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Antidiabetic activity of some common medicinal plants

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ABSTRACT

Diabetes mellitus (DM) is a chronic metabolic disease characterized by elevated blood sugar, malfunctional insulin, resistance, and lipid metabolism. DM is a major global health that causes a burden on the individual and society. Despite advances in clinical management, late-onset complications of diabetes remain challenging to control. Antidiabetic medications can cause weight gain or loss, and adverse gastrointestinal effects, highlighting the need for alternative, effective therapies with fewer side effects. Natural products have been widely investigated as antidiabetic agents, and many have been shown to have direct or indirect effects on DM pathways. These products contain chemical components, such as flavonoids, terpenes, alkaloids, coumarins, and phenolic compounds, which may be used to develop new antidiabetic drugs. This review provides an overview of the evidence surrounding some commonly used natural products that affect DM management.

Keywords: Diabetes mellitus, Medicinal plants, Antidiabetic effect, Hypoglycemia, Natural products.
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Introduction

Diabetes mellitus (DM) is a major global health risk, which is a group of metabolic disorders characterized by the presence of hyperglycemia. It has been reported that 424 million adults worldwide had diabetes, which is projected to grow to 629 million by 2045 (Afroz et al., 2019). International Diabetes Federation (IDF) estimates that 1.1 million children and adolescents aged 14–19 years have type 1 diabetes (T1-DM) (Grabia et al., 2021). According to the current classification, there are two major types: T1-DM and type 2 diabetes (T2-DM) (Fig. 1). The difference between the two types has been based on age, degree of loss of β-cell function, degree of insulin resistance (IR), presence of DM-associated autoantibodies, and the requirement for insulin treatment (Punthakee et al., 2018).

The long-term consequences of DM include retinopathy, nephropathy, and neuropathy. Also, people with diabetes are at great risk of cardiovascular disease, obesity, cataracts, and fatty liver disease (Chawla et al., 2016). DM can cause several characteristic symptoms, including thirst, polyuria, blurring of vision, and weight loss. If diabetes is not effectively treated, it can lead to serious complications, including ketoacidosis, dehydration, coma, and death (Kitabchi et al., 2009). Oral hypoglycemic medications are commonly used to manage T2-DM including metformin (Met), thiazolidinediones, alpha-glutamyl transferases, and sulphonyl urease.

Hypoglycemia, fatigue, diarrhea, and anemia risk are all associated with these therapies (Mahankali et al., 2022). Met remains the first choice of treatment for most T2-DM patients, however, it causes vitamin B12 deficiency. Therefore, other alternative or second-line treatment options should be individualized depending on the characteristics of each patient (Marín-Peñalver et al., 2016).

Natural product-derived drugs are more affordable with fewer side-effects compared to conventional therapies, research is increasingly leaning towards the discovery of new antidiabetic drugs from natural products targeting pathways or components associated with T2-DM (Alam et al., 2018).

Blood glucose homeostasis

Insulin and glucagon are pivotal hormones that play a crucial role in regulating blood glucose levels and ensuring the body's glucose homeostasis. Insulin, primarily produced by pancreatic β-cells, is released in response to elevated blood glucose levels following a meal (Rahman et al., 2021). Its primary function is to lower the blood glucose levels through various mechanisms. First, insulin facilitates glucose uptake by muscle and adipose tissue cells, allowing glucose utilization for energy or storage efficiently. Second insulin encourages the breakdown of glucose through glycolysis for ATP production in cells that helps to utilize glucose effectively. Finally, insulin promotes glycogenesis in the liver and muscle cells (Qaid et al., 2016). Glycogen is a storage form of glucose, readily available (Qaid et al., 2016). In contrast, glucagon is released by pancreatic α-cells in response to declining blood glucose levels during fasted state. Its primary role is to stimulate the liver, prompting the conversion of glycogen into glucose, thus increasing glucose availability in the bloodstream. This dynamic interplay between insulin and glucagon forms a vital regulatory cycle. While glucagon works to elevate blood sugar levels through its interactions with the liver, insulin plays a complementary role in reducing blood sugar by facilitating glucose utilization within cells (Röder et al., 2016). The physiological consequences of defective insulin secretion or function are the main causative of the T2-DM pathology (Skyler et al., 2017).

Insulin and its receptor

Insulin is a peptide hormone consisting of two chains, linked by disulfide bridges between cysteine residues. Insulin mediates its actions by binding to the insulin receptor (INSR) and activating intracellular signal transduction cascades. The INSR is a heterotetrametric with four subunits: two α subunits and two β subunits (Boucher et al., 2014). The subunits are linked by disulfide bonds and are located on the cell membrane. Insulin binds to the extracellular α subunit, which triggers a conformational change that allows adenosine triphosphate (ATP) to bind to the intracellular component of the β subunit. ATP binding triggers phosphorylation of the β subunit, giving it tyrosine kinase activity. This enables the β subunit to phosphorylate tyrosine residues on intracellular substrate proteins known as insulin-responsive substrates (IRS). The IRS can then bind to other signaling molecules mediating further insulin cellular actions (Boucher et al., 2014).

