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Review Article

Exploring the Potential of Anti-Diabetic Medicinal Plants and Phytocompounds

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ABSTRACT

Diabetes mellitus is a long-term metabolic disease that prolonged hyperglycemia can cause serious side effects that impact several organs and systems, such as peripheral neuropathy, retinopathy, and nephropathy. While insulin and oral hypoglycemic drugs continue to be useful in controlling hyperglycemia, their inability to address disease-related variables including insulin resistance and hypertension makes the quest for new therapeutic strategies necessary. This has led to a worldwide interest in natural products, especially those derived from plants, which have long been used to treat diabetes. Diabetes has a complicated etiology, necessitating multimodal treatment approaches that may include antidiabetic drug combinations. The potential of plant-derived chemicals as lead molecules for the development of innovative antidiabetic medicines is highlighted in this study, which examines the historical and current roles of natural products in the treatment of diabetes.

Keywords: Diabetes Mellitus, Hypoglycemic Drugs, Phytocompounds.

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INTRODUCTION

Diabetes, a long-term and often inherited condition affecting the body's hormone system, can seriously impact health and even be life-threatening. It's marked by high blood sugar levels, eventually leading to sugar in the urine. This happens because the body's tissues struggle to properly process sugars, fats, and proteins. There are two main types of diabetes: Type 1, where the body doesn't produce insulin and often involves an autoimmune reaction destroying cells in the pancreas, and Type 2, which is much more common (over 90% of cases) and largely linked to obesity and inactivity. Type 2 diabetes involves both poor insulin production and a resistance to the insulin that is produced. Family history increases the risk for Type 1 diabetes.

Chronic hyperglycemia can seriously harm the heart, blood vessels, kidneys, nerves, eyes, and other body systems. Retinopathy, nephropathy, and peripheral neuropathy are among the severe macrovascular and microangiopathy consequences that may arise from this.[1]

Even while insulin and oral hypoglycemic medications work well to treat hyperglycemia, disease-related variables such insulin resistance, hyperinsulinemia, hypertension, decreased insulin production, and elevated cholesterol make using them more difficult. Numerous drugs have significant negative effects and don't significantly alleviate the complications associated with diabetes. The effectiveness, patient compliance, and side effects of the available insulin therapy and oral hypoglycemic drugs are limited. This has sparked a global search for novel treatments for this metabolic disorder.

The complex pathogenesis of diabetes mellitus necessitates a multimodal therapy strategy. It may be necessary for future treatment approaches to combine several kinds of antidiabetic medications.

Insulin was one of the many treatments and medications used to treat type 2 diabetes throughout history, a synopsis of insulin's history is given in Figure 1. Even before its mechanism of action was understood. While some of them are utilized as supplemental therapy for individuals with hyperglycemia, others have been added to the medical arsenal of therapeutics. Numerous of these substances have been isolated from microorganisms or plants. Classic examples are acarbose, miglitol, and voglibose from bacteria, and galegine, phenolic compounds, and pycnogenol obtained from plants.

Since the Middle Ages, diabetes mellitus has been treated using *Galega officinalis* L. (Fabaceae), the first medicinal plant with a proven antidiabetic effect. Galegine, a guanidine derivative, was isolated from the plant that goes by a number of names, including Italian fitch, French lilac, and goat's rue. The plant extract's ability

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to lower blood glucose is due to this compound, whose chemical structure is similar to that of the antidiabetic drug metformin.

The historical treatments for the diseases referred to as "diabetes," encompassing both type 1 diabetes (autoimmune destruction of insulin-secreting β-cells in the pancreas) and type 2 diabetes (insufficient insulin production and/or insulin resistance, though the specific mechanisms are unclear), will be examined to help save lives and support individuals suffering from this condition. The details given will illustrate the roles that natural products have served in the advancement of contemporary medications for these ailments as well as earlier treatments (primarily insulin)

- Diabetes mellitus is a collection of metabolic diseases rather than a single illness, signs that indicate the presence of metabolic syndrome is given in Figure 2.
- Diabetes 1 (autoimmune loss of the pancreatic β-cells that produce insulin).
- Diabetes type 2 (insufficient insulin synthesis and/or insulin resistance; the precise processes underlying these conditions are unclear).
- "Variants" of the illness.
- Individuals with Type 1 Diabetes (T1DM) produce minimal to no insulin from the pancreas.
- Type 2 Diabetes (T2DM): This condition changes how the body produces glucose.
- Current Potential Insulin-Based Treatments for Type 2 Diabetes T1DM and T2DM treatments that are not insulin-linked.[2]

Lead growth problems for complex natural product design

Both inside and beyond the Rule-of-5 chemical space, synthetic medications and chemical leads differ from natural molecules in their structures. Since they are made biosynthetically, their structures don't undergo significant chemical modifications.

