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Review

Exploring the plant-derived bioactive substances as antidiabetic agent: An extensive review

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ABSTRACT

Diabetes mellitus (DM) is a metabolic syndrome. Diabetes has become more common in recent years. Chemically generated drugs are used to lessen the effects of DM and its following repercussions due to unpleasant side effects such as weight gain, gastrointestinal issues, and heart failure. On the other hand, medicinal plants could be a good source of anti-diabetic medications. This article aims to determine any plant matrix's positive potential. Food restriction, physical activity, and the use of antidiabetic plant-derived chemicals are all being promoted as effective ways to manage diabetes because they are less expensive and have fewer or no side effects. This review focuses on antidiabetic plants, along with their bioactive constituent, chemically characterization, and plant-based diets for diabetes management. There is minimal scientific data about the mechanism of action of the plant-based product has been found. The purpose of this article is to highlight anti-diabetic plants and plant-derived bioactive compounds that have anti-diabetic properties. It also provides researchers with data that may be used to build future strategies, such as identifying promising bioactive molecules to make diabetes management easier.

1. Introduction

Diabetes mellitus (DM) is defined by serious higher glucose levels occurring due to abnormalities in the production of insulin, or insulin resistance also some individuals can have both reasons [1]. Diabetes affects roughly 29.1 million people each year and is the 7th largest death in the US, obtained to the report CDC [2]. It will be one of the primary causes of mortality in 2030, according to the WHO, with a death rate doubling between 2005 and 2030 [3]. There are two different types of diabetes such as type 1 diabetes mellitus (T1DM) (lack of insulin production) type 2 diabetes mellitus (T2DM) (resistance to insulin activity) and gestational diabetes mellitus is a term used to describe diabetes that develops during pregnancy [4]. T1DM patients make for 5–10% of all diabetics, with type 2 diabetes (Fig. 1) accounting for the rest [5]. On the other hand, the production of insulin is reduced due to the failure of pancreatic-cell (Fig. 2) failure [6]. Gestational diabetes mellitus is defined as "a kind of glucose intolerance that develops in the second and third trimesters of pregnancy, resulting in hyperglycemia of varying severity" [7]. Characteristics that are shown by diabetic patients like as desire for drinking water, polyuria, blurred eyesight, and weight loss. Ketoacidosis or a non-ketotic hyperosmolarity can cause a person to suffer a lack of water in the body and, insufficient treatment can cause mortality [8].

Along with physical activity, a healthy diet is critical for diabetes management [9]. If the treatment is properly administered, all types of oral hypoglycemic medications and insulin are safe in older patients, each medicine has some restrictions related to hypoglycemia risk or co-morbidities [10]. According to Curtis (2007), despite the availability of numerous effective oral hypoglycemic medications 5–10% of case develops secondary failure. Secondary failure occurs when beta-cell activity deteriorates, medication adherence is poor, weight gain, less exercise, dietary changes, or illness occurs [11]. In underdeveloped nations (especially in rural regions), pharmaceutical medications and insulin used to treat diabetes are rare, expensive, and have substantial side effects. Treatment costs are expensive and unaffordable in developing nations, which is a major basic barrier for DM. In light of this,

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phototherapy and the use of natural items with anti-diabetic properties are often the first lines of treatment and care [12].

Herbal medicine can be a good way to counteract the negative effects of synthetic drugs. Diabetes has traditionally been treated with a variety of medicinal plants [13]. Bioactive compounds are the basic essential component of current medicines, mainly in rural areas, due to their availability, low side effect, and cost-effectiveness [14]. Human pancreatic α-amylase is the digestive system's major enzyme, hydrolyzing starch, glycogen, and different oligosaccharides into smaller oligosaccharides such as maltose, maltotriose, and a variety of - (l-6) and - (1−4) oligoglucans. α -Glucosidase, which is found in the small intestine's brush border, breaks down disaccharides further, making them available for intestinal absorption. The breakdown of dietary starch occurs quickly, resulting in a postprandial spike in blood sugar [15,16]. Inhibition of α-amylases and α-glucosidases is one of the treatment procedures for post-prandial hyperglycemia. Synthetic medications such as acarbose and miglitol block -amylase and -glucosidase, however, they can cause stomach distention, gas, vomiting, and diarrhea [17]. Different types of tannin, flavonoid, catechin, and gallic acids, are identified as antioxidant and hydrolytic enzyme inhibitors α-amylase and α-glucosidases which help to maintain -cell function and lower blood glucose levels [18,19].

One of the main ideas offered to explain the hyperglycemia-induced beginning of diabetic complications is that it is caused by an imbalance between reactive oxygen species capacity and antioxidant defense capability [20]. The production of ROS enhance in all types of diabetic conditions, and diabetic onset is connected to oxidative stress, which is caused by oxidation, no enzymatic protein glycation, and oxidative breakdown of glycated proteins [21]. Because it plays an important part in diabetes etiology, antioxidant treatments may be useful in its therapy [22].

T2DM is becoming more common, with numerous Asian countries ranking in the top ten countries with the greatest number of diabetics [23]. In diabetes therapy, chemical elements taken from plants, called phenolic polyphenols, can reduce amylase absorption [24]. A variety of new compounds from diverse distinct plants have been discovered to have antidiabetic actions [25]. Even though there are over 400 plant species with hypoglycemic action in the literature, researching new antidiabetic medications from natural plants remains appealing as they consist of phytoconstituents that can be used for DM [26]. Thus, the discovery of the best pharmacological component, as well as an effective therapeutic system for the treatment of this condition [27].

This study aims to discuss the possible active compound of natural plants with anti-diabetic properties which could serve as an alternative to diabetes management.

2. Pancreatic β-cell physiology: insulin biosynthesis

Insulin is made up of 51 amino acids and has a molecular weight of 5.8 kDa. The insulin gene, on the other hand, produces preproinsulin, a 110-amino-acid precursor. Preproinsulin contains a hydrophobic N-terminal signal peptide that interacts with cytosolic ribonucleoprotein signal recognition particles (SRP) [30], as do other secreted proteins. Preproinsulin translocation over the rough endoplasmic reticulum (rER) membrane into the lumen is facilitated by SRP. This happens through the peptide-conducting channel [31,32]. where a signal peptidase cleaves the signal peptide from preproinsulin to produce proinsulin [33]. Proinsulin is next folded and three disulfide bonds are formed [5], a process that requires a variety of endoplasmic reticulum (ER) chaperone proteins, including the protein-thiol reductase [34]. The folded proinsulin is transported from the ER to the Golgi apparatus, where it enters immature secretory vesicles and is broken to release insulin and C-peptide after maturity of the three-dimensional shape. Insulin and C-peptide, as well as islet amyloid polypeptide (IAPP or amylin) and other less abundant β-cell secretory products, are then deposited in these secretory granules [35,36]. Despite the fact that several factors influence insulin production, glucose metabolism is the most critical physiological event that increases insulin gene transcription and mRNA translation [37]. Glucose infusion increased relative proinsulin mRNA levels by three to fourfold within 24 h in 3-day fasting rats, and this effect was prevented by pharmacological transcription inhibition with actinomycin D [38]. These findings imply that glucose plays a key role in insulin biosynthesis regulation, which is influenced at least in part by changes in proinsulin mRNA expression. Furthermore, glucose has a crucial role in the stability of insulin mRNA. Insulin mRNA stability was reduced at lower glucose concentrations and enhanced at higher glucose concentrations, according to in vitro investigations [39,40]. Surprisingly, increasing intracellular cAMP levels prevents this decrease [41]. The insulin gene is only found in a single copy in most species, while rats have two non-allelic insulin genes (insulin I and II). Their number of introns and chromosomal sites varied [42]. The 5′-flanking region of all insulin genes determines tissue and cell type specific expression [43]. In

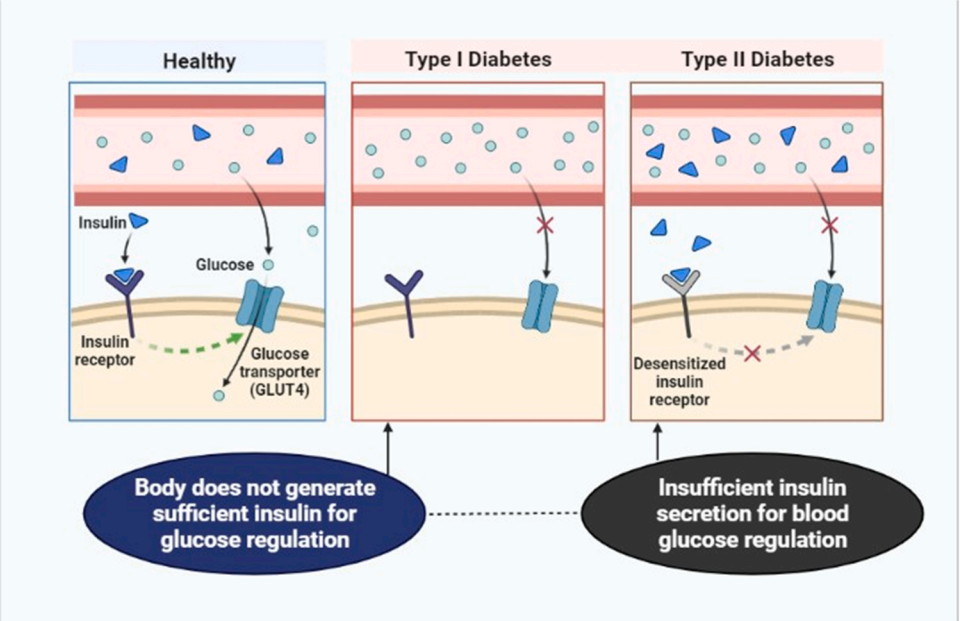

Fig. 1. Different types of diabetes and their symptoms. The pancreas does not manufacture insulin inside the body in type 1 diabetes, resulting in a weakened immune system. As a result, the person is unable to produce insulin on their own. In type 2 diabetes, the amount of insulin produced by the pancreas is insufficient to maintain the body's glycemic profile. The significant development in Type 2 Diabetes cases at an earlier age, which has overweight children even before puberty, has caused alarm for diabetic people, particularly in developing countries. Insulin is required for type 1 diabetic patients to maintain blood glucose control. Patients with type 2 diabetes can keep their glucose levels under control by eating a healthy diet and exercising regularly [28].

both rat and human insulin genes, transcriptional factor binding sites that determine insulin's exclusive production in β-cells are positioned between − 520 and + 1 base pairs (bp) from the transcription start site (TSS) [37,43,44] There is a conserved region between − 350 bp and the TSS of mammalian insulin genes that affects cell-type-specific insulin production. Interactions within these conserved regions are responsible for the majority of transcriptional control. The stretch between − 340 and + 91 has been identified as the main insulin gene transcription enhancer region [45–50], which determines cell-specific and glucose-regulated insulin gene expression (Fig. 3).