The role of insulin in blood glucose homeostasis

Throughout the process of digestion, carbohydrates within food are transformed into glucose, resulting in an elevation of blood glucose levels. This surge in blood glucose triggers the pancreas's β-cells to release insulin. Insulin plays a pivotal role by acting on multiple fronts: Firstly, it acts within the pancreas to suppress glucagon secretion, another key hormone involved in blood glucose regulation. Moreover, insulin influences three primary sites within the body: the liver, muscle tissue, and adipose tissue. Its mission is to facilitate the removal of excess glucose from the bloodstream, ultimately restoring blood glucose levels to a healthy, balanced range (Dimitriadis et al., 2021).

Glucose hemostasis, liver, muscles, and adipose tissues

Hepatocytes play a crucial role in mediating glucose uptake through the utilization of GLUT-2 transporters. Importantly, these

transporters do not respond to insulin sensitivity, as evidenced by research. Consequently, glucose uptake within liver cells proceeds independently of insulin, indicating that insulin does not directly impact hepatocyte glucose uptake (Navale and Paranjape, 2016). Within the liver, insulin assumes a multifaceted role. It fosters glycogen synthesis through glycogenesis by activating glycogen synthase, reducing blood glucose levels. Additionally, insulin serves as an inhibitor of both gluconeogenesis and glycogenolysis (Barthel et al., 2003)

Within muscle tissue, insulin is pivotal in facilitating glucose uptake by promoting the translocation of GLUT-4 transporters to the cell surface. This action enhances the insulin-stimulated uptake of glucose by the muscle cells. In addition, insulin contributes to heightened glucose uptake through the processes of glycolysis and glycogenesis while concurrently inhibiting glycogenolysis. Consequently, these multifaceted effects of insulin collectively contribute to reducing blood glucose levels (Petersen and Shulman, 2018; Chadt and Al-Hasani, 2020).

Adipocytes, the cells found in fatty tissue, notably express the insulin-sensitive GLUT-4 transporter. Consequently, insulin positively influences glucose uptake within adipose cells by enhancing the expression of GLUT-4, thereby promoting glycolysis. Furthermore, insulin stimulates the process of lipogenesis while concurrently inhibiting lipolysis. These coordinated actions by insulin are instrumental in maintaining a healthy equilibrium of serum lipids (Morigny et al., 2016).

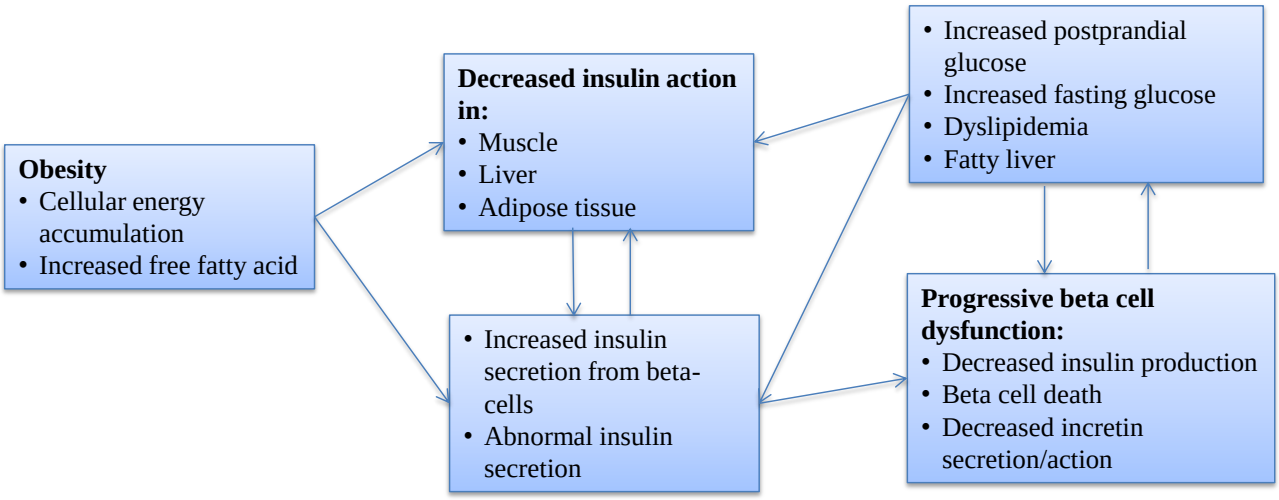

Fig. 1. Pathophysiology of type 2 diabetes (T2-DM) adapted from (Campbell, 2011)

Insulin resistance

Insulin resistance (IR) is a defining characteristic of diabetes, and it's marked by the inability of insulin-sensitive cells to respond adequately to normal physiological concentrations of insulin. This failure results in impaired insulin-induced glucose uptake and subsequent metabolic processes within the cells. Consequently, this resistance reduces glucose uptake in muscles and diminishes liver glycolysis and fatty acid oxidation, initiating a cascade of alterations in the insulin signaling pathway (Li et al., 2022). Numerous factors can exacerbate IR, including genetic predisposition, the natural aging process, ethnic background, excessive body weight, visceral obesity, physical inactivity, and smoking (Kolb et al., 2018). As tissues and organs become increasingly resistant to insulin, pancreatic β-cells compensate by increasing insulin production to sustain normal blood glucose levels. This compensatory mechanism leads to hyperinsulinemia, characterized by elevated plasma insulin levels. However, the chronic strain on β-cells eventually disrupts their function, resulting in β-cell dysregulation and, ultimately,

failure, leading to insulin deficiency. Both IR and insulin deficiency contribute significantly to hyperglycemia, which, if left unchecked, progresses to glucose intolerance and eventually diabetes (Prentki and Nolan, 2006).