Total synthesis

Semisynthesis

The standard Rule-of-5 lead advancement involves enhancing ligand efficiency, selectivity, ADME, and other properties as lead molecules or fragments are advanced from the target. Although natural product leads may be sufficiently strong and selective, they may not meet ADME, safety, pharmacokinetic, pharmacodynamic, or financial requirements.

Chemical change of a 500-1000 molecular weight molecule may not significantly improve ligand efficiency, but it may improve other critical therapeutic qualities for lead development. Biosynthetic techniques can be useful instruments for attaining structural changes in natural products, which in turn facilitates the advancement of natural product leads.

Guanidines: Substances Originally Used as Herbal Medicines

Pharmaceuticals have historically mostly come from plants, and a large number of the pharmaceuticals on the market today are either directly or indirectly derived from plants.

Through the "Project Gutenberg" ebook series, Culpeper's Complete Herbal as of 1850 is available.

Werner and Bell published the first metformin synthesis in 1922.

The use of partially purified extracts as therapies was documented in French literature as late as the mid-1930s.

Metformin was "rediscovered" in the early 1940s while looking for antimalarial drugs.

The French doctor Jean Steme was the first to remark on its promise as a diabetic treatment for adults in 1957.[10-13]

Several medicinal plants and their byproducts (natural principles, active compounds, and crude extracts) have been described in the literature as being used in the Indian traditional medical system known as "Ayurveda" to treat diabetes, T2DM medications approved between 1997 and 2019 that aren't guanides plants is given in Figure 3. Regarding diabetes and its complications, the following species are regarded to be more effective and have been investigated in greater depth: *Allium cepa, Allium sativum, Aloe vera, Coccinia indica, Caesa-piniabonducella, Eugenia jambolana, Ficus bengaensis, Gymnema sylvestre, Momordica charantia, Mucuna prurins, Ocimum sanctum* syn. *Tenui orum, Pterocarpus marsupium, Swertia chirayita, Syzigium cumini, Tinospora cordifolia,* and *Trigonella foenum-graecum.*

Here are the primary types of diabetic treatment. However, the fundamental reason for the growing number of people looking for alternative treatments with fewer or no bad effects is the well-known side effects of pharmaceuticals. As a result, plant-based herbal drugs or botanicals are becoming increasingly important in comprehensive diabetes management regimens.

Plants have historically been the primary source of medications, and many of the drugs on the market today are either directly or indirectly produced from plants.

Galega officinalis is the source of the popular diabetic medicine glucophage (metformin)

The 45 medicinal plants include *Allium cepa, Allium sativum, Aloe vera, Cajanus cajan, Coccinia indica, Caesalpinia bonducella, Eugenia jambolana, Ficusben galenesis, Gymnema sylvestre, Momordica charantia, Murraya koeingii, Ocimum sanctum* syn. *tenuitarum, Pterocarpus marsupium, Swertia chirayita, Syzigium cumini, Tinospora cordifolia,* and *Trigonella faenum-graecum.*

There have been extensive studies of Indian medicinal herbs used to treat one or more diabetes-related issues published.[15]

Herbal Remedies for Diabetes

Traditional therapy for diabetes mellitus probably focuses mostly on managing the disease's obvious symptoms, like polyuria and extreme thirst.[16] The Sushruta Samhita and CharakaSamhita, two ancient Ayurvedic medical texts, recognized glycosuria as an indication of diabetes. Diabetes can be treated by addressing acute thirst, according to the Greek physician Aretaeus.

The world has benefited from the valuable medications found in the Indian subcontinent's indigenous pharmacopoeia, such as reserpine from *Rauvolfia serpentina*, which is used as a sedative and antihypertensive. Other medicinal systems from the subcontinent include Ayurvedic, Unani, and folklore. It is demonstrated that both hyperglycemic and normal animals experience hypoglycemia when given serpine. New anti-diabetic drugs for the international market may be developed from Indian traditional medicine.

Indian Medicinal Plants that May Help Avoid Diabetes

Natural plants have been a significant source of medicine since ancient times. About 80-85% of individuals in both industrialized and developing nations receive their primary care from traditional medicine made from medicinal plants. Traditional medicine is believed to use large doses of active substances or plant extracts. Before insulin was discovered, the main treatment for diabetes was the use of medicinal herbs. Today, the most widely used conventional medication for treating non-insulin-dependent diabetes is metformin, which is produced from the medicinal plant *Galega officinalis*.