3. Medicinal plants in diabetes prevention

From ancient times in our traditional system, various preparations of plants have been used in the treatment of diabetes mellitus. Further research on finding new plant-derived active compounds could bring a revolutionary change in the pharmaceutical sector or to the existing dietary supplements shortly. Table 1 shows data of some widely available plants which exhibit anti-diabetic properties with their details [52].

4. In-vivo studies in developing antidiabetic agents

Diabetes impacts a variety of metabolic processes in human tissues, many of which can be treated with drugs [84]. Animal models are better suited to assessing medicinal plant's anti-diabetic capabilities in this respect.

Here we have described the detailed in-vivo test information about some of the plants containing anti-diabetic effects;.

4.1. *Vernonia amygdalina Del. (Asteraceae)*

Vernonia is the most often used plant in the Vernonia genus. *Azadirachta indica* (neems) effects against diabetes were shown by the ethanolic extraction were discovered in an animal. The plasma glucose decreases in an animal in a given extraction mixture and acrid leaves directly differentiate between chlorpropamides and non-diabetic controls. These discoveries supported a previous study that found a low glycemic effect in diabetic animals tested with *Vernomia amygdalina* extraction [85].

4.2. *Hypoxis hemerocallidea Fisch. (Hypoxidaceae)*

Hypoxis hemerocallidea is the most extensively employed in African treatment plants. There are few scientific findings on the anecdotal assertion that hemerocallidea has anti-diabetic properties. Streptozotocin was treated with aqueous extraction and the effect on diabetics was shown in diabetic rats which were further evaluated by the investigation of Zibula & Ojewole and Ojewole, who found significant drops in the animals' blood glucose levels [86].

4.3. *Gymnema sylvestre (Apocynaceae)*

Gymnema sylvestre (Asclepiadaceae*)* is a woody climber identified in India's central and southern tropical forests. By rebuilding pancreatic islets and beta cells in diabetic rats, a water-soluble extract of *Gymnema sylvestre* leaves lowered blood glucose levels. The glycogen level of the tissue in glucose-fed rats was reduced by an aqueous dissolved fraction of alcohol extraction of *Gymnema sylvestre* leaves, but it was not affected in normal rats [87]. In T2DM, a daily dose containing 400 mg water-soluble extract of Gymnema sylvestre significantly reduced insulin demands while also lowering HbA1c levels [88].

5. In-vitro evaluation of antidiabetic agents

One of the most common methods for managing blood sugar levels is to inhibit critical enzymes. *Abelmoschus moschatus, Alangium salvifolium, Boerhaavia diffusa, Capsicum frutescens, Mangifera indica, Momordica charantia, Ocimum sanctum, Punica granatum, and Zingiber officinale* have all shown enzymes inhibition effect with potential benefits on diabetes and hyperglycemia [89].

5.1. *In vitro studies on glucose uptake*

In HIT-T15 Hamster pancreatic â-cells, an aqueous extract of *Momordica charantia* demonstrated strong cell mending actions and the promotion of insulin secretion [90]. *Pterocarpus marsupium* methanol extracts exhibited glucose transportation activity in the PPARa mediated PI3 kinases dependent manner, while *Pterocarpus marsupium* isoflavone showed glucose transportation effect in a PPARa mediated but PI3 kinase-independent manner [91].

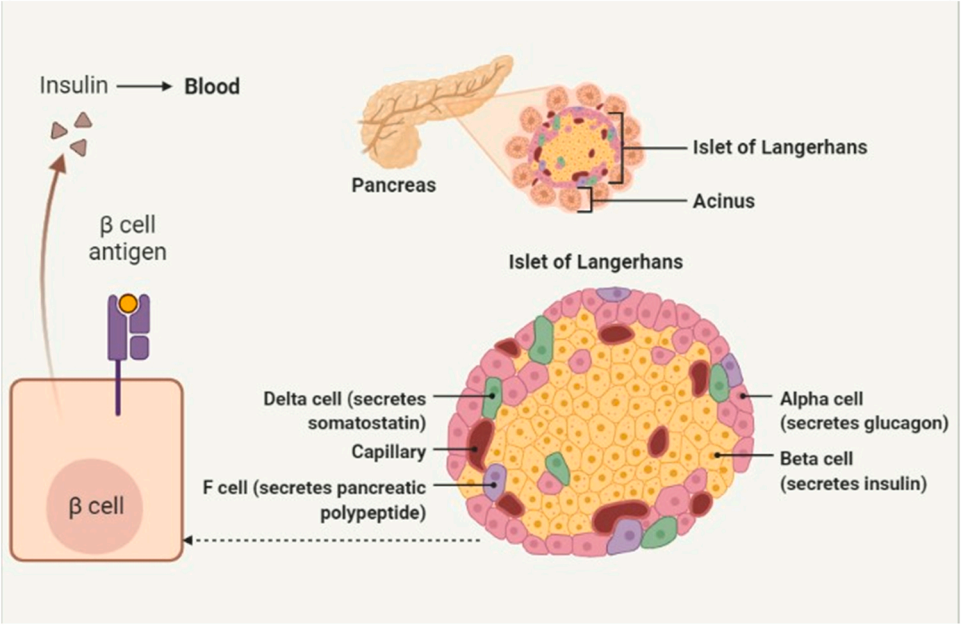

Fig. 2. Representation of pancreatic cells and the release of insulin. Pancreatic endocrine tissue is organized as clusters of cells dispersed throughout the exocrine pancreas and makes up less than 1% of the pancreas. The islets of Langerhans are heterogeneous cell clusters made up of three main cell types that release different hormones. The bulk of islet cells is insulin-secreting cells that also serve as glucose sensors, releasing insulin in response to elevated blood glucose levels. The right panel depicts the process that regulates insulin production from β cells [29].

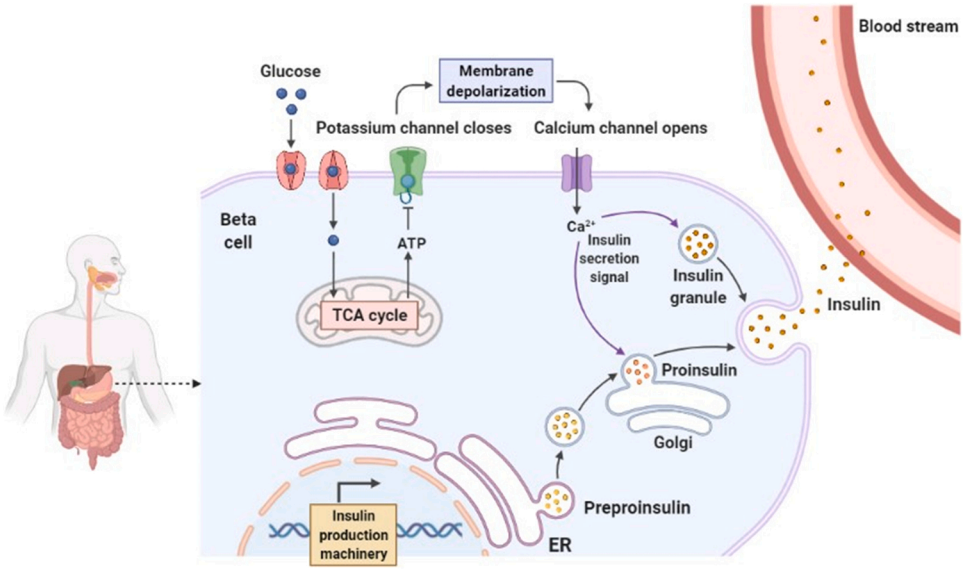

Fig. 3. Glucose-induced insulin secretion pathways. Glucose enters the beta cell quickly via specialized glucotransporters and is phosphorylated by glucokinase, which controls metabolic flux via glycolysis. The tricarboxylic acid cycle produces reducing equivalents once pyruvate enters the mitochondria. After then, ATP is produced, and the increased ATP/ADP ratio induces the ATP-sensitive K+ (KATP) channels in the membrane to close. The influx of extracellular Ca2 + and activation of exocytosis are caused by sequential depolarization of the plasma membrane. Insulin may be affected by other chemicals produced in the mitochondria [51].

5.2. *In vitro studies using α-amylase inhibition assay*

α -amylase is an enzyme that breaks down starch into simpler sugars and is essential in the human body. Decomposition of carbohydrates may help persons with diabetes manage their insulin resistance and glycemic index [92]. Citrus *macroptera Montr.* Methanol extract had an IC50 of (3.6380.190) mg/mL, whilst normal acarbose had an IC50 of (0.9120.015) mg/mL. Methanol extract, like acarbose, strongly reduced α -amylase activity in a dose-dependent manner. As a result, *C. macroptera* extract has a mild anti-amylase activity [93]. *Andrographis paniculata* ethanolic extract inhibited α -glucosidase activity in a concentration-dependent mode. It also had a mild inhibitory effect on á-amylase. *Andrographis paniculata* was addressed as a promising choice to treat T2DM, according to the findings [94].

5.3. *In vitro studies using insulin- secreting cell lines*

The presence of insulin secretagogue in *Tinospora cripa* extract caused a rise in cytosolic ca2 + uptake from the extracellular medium while suppressing ca2 + efflux from the cytosol, resulting in insulinotropic action in HIT-T15 cells. HIT-T15, MIN6, AND RINm5F are a few examples. Insulin secretion is triggered by permeabilization of the beta-cell plasma membrane and channel-independent Ca2 + influx into the beta-cells. Aqueous extract of *Viscum album* (mistletoe) increase secretion in clonal BRIN-BD11 pancreatic beta-cell in a dose-dependent manner [95].

6. Importance of herbs in diabetic management

Diabetes mellitus is a serious metabolic illness, and medicinal herbs play an important part in its therapy. Traditional plants have been shown to offer potent anti-diabetic capabilities with no negative side effects [96]. According to studies, traditional plants are used as the first-line treatment for eighty percent of people in underdeveloped countries. In many poor nations, traditional medicines play an essential role in primary health care [97].