Different therapies for T2-DM

Different pharmaceutical therapies are designed to manage T2-DM, each operating through distinct mechanisms. For instance, sulfonylureas and meglitinides fall into the insulin secretagogues category, as they stimulate insulin secretion from pancreatic β-cells. In contrast, biguanides and thiazolidinediones function as insulin sensitizers (Nanjan et al., 2018). They enhance the response of tissues to insulin, making the body more efficient in utilizing the available insulin. Another noteworthy medication is acarbose, which acts as an α-glucosidase inhibitor within the small intestine's lumen. Its mechanism involves slowing down the digestion and absorption of dietary carbohydrates (Chiasson et al., 2002). The diverse array of these pharmaceutical treatments provides clinicians with various options to tailor therapy to individual patient needs and responses. Another class of anti-diabetic therapies centers around the activity of incretin hormones. Incretins constitute a group of metabolic hormones that can remarkably lower blood glucose levels (Kim and Egan, 2008). These hormones are released following a meal and orchestrate several essential actions, including promoting insulin secretion and inhibiting glucagon release from alpha pancreatic cells, as illustrated in Fig. 2. Moreover, they exert control over the pace at which nutrients are absorbed into the bloodstream by slowing gastric emptying and may even directly suppress appetite, functioning as appetite suppressors.

The key players among incretin molecules are the intestinal peptides known as glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP, also referred to as glucose-dependent insulinotropic polypeptide) (Nauck et al., 2018). These peptides are synthesized by enteroendocrine cells in the gastrointestinal tract but are swiftly broken down by an enzyme called dipeptidyl peptidase-4 (DPP-4).

In therapeutic interventions for T2-DM, GLP-1, GIP analogs, and DPP-4 inhibitors have emerged as effective options (Rizzo et al., 2009). These medications leverage the intricate biology of incretin hormones to help manage and control T2-DM effectively.

A cutting-edge category of anti-diabetic medications includes sodium-glucose cotransporter (SGLT) inhibitors. These inhibitors target SGLT-2 proteins situated in the renal proximal tubules, which are responsible for reabsorbing glucose from the glomerular filtrate into the bloodstream (Hsia et al., 2017). When SGLT-2 is inhibited, it eliminates glucose through urine by preventing its reabsorption in the kidneys (Hsia et al., 2017, Wanner and Marx, 2018). Conversely, SGLT-1 proteins function as glucose transporters engaged in glucose absorption within the small intestines. Inhibiting SGLT-1 protein activity slows intestinal glucose absorption, lowering postprandial blood glucose levels. While SGLT-1 inhibitors remain in the research phase, dual SGLT1/SGLT2 inhibitors are presently under investigation and hold the potential to become the first oral medication suitable for both T1-DM and T2-DM (Musso et al., 2019).

Insulin secretagogues and sensitizers are prominent among the most commonly prescribed anti-diabetic therapies. Notably, Met is the foremost medication for T2-DM and is typically prescribed for diabetic patients who are overweight or obese. The mechanism of Met action involves enhancing insulin sensitivity by promoting glucose uptake and utilization in muscle cells, while concurrently inhibiting gluconeogenesis in the liver, as depicted in Fig. 3 (Madiraju et al., 2018).

Side effects of anti-diabetic medications

A diverse array of anti-hyperglycemic agents is available to healthcare providers, allowing them to tailor therapy choices according to individual patient needs while carefully considering the potential side effects of these medications (Chaudhury et al., 2017). While these therapies for T2-DM are vital in managing blood glucose levels and alleviating diabetes symptoms, they can also lead to undesirable side effects. For instance, insulin therapy and insulin secretagogues may inadvertently drive blood glucose levels to dangerously low levels, resulting in hypoglycemia (Sena et al., 2013). Sulfonylureas and thiazolidinediones, on the

other hand, are associated with weight gain, while biguanides, α-glucosidase inhibitors, and incretin-related therapies often trigger adverse gastrointestinal effects. Given these concerns, there is a growing need for alternative, effective therapies to manage T2-DM with fewer adverse side effects effectively (Sena et al., 2013).

Natural products to combat diabetes mellitus

Individuals grappling with chronic medical conditions, such as diabetes, frequently exhibit a heightened inclination towards the utilization of natural products when compared to the general population, seeking these remedies to manage their health. Natural products encompass herbal plants and traditional medicines, often considered safe for consumption without the need for direct supervision by a healthcare professional or a prescription for purchase. This growing interest in herbal medicine among the general public has sparked an increased scientific curiosity, driving extensive research endeavours to unravel and comprehend the pharmacologically active components within medicinal plants (Ekor, 2014; El-Sawy et al., 2023).