Medicinal Plant's Phytoconstituents

Plants exhibit antidiabetic characteristics due to the variety of phytoconstituent types they contain. The phytoconstituents found in medicinal plants are mentioned below:

- Flavanoids are antidiabetic compounds that lower blood glucose levels, significantly lower plasma cholesterol

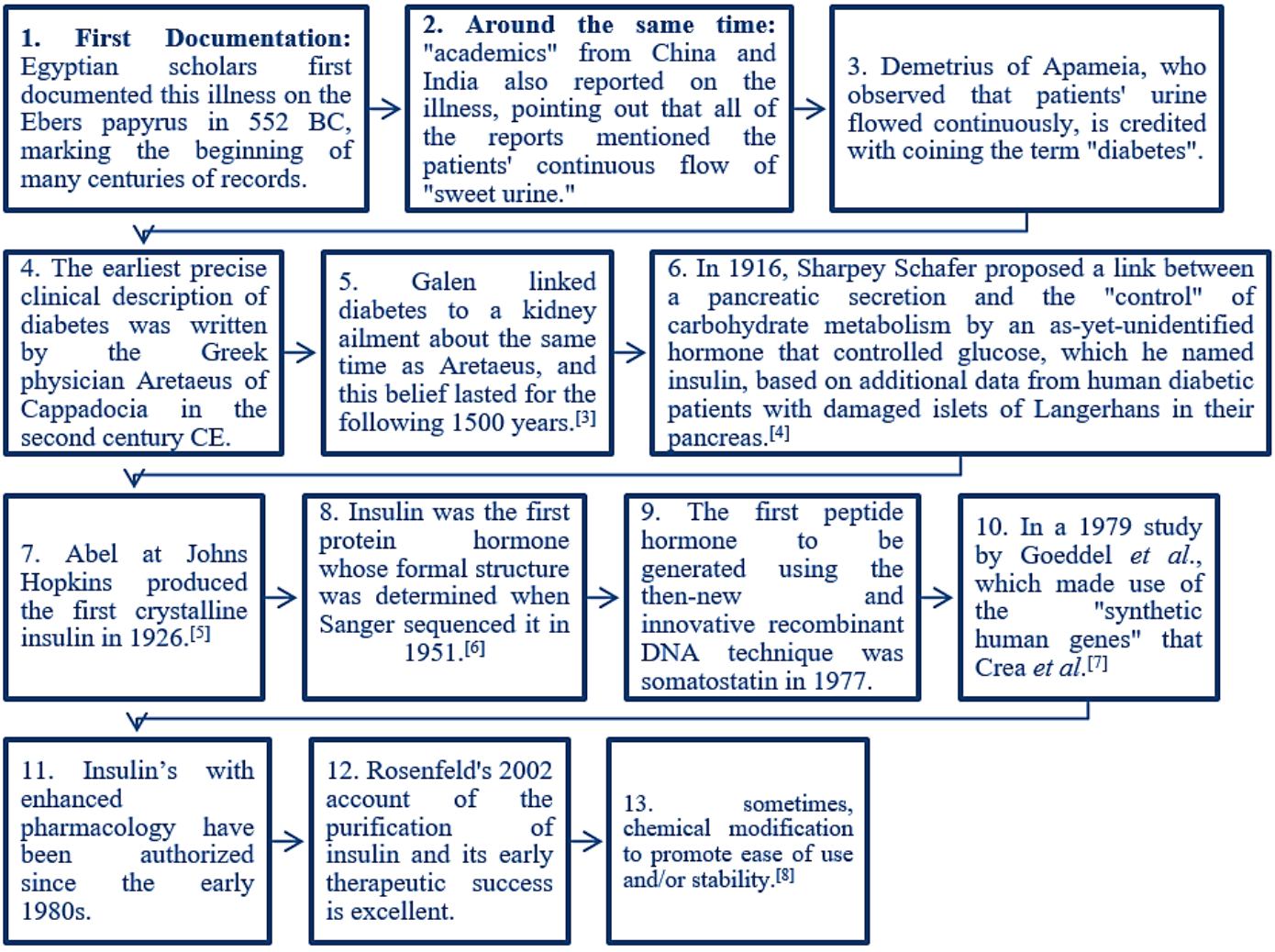

Figure 1: A Synopsis of Insulin's History.

and triglycerides, and raise hepatic glucokinase activity-possibly by improving insulin production.

