. Indian herbal medicines introduced to the modern system will be required to adhere to the requirements of the Drug Controller General of India (DCGI). Furthermore, the Pharmacovigilance Programme for AYUSH (PvP-Ayush), set up recently (2017), has developed a national system for the evaluation of adverse drug reactions (Table 2) [74,75].

Table 2. Global Regulatory Comparison of Herbal Antidiabetic Products.

S. No.	Region	Classification	Clinical Evidence Required	Pre-Market Approval	References
1.	EU (EMA)	Traditional Herbal Medicinal Products (THMPD), Well-established use	Bibliographic evidence (long-term use)	Required (simplified registration)	[76]
2.	India (AYUSH/CDSCO)	Classical / Proprietary herbal medicines	Limited (based on traditional use, additional data for proprietary drugs)	Partial	[75,77]
3.	USA (FDA)	Dietary supplements (DSHEA), Botanical drugs	Not required for supplements, Required for botanical drugs	Not required for supplements, Required for drugs	[78]
4.	Global (Comparative Insight)	Varies by region	Increasing emphasis on safety, quality, efficacy	Strengthening regulatory frameworks globally	[79,80]

8.3. Clinical Evidence Requirements for Approval

Clinical assessment of herbal medicinal products should be preceded by gathering relevant preclinical data on pharmacology and toxicology and obtaining approval from appropriate health authorities and ethics committees before the start of any human studies. Clinical trials are conducted in phases to assess safety and efficacy, using procedures similar to those used for conventional drugs. WHO operational guidelines recommend regulatory requirements to justify the clinical testing of herbal products, giving assurance on quality and standardized assessment. Data submitted for the registration of drugs may include pharmaceutical, pharmacological, toxicological, and clinical documentation. In the United States, all antidiabetic drugs go through a regulatory pathway, such as the Investigational New Drug (IND) and New Drug Application (NDA) processes, through the FDA. Regulatory requirements, such as size and safety evaluation in clinical trials, differ among regions, which would make a difference in the process of approval [81,82].

8.4. Labelling, Claims, and Post-Marketing Surveillance

Once a drug receives marketing authorization, it will go through controlled post-marketing surveillance to assess ongoing safety and unwanted effects of the product through structured Pharmacovigilance systems. From Spontaneous reports, clinical trials, meta-analyses, individual case reports, and large databases, etc., safety signals can arise. Regulatory agencies may take action as needed; these actions can include regulating changes to the product labelling or packaging insert, adjusting dosing, restricting uses, providing boxed warnings, and having the drug removed from the market if the risk is greater than the benefit. Communication by Regulatory Agencies of Safety and Risks to healthcare professionals and consumers occurs through either updating the labelling, providing warnings, or sending out official notifications [83]. All Pharmacovigilance systems in Europe, the United States, and India focus on the three key components of regulatory oversight; structured adverse event reporting, signal detection, and benefit-risk evaluation. As a result, post-marketing surveillance provides an essential component of protecting the safety of patients and maintaining an optimal benefit-risk ratio of marketed medicinal products [84].

9. Regulatory Challenges and Gaps

9.1. Lack of Harmonized Global Regulations

Requirements for regulation of herbal substances vary widely depending on the country where they will be sold, so their classification is inconsistent from place to place and even within a single jurisdiction (when products are classified similarly). The requirements for the submission of toxicological evidence also differ widely between jurisdictions; for example, there are different types of clinical trial data and ways to document adverse effects, some jurisdictions will consider the history of traditional uses as part of the regulatory process. Manufacturers frequently experience challenges in delivering a consistent product to the global market due to differences among each jurisdiction's regulatory requirements, initiatives to develop a uniform standard for regulation of herbal medicines are being undertaken at an international level by entities such as the World Health Organization [9,74].