Herbal medicine is now frequently utilized to treat diabetes due to the lower cost and easier accessibility of medicinal plants over conventional drugs. With low adverse effects, this therapeutic alternative can be utilized as an anti-diabetic treatment when combined with other anti-diabetic medications or insulin [98]. Clinicians should employ herbal medications to treat DM and associated complications, according to the World Health Organization. Apart from their hypoglycemic activity, research has shown that a variety of antidiabetic plants have other helpful qualities such as antihypertensive, nephroprotective, and retinoprotective activities, which may be useful against the most prevalent complications of diabetes. As a result, eating these plants could be beneficial in the treatment of diabetes and its consequences [99].

7. Natural products for the prevention of insulin resistance in diabetic conditions

Type 2 diabetes mellitus occurs in 90% of individuals, with insulin resistance (IR) being the primary pathophysiological sign. In adipose cells and skeletal muscle cells, IR was mostly attributed to the malfunction of glucose. IR is mainly ascribed to the dysfunction of glucose transporter 4 (GLUT4) moving from the cytoplasm to the membrane, which was linked to an aberrant insulin signaling pathway [100]. Adipose tissue has been proven in numerous studies to aid maintain glucose homeostasis by boosting glucose absorption in skeletal muscle and lowering glucose production in the liver. As a result of insulin resistance, the incretin action is reduced, glycogenesis is reduced, and proinflammatory proteins and cytokines are produced in greater quantities (Fig. 4). After the insulin combines with its receptor, the downstream signal transduction is mainly controlled by insulin receptor substrate-R-as-mitogen-activated protein kinase (IRS-RaS-MAPK) and IRS-1- phosphoinositide-3-kinase-protein kinase B (PKB, known as Akt) IRS-1-PI3K-Ak [101–103]. The former plays a significant role in various biological processes–glycogen synthesis, metabolism, glucose transport, and utilization, which are indispensable in the occurrence and development of IR, while the latter regulates the growth and apoptosis of cells [104–106].

Medicinal substances can be used to convert resistance to sensitivity in cells [107]. *Urtica dioica* leaves extraction by hydro alcohol substance layout a low glucose action in male wistar rat by fructose generated resistance of insulin. Two weeks later different intraperitoneal administration of *Urtica dioica* extraction dosages, the examined animal displayed a significantly low level of plasma glucose count & fasting insulin resistance index and the effect were dose-depended. Furthermore, the treatment group's serum insulin concentration was much lower than the control group's, indicating that the usage of leaf extract boosted tissue and cell sensitivity, as indicated by the lower plasma glucose level [108].

In STZ-induced neonatal diabetic animals, an *Anacardium occidentale* leaves ethanolic extraction has anti-diabetic properties. Fasting glucose count of insulin in serum was (11.60 0.89 IU.mL1), and Fasting insulin

Table 1
Medicinal plants in diabetes prevention with respective mechanisms and clinical interventions.

Scientific Name	Family	Place of Study	Used Parts	Preparation	Active Ingredient	Mechanism of Action	Route	Dose	Type of Study	Ref.
Acalypha godseffiana	Euphorbiaceae	Nigeria	Leaves	Acetone, Aqueous, Ethanol and Methanol extract.	Flavonoids; Proanthocyanidins	Inhibits the α-glucosidase enzyme.	Oral	1.38 mg/mL	in vitro	[53]
Allium sativum L.	Amaryllidaceae	–	Bulb	Crushing or Cutting	Allicin	Anti-hyperglycemic	Oral	0.5 mg/mL	in vivo	[54]
Aloe barbadensis	Asphodelaceae	Mexico	Leaves	Methanolic extract	Polysaccharides	Inhibited the α-amylase and α-glucosidase enzyme.	Oral	5 mg/mL	in vitro	[55]
Amaranthus hybridus L.	Amaranthaceae	India	Leaves	Ethanolic extract	Flavonoids, glycosides, terpenoids, saponins, alkaloids, tannins, and steroids.	Reduces the level of high glucose in the blood.	Oral	200 and 400 mg/kg	in vivo	[56]
Angiopteris helferiana	Marattiaceae	Nepal	Rhizome	Aqueous extract.	Lactones	Inhibited the enzyme α-glucosidase	Oral	150 mg/kg/day and 300 mg/kg/day	in vivo	[57]
Areca catechu	Arecaceae	Indoneisa	Seed	Ethanolic extract.	Pyridine and piperidine alkaloids	Positive glucose tolerance test.	Oral	22.5 mg; 45 mg and 180 mg per 200gr body weight	in vivo	[58]
Azadirachta indica	Meliaceae	Kenya	Leaf	Aqueous extract.	Flavonoids; Tannins; Sterols; Saponins, Anthraquinones; Alkaloids	Hypoglycemic	IntraperIntraperitoneall.	25 mg/kg, 48.4 mg/kg, 93.5 mg/kgb, 180.9 mg/kg and 350 mg/kgbwt	in vivo	[59]
Barringtonia acutangular (L.)	Lecythidaceae	–	Bark and seed	Aqueous extract	Triterpene saponins	Anti-hyperglycemic	Oral	–	in vivo	[60]
Barleria prionitis	Acanthaceae	India	Leaf and root	Alcoholic extract.	Further studies are required.	Hypoglycemic	Oral	200 mg/kg	in vivo	[61]
Bauhinia holophylla	Fabaceae Lindl.	Brazil	Leaves	Aqueous extract	Kaempferitrin	Reduces body weight.	Oral	400 mg/kg		[62]
Benincasa hispida	Cucurbitaceae	Japan	Stem	Chloroform extract.	Volatile oils; Flavonoids; Glycosides.	Anti-hyperglycemic	Oral	250 mg/kg and 500 mg/kg	in vivo	[63]
Carica papaya	Caricaceae	Nigeria	Leaves	Ethanolic extract.	Flavonoids; Alkaloids; Glycoside; Phenols.	Hypoglycemic	Oral	200 mg/kg, 400 mg/kg and 600 mg/Kg	in vivo	[64]
Carthamus tinctorius	Asteraceae	Pakistan	Flower	Ethanolic extract	Neocarthamin; Cathamidin; Carthanin; Lignans and Polysaccharides.	Anti-hyperglycemic	Oral	200 mg/kg and 300 mg/kg	in vivo	[65]
Coccinia grandis	Cucurbitaceae	Bangladesh	Leaves	Ethanolic extract.	–	Reduced body weight Anti-hyperglycemic	Oral	750 mg/kg	in vivo	[66]
Coriandrum sativum	Apiaceae	Thailand	Seeds	Ethanolic extract	Linalool	Hypoglycemic Increased pancreatic β-cells activity Increases release of insulin.	Intraperitoneal	200 mg/kg and 250 mg/kg	in vivo	[67]
Cuminum cyminum	Apiaceae	Egypt	Seeds	Ethanolic extract	Phenols; Flavonoids.	Anti-hyperglycemic Increased insulin sensitivity.	Oral	200 mg/kg	in vitro	[68]
Diospyros peregrina	Ebenaceae	India	Fruit	Aqueous extract	–	Hypoglycemic	Oral	50 mg/kg and 100 mg/kg	in vivo	[69]
Elaeocarpus grandiflorus	Elaeocarpaceae	Thailand	Leaves; Twigs; Fruits	Aqueous extract.	Further studies are required.	Hypoglycemic	Oral	0.0001, 0.001 or 0.01 g/kg	in vivo	[70]
Emblica officinalis	Phyllanthaceae	Pakistan	Fruit	Methanolic extract.	Ellagic acid	Decreased fasting glucose in blood	Oral	250 or 500 mg/kg	in vivo	[71]

(*continued on next page*)

Table 1 (*continued*)

Scientific Name	Family	Place of Study	Used Parts	Preparation	Active Ingredient	Mechanism of Action	Route	Dose	Type of Study	Ref.
						Increased insulin in serum.				
Ficus Recemosa L.	Moraceae	India	Unripped fruit	Ethanolic extract	Bioflavonoids; Glycosides; Alkaloids; Tannins.	Hypoglycemic	Oral	400 mg/kg	in vivo	[72]
Fraxinus ornus	Oleaceae	Egypt	Leaves	Hydroethanolic extracts	Tannins; Flavonoids; Saponins; Alkaloids.	Anti-hyperglycemic	Oral	10 mg/kg and 50 mg/kg	in vivo	[73]
Gynura procumbens	Asteraceae	Malaysia	Leaves	Aqueous extract.	Kaempferol-3-O-rutinoside; Astragalin.	Decreased fasting glucose in blood	Intraperitoneal	500 mg/kg or 1000 mg/kg	in vivo	[74]
Hibiscus sabdariffa	Malvaceae	Nigeria	Leaves	Aqueous extract.	Flavonoids;	Anti-hyperglycemic.	Orally	200 mg/kg, 400 mg/kg and 600 mg/kg	in vivo	[75]
Ilex paraguariensis	Aquifoliaceae	Uruguay	Leaves and stems	Aqueous extract	Theobromine; Chlorogenic Acid; Caffeic acid; Caffeine.	Anti-hyperglycemic; Anti-oxidant.	Oral	580 mg/kg	in vivo	[76]
Jatropha curcas	Euphorbiaceae	Nigeria	Leaves	n-Hexane extract	–	Hypoglycemic; Reversed Increased level of nitric oxide.	Oral	200 mg/kg	in vivo	[77]
Lavandula stoechas L.	Lamiaceae	Tunisia	Flower	Boiling; Distillation (Essesntial Oil)	Linalool	Hypoglycemic	Intraperitoneal	50 mg/kg	in vivo	[78]
Leucas aspera (Willd)	Lamiaceae	India	Leaf and stem	Ethyl acetate, Acetone and Hydro alcoholic extracts	Flavonoids; Polyphenols; Tannins; Alkaloids; Glycoside; Saponins; Phytosterols and Triterpenoids	Inhibition of glycosylation.	oral	10 μg/mL	in vitro	[79]
Mangifera indica L.	Anacardiaceae	Vietnam	Leaves	Ethanolic extraction	Mangiferin	Inhibited the enzyme α-amylase	oral	200 μg/mL	in vitro	[80]
Melissa officinalis	Lamiaceae	South Korea	Leaves	Aqueous extract	Monoterpene hydrocarbons; Oxygenated monoterpenes; Sesquiterpene hydrocarbons	Anti-hyperglycemic. Showed an improvement in glucose tolerance.	Oral	250 mg/kg	in vivo	[81]
Mentha × piperita L	Lamiaceae	India	Leaves	SA-elicited peppermint infusion	–	Hypoglycemic. Reduced urine, urine urea, uric acid and microalbumin.	oral	100 g/L	in vitro	[82]
Tagetes erecta L.	Asteraceae	China	Inflorescence	Ethanolic extraction	Rutin; Quercetin; Quercetagetin	Inhibited the α-amylase and α-glucosidase enzyme	oral	250 mg/kg	in vitro	[83]

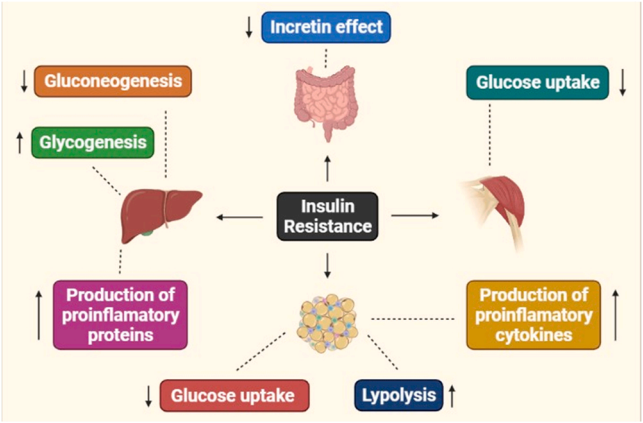

Fig. 4. Mechanism of action of insulin resistance in the human body.

resistance index levels were significantly reduced after oral application of 99.99 mg/kg weight in *Anacardium occidentale* extraction in one month[109].