- Polysaccharides decrease blood glucose by increasing serum insulin levels.
- Ferulic acid causes insulin to be released, while saponins trigger the release of insulin, which lowers blood glucose levels.
- Dietary fibers can reduce postprandial blood glucose levels by slowing down the pace at which glucose is absorbed.
- Some plants may be able to prevent diabetes, according to reports based on ethnobotanical research. Many plants have active ingredients that can be employed directly as pharmacological agents, lead compounds, or medications.

Important Herbal Plants Looked into for Possible Diabetes Treatments

Ficus religiosa

The plant *Ficus religiosa*, often known as peepal, is a member of the Moraceae family. Numerous significant chemicals found in *F. religiosa* can be used to treat conditions like diabetes, lung conditions, skin conditions, and abnormalities of the central nervous system.[17]

Chemicals in *Ficus religiosa* that are Bioactive

The bioactive substances found in *Ficus religiosa ficus* contains a variety of bioactive substances that have potent antidiabetic properties.

alkaloids, flavonoids, lanosterol, lupen-3-one, methyl oleanolate, noctacosanol, phenols, Steroids, β-sitosteryl-d-glucoside, stigmasterol, tannins, and vitamin K are among the phytoconstituents of *F. religiosa* stem bark that have been found. These fall under the category of antidiabetic inaction.[18]