Natural plant components with anti-diabetic activity: their biological modes of action

Numerous plant-derived substances, encompassing flavonoids, terpenes, alkaloids, coumarins, and phenolic compounds, hold significant potential for advancing the development of novel drugs or therapeutic interventions (El-Naggar et al., 2007). These natural products may be used for conditions like diabetes and its associated complications, as illustrated in Fig. 4 (Lamba et al., 2000). These compounds have demonstrated promise in the realm of diabetes treatment. Herbal treatments for diabetes have found utility among patients dealing with both insulin-dependent and non-insulin-dependent diabetes, extending their application to conditions such as diabetic retinopathy and diabetic neuropathy. These natural remedies have thus emerged as valuable options in the broader spectrum of diabetes management. Plant extracts presenting hypoglycemic activity were summarized in table (1)

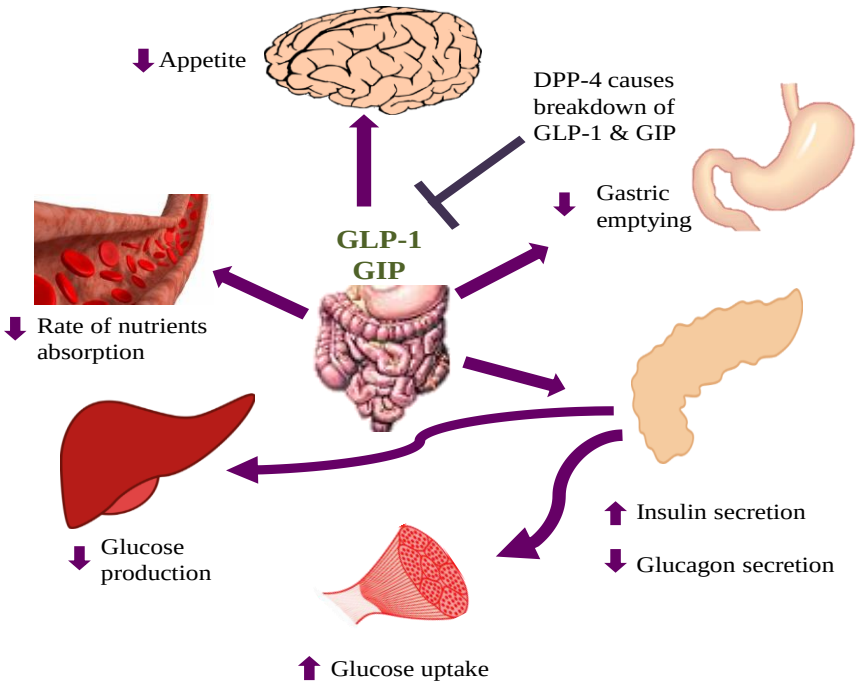

Fig. 2. Mechanisms of incretin hormones. The gut secretes incretin hormones in response to food intake and acts to increase insulin secretion and decrease glucagon release from the pancreas. Incretin hormones, especially GLP-1, stimulate insulin release from the beta cells in a glucose-dependent manner. GLP-1 suppresses the release of glucagon, incretin hormones can slow the emptying of the stomach contents into the small intestine and effects on appetite and food intake.

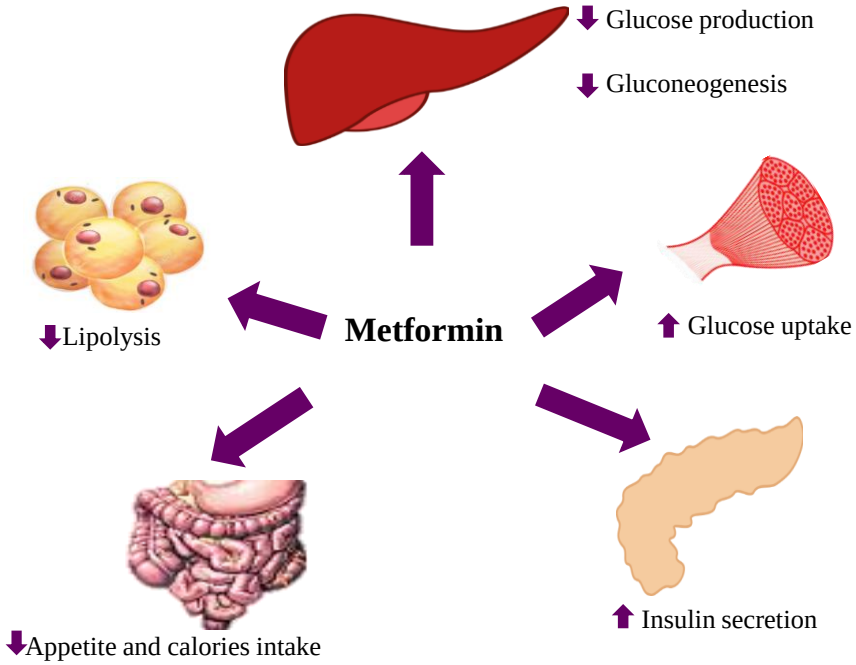

Fig. 3. Mechanism of Met action. Met primarily works in the liver and reduces its ability to produce glucose. In fasting, the liver releases glucose into the bloodstream to maintain blood sugar levels. Met decreases hepatic gluconeogenesis, leading to lower fasting blood glucose levels. Met improves the body's sensitivity to insulin, which is essential for cell glucose uptake. By increasing insulin sensitivity in muscle and adipose tissue, Met helps these tissues absorb and utilize glucose more effectively, lowering blood sugar levels.