Symplocos cochinchinesis bark ethanolic extraction has been demonstrated to show insulin resistance inhibition properties. On day 20, diabetic caused rats with insulin resistance received by an oral dosf *Symplocos cochinchinesis* extraction of two hundred and fifty and five hundred mg kg1.day1 [110]. Concurrently, it was found that in the treatment group, plasma insulin levels and the HOM-IR were significantly reduced than in the group, implying better cell susceptibility to endogenous insulin [110].

7.1. Terpenoids

Protopanaxatriol is a novel antagonist of peroxisome proliferators-activated receptor-ɣ (PPAR ɣ), which regulates metabolic and inflammatory gene expression such as interleukin, 1interleukin-10 (IL-10), interferon-ɣ (IFN- ɣ), inducible nitric oxide synthase (iNOS) and CD68 improving insulin sensitivity, dyslipidemia, and steatosis [111]. Cucurbitacin B is a kind of tetracyclic triterpenoid isolated from *Trichosanthes dioica*. Cucurbitacin B improved insulin tolerance and glucose utilization through translocation of GLUT4, which was related to the activation of the PI3K/Akt signaling pathway [112]. Guavenoic acid (0.3–30 nmol/L) could significantly improve the insulin resistance of INS-1 cells, which was related to the down-regulation of protein tyrosine phosphatase 1B (PTP1B) gene expression and up-regulation of PPAR gene expression [113]. Deoxyandrographolide is mainly derived from the Andrographis paniculata, which concentration-dependently induced glucose uptake by increasing the translocation of GLUT4 on the cell surface and activating PI3K and AMPK dependent signaling pathway [114]. Ginsenoside Rb1 induced translocation of GLUT4 by upregulation of leptin receptors and activation of PI3K, which improved insulin sensitivity and glucose metabolism in skeletal muscle cells [115,116].

7.2. Alkaloids

Berberine is an isoquinoline alkaloid isolated from *Coptidis rhizoma* or CortePhellodendronri, two Chinese herbs. Berberine may improve glucose tolerance by influencing critical molecules such as AMPK and PKC (paroxysmal kinesigenic choreoathetosis) in the insulin signaling pathway, as well as AS160 phosphorylation and GLUT4 translocation, resulting in increased glucose uptake in insulin-resistant cell Mahanine has been reported to be a major bioactive carbazole alkaloid. Mahanine (5–10 mol/L) could improve glucose metabolism in L6 myotubes and adipocyte cells via modulation of the Akt signaling pathway and then raised plasma membrane GLUT4 content [117]. Capsaicin is a pungent principal compound of hot chili peppers. It was demonstrated that promoted glucose utilization in C2C12 muscle cells by modulating AMPK, ROS (reactive oxygen species), and the p38 MAPK signaling pathway [118,119].

8. Advantages of plant-based bioactive compounds

Phenolics and carotenoids are two essential bioactive molecules that can help to keep improve human health. Food comprises a wide range of nutritional components which are required to survive, also several substances with bioactive quality that aid in the improvement of health and illness prevention. Secondary metabolites aren't required for a plant's overall growth or functioning, but they often contain therapeutic properties that make them useful in the treatment of diabetes. Natural food components contain Mg, Ca, and K including phytocompound, dietary fibers, carotenoids, and vitamins.

The current treatment for diabetes mellitus (DM) focuses on maintaining and reducing plasma glucose count within normal levels [120]. Nowadays 6 basic types of contemporary medications, and also two classes of injections, are being used to regulate blood glucose levels all around the world. Biguanides, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, and DPP-4 inhibitors are all names for the tablets. Incretin mimetics and insulin are two types of injectable drugs [121–124]. As of now, different techniques for managing DM, such as diet restriction, physical activity, and plant-derived molecules such as antidiabetes are recommended because they are less expensive and have fewer or no adverse effects [125]. According to the World Health Organization, roughly 75–80% of the global total, mostly in developing nations with diverse plant life, still rely on a plant-based traditional medical system. Conventional drugs are generally the 1st option to use in health lines in impoverished states as they're more culturally acceptable, and more suitable due to fewer adverse effects compared to contemporary treatments. Certain medicinal plants have lately been discovered to be effective in the treatment of diabetes, and they have been utilized as antidiabetic medicines all around the world. There are over 400 plant species that exhibit hypoglycemic action [126]. Previous studies have discovered a connection between the consumption of a particular herbal product and the development of diabetes, also diet plans help to maintain a good life. Fruit, vegetable consumption [127], and whole grains are inversely related to the development of diabetes [128,129].

9. Natural antidiabetic bioactive compound's mechanism of action

Diabetes is an oxidative stress-related disease characterized by a mismatch between the reactive oxygen species (ROS) generation in cells. The substances that are obtained from the live organism are known as natural compounds. Plants are principal suppliers of natural chemicals. Secondary metabolites are a wide category of natural substances that plants create. Phytoconstituents & active compounds derived from them could be effective treatments for diabetes and serious comorbidities with very few negative impacts. Anti-diabetic characteristics have indeed previously been identified in a wide range of effective medicinal herbs and their endogenous bioactive components, and they are presently more of it in need over manufactured drugs for the treatment of hyperglycemia due to their wide accessibility, potency, and lack of adverse effects (Table 2) [130].

Apigenin is a natural flavonoid [132]. that decrease IL-6, IL-1, and TNF through the alteration of the various intracellular signaling pathway of macrophage, reducing hyperglycemia and increasing antioxidants through oxidative stress-related anti-inflammatory options.

Hesperidin is a glycoside [133]. that reduces the symptoms of diabetes by lowering the release of all pro-inflammatory cytokines by controlling hyperglycemia and hyperlipidemia levels. Hesperidin reduces oxidative stress and increases insulin resistance by having a high antioxidant capacity and associated enzymes [134].

Table 2
Plant-based bioactive compound classes along with the mechanism of action for diabetics [131].

Class of active compound	Compounds name	Sources	Mechanism of Actions
flavone	apigenin	parsley, celery, rosemary	ERK1/2 stimulation also causes the reduction of the synthesis of pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α
	diosmin	lemon, orange	NF-κB targets are deactivated and (MCP-1), tumor necrosis factor (TNF-α), and interleukins (IL-1β and 6) are all suppressed
flavonol	quercetin	capers, onion cranberries	NF-κB system inactivation and TNF-α and CRP serum level is decreased
	kaempferol	tomato, green tea	AMPK activation as well as fasting blood glucose level is reduced, and insulin resistance is reduced.
	eriodictyol	mountain, balm	the NF-κB system activation is suppressed TNF-α, intercellular adhesion molecule 1 (ICAM-1), vascular endothelial growth factor (VEGF), and endothelial NOS (eNOS) is reduced
flavanone	naringenin	orange, tomato	AMPK activates and NF-κ pathways suppression And the glucose tolerance is increased and insulin sensitivity is caused
	hesperetin	Orange, peppermint	NF-κB system was activated is reduced also pro-inflammatory cytokines and oxidative stress indicators is reduced.
	chrysin	skullcap, honey	TNF-α production reduced and cause NF-κB activation as well as L-1β and IL-6 serum level reduction.
phenolic acid	curcumin	turmeric, curry powder mango Ginger	ICAM-1 expression is reduced & ROS improves also vascular inflammation Inhibits MCP-1 &ICAM-1 expression.
	colchicine	saffron, colchicum	Mitigates inflammatory cell infiltration, Suppression of MCP-1 and ICAM-1expression
stilbene	resveratrol	grapes, wine, grape	The NF-κB signaling activation pathway reduction. COX-2 gene expression enhanced the release of pro-inflammatory mediators
	emodin	rhubarb, buckthorn	Cause the suppression of NF-κB system activation Down-modulated the adhesion molecules includingICAM-1, and VCAM-1.

Diosmin is also a flavone. Diosmin supplements reduced the DM-convinced reactive oxygen species, and also cause the inhibition of NF-B-linked MCP-1 [135]. Kaempferol is found in nature that lowers fasting blood glucose and improves the resistance of insulin. It's also triggered through the enhancement of AMPK. Naringenin causes the prevention of diabetes response by the regulation of 51 AMPK. High blood glucose stimulates innate immunity, causing inflammation and diabetes. Chrysin decreased IL-1β and IL-6 levels in the blood. As a result of its anti-inflammatory properties, chrysin reduces the development of diabetes by particularly targeting the TNF pathway. Catechin's inhibitory actions play an important role in its anti-diabetes treatment efficacy. Emodin inhibits the breakdown of IB, and so has anti-diabetic effects. When added to endothelial cells, emodin inhibited the sticking compound such as ICAM-1, & VCAM-1 contain NF-B attaching site to its promoter site, which may help to lessen the impact of diabetes [136].