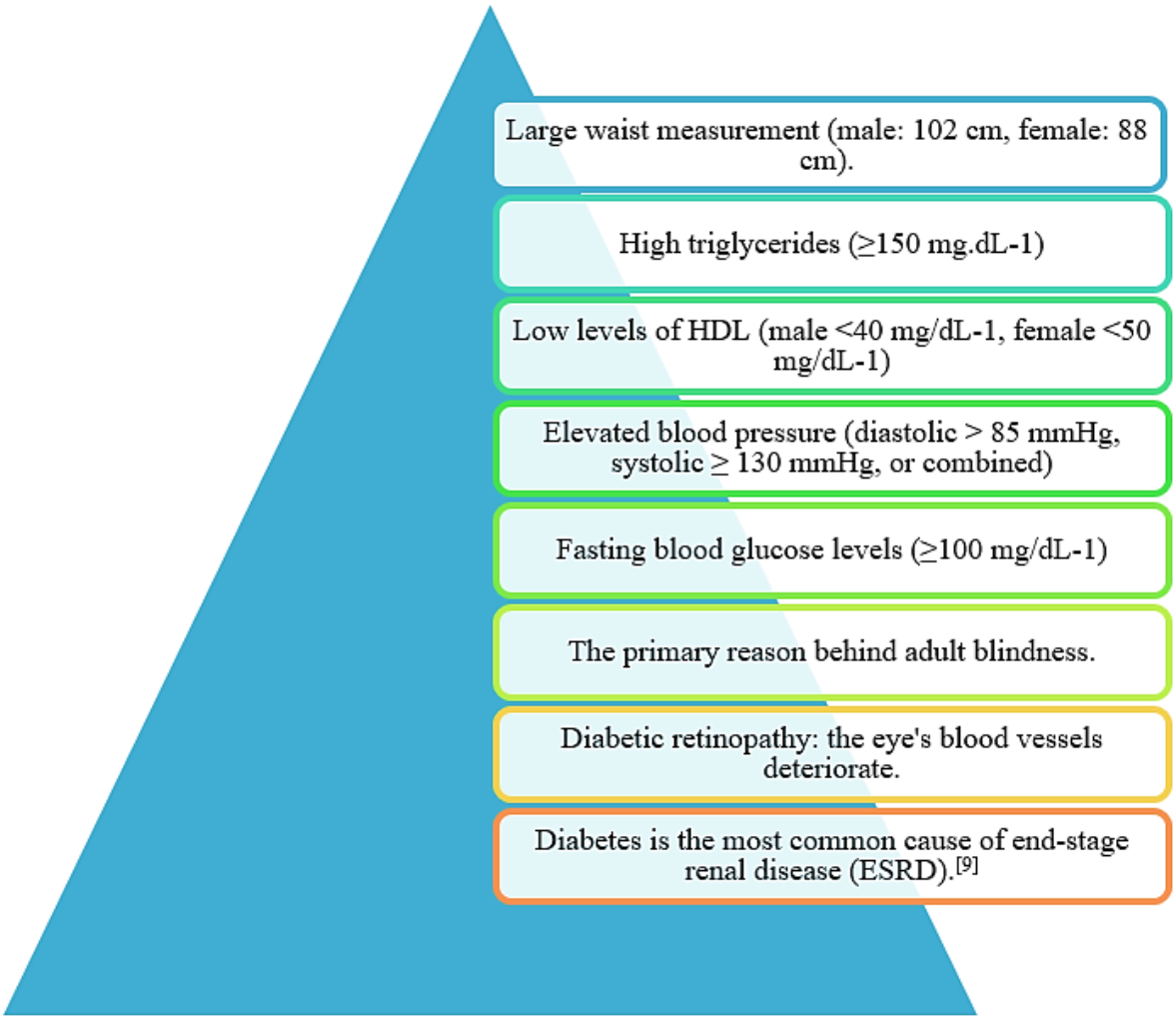

Figure 2: Syndrome Metabolic (Signs that indicate the presence of metabolic syndrome.) Standard Criteria.

Anti-Diabetic Activity

It has been shown that the aqueous extract of *F. religiosa* significantly reduces blood glucose levels at doses of 50 and 100 mg/kg. Glibenclamide, a well-known hypoglycemic drug, was used as a comparative control. The *F. religiosa* aqueous extract then caused a progressive increase in the experimental diabetic rats' body weight, skeletal muscle, liver glycogen content, and blood insulin levels. At the bark root, the blood sugar level dropped the most.

When taken orally, the aqueous extract of *F. religiosa* reduces blood glucose levels during fasting and regulates the antioxidant defense system's enzymes to prevent oxidative stress. The rise in glutathione levels and its capacity to prevent the synthesis of malondialdehyde showed its potential as an antioxidant and antidiabetic medication.[19]

Eugenia jambolana

Eugenia jambolana belongs to the Myrtaceae family and is also referred to as jamun or black plum. This species has long been found in South Asian countries like Bangladesh, Indonesia, Nepal, Burma, Pakistan, and Sri Lanka, as well as the Indian subcontinent.

Antidiabetic Inaction because the jambul fruit directly affects the pancreas; it is an important diabetic treatment.[20]

Bioactive Compounds in *Eugenia jambolana*

Anthocyanins, ellagic acid, glucoside, hydrolyzable tannins, isoquercetin, myricetin and kaempferol are among the many bioactive substances present in the plant.

Anti-Diabetic Activity

- Jamboline, a glycoside found in jambul seeds, prevents starch from becoming sugar when blood sugar levels are