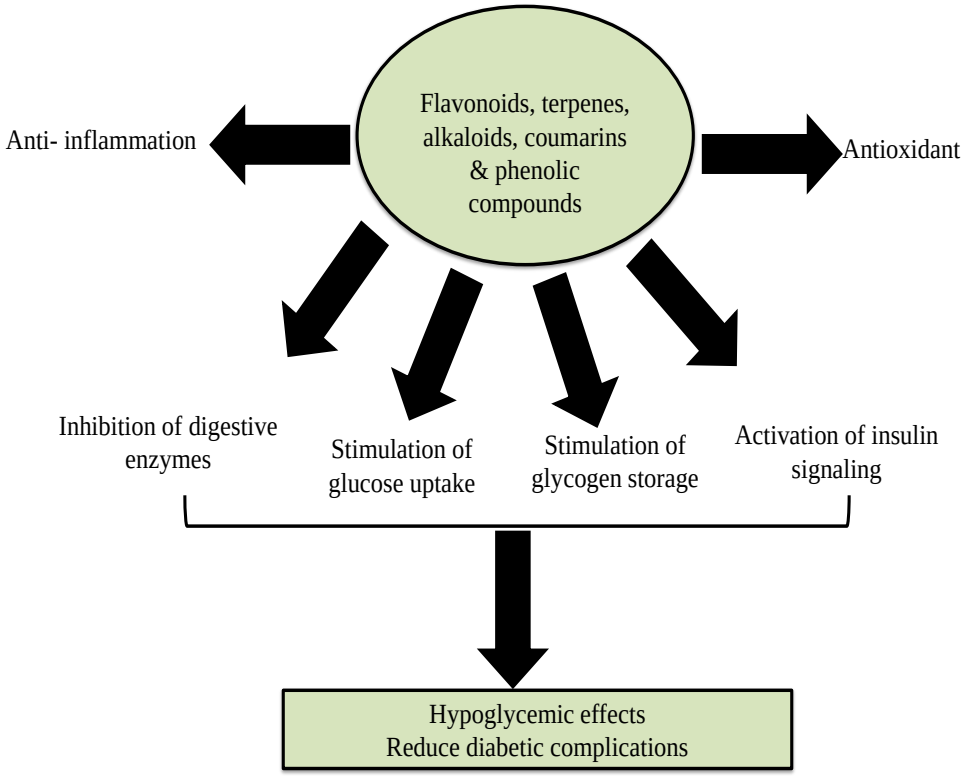

Fig. 4. Mechanism of natural plants components as an anti-diabetic effect**.**

Table 1. Plant extracts presenting hypoglycemic activity

Plant name	The active constituents	Mode of actions	Side effects	Effective dose
Fenugreek	Saponins, Coumarin Nicotinic acid.	Reduce fasting plasma glucose. Reduce postprandial plasma glucose. Control HbA1C.- Reduce LDL Cholesterol and triglycerides.	It may increase bleeding when taken concurrently with antiplatelet or anticoagulant drugs	100 g daily
Gymnema	Gymnemic acids water-soluble acidic fractions	Increase insulin secretion. Protect pancreatic cells. Increase the utilization of glucose. Inhibit glucose absorption from the intestine.	No significant side effects have been reported	400 to 500 mg daily for 3 months or more
Bitter melon	Triterpenes, alkaloids phenolic Polypeptide-p, an insulin-like plant protein	Decrease blood glucose levels. Protect pancreatic beta cells. Stimulate insulin secretion. Regulate postprandial glucose. Stimulate glucose uptake by skeletal muscle.	No significant side effects have been reported	2 to 3 g/day or 2 oz of fresh juice for 30 days
Cinnamon	Amethylhydroxyc-halcone polymer	Insulin-like effects in reducing blood glucose levels. Improve the lipid profile.	Large doses increased the risk of hepatotoxicity Not recommended with methotrexate drug	112 mg of aqueous extract 3 times daily
Milk thistle	Silymarin	Reduce blood glucose levels. Reduce insulin requirements. Improve the lipid profile. protect against kidney damage	Safe with very few gastrointestinal effects.	600 mg of silymarin
Reishi mushroom	Polysaccharides, Proteoglycans Triterpenoids	Increase plasma insulin. Decrease plasma glucose levels.	Safe Higher dose (3000mg per day)	1800 mg of the hot water extract form 3 times daily
White mulberry	Iminosugars, specifically 1-deoxynojirimicin, Polysaccharides Flavonoids	Alpha-glucosidase inhibitor. Prevent the digestion and absorption of simple carbohydrates in the intestine. Decrease the postprandial glucose.	No significant side effects have been reported	3 to 9 mg of deoxynojirimicin 3 times daily before meals
Aloe vera	Saponins, Vitamins A, C and E, phenolic compounds	Maintained glucose homeostasis by it is the effect on carbohydrate metabolizing enzymes.	No significant side effects have been reported	130 mg/kg body weight per day for 4 weeks
Moringa oleifera	Oleic acid Ascorbic acid, Phenols Flavonoid	Reduce blood glucose levels. Improve the lipid profile. Protect to islet cells from damage.	Toxic at 3000 mg/kg body weight	150 or 300 mg/kg for 21 days
Portulaca oleracea	Polyunsaturated Fatty acids, Flavonoids, and Polysaccharides	Decrease the insulin resistance Hypoglycemic Hypolipidemic effects	1040 mg/ kg	50-1000 mg/ kg
Tamarindus indica		Decrease blood glucose levels.		250 mg/kg and 500 mg/kg for 21 days