10. In- silico study of the bioactive compound against diabetes receptor

Bioactive chemicals, particularly poly-phenols consumption has been found to have anti-diabetic characteristics, reducing insulin resistance or secretion through various signaling pathways. This action is linked to poly-phenols ability to modulate genome expression. PDBsum, a graphical library of 3d shapes in the Protein Data Bank database, is used to define the binding plot. A complex docking of the binding plot was formed, and the amino acid inside 100 A was calculated via imagining an attentive ligand in the middle [137]. *Moringa oleifera* is an important pharmacological target for diabetic mellitus treatment. To identify unique structural properties and scaffolds, the ligand cellular docking technique was used. Every ligand's pharmacophoric feature was evaluated, and all phytochemical substances (ligands) were loaded to generate pharmacophore information [137].

Insulin receptor kinases are mutant proteins with concrete strength of 35848.66, several atoms of 2480, a residue count of 307, and just one distinct protein chain. The below image is a complex insulin receptor kinase molecular level drawing having cis-(R)− 7-(3-(azetidine-1-ylmethyl) cyclobutyl) - 5-(3-((tetrahydro-2 H-pyran-2-yl) methoxy) phenyl)− 7 H-pyrrolo [2, 3-d] pyrimidine-4-amine. The 5HHW protein depicted two mutations i.e., C5S, and D156N (Fig. 5).

Regarding X-beam clarity, the experimental strategy was chosen as X-beam crystallographic with the claims of 2.18 A. The insulin receptor kinase domain molecular structure in combination with cis-regulatory proteins (R) 3-(azetidine-1-ylmethyl) cyclobutyl) − 7-(azetidine-1-ylmethyl) cyclobutyl) − 7-(azetidine-1-ylmethyl) 3-((tetrahydro-2 H-pyran-2-yl) methoxy) phenyl) − 5-((tetrahydro-2 H-pyran-2-yl) methoxy) phenyl) − 5-((tetrahydro-2 H- It was possible to recover −7 H-pyrrolo [2, 3-d] pyrimidine −4-amine (5HHW). The primary chemicals accountable for M. Garantia's anti-diabetic function were discovered to be monordicosides D (TGR5 agonist), cucurbitacin (GLP-1r agonist), and charantin (DPP-4 inhibitor) in this investigation. This study reveals that the plant's antidiabetic impact is mediated through TGR5 activation, GLP-1 release, inhibition of DPP-4, and release of insulin, resulting in improved insulin sensitivity and glucose uptake in skeletal muscle and white adipose tissues, validating its usage as an antidiabetic (Fig. 6).

11. Antioxidant effect of the bioactive compound in diabetes

Free radicals which affect different types of diseases, including hepatic cirrhosis, heart disease cancer, and diabetes & chemicals that can collect free-radical show a lot of promise in treating these conditions. Diabetes is indeed a widespread issue due to its high rate of morbidity and mortality, as well as higher medical costs in diagnoses and prevention. On the worldwide scale, the condition usually occurs in low - and - middle nations, with nearly 50% of cases going undetected. Untreated diabetic occurrences are common in South Africa (69.2%), and 73.7% of any diabetes-related deaths happen under the age of 60, demonstrating the extent to which diabetes is eliminating the continent's worker population. In South Africa, the prevalence of diabetes is quickly rising, with an estimated 1.8 million individuals suffering from diabetes and another 1.5 million persons remaining untreated. One of the primary variables for the development of diabetes has been identified as oxidative stress. The activity of oxygen-free radicals cause lipid peroxidation, which can lead to the glycation of protein, changes in the structure and function of collagen, basement, and other membranes, changes in the structure and function of collagen, basement, and other membranes, all of which contribute to the long-term difficulties of diabetes. Mulberry fruit polysaccharides, for example, showed excellent antioxidant activity in vitro by having a higher DPPH radical scavenging activity and radical - scavenging rate are both high. Typical poly-

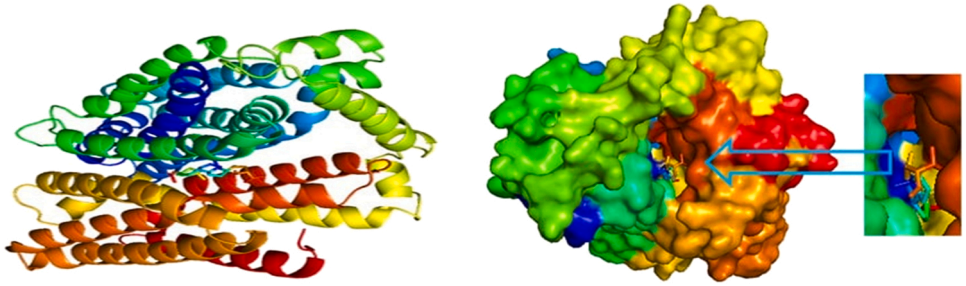

Fig. 5. 3D representation of the docking position of β-orbital with human glucose transporter (PDB 4PYP).

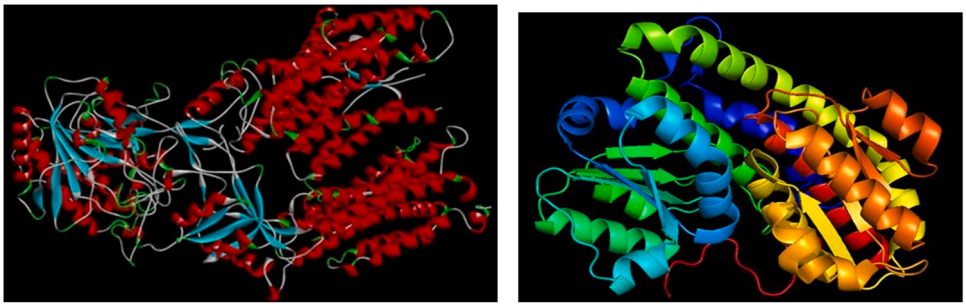

Fig. 6. Crystal structure of glucose-fructose-6 phosphate aminotransferase (PBD2ZJ3).

phenolic compounds present in the fruit includes gallic acid, protocatechuic acid, ellagic acid, ferulic acid, caffeic acid, p-coumaric acid, and chlorogenic acid. These are potent antioxidants with considerable anti-diabetic properties. These could be able to successfully improve carbohydrate absorption & gluconeogenesis, hence alleviating diabetes glucose levels & consequences [138–141]. Phenolic-rich litchi or lychee pulp preparations protect the pancreatic cell [142]. in STZ- induced diabetic animals oxidative stress, apoptosis, and diabetes-induced hepatic damage in animal were also studied [143].

12. Bioactive compound's biomarker discovery for the development of antidiabetic drug

A biomarker is a trait that may be measured and assessed objectively as a sign of normal biologic activities, pathogenic processes, or pharmacologic reactions to a therapeutic intervention". Biomarkers have significant economic and medical potential are appropriate monitoring utilizing biomarkers could reduce medication attrition throughout clinical phases as well as overall development expenses. In insulin resistance and diabetes conditions, metabolic investigations have revealed previously unknown alterations in metabolic pathways. The relationship between improper metabolism of amino acids and resistance of insulin is one of the most significant of these discoveries. Branched-chain amino acids and branched-chain keto acids are shown to be higher in the blood of diabetic patients [144].

Metabolite profiling has found significant variations between diabetes and non-diabetic individuals also alanine, formic acid, and trigonelline, betaine among other urine metabolites. Investigating the metabolic pathways that involve these metabolites could yield new insights into the pathophysiology of diabetes and how these metabolites play a role. Other diabetes-related biomarkers discovered recently include phosphatidylcholines, 2-hydroxyethanesulfonate methyl succinate, guanidinoacetate, methyl guanidine, and hippurate. The retinoid family of phytochemicals includes the phytochemicals boeravinone E and boeravinone D, which are plentiful in Boerhaavia diffusa and have significant medicinal promise. The phytochemicals boeravinone E and boeravinone D, which are abundant in Boerhaavia diffusa and have great therapeutic potential, belong to the retinoid family of phytochemicals. Both compounds were discovered to be deeply lodged in the active pocket and to interact with Glu63 in the surrounding region, allowing new anti-diabetic drug development. Annona glabra contains a lot of squamosamide, and a derivative of it is quite effective against diabetes. It protects pancreatic -cells from glucose toxicity by increasing the Akt-FOXO1 pathway, which has substantial hypoglycemic and anti-inflammatory effects [145].

13. Functional food management for a diabetic and pre-diabetic condition

Pre-diabetes is a state in which blood glucose concentration is above baseline but maybe not excessive enough to be confirmed as diabetes [146]. Pre-diabetes condition is a serious risk factor for diabetes that is characterized by moderate hyperglycemia [147]. Diabetes is unavoidable for persons with pre-diabetes, the chance of developing diabetes can be minimized by implementing early action [148].

According to the International Diabetes Federation, there will be 471 million people globally with pre-diabetes in 2035 [146]. One of the most important features of a functional food supply is that it is high in nutritional content and low in calories, both are beneficial to human health. Increase Easy availability of foods that are high in preventive nutrients is also beneficial in treating illnesses. Functional food security in combination with increased moderate exercise, which is an effective weight loss technique, may be the key to considerable success in the treatment of obesity and type 2 diabetes. It is widely recognized that Mediterranean-style dietary patterns include excessive intake of functional foods (vegetables, legumes, whole grains, fruits, nuts, and olive oil), moderate consumption of fish and wine, and low consumption of red and processed meat, as well as whole-fat dairy products; this is widely recognized as a healthy dietary pattern, rich in functional foods, and similar to the Paleolithic diet; this is widely recognized as a healthy dietary pattern, rich in functional foods, and similar to the Pale [149–153].

13.1. Quinoa seeds

Quinoa seeds (*Chenopodium quinoa*) are widely grown in South

America. They have a high nutritional profile and are resistant to climate change, making them a crucial seed for the future food sector [154]. The Bolivian culture called it 'jupha,' or 'quinia.' Near 5000 years ago, the species was domesticated in the South American range zone around Titicaca Lake. It now stretches to the north and south of the continent along with a mountain range, from Colombia to Chile's south, where it can be found growing wild or cultivated [155]. It is said to assist high-risk patient groups, such as those with diabetes, dyslipidemia, and obesity, due to its high nutritional content, therapeutic properties, and gluten-free status. Minerals, fibers, vitamins, fatty acids, antioxidants, and phenolic, all of which have a substantial impact on human nutrition and well-being, are closely linked to the levels of minerals, fibers, vitamins, antioxidants, and phenolic in its seeds [156]. Quinoa consumption decreased blood glucose and insulin resistance in test subjects, implying that it had a substantial role in diabetic treatment [157].