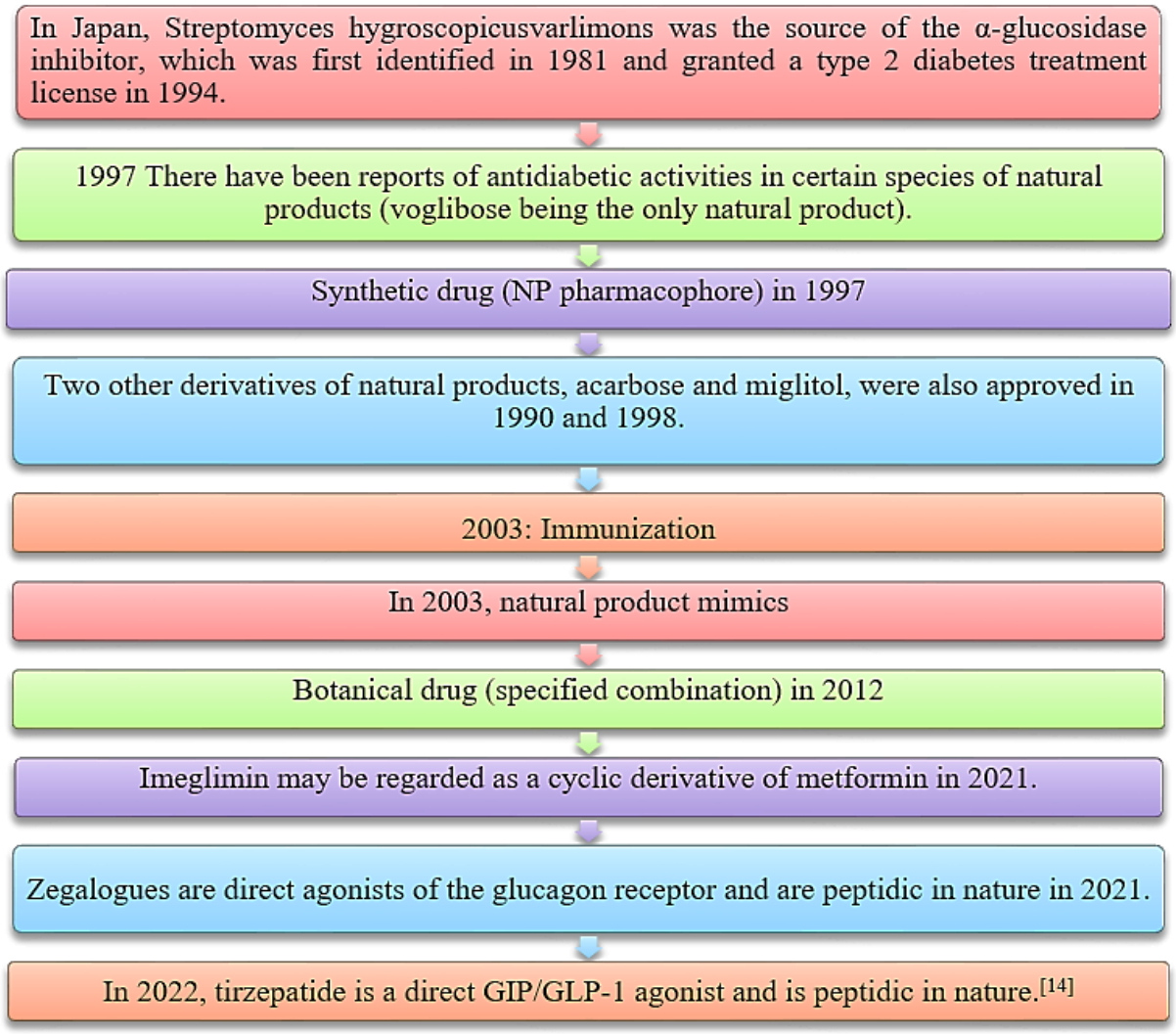

Figure 3: T2DM medications approved between 1997 and 2019 that aren't guanides Plants.

high. It also causes the pancreas to secrete more insulin by inhibiting the breakdown of insulin.

- The jambul tree's dried bark ash can help manage the symptoms of diabetes.
- In rats given alloxan to induce diabetes, *Eugenia jambolana* seed powder and ethanolic extract significantly reduced blood sugar levels and improved pancreatic islet histology.[21]

Momordica charantia

Momordica charantia, sometimes referred to as the bitter gourd or karela, is a fruit that is widely grown in Asia, East Africa, and South America. It belongs to the Cucurbitaceae family and can be used to treat diabetes, heart disease, and other associated ailments. Although the anti-diabetic activity has drawn a lot of attention, antibacterial, antiviral, and anticancer capabilities have also been demonstrated.[22]

Bioactive Compounds in *Momordica charantia*

M. charantia has the following unique chemical constituents: spinasterol, nerolidolcitrulin, galacturonic acid, momordicin, charantin, and linoleic acid.[23,24]

Anti-Diabetic Function

M. charantia produces specific hypoglycemic effects through a variety of pharmacological pathways. It has bioactive ingredients with anti-diabetic properties, including as vicine and some antioxidants. By blocking glucosidase, it prevents the absorption of glucose. It helps initiate insulin release and enhances insulin signaling or sensitivity by mending damaged β-cells.

- It facilitates the activation of hepatic glucose-6-phosphate dehydrogenase activity and the inhibition of glucose-6-phosphatase. It also shows inhibitory effects on α-amylase and α-glucosidase. Saponins also promote the release of insulin.[25]

Aloe barbadensis

Ghritkumari, or *aloe vera*, is another name for *Aloe barbadensis*. In the dry regions of India, it is commonly utilized to make hedgerows. It is mentioned in Arabian Peninsula traditional medicine as a treatment for diabetes and is used as an Ayurvedic medication to help people cope with painful ailments.[26]

Bioactive Compounds in *Aloe barbadensis*

Anthranol, aloin A and B, aloetic acid, aloe-emodin, isobarbaloin, emodin, and ester of cinnamic acid are just a few of the plant's many active phytoconstituents.[27]

Anti-Diabetic Activity

The primary benefits of Ghritkumari are its anti-inflammatory and antidiabetic properties. Long-term blood sugar stabilization is aided by it.

At 200 mg/kg, aloe vera gel exhibits remarkable anti-diabetic and cardioprotective properties, maintaining normal levels of catalase and superoxide dismutase activity and increasing reduced glutathione in diabetic rats by four times. The application of leaf pulp extract, which demonstrated specific hypoglycemia effects, can improve the effectiveness in type II diabetic rats.