Flavonoids

Flavonoids, natural pigments abundantly found in fruits, vegetables, cereals, and various parts of plants, including roots, leaves, and stems, exhibit intriguing properties in diabetes management. Certain flavonoids have the remarkable ability to enhance the release of insulin from isolated islets of Langerhans in a concentration-dependent manner (Koshy and Vijayalakshmi, 2001). Moreover, specific flavonoids, such as rutin, quercetin, chlorogenic acid, and silibin isoform 3, possess hypoglycemic properties (Abd El-mawla et al., 2011, Kazazis et al., 2014). Additionally, to their hypoglycemic effects, flavonoids are renowned for their potent antioxidant activity. Numerous studies have illuminated the hypoglycemic actions of flavonoids, attributed to their capacity to safeguard pancreatic β-cells against oxidative stress, thus mitigating the adverse impact of oxidative damage on insulin-producing cells (Martín and Ramos, 2021). This multifaceted role underscores the potential of flavonoids as valuable components in managing diabetes.

Terpenes

Terpenes encompass a diverse group of compounds characterized by the general chemical formula $(C_5H_8)_n$ and grounded in the fundamental isoprene molecule structure. Certain diterpenes, triterpenes, and sesquiterpenes have demonstrated the ability to stimulate insulin release and concurrently reduce oxidative stress (Lai Shi Min et al., 2022). This dual action contributes to normalizing blood glucose levels, making them potentially valuable in managing and treating diabetes. Furthermore, these terpenes also exhibit hypolipidemic activity, implying their potential to assist in regulating lipid levels in the body. Given these multifaceted attributes, these substances hold promise as beneficial components in the comprehensive control and treatment of diabetes (Eliza et al., 2009).

Coumarins

Coumarins, secondary metabolites present in various plants, comprise aromatic heterocyclic structures characterized by fused benzene and α-pyrone rings. Among their notable properties, coumarins demonstrate hypoglycemic activity and exhibit inhibitory effects on the enzyme aldose reductase and platelet aggregation (Ghosh et al., 2022). These actions are particularly significant as they are believed to underlie the mechanisms behind diabetic complications (Venugopala et al., 2013).

Alkaloids

Alkaloids, cyclic amines featuring heterocyclic rings incorporating nitrogen, wield notable antidiabetic effects. They achieve this by both promoting insulin secretion and enhancing the uptake of blood glucose in peripheral tissues (Shehadeh et al., 2021). Additionally, alkaloids hold promise in preventing diabetic complications, including neuronal and renal damage (Tiong et al., 2013).

Phenolic compounds

Phenolic compounds derived from plants are crucial in mitigating diabetes complications, primarily by curbing the formation of reactive oxygen species and safeguarding kidney function. Several studies have even suggested that polyphenols can lower blood glucose levels (Deka et al., 2022). Specifically, isoferulic acid has been identified for its hypoglycemic activity, making it a potential candidate for managing T1-DM (Hurst et al., 2011). These findings underscore the significance of phenolic components in diabetes prevention and management.

Hypoglycemic plants

This section showcases some of the most promising medicinal plants with hypoglycemic properties that have undergone testing and research.

Fenugreek *(Trigonella foenum-graecum)*

Fenugreek, one of the oldest medicinal plants, boasts a native habitat spanning the Mediterranean, Asia, North Africa, and Europe (Marles and Farnsworth, 1995). Its hypoglycemic effects can be attributed to active constituents such as saponins, coumarin, and nicotinic acid. Extensive research has shown that Fenugreek significantly reduces key diabetes-related parameters, including fasting plasma glucose, postprandial plasma glucose, glycosylated hemoglobin (HbA1C), LDL cholesterol, and triglycerides (Neelakantan et al., 2014). Fenugreek has demonstrated antiplatelet effects, which may lead to increased bleeding

when taken concurrently with antiplatelet or anticoagulant medications (Abebe, 2019). Additionally, its interaction with hypoglycemic drugs can result in an additive effect, necessitating cautious us.

Gymnema *(Gymnema sylvestre)*

Gymnema, a sturdy perennial plant, originates in central and western India, parts of Africa and Australia. This remarkable herb has a longstanding history of use in herbal medicine for addressing diabetes mellitus. The active constituents responsible for its hypoglycemic effects are the gymnemic acids and water-soluble acidic fractions extracted from the plant's leaves (Venkatesan et al., 2020). Research has revealed that these Gymnema constituents exert their hypoglycemic influence by enhancing insulin secretion, safeguarding pancreatic cells, promoting glucose utilization, and inhibiting glucose absorption from the intestine (Kumar et al., 2013). Studies have shown that a daily dose of 400 to 500 mg of Gymnema can yield positive outcomes concerning postprandial blood glucose levels and a reduction in HbA1C, especially when administered for a duration of three months or longer. However, it's worth noting that the sample sizes in these studies tend to be minor, (Shanmugasundaram et al., 1990).