13.2. Chia seeds

Chia (*Salvia hispanica L.*) seeds are an annual herbaceous plant that can be found in Northern Guatemala and Southern Mexico. Its name stems from the Latin word "salvere," which refers to the medicinal and culinary characteristics of the well-known *Salvia officinalis* herb, often known as *Mexican chia* or *Salba chia* [158]. As a Vita food, chia seeds play a prime role. The content and concentration of its bioactive components are affected by circumstances such as climate, geographical origin, and extraction processes. Chia seeds are high in -linolenic acid (ALA), a fatty acid that reduces the resistance of insulin in T2DM and its complications. It also helped to treat diabetes by lowering serum glucose, cholesterol, and triglycerides levels, and postponing the onset of diabetes in borderline test subjects [159]. Chia seeds have recently been designated the finest source of fatty acids. They're also abundant in bioactive substances including phenolic compounds and tocopherols, both of which have anti-diabetic properties [160].

13.3. Hab El-Rashad seeds

Hab El-Rashad seeds, also known as *Lepidium sativum L*are an edible plant that belongs to the cruciferous plant family. This species was used as a grain in ancient Greece. Long before the advent of bread, *L. sativum* was a nutritional source for ancient Egyptians, who utilized it as a staple diet Hab El-Rashad is the Arabic name for *L. sativum*, which is widely used in Egypt and Saudi Arabia. Hab ElRashad seed powder and alcoholic extracts demonstrated a cytoprotective impact in pancreatic islets in a high-fat diet rodent model, maintaining the integrity of the cell that controls appropriate insulin secretion and maintaining glucose levels to normal in test subjects, according to recent studies [161]. the extraction of Hab ElRashad seeds stabilizes diabetes by enlarging antioxidant activity, decreasing oxidative stress, and improving lipid profile, as well as regulating insulin pancreatic secretion from pancreatic islet cells, which is linked to lower glucose, urea, triglycerides, and cholesterol levels [162].

13.4. Pumpkin seeds

Pumpkin seeds (*Cucurbita pepo L.*) are high in phytosterols, proteins, vitamins, and minerals, they are widely utilized in edible seeds all over the world [163]. According to recent studies, pumpkin seeds have piqued the interest of the food sector, which is looking for healthier alternatives. Proteins, crude fibers, calcium, carotene, and vitamin C were discovered to have a high nutritional profile in the seeds, which aid in weight loss. It was claimed that the ingestion of natural bioactive substances with a documented anti-obesity activity has gained special attention in scientific circles because of its capacity to control weight growth and aid in weight loss [164]. Pumpkin seeds have anti-diabetic properties, thanks to their hypoglycemic and hypolipidemic properties. According to current research, diabetic rats' cellular insulin absorption was boosted, indicating that the cells' ability to use insulin and glucose was greatly increased. It was also discovered that alcoholic extracts of pumpkin seeds could block -amylase, while aqueous extracts exhibited considerable inhibition of amylase and -glucosidase, both of which are directly linked to the antidiabetic action that has lately been considered for pumpkin seeds [165].

13.5. Fenugreek seeds

Fenugreek seeds are a yearly bean crop farmed primarily for use as a spice in many regions of the world. The plant is a scented herbaceous annual that is extensively grown in Mediterranean and Asian nations [166]. Recent pharmacological research has revealed that fenugreek includes several active compounds that modulate glycolipid metabolism and improve insulin resistance. In addition, 4-hydroxy isoleucine was discovered to have a significant impact on lowering insulin resistance, which aids in the reduction of obesity in test individuals. However, the exact mechanism is unknown, and more research into this seed's anti-obesity properties is needed [167]. Alkaloids, essential oils, proteins, steroidal saponins, mucilaginous soluble fiber, and insoluble fibers) are present in fenugreek seeds and are responsible for their biological activity. In test individuals, these ingredients aid in lowering serum glucose levels and inflammatory mediators that cause mild inflammation which is one of the main reasons for obesity and insulin resistance. As a result, the fenugreek seed is a promising anti-obesity candidate. Phytomedicine [168–172]. A range of elements in fenugreek seeds, including galactomannan, phenolic compounds, and fibers, have been discovered to have hypoglycemic effects. Clinical investigations have indicated that 2–3 g of fenugreek gum per day is beneficial in managing blood sugar levels, although other food fiber requirements are substantially higher (up to 20 g). The fenugreek gum thickens and creates a gel in the stomach, trapping sugars, lipids, and starch-hydrolyzing amylase enzymes, resulting in a slowdown of sugar absorption, which is beneficial to diabetic and obese people [145, 173–178].

14. Wild edible plants in diabetes management

14.1. Artemisia annua L. Leaves

In vitro, the caffeoylquinic acid derivatives inhibited the activity of the DPPIVI, -amylase, and -glucosidase enzymes. These effects may account for Artemisia annua's well-known antidiabetic activity by the enhancement of insulin release, preserving pancreatic -cells, delaying glucose absorption and lowering postprandial glucose excursion. Surprisingly, some of these substances aided wound healing [179].

14.2. Brassica juncea

B. juncea (Cruciferae). *B. juncea* has been ingested in all countries. The parts that are used include leaves and seeds. Its various parts can be utilized to make vegetables and seeds can be used as a condiment or a source of oil. These components contain glucosinolates, isothiocyanates, phenolics, Kaempferol, glycosides, and flavonoids [180]. In STZ-induced diabetic rats, aqueous seed extract resulted in a remarkable reduction of blood glucose levels and a rise in serum insulin in a dose-dependent way [181].

14.3. Nigella sativa (N. sativa; Ranunculaceae)

Nigella sativa is primarily grown in the Middle East and Southwest Asia. Powder, extract, and seed oil were all used. Thymoquinone (the major component), flavonoids, unsaturated fatty acids, nigellone, p-cymene, and carvone are some of the compounds found in thymoquinone [107,182]. *N. Sativa's* action mechanism has been demonstrated in human and animal research to include effects on antioxidants, enzymes,

insulin secretion, glucose absorption, gluconeogenesis, beta-cell function, and gene expression [182–186].

15. Plant-based nanoparticles in diabetes management

15.1. Ginger nanomaterials

High-fat diet-fed mice were given ginger-derived nanoparticles (GDNP) in their drinking water for at least one year or the rest of their lives. The gene expression profile of GDNP-treated mice was analyzed using a microarray profile of their intestine, liver, and fat tissue. The interaction between the Foxa2 protein and phosphatic acid-lipid nanoparticles was studied using surface plasmon resonance (SPR). Obesity has spread over the world for overconsumption of high-fat diets (HFD), which is the main reason for major chronic diseases like type 2 diabetes. Dietary management is the cornerstone of obesity and diabetes prevention. However, the molecular mechanisms of diet-based prevention of insulin resistance are still unknown. Treatment with GDNP reduces the resistance of insulin in rats fed a high-fat diet by restoring balance in gut epithelium Foxa2 mediated signaling (HFD). By protecting Foxa2 from Akt-1-mediated phosphorylation, GDNP therapy can prevent HFD-induced obesity and insulin resistance [5,187,188].

15.2. Curcumin nanomaterials

Diabetes is a complex metabolic condition that necessitates lifelong pharmacological therapy as well as lifestyle adjustments. Curcumin is one of the most researched bioactive components in traditional medicine, although it has poor solubility, absorption, and activity due to its physicochemical properties. Curcumin's low bioavailability can be overcome by nanotechnology-based pharmaceutical formulations, which can boost its anti-diabetic properties. Nanocurcumin's anti-diabetic properties are attributable to multiple pharmacological pathways that reduce DM's hallmark hyperglycemia. Nanocurcumin may be considered a possible drug in the pharmacotherapeutic management of diabetic patients in light of these findings [189–191].

15.3. Selenium nanoparticles

The principal aspect of the diabetes treatment and management process is the lowering of hyperglycemia following carbohydrate consumption, which can be accomplished by inhibiting alpha-amylase. Diabetic rats were given the extract that produced the best outcomes in vivo trials. In a diabetic rat trial, the brewed extract had a substantial effect on fasting glucose reduction and a non-significant effect on triglyceride, cholesterol, and LDL decrease [192].

Some data from human studies and medicinal plants in the management of type 2 diabetes mellitus in ASEAN countries are shown in Table 3.

16. Plants having an anti-diabetic effect

16.1. Albizzia lebbeck (Fabaceae)

Streptozotocin-induced diabetic rats received a different dose of a methanol/ extract from *Albizzia lebbeck* stem bark for 30 days [194]. The therapy reduced fasting blood glucose and glycated hemoglobin while increasing plasma insulin. It also reduced TC, triglyceride low-density lipoprotein, and VLDL LDL while increasing high-density lipoprotein. In streptozotocin-induced diabetic rats, the therapy increased and reduced glutathione peroxidase, CAT, glutathione, and SOD levels while decreasing lipid peroxidation. The therapy also protected the liver, pancreas, liver, and heart of the diabetic rats and reduced lesions in a dose-dependent way. *Albizzia lebbeck* bark methanolic extract has toxicological effects on diabetic rats caused by streptozotocin and nicotinamide [195].

Table 3
Completed summary of data extraction of selected published literature articles on human studies and medicinal plants in the management of type 2 diabetes mellitus in ASEAN countries [193].