- *Aloe gibberellins* and *Aloe vera* (at doses ranging from 2 to 100 mg/kg) both improve wound healing and decrease inflammation in dose-responsive manner in STZ diabetic mice.
- It was evident that aloe helped diabetic patients control their blood sugar levels and prevent atherosclerotic heart disease.
- The plant's dried sap helped to demonstrate the hypoglycemic effects.[28]

Brassica juncea

In India, *brassica juncea*, also referred to as rai, is a common spice used in many different dishes. The plant is grown all over India, however primarily in Bihar and Uttar Pradesh. India ranks third globally in terms of rapeseed and mustard production. Its impact was linked to an increase in glycogen synthetase, which raised the amount of glycogen in the liver and decreased the levels of other glyconeogenic enzymes and glycogen phosphorylase in the body of the animal.

Compounds in *Brassica juncea* that are bioactive

Brassica contains cyaniding, isorhamnetin, kaempferol, and quercetin as its main phytoconstituents.[29]

Anti-Diabetic Action

When normal rats were fed *Brassica juncea* orally for 60 days, the results were notable hypoglycemia effects.

• *B. juncea* aqueous seed extract has strong hypoglycemic effect; this was tested in male albino rats with STZ-induced diabetes.

• Certain polyphenols in *Brassica* vegetables exhibit strong antioxidant properties. The hepatic glycogen content rises as a result of the hypoglycemic impact of the seed extract, whereas other gluconeogenic enzymes such as glycogen phosphorylase and others are decreased.[30]

Allium cepa

Onions, or *Allium cepa*, are widely grown throughout Central Asia. It is one of the most important dietary components and is grown all over India. In diabetic rabbits, a number of the

soluble and insoluble ingredients in dried onion powder show anti-hyperglycemic properties. Allium cepa has antioxidant and hypolipidemic qualities as well. *Allium cepa* also has antioxidant and hypolipidemic qualities.[31,32]

Bioactive Compounds in *Allium cepa*

Phytoconstituents such ajoene, allin, allicin, di-allyl-tri-sulphide, and S-allyl cysteine are abundant in the plant.

Anti-Diabetic Action

Onions help control blood sugar levels. Giving onions to diabetics improves their metabolic status because they are hypoglycemic and hypocholesterolemic.

• In individuals with diabetes, the levels of thiobarbituric acid reactive compounds and glutathione S-transferase activity in the plasma, liver, brain, and kidney are often elevated; however, onion extract reduces these levels. Its strong antioxidant properties could also account for its hypoglycemic propensity.

• In individuals with diabetes, onion extract reduces body weight and plasma glucose levels;

• In diabetic rats fed a high-fat diet, supplementing with onion powder stimulates the generation of insulin.[33]

Acacia arabica

This plant, also known as "Babool" in India, has a variety of therapeutic uses, including treating skin, stomach, and dental ailments. In Indian traditional medicine, the fresh plant parts of *Acacia arabica* are valued for their aphrodisiac, antibacterial, anthelmintic, astringent, antidiarrheal, and nutritive properties.[34]

Compounds in *Acacia arabica* That Are Bioactive

The majority of *Acacia arabica's* phytochemicals include kaempferol, epicatechin, procatechinic acid, tannins, alkaloids, and glucosides.[35]

Antidiabetic In action

It is both cultivated and found all over India. 94% of the seed meals caused a significant hypoglycemia impact in normal rats compared to controls.

Alloxanized rats were shown to have no hypoglycemia impact, suggesting that the plant functions via releasing insulin.

When insulin release from pancreatic beta cells was started, a notable hypoglycemia effect was also seen in normal rabbits. Acute toxicity and behavioral abnormalities were not seen at these dosages.[36]

Azadirachta indica

It is frequently called neem. This particular plant is indigenous to the Indian subcontinent and belongs to the genus *Azadirachta*. Tropical and subtropical locations are the primary habitats for its growth. Among its many uses is the maintenance of good hair. Neem promotes better liver function, blood sugar control, and blood purification. A wide range of products, including toothpaste, body lotion, skin creams, shampoos, and soaps, are also made with it. It also works as a skin-benefiting tonic and heals eczema.[37]

Bioactive Compounds in *Azadirachta indica*

Numerous bioactive substances, including quercetin, nimbin, and nimocin, are abundant in the plant.

Anti-Diabetic Activity

Blood sugar levels are suppressed by neem root bark extract, which also lessens hypoglycemic and antihyperglycemic effects.

The ethanolic extract of *Azadirachta indica* was found to significantly lower elevated blood glucose levels.