9.2. Safety Monitoring and Pharmacovigilance Issues

The existing pharmacovigilance systems have come a long way; however, they still face some challenges, such as underreporting of adverse drug reactions (ADRs), inconsistent quality, and discrepancies in regulations by jurisdiction. There are many limitations to pre-marketing clinical trials, like small sample sizes, limited timeframes, and selective populations, which require strong post-marketing surveillance to establish the safety profile in real-world conditions. While spontaneous reporting systems and signal detection methods help identify potential risks, it is important that they are not impacted by factors such as false positives, poor reporting, and inconsistent data formats that would impede an accurate determination of product safety. Strengthening infrastructure for safety surveillance, improving education and awareness about pharmacovigilance, and promoting regulatory convergence will all contribute to addressing these challenges [85,86].

According to WHO guidance, providing structured quality controls and regulatory oversight of herbal medicines during their life cycle will help safeguard the public's health and provide protection from unsafe or ineffective products [70].

9.3. Intellectual Property and Patent Challenges

The legal rights associated with the creations of the mind found in the nutritional supplement industry can act as a catalyst for innovation, but also as an obstacle to market entry through patent and regulatory hurdles. The high expense of research and development, lengthy litigation times, licensing fees and the disparate application of intellectual property law throughout the world create challenges for small and medium enterprises entering global markets. Emerging markets have also experienced increased risk of intellectual property theft and limited enforcement of intellectual property laws. In addition, the use of exclusivities linked to intellectual property rights limits the accessibility to affordable products, particularly in developing markets; thus, requiring that balanced intellectual property systems be implemented so that innovation can be protected while also providing access to markets for all companies equally [87].

9.4. Ethical Concerns and Consumer Protection

Trust by consumers in the safety and efficacy of Nutraceuticals (including vitamins, minerals, herbal foods) and Traditional Chinese Medicine (TCM) has been damaged by regulatory fragmentation, resulting in discrepancies within various regions in all areas of regulation, including ingredient approval, evidentiary standards, and risk management. The perceived safety of natural products leads to increased misuse, self-medication, and under-reporting of harmful effects related to the use of TCM and nutraceuticals. There are too many nutraceuticals and complementary medicines (TCM) on the market, and insufficient standardization of their ingredients, contamination or adulteration, combined with a lack of adequate pre-clinical and clinical testing, create a higher incidence of health problems associated with their use; thus, the use of uniform and enhanced regulatory oversight, quality assurance, and pharmacovigilance systems is necessary to enhance consumer protection and promote responsible business practices [88,89].

10. Emerging Trends and Future Perspectives

10.1. Integration of Herbal Products into Evidence-Based Diabetes Care

The amalgamation of traditional and conventional medicine in the management of diabetes focuses on a holistic approach that incorporates both traditional and conventional aspects of medicine. There is a consensus that the management of diabetes with conventional antidiabetic agents in combination with traditional remedies, taking

into account possible interactions of these agents with conventional drugs, has helped in the management of contemporary outcomes in diabetes [90]. New pharmacological studies indicate that the use of herbal formulations in the management of diabetes has a multicomponent, multitarget mechanism of action, which aligns with the systems approach to therapy rather than the single-target drug approach. Advances in the science of network pharmacology, metabolomics, artificial intelligence, and molecular docking have helped in the validation of the mechanisms of herbal formulations, which can then be incorporated in the management of disease in contemporary healthcare. Although new therapeutic agents in the management of diabetes are being discovered, the inaccessibility of these agents and the side effects of conventional agents emphasize the need to explore complementary herbal therapies in the management of disease in evidence-based practice [91,92].

10.2. Advances in Formulation and Drug Delivery of Herbal Actives

The limitations associated with using plant-derived antidiabetic medicines are primarily due to their poor solubility, permeability and physicochemical stability leading to low bioavailability. To help alleviate these issues, researchers are developing a wide variety of nanoscale-based systems to deliver antidiabetic medicines, including liposomes, niosomes, polymeric nanospheres, nanoemulsions, solid lipid nanospheres and metallic nanoparticles [93]. Nanoscale-based drug delivery systems have exhibited great promise as possible methods to improve the stability and bioavailability of antidiabetic medications and allow for sustained release through improved delivery techniques. In addition, many of the newer drug delivery methods, such as polymeric nanoparticles, lipid-based nanoparticles, nanocrystals, nanosuspensions, and inorganic nanoparticles, have been designed to enhance the pharmacokinetic properties of both traditional and alternative [i.e., herbal] antidiabetic agents [94]. Finally, natural nano-based products produced from plants and their derivatives appear to be viable options to enhance both the bioavailability and targeted delivery characteristics of plant derived antidiabetic agents through the use of innovative delivery systems.