Plant name and type of extraction	Duration and type of treatment	Study outcome	Short methodology
Rosella with stevia As ready-to-brew rosella-stevia bags (i) 5 g rosella powder (ii) 125 mg stevia sweetener Each rosella-stevia tea bag is brewed with 250 mL of boiling water for 5 mins and cooled down for 20–30 min before consuming	14 days treatment (1) Fast for 8 h the night before the first day of treatment, to withdraw participants' blood for fasting blood glucose readings (2) Each participant was given 75 g sugar in 250 mL water and rested for 2 h, for 2nd blood withdrawal as 2-hour post-prandial blood glucose (3) Treatment group (i) (i) Ready-to-brew rosella-stevia tea 2x per day for 14 days	Post-treatment Tea consumption significantly lower FBG level but not the 2-hour PBG level	Venous blood samples were collected for FBG and 2-hour PBG
M. charantia (Bitter melon) *As charantia ampalaya* capsules vs. placebo capsules	3-month treatment: (1)*M. charantia* capsules or placebo: (i) 2 capsules, 3 times per day after meals for 3 months (ii) Monthly follow up	No significant effect on mean FBG, total cholesterol, and weight or serum creatinine, ALT, AST, sodium, and potassium	Each monthly visit: (i) Capillary blood sugar levels (ii) Interviewed on compliance and adverse events (iii) Diet and medications reinforced Lab test: (i) HbA1C (ii) Fasting blood glucose (iii) Serum cholesterol (i)WeightExtra: (i) Serum creatinine, AST, ALT, sodium, potassium Adverse event
Curcuma longa (turmeric) with *A. sativum L.* (garlic) (1) AC group: (i) 200 mg of turmeric ethanolic extract, 200 mg of	For 12-week treatment: (1) AC group: (i) 2.4 g Allium curcuma capsules (ii) 2 times, 3 capsules per day after meal	(i) Significant decrease in FBG of AC group (192.76 vs. 141.71 mg/dL) and 2 h postprandial blood (ii) Significant decrease in	Evaluated every 2 weeks for 12 weeks (i) Fasting blood glucose (ii) 2 h postprandial (iii) Lipid profile examination

(*continued on next page*)

Table 3 (*continued*)

Plant name and type of extraction	Duration and type of treatment	Study outcome	Short methodology
garlic aqueous extract Vs. Oral drug (ii) 5 mg glibenclamide	(2) Glibenclamide group: (i) 2 times 3 capsules per day (ii) But for the morning-after meal, each consumed 1 capsule of 5 mg	HbAlC 10.41 vs. 8.09)	Oral drug (i) HbA1C. Fasting insulin, liver function, renal function, complete hematology, urine, and heart function

16.2. *Aloe vera*

Aloe vera extract was examined in stz-induced diabetic mice and mouse embryonic NH/3T3 cells [196]. When an extract was given to rats at a dose of 130 mg/kg per day for four weeks, blood glucose, triglycerides, LDL cholesterol, and total cholesterol were all significantly reduced, a result that was comparable to that of metformin. Furthermore, this study discovered that a lyophilized aqueous aloe extract (1 mg/mL) increased the synthesis of GLUT-4 mRNA in NIH/3T3 cells, which was previously unknown. Many studies show that *Aloe vera* extract improved pancreatic-cell function and insulin secretion while restoring pancreatic islet mass in stz-induced diabetes [197].

16.3. *Amaranthus tricolor (Amaranthaceae)*

In the OGTT test, methanolic extracts of the whole plant of *Amaranthus tricolor* were delivered at a different dosage one hour before glucose delivery [14]. Anti-hyperglycemic action in glucose-loaded mice was shown to be substantial at every dosage the largest effect recorded at the maximal dose tested and an effect comparable to glibenclamide.

16.4. *Anacardium occidentale*

Anacardium occidentale was found to reduce blood glucose levelevelsdiabetic rats produced with streptozotocin [198]. It was given twice a day to the rats, beginning two days before the injection of stz. Prior treated rats had considerably lower blood glucose levels than diabetic control rats three days following streptozotocin treatment. Streptozotocin-induced diabetic rats received a defined dose of methanol extract, and their blood glucose levels decreased, showing effects similar to those of the conventional medication Pioglitazone [109].

16.5. . *Barleria prionitis*

Alloxan-induced diabetic rats showed anti-diabetic action of *Barleria prionitis* leaves ethanolic extraction [199]. Leave extracts reduced glycosylated hemoglobin and blood glucose levels in animals. Serum insulin and hepatic glycogen levels were also elevated.

16.6. *Bauhinia thoningii (Fabaceae)*

It was discovered in a study on alloxan-induced diabetic rats [200] that *Bauhinia thoningii* plant leaves extract in water form has an anti-diabetic effect. Using an oral dose, the extract caused a substantial reduction in blood glucose, low-density lipoprotein cholesterol, and heart disease in the participants.

16.7. *Camellia sinensis (Theaceae)*

Mice with diabetes caused by streptozotocin were given the crude tea leaf extract from *Camellia sinensis* to test for hypoglycemic action [201]. Diabetes rats were fed tea for 20–25 days, and the hypolipidemic and anti-hyperglycemic effects were seen. Other benefits were a decrease in body weight and the return to normal of several abnormal hematobiochemical markers.

16.8. . *Moringa oleifera (Moringaceae)*

Experiments on diabetic rats were conducted to examine the anti-diabetic and antioxidative effects of *Moringa oleifera* methanol extracts [202]. Nitric oxide and serum glucose levels dropped significantly at both doses, whereas protein and insulin levels rose. Even more remarkable, a histologic study of the pancreas revealed considerable islet cell histoarchitectural repair after therapy with *Moringa oleifera*. *Moringa oleifera* leaves have been shown to have a hypoglycemic impact and prevent weight loss in rats that have been given alloxan [203].

16.9. *Murraya koenigii (Rutaceae)*

Alloxan-induced diabetic mice were given Water extraction of *Murraya koenigiileaf* were given to alloxan-induced diabetic rats and the results showed that the extract had a substantial influence on blood sugar levels also carbohydrate metabolism [204]. Furthermore, an ethanolic extract of this plant has been shown to alleviate dexamethasone developed hyperglycemia and resistance to insulin as a result of increased skeletal muscle glucose absorption. [205].

16.10. *Opuntia ficus-indica (Cactaceae)*

Researchers tested a conventional drug on the treated group (streptococci-induced diabetes) (dimethyl biguanide, 100 mg/kg) and an edible Opuntia ficus-indica extraction on those same diabetic animals [206]. All but the aqueous extract drastically lowered blood glucose levels while preserving body weight. Reduced fasting sugar levels were the primary benefit of using petroleum ether extraction.

16.11. *Origanum vulgare (Lamiaceae)*

Extraction of the *Origanum vulgare* demonstrated substantial phenol content and in vitro antioxidant activity in DPPH tests [207]. To test the extract in humans, researchers used stz - induced diabetic rats. The methanol extracts had anti-inflammatory and cytoprotective properties.

16.12. *Momordica saponins*

Momordica saponins improve uric acid and creatinine levels in STZ-induced T2DM rats, while MCP improves antioxidant capacity [208]. In STZ-induced diabetic rats, *Momordica saponins* reduce oxidative stress and regulate the HO-1/Nrf2 pathway [209]. MC extract protects kidneys from oxidative damage, prolonging diabetic nephropathy [210]. Conversely, a bitter gourd diet prevents renal problems by reducing glycoconjugates and increasing heparan sulfate in diabetics [211]. Another study found that MC extract reduces retinal ganglion cell death in T2DM rats by decreasing Bax and increasing Bcl-2 mRNA and protein expression [212]. Also, *Momordica saponin* [208], MC ethanol extract [213], and MC leaf extract [109] have hypo-lipidemic action. MC seeds may lower blood lipids and uric acid levels [214].

16.13. *Catharanthus rose*

The Apocynaceae family includes *Catharanthus roseus*, an ever-blooming herb. There is a considerable effect on the lipid profile and insulin sensitivity of *Catharanthus roseus* leaf extract [215]. Diabetes-related blood glucose levels were significantly reduced in diabetic mice treated with ethanolic extract of *Catharanthus roseus* (200 mg/kg b.w) in the present study. Alloxan was administered to start

the body's insulin production. Diabetic animals received leaf extract from *Catharanthus roseus*. In rats, the aqueous extract solution of *Catharanthus roseus* was given for 60 days and significantly reduced glucose levels [216]. It was shown that *Catharanthus roseus* suspension had a substantial effect on diabetes. The long-term usage of *Catharanthus roseus* prevents insulin resistance in the body, according to a study. Pre-diabetic patients may benefit from using *Catharanthus roseus* as a supplement to prevent or control insulin resistance [217].

16.14. *Anacardium occidentale*

Because the entire tree produces resources and goods, *Anacardium occidentale* is considered a multipurpose tree. Medicinal uses include the leaf, bark, root, and nutshell oil [218]. Hyperglycemia is a hallmark of diabetes, and the oxidative stress that results from it is a major cause for concern because it can lead to a wide range of issues. antihyperglycemic and antioxidant properties of *A. occidentale* root extracts have been studied. Analyses of cytotoxicity and antidiabetic potential were carried out on MIN6 pancreatic -cells using MTT assay and ELISA at a higher glucose concentration. qRT PCR was used to investigate the impact of 80% MAO on INS gene expression. Antihyperglycemic and antioxidative capabilities of *A. occidentale* root extracts were found to be efficient in this investigation, along with the ability to normalize the insulin secretory system of -cells. This material's active principles and in vivo effects in *A. Occidentale* root extracts need to be further investigated. It is hoped that the root extracts of *A. occidentale* would yield new medication leads for the treatment of diabetes [219].

16.15. *Syzygium cumini*

Myrtaceae is a family of plants that includes the *Syzygium cumini* tree, often known as Eugenia jambolana. Antidiabetic effects of SC seed extracts and mycaminose compound were evaluated in this study. The blood sugar levels of diabetic rats decreased significantly after 15 days of therapy with extracts of SC. According to these findings, the traditional usage of SC seed as an anti-diabetic has been proven by modern research. Inhibition of insulin production from BETA-cells in the islets of Langerhans may be one method by which seeds lower blood sugar levels by boosting insulin secretion from the pancreas or releasing insulin from its bound state. The insulin-release stimulatory properties of a variety of different plants have been documented to produce hypoglycemic effects. This study's findings support the traditional usage of S. cumin seed in Indian medicine to treat diabetes [220].

16.16. *Lupinus albus L*

Lupinus albus L. seed proteins are expected to release some of the bioactive peptides that are thought to play a significant role in the progression of cardiovascular disease, type 2 diabetes, and obesity. In general, the seeds contain anything from 6% to 13% oil, 34–39% fibers, and 33–47% proteins [221,222]. Materials containing seeds of *Lupinus albus L.* were obtained from a spice shop and dried in the shade. Before extraction, every seed was roasted and then ground into a powder. After letting the mixture sit for 48 h, 100 g of powder were filtered out of 500 milliliters of ethanol. The ethanol that was extracted was evaporated under a vacuum (at 40 degrees Celsius with a rotating evaporator). The organic solvent evaporation-dried extracts that were made under lower pressure and temperature were kept at a temperature of 4 degrees Celsius until they were used. Before application, 1 milliliter of distilled water was used to dissolve the extract. Animals were given the extract at a dose of 10 mg/kg of body weight through an intragastric tube for 20 days [223]. Glycosylation reduces the synthesis and activity of numerous antioxidant enzymes, namely SOD and GPx. The liver, kidney, and pancreas were normal in the control and LA groups. The STZ group diabetic rats' liver, kidney, and pancreatic tissues showed severe deterioration. The regeneration of the liver, kidney, and pancreas in rats given *Lupinus albus L.* seed extract and STZ reveals the strong protection conferred by *Lupinus albus L.* seed extract against diabetes. Unlike the STZ group, this group did not show severe deterioration. Increased production of lipid peroxides and ROS causes membrane damage and pathological alterations in the liver, kidney, and pancreas. These findings suggest that *Lupinus albus L.* seed extract may be an anti-diabetic, antioxidant, and anti-oxidant. Extract after roasting *Lupinus albus* seed is a pioneer in literature and ethnomedicine for diabetes [223].