The intestinal glucosidase activity is suppressed and oral glucose tolerance is enhanced by *A. indica* chloroform extract. Additionally, it contributes to the renewal of cells that produce insulin. Short-term blood glucose reduction is one of the benefits of neem oil. It enhances glucose tolerance as well.[38]

Tinospora cordifolia

It is commonly referred to as "guduchi" or "giloy." The tropical areas of India, Sri Lanka, and Myanmar are home to this herbaceous vine. *T. cordifolia* contains a wide variety of advantageous compounds. Some provide antioxidant qualities, while others might strengthen the body's defenses.[39]

Chemicals in *Tinospora cordifolia* That Are Bioactive

Among the several bioactive compounds found in abundance in the plant are berberin, palmative, and columbinas.

Anti-Diabetic Activity

Oral T. cordifolia extracts lower blood and urine glucose and serum lipid levels

Additionally, it reduces body weight. Blood glucose levels are decreased by its aqueous extract. Additionally, the methanol extract from it lowers the level of glycosylated hemoglobin and suppresses blood glucose.[40]

Allium sativum

Garlic, or *Allium sativum*, is a common ingredient in both traditional and modern medicine. It is also used as a raw ingredient in cooking. It can be eaten raw or processed into products like garlic oil or powder, which have a different chemical and biological composition. It is considered to be one of the many sources of phenolic compounds.[41]

Allium sativum's Bioactive Compounds

The unique flavor of garlic products, which is the consequence of multiple biochemical processes, is considered to be their main quality attribute. Alliin, allicin, 1, 2-vinyldithin, allyl sulfide, and sulfur-containing non-volatile amino acids, or thiosulfinates, are the main bioactive compounds.[42]

Anti-Diabetic Action

Glyburide, an anti-diabetic drug that also lowers serum glucose levels and belongs to the sulfonylurea family, has shown that S-allyl-cysteine sulfoxide, also known as alliin, has hypoglycemic effects.

Garlic enhances insulin sensitivity and increases β cell-mediated pancreatic insulin production, which releases bound or attached insulin and contributes to the hypoglycemia state.

It has an ingredient called allicin, which when combined with other ingredients like cysteine, improves serum insulin levels and frees insulin from S-H group interactions, which frequently result in insulin inactivation.[43]

Ocimum sanctum

Its leaves, commonly referred to as *tulsi*, are prized and utilized in Hindu religious ceremonies. In terms of their chemical makeup and therapeutic qualities, the two primary varieties-green and black-are identical. Tulsi leaves have long been used to cure a variety of ailments, including inflammation and respiratory tract infections. This plant's essential volatile oils are what give it its distinctly characteristic aroma. Terpenes, phenols, and aldehydes are the primary constituents of this volatile oil that is extracted from the seeds. In addition to oil, the plant has alkaloids, glycosides, saponins, and tannins; ascorbic acid and carotene are abundant in the leaves.[44]

Bioactive Compounds in *Ocimum sanctum*

About 0.7% of the plant's volatile oil, which is made up of 71% eugenol and 20% methyl eugenol, is found in the leaf. Moreover, several phenolic chemicals, including as orientin, vicenin, eugenol, urosolic acid, and apigenin, are isolated from the fresh leaves and stem of tulsi using aqueous leaf extracts.

Anti-Diabetic Activity

Alcohol and several organic solvent extracts boost the amount of insulin released by the clonal pancreatic β cells and the pancreas itself.

In addition to their well-known ability to lower blood sugar, tulsi extracts also contain aldose reductase activity, which helps to lessen the problems associated with diabetes. *Tulsi* extracts directly mobilize intracellular calcium ions and facilitate their entrance by stimulating Adenylatecyclase (cAMP), which in turn increases insulin secretion.[45]

CONCLUSION

Particularly in the context of traditional Ayurvedic medicine, the use of medicinal plants in the management and treatment of diabetes has attracted a lot of attention. Plant-based options that have fewer or no negative effects are becoming more and more popular as worries about the side effects of traditional pharmacological therapies grow.

Many therapeutic substances have historically been obtained from plants, and even contemporary drugs, like metformin (which comes from *Galega officinalis*), have roots in medicinal plants. By increasing insulin production, controlling blood glucose levels, and optimizing metabolic function, the bioactive substances present in these plants-such as flavonoids, polysaccharides, and saponins-display strong antidiabetic effects.

The phytochemicals found in these plants could result in the creation of innovative, safe, and efficient diabetes treatments when further research is conducted. As a result, the use of medicinal plants in the treatment of diabetes presents an interesting new avenue for complementary and alternative medicine.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

T1DM: Type 1 diabetes, **T2DM:** Type 2 diabetes, **ADME:** Absorption, distribution, metabolism, excretion.

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