10.3. Role of Systems Biology, Metabolomics, and AI in Herbal Research

Network Pharmacology combines Systems Biology, Bioinformatics, and Pharmacology to develop compound-target-pathway networks that allow researchers to analyze the multicomponent and multitarget properties of herbal products. Metabolomics will allow researchers to create complete profiles of the biochemical changes induced by herbal treatments through the use of a variety of platforms, including HPLC, NMR and Mass Spectrometry [89]. Artificial Intelligence and Machine Learning-based virtual screening, predictive modelling, and large-scale data analysis will allow researchers to use Natural Products in their research. The combination of omic technology with computational methods will help researchers through systematic validation of herbal medicines and accelerate the discovery of bioactive compounds [95].

10.4. Strategies to Strengthen Clinical and Regulatory Acceptance

Using a combination of clinical or regulatory standards, both homemade and store-bought natural and herbal medicines could increase both the method and manner of standardising the use of all-natural products with respect to modern science. The use of all-natural substances in the creation of drugs should consider using a systems biology (biological sciences) perspective in creating a whole/natural source of drug development, rather than an isolated chemical molecule source. Whole systems biology is made possible with advanced technologies such as genomic identification (e.g., DNA barcoding), proteomic analysis, metabolomic analysis and high throughput screening that can confirm authenticity, quality assurance and confirmation of the mechanics of action of natural medicine. The use of new and emerging technologies such as artificial intelligence, computational modelling and newer forms of analytical tools will expand and enhance the avenues for designing new drugs, evaluating their safety and identifying their molecular targets. In a collective manner, the combination of data-driven technologies with standardized methods of evaluation of traditional natural product therapeutics will provide greater capability for translational (whereby both types of products become interchangeable) development of their applications and to have broader regulatory recognition of natural product-based therapies [96].

11. Conclusions

Herbal products can be an effective way to manage diabetes and have multiple ways that they may help by increasing insulin production, enhancing sensitivity to insulin, decreasing the breakdown of carbohydrates by enzymes, speeding up how glucose enters cells, and providing antioxidants and anti-inflammatory effects. Preclinical studies that have been conducted using *in vitro* screening and *in vivo* in animals support that there are

mechanisms by which these products work, as do toxicology studies that show early safety when they are used under controlled settings. Clinical studies have shown that using herbal products along with other diabetes medications will result in improved blood sugar levels and improve the overall health of people with diabetes. Although there may be differences in the phytochemicals present in herbs, poorly designed studies, a lack of research into the interactions between the herb and other medications used, and a lack of adequate regulations make it difficult to find a smooth transition from research to actual use of these herbal products for managing diabetes.

Standardization of herbal products with the use of marker-based methods, following the guidelines of Good Agricultural Practices (GAP) and Good Manufacturing Practices (GMP), strong analytical methods for evaluation, and providing a system to identify potential adverse drug reactions will assist in the production of safe and effective herbal products. New advances in systems biology, metabolomics, artificial intelligence, and nanotechnology systems for delivering herbal medicines will help to provide more complete knowledge about the way that herbal products work, will support the use of herbal products to treat diabetes, and will support the efforts to develop regulatory guidelines for the use of these products. Continued efforts to strengthen the harmonization of globally accepted regulatory systems and the integration of these regulations based on sound scientific evidence will support a greater realization of the full therapeutic effect of herbal products for managing diabetes.

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Conflicts of Interest

The authors declare that with regard to the reported data in the manuscript, the authors have no conflict of interest with respect to any entity or individual.

Use of AI and AI-Assisted Technologies

During the preparation of this work, the author(s) used ChatGPT and Quillbot in order to improve language and readability. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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