16.17. *Tecoma stans*

Herbarium mixtures have been used empirically, and their qualities are unknown. The purpose of this study was to see how the oral administration of a herbarium mixture (*Guazuma ulmifolia [G. ulmifolia]/Tecoma stans [T. stans*]) affected individuals with type 2 diabetes mellitus metabolic profile (T2DM). In 40 T2DM patients, a randomly selected, double-blind, placebo-controlled clinical trial was conducted. They were between the ages of 40 and 65, with a BMI of 25.0–34.9 kg/m2 and an HbA1c of $> 7.0\%$. The following measurements were taken: BMI, mass index, fasting blood glucose, HbA1c, lipids, kidney, and liver function. For 90 days, the patients were given either the herbarium combo (*G. ulmifolia/T. stans*) before each meal that enhanced the glycemic profile in T2DM patients. This clinical trial supports the traditional usage of *G. ulmifolia/T. stans* in the treatment of T2DM by demonstrating that the combination of these phytopharmaceuticals can lower glucose and HbA1c in patients with T2DM. This type of clinical investigation must be continued with larger sample numbers for longer periods to determine its effectiveness and long-term safety [224].

16.18. *Taraxacum officinale*

Herbs and their mixtures might impact many links of the pathogenetic system of diabetes mellitus or its consequences due to their extensive variety of biologically active compounds. One of these combinations is an antidiabetic herbal mixture containing an insulin-containing component – *Taraxacum officinale L.* roots – that has been shown to have hypoglycemic, hypolipidemic, antioxidant, hepatoprotective, and pancreatoprotective activity in previous pharmacological studies in vivo. The goal of this study was to find out how much inulin and fructans there were in *Taraxacum officinale L.* The difference between fructose, a product of enzymatic hydrolysis, and D-fructose, a constituent of sucrose and free D-fructose, as well as the empirical factor for the conversion of D-fructose from inulin, was used to calculate the quantity content of inulin. After conversion into volatile derivatives like aldononitrile acetate, carbohydrates employed in the computation of inulin were separated by gas chromatography-mass spectrometry. *Taraxacum officinale L.* roots contain 436.29 mg/g of inulin, according to the findings. As a result of acid hydrolysis of 5-(hydroxymethyl)furfural, the total concentration of fructans was measured by spectrophotometric analysis. The roots of *Taraxacum officinale L.* contain 39.49% fructans, according to the findings. The findings show that this plant component should be included in herbal antidiabetic mixtures since it has hypoglycemic, hypolipidemic, and detoxifying properties due to the presence of fructans and inulin [225].

16.19. *Black carrot*

The Type 2 diabetes healing properties of black carrots are due to the presence of phenol in them. The goal of this research is to figure out how phenol interacts with enzymes that might act against diabetes. Pure extraction of black carrot and the conventional inhibitors acarbose and vildagliptin, respectively, were used in an in vitro experiment on glucosidase, amylase, and DPP-IV inhibition. For a better understanding of interactions, the inhibitory activity of chosen phenolic compounds was investigated using in silico docking with all three enzymes. In addition, pure black carrot extract was encapsulated. The purified

extract had a higher in vitro IC50 value than the usual inhibitors acarbose for -amylase and -glucosidase, and vildagliptin for DPP-IV. Similarly, the docking scores of a few anthocyanin compounds were found to be greater than those of their inhibitors, implying that the inhibition was more effective. Among the anthocyanin compounds present in black carrots, cyanidin 3-xylosyl galactoside was discovered to be a possible medication to block these enzymes, whereas dipeptidyl peptidase IV was revealed to be the greatest target for the controlling diabetes with anthocyanins. Anthocyanins from black carrots have been found to help regulate diabetes, and for the first time, we propose that cyanidin 3-xylosyl galactoside is the best prospective molecule for inhibiting glucose metabolism enzymes. The work also demonstrates the use of -cyclodextrin to encapsulate anthocyanin pigments [226].

17. Conclusions and future directions

Herbal plants have utilization to treat communicable and non-communicable illnesses. At present many effective medicines are produced from naturally generated lead compounds or acquired directly from plant sources. Scientific interest in the plant's product in drug discovery and development has resurfaced, indicating that it could be a prime source of novel medicines in the future. A lot of innovative techniques have been developed as a result of medicinal chemists' interest in natural product drug discovery. These innovative approaches have the potential to reduce the technical limitations of natural product development while also addressing the obstacles that come with discovering and developing novel natural products due to their complicated nature. Technological advancements allowed researchers to investigate the phytoconstituents, resulting in the isolation or synthesis of several successful medicinal medications and innovative lead compounds that potentially serve as a foundation for future drugs. For good results in this area, it is very vital to take a cross-disciplinary attitude that includes traditional and pharmacological knowledge, phytochemistry, botany, analytical chemistry, appropriate biological screening methodologies, and modern drug development tools. Innovative natural product marketing strategies; the use of novel compounds from plants and chemical libraries based on natural products will be expanded in the drug discovery process in the future, reducing hurdles and improving success rates. It has the potential to make a significant contribution to the creation of novel drugs and the resolution of global health issues.

Diabetes is a severe public health issue, but there is good news: significant progress is being made in diabetes prevention, detection, and treatment. Patients with type 1 diabetes must take insulin 3–4 times a day for the rest of their life, and their blood sugar levels must be closely checked to avoid consequences such as retinopathy and cardiovascular disease risks. Around 1300 patients with type 1 diabetes are predicted to receive a whole organ (pancreas) transplant and no longer require insulin, however demand for organ transplantation outnumbers supply. Rejection of the transplanted organ is another risk factor; as a result, the patient is given powerful immunosuppressive medicines, which can lead to additional catastrophic disorders. Glycemic control must be closely managed in the treatment of type 2 diabetes. Controlling the progressive decline of β cell function is critical because it can lead to glycemic control loss. Conventional medicines and insulin can help, but they can't fix the underlying metabolic and glucoregulatory issues. Diabetes is becoming more prevalent every day, necessitating aggressive and focused combinational medication, notably incretin-based therapy and peptide analogs. This may help to restore and maintain β cell function while also slowing the progression of type 2 diabetes In today's world, a new drug's usefulness and success will be determined by its capacity to treat/relieve one or more metabolic abnormalities, such as increased insulin production or improved glucose absorption and utilization by peripheral tissues, notably skeletal muscle.

Aside from novel therapeutic generations, numerous other classes have been described as alternative ways of treating diabetes, either alone or in combination. The future of leptin therapy is one of the newest concepts in diabetes management. It's a hormone produced by adipocytes that affects the central nervous system's neurons. This hormone has various functions, including preventing excessive weight gain by reducing food intake and increasing energy expenditure. Leptins also activate leptin receptors (LEPRs), which regulate glucose homeostasis. With reference to type 1 diabetes, it has been established that the central nervous system modulates leptins' sugar-lowering effect; it was hypothesized that leptins' antidiabetic action could have been affected by neurons in the brain. In mice with insulin-deficient type 1 diabetes, leptin treatment improves their condition through CNS-dependent pathways. Designing and using mucoadhesive microcapsules of various medications, such as glipizide, to enable controlled drug release and successful targeting is another area of drug development. Mucoadhesion is a unique strategy in drug delivery design because it causes the drug to release slowly at the action or absorption site, enhancing the drug's interaction with the underlying tissue forms and thereby increasing drug bioavailability. The number of drug delivery techniques that have been tried as a possible diabetes treatment is endless. Transdermal insulin delivery (which was developed as a result of painful and difficult insulin therapy) maintains stable insulin levels without the insulin deposits that are common with subcutaneous insulin injections. Odegaard and colleagues discovered that activated macrophages have a beneficial function in the regulation of nutritional homeostasis, implying that polarizing macrophages to the alternate state could be a valuable option in the treatment of type 2 diabetes. Clinical advances have been achieved in the prevention, development, and treatment of the condition, but no therapeutic strategy has yet proven to be effective. With new technologies altering treatment options, finding an effective drug will not be difficult. Extensive research that led to the discovery of disease-causing pathway genes and the sequencing of entire genomes has changed diabetes research. The introduction of tools such as PCRs, DNA microarrays, and gene knockouts with silence has opened up a new field in identifying faulty genes/mutations in an organism's genome. The rising prevalence of diabetes around the world is putting a financial strain on each country's economy. Diabetes, unlike some other diseases, has a treatment that, when properly managed, can significantly reduce complications such as heart attacks, amputations, blindness, and kidney failure. With constant research, finding the proper therapy for diabetes treatment is not impossible.

Diabetes and its consequences are currently on the rise throughout the world, and it is projected to climb much further in the future. Plant-based remedies, particularly traditional medicinal mixes, have been stressful in the treatment of diabetes, despite the availability of antidiabetic medicines. As a result, traditional plant-derived bioactive chemical treatments for diabetes are currently being promoted due to their safety and lack of adverse effects when compared to manufactured drugs. These investigations will greatly aid research into the discovery of antidiabetic medications from innovative natural product leads utilizing medicinal chemistry methodologies, as well as the exploration of their mechanistic activities via pharmacological studies.

As a result, this study briefly summarizes the active components and pharmacological effects of various commonly used plants in diabetes treatment. Furthermore, herbal extracts can now be used with conventional pharmaceuticals for combinatorial therapy. Each herb has its unique components that can help reduce diabetic complications and lower blood sugar levels. The goal of this review is to provide the required information for diabetes management. We have provided a comprehensive list of anti-diabetic herbs in our review. The isolation and identification of bioactive phytochemicals from these plants will help researchers better understand how to build anti-diabetic functional foods and drugs. The mechanism of action of the reported phytochemicals and/or plant extracts attributed to antidiabetic activity has also been discussed in order to focus on the potential phytochemicals and phytosources for further studies in the discovery and development of novel antidiabetic therapies.

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Conflicts of interest

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