Bitter melon *(Momordica charantia)*

Bitter melon, a tropical fruit with a rich history of medicinal use across Asia, South America, India, and East Africa, holds promise in managing diabetes. Its active constituents include triterpenes, alkaloids, and phenolic compounds (Joseph and Jini, 2013). Notably, bitter melon contains Polypeptide-p, an insulin-like plant protein that can lower blood glucose levels when administered subcutaneously to individuals with T1-DM (Joseph and Jini, 2013). Moreover, bitter melon offers a multifaceted approach to diabetes management. It has been shown to protect pancreatic beta cells, stimulate insulin secretion, regulate postprandial glucose absorption in the gastrointestinal tract, and enhance glucose uptake by skeletal muscle. The recommended effective dose typically ranges from 2 to 3 grams per day or the equivalent of 2 ounces of fresh juice for a duration of 30 days, yielding reductions in blood glucose levels ranging from 13% to 50% (Joseph and Jini, 2013). Importantly, bitter melon is generally considered safe for diabetes management, with no serious side effects reported at therapeutic dosages (Dans et al., 2007). This natural remedy underscores its potential as a valuable component in diabetes care.

Cinnamon (*Cinnamomum cassia*)

Cinnamon, widely known for its culinary uses in the Western world as a delightful spice and flavoring agent, also has a rich history in herbal medicine for managing diabetes mellitus (Nabavi et al., 2015). The active constituent within Cinnamomum cassia is a methylhydroxychalcone polymer, which possesses insulin-like properties capable of reducing blood glucose levels (Medagama and Bandara, 2014).

Notably, cinnamon's effectiveness in lowering plasma glucose appears most pronounced in individuals with poorly controlled diabetes (Medagama and Bandara, 2014). Studies have indicated that an effective dose consists of 112 mg of aqueous extract taken three times daily, equivalent to a daily intake of 3 grams of Cinnamomum cassia (Kizilaslan and Erdem, 2019). Furthermore, research, including the work of Allen and colleagues, underscores the benefits of cassia cinnamon in reducing fasting plasma glucose levels compared to a placebo. Additionally, it demonstrates favorable impacts on total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol levels (Allen et al., 2013).

While cinnamon is generally safe when consumed at recommended doses, caution is warranted when consuming large quantities, as excessive intake has been associated with a heightened risk of hepatotoxicity (Gu et al., 2022). Moreover, individuals with pre-existing liver conditions or those taking hepatotoxic medications like methotrexate should exercise caution and may consider avoiding cinnamon (Felter et al., 2006).

Milk thistle *(Silybum marianum)*

Milk thistle, a member of the aster family, which includes common daisies and various thistle plants, is native to Europe and North America. Historically, this resilient herb has been employed to treat liver and gallbladder disorders (Giese and Associates, 2001). Its active component, found in the seeds of the milk thistle plant, is silymarin. A previous research has

unveiled the potential of milk thistle in managing hyperglycemia and hyperlipidemia among individuals with diabetes mellitus. For instance, studies conducted by Kazazis and colleagues have indicated that a daily dose of 600 mg of silymarin significantly reduces fasting blood glucose levels, daily blood glucose fluctuations, and insulin requirements by up to 20%, and HbA1C by 0.5% in diabetic patients (Kazazis et al., 2014). Furthermore, milk thistle remarkably can lower total cholesterol, LDL cholesterol, triglyceride, aspartate aminotransferase, and alanine aminotransferase levels (Huseini et al., 2006). It also exhibits protective effects against kidney damage (Sonnenbichler et al., 1999). Notably, milk thistle is considered a safe herbal remedy, with very few gastrointestinal side effects such as diarrhea and nausea reported (Fried et al., 2012).

However, it's crucial to exercise caution, as milk thistle can theoretically enhance the hypoglycemic effects of certain medications when taken concurrently with hypoglycemic agents and some other drugs (Kazazis et al., 2014).

Reishi mushroom *(Ganoderma lucidum)*

Reishi mushroom, a white rot Oriental fungus native to China, Japan, and various Asian regions, has garnered attention for its potential in diabetes management. The active constituents responsible for its hypoglycemic effects encompass polysaccharides, proteoglycans, proteins, and triterpenoids (Benzie and Wachtel-Galor, 2011). These constituents have demonstrated the ability to elevate plasma insulin levels while concurrently reducing plasma glucose levels, as evidenced in both animal and human studies (Benzie and Wachtel-Galor, 2011). Furthermore, Gao et al. reported significant reductions in HbA1C by 0.8% and postprandial blood glucose levels when Reishi was used for 12 weeks compared to a placebo group. The recommended dosage for Reishi mushroom typically consists of 1800 mg in the form of a hot water extract, taken three times daily (Gao et al., 2004).

Reishi mushroom is generally considered safe; however, higher doses (e.g., 3000 mg per day) in individuals with low platelet counts have been associated with reduced platelet aggregation and symptoms such as dry mouth, nasal dryness, itchiness, and stomach upset. Moreover, it's essential to exercise caution, as Reishi mushroom may theoretically enhance the blood glucose-lowering effects of hypoglycemic agents when taken concurrently (Wińska et al., 2019).

White mulberry *(Morus alba)*

White mulberry leaves have a rich history as antidiabetic agents utilized across the globe. The active constituents responsible for their hypoglycemic effects encompass iminosugars, particularly 1-deoxynojirimicin, polysaccharides, and flavonoids (Kojima et al., 2010). Remarkably, 1-deoxynojirimicin, as indicated by Kojima and others, functions as a potent alpha-glucosidase inhibitor, effectively impeding the digestion and absorption of simple carbohydrates within the intestine (Kojima et al., 2010).

Numerous studies have explored the impact of mulberry on postprandial blood glucose levels, consistently revealing improvements in glycemic control by lowering postprandial glucose levels. However, these studies have not significantly improved HbA1C or fasting plasma glucose values (Lown et al., 2017). The recommended effective dose for white mulberry typically ranges from 3 to 9 mg of deoxynojirimicin, administered three times daily before meals (Mudra et al., 2007). It's noteworthy that mulberry plant extract does not produce the same effects. While white mulberry is generally considered safe, it's essential to be cautious of potential interactions with other hypoglycemic drugs, which could theoretically lead to additive effects. Nevertheless, no concrete evidence supports such interactions in humans (Kimura et al., 2007).

Aloe vera

Aloe Vera, a succulent plant species belonging to the Aloe genus, thrives in wild environments across tropical, semi-tropical, and arid climates worldwide. Its medicinal applications have been harnessed for millennia, dating back thousands of years (Manvitha et al., 2014). Previous research by Kumar et al. (2011) unveiled compelling findings regarding Aloe Vera's potential in diabetes management. In their study, the administration of A. vera extract at a dosage of 130 mg/kg body weight per day over 4 weeks led to a significant reduction in blood glucose and total cholesterol levels in diabetic mice induced

by streptozotocin (60 mg/kg body weight). Intriguingly, the hypoglycemic effects of Aloe vera were compared with Met, a commonly prescribed diabetes medication. Following this treatment, the activities of carbohydrate metabolizing enzymes returned to near-normal levels, ultimately contributing to the maintenance of glucose homeostasis (Kumar et al., 2011). These findings underscore the therapeutic potential of Aloe Vera in the realm of diabetes management.

Moringa oleifera

Moringa, a plant thriving in tropical regions across India, Pakistan, Bangladesh, Afghanistan, and beyond, offers a plethora of medicinal applications. Its leaves, bark, flowers, fruit, seeds, and roots are used to create various forms of medicine. The active components responsible for its hypoglycemic and protective effects encompass flavonoids, phenolic compounds, oleic acid, and ascorbic acid (Elbakry et al., 2019, Mthiyane et al., 2022). Intriguingly, treatment involving 150 or 300 mg/kg of methanolic extracts derived from *M. oleifera* pods administered over 21 days yielded significant reductions in diabetes progression, serum glucose levels, and nitric oxide levels. Simultaneously, there was an increase in serum insulin levels, glucose uptake in peripheral tissues, and the expression and regulation of enzymes involved in carbohydrate metabolism (Mthiyane et al., 2022). These methanolic extracts also elevated antioxidant levels within pancreatic tissue while concurrently reducing the levels of thiobarbituric acid reactive substances, effectively mitigating oxidative stress damage. Moreover, protein levels within treated animals increased. Furthermore, histological examinations of the pancreas in diabetic rats revealed degenerative changes in β-cells, but the administration of methanolic extracts from *M. oleifera* pods significantly ameliorated this histoarchitectural damage to islet cells (Gupta et al., 2012). These findings illuminate the promising therapeutic potential of Moringa in diabetes management and its role in protecting pancreatic tissue from oxidative stress-induced damage.

Portulaca oleracea

Portulaca oleracea, often regarded as a weed in field crops and lawns, holds surprising health benefits. This resilient plant can be naturally found across Europe, Asia, and the Mediterranean region, making it widely distributed (Uddin et al., 2014). The active constituents responsible for its hypoglycemic effects include a high content of polyunsaturated fatty acids, flavonoids, and polysaccharides. Notably, El-Sayed's research has demonstrated that treating patients with T2-DM using *Portulaca oleraceae* seeds can effectively reduce IR. Additionally, it leads to significant hypoglycemic and hypolipidemic effects, showcasing its potential as a valuable natural remedy in managing diabetes (El-Sayed, 2011).

Tamarindus indica

Tamarindus indica, a leguminous tree known for its delectable fruits, originates from tropical Africa. In a previous research, an alcoholic extract derived from Tamarindus indica exhibited noteworthy antioxidant activity in vitro, effectively countering 2,2-diphenyl-1-picrylhydrazyl, nitric oxide, and hydroxyl radical-induced oxidative stress (Agnihotri and Singh, 2013). Excitingly, when administered orally to diabetic rats over 21 days, this alcoholic extract from Tamarindus indica yielded substantial reductions in blood glucose levels at doses of 250 mg/kg and 500 mg/kg. These findings underscore its remarkable potential as an antidiabetic agent (Agnihotri and Singh, 2013).

Conclusions

Numerous natural products with antidiabetic properties have undergone rigorous testing in both experimental models and clinical practices. However, it's important to note that the natural products discussed in this review represent just a fraction of the possibilities. Many others hold the potential to influence blood glucose levels, though the evidence supporting their efficacy is less robust. In some cases, these botanicals showcase promise for developing compounds that could be pivotal in diabetes treatments. The diverse array of active components found in these natural products underscores the multifaceted mechanisms at play. These mechanisms include stimulating insulin secretion from pancreatic β-cells and enhancing glucose uptake in peripheral tissues. While certain substances derived from medicinal plants exhibit therapeutic potential,

others may induce hypoglycemia as a side effect and, in some instances, may even pose a risk of toxicity, particularly to the liver. Consequently, future research should elucidate the biologically active components and their underlying Abebe mechanisms. This will pave the way for developing clinically effective and safe compounds, ultimately enhancing the arsenal of available antidiabetic therapies.

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