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Novel antidiabetic therapeutics from some Indian medicinal plant kingdom

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Abstract

Diabetes mellitus (DM) has become a serious global problem as it is responsible for 1.5 million deaths. The extreme change in food habits and the fast lifestyle causes metabolic or endocrine disorders, which leads to Diabetes Mellitus (DM). The presently available synthetic drugs possess numerous side effects. They are very costly and limited ease of use, efficiency, and acceptability. Natural products are playing a major role in the treatment of numerous chronic diseases and drug discovery processes. The superiority of natural product drugs over synthetic drugs is because the former are safer and easily available. For this reason, researchers are now trying to find novel and more potent antidiabetic drugs from traditional medicinal plants. A number of plant-generated chemical compounds, especially polysaccharides, glycosides, terpenes, flavonoids, and polypeptides possessing antidiabetic activity, are isolated from various medicinal plants worldwide. These natural antidiabetic medications alter metabolic imbalances through a number of cellular and molecular pathways, preventing diabetic problems from developing. Nowadays, a great scientific interest has been aimed at the use of traditional antihyperglycemic medicinal plants as a daily food supplement. Inspired by the virtues of nature-based medicines, pharmacologists, phytochemists, and pharmacognosists are extensively engaged in further research for the development of natural

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antidiabetic drugs from nature. They advocate for the use of antidiabetic agents from nature's pharmacy, especially from plants, for the long-term remedy of diabetic patients.

Keywords: Antidiabetic activity, Diabetes mellitus, Flavanoids, Phenolic compounds, Phytochemical compounds, Medicinal plants.

Introduction

Diabetes mellitus (DM), the prevalent condition within the endocrine system, has become a serious concern to many people in developing countries. DM is considered the fifth chief source of death globally due to the changes in the human environment, activities, and way of life and globalization industrialization [1, 2]. This heterogenous disorder is due to insulin deficiency or impaired insulin function by the pancreas [3, 4]. Diabetes is divided into four types: type 1 diabetes, type 2 diabetes, gestational diabetes, and MODY or prediabetes, which together cause diabetic individuals to die young. [5]. Insufficient insulin leads to type 1 diabetes, while type 2 diabetes results from insulin resistance. Insulin resistance contributes to hyperglycemia and dyslipidemia [6]. Maturity-onset diabetes of the young (MODY) is a hereditary condition that typically appears before age 25. It's characterized by impaired insulin production in the pancreas, leading to high blood sugar levels but without the ketone buildup seen in other types of diabetes. MODY is caused by specific gene mutations. Common types of MODY include HNF4-α (MODY-1), glucokinase (MODY-2), HNF1-α (MODY-3), HNF1-β (MODY-5), and CEL gene (MODY-8). Unlike type 2 diabetes, MODY is not related to obesity or high blood pressure. People with MODY often have normal weight and experience symptoms like frequent urination, excessive thirst, dehydration, blurred vision, and recurring skin or yeast infections. Studying MODY at the genetic and clinical levels can help scientists understand how more complex forms of diabetes, like type 2, develop. On the other hand, prediabetes is a condition where blood sugar levels are elevated but not yet at the level of type 2 diabetes. This can happen because the body isn't effectively using insulin (insulin resistance) or because the pancreas isn't producing enough insulin. Prediabetes often has no noticeable symptoms, but some people might experience increased thirst, frequent urination,

excessive hunger, tiredness, blurry vision, numbness or tingling, frequent infections, slow-healing wounds, and unexplained weight loss. Having prediabetes significantly raises your chances of developing type 2 diabetes, heart disease, or stroke [7, 8].

People with persistently high blood sugar levels can develop a range of serious health problems affecting their organs, such as those related to blood vessels, heart, kidneys, nerves, eyes, and limbs, potentially leading to amputations and blindness. [9]. In the year 2019, around '463 million people globally had diabetes, with this figure projected to rise dramatically to '578 million by 2030' and '700 million by 2045'. With over half a billion people currently affected, there's an urgent need for coordinated efforts to combat diabetes [10, 11]. The report of 'The International Diabetes Federation (IDF) Diabetes Atlas 2021' shows that diabetes mellitus (DM) affects 537 million adult people in worldwide [12, 13].

Recently used antidiabetic drugs developed the overall glycemic control via different mechanisms. Some of them reduce the fasting plasma glucose level. Some agents primarily lower postprandial plasma glucose excursions. Some work by combining the two mechanisms. Sulfonylureas and Meglitinides boost β-cell insulin secretion through a mechanism independent of glucose levels. Dipeptidyl peptidase 4 (DPP4) inhibitors and glucagon-like peptide 1(GLP1) receptor agonists raise insulin secretion by a glucose-dependent mechanism. Insulin resistance is reduced with metformin and thiazolidinediones. α-Glucosidase inhibitors and Colesevelam operate in the gastrointestinal tract to reduce postprandial glucose fluctuations [14]. Bromocriptine activates D2 dopamine receptors in the brain, leading to a reduction in plasma glucose levels [15]. Most of them possess severe side effects, e.g., sulfonylurea, a drug for hypoglycemia, can cause weight gain, fatal complications, and mild headaches [14, 16]. The biguanide medication Metformin may cause abdominal discomfort, loss of appetite or diarrhea, temporary nausea, and lactic acidosis in cases of severe renal impairment and renal hypoperfusion [16-18]. Common symptoms include gastrointestinal issues, weight gain, anemia, headaches, changes in vision, dizziness, blood in the urine, erectile dysfunction, and occasionally fatigue. The side effects of Thiazolidinediones include

sleeplessness, vertigo, hypoglycemia, and proteinuria [19-21]. Besides this, the "UK Prospective Diabetes Study (UKPDS)" and "A Diabetes Outcome Progression Trial (ADOPT)" report that the response of patients to a particular antidiabetic agent is reduced over time. To overcome this problem, they recommended the use of composite regimens with multiple drugs with diverse mechanisms of action will be essential to sustain target HbA1c [22]. Combining lifestyle changes with contemporary pharmacological treatments can help achieve metabolic control targets in many patients with type 2 diabetes mellitus (T2DM) [21].

This review will discuss some novel antidiabetic agents from natural resources, mainly from the Indian plant source, and their structure, antidiabetic activity, and their mechanisms of action draw the interest of pharmacologists, phytochemists, and pharmacognosists for further scientific exploration into endocrine metabolic disorders.

Currently used synthetic antidiabetic drugs:

Antidiabetic medications are primarily used to treat immediate symptoms and life-threatening conditions related to diabetes. Additionally, certain drugs are used to reduce the risk of long-term complications and improve overall life expectancy by addressing various risk factors associated with diabetes. This is achieved by reducing blood glucose levels through the use of antidiabetic drugs. The vast majority of antidiabetic medications are taken by mouth, which is why they are often referred to as oral hypoglycemic or antihyperglycemic agents. There are a few exceptions of oral antihyperglycemic agents like insulin, pramlintide, liraglutide, and exenatide. The categorization and choice of antidiabetic medications depend on the type of diabetes, age, individual condition, and other considerations. Since Type 1 Diabetes Mellitus (T1DM) results from insulin deficiency, insulin administration is necessary for patients with T1DM. On the other hand, T2DM is caused by insulin resistance by the cell. The remedy of T2DM can be done in three ways: (i) agents that enhance the insulin secretion activity of the pancreas, (ii) substances that improve the body's ability to use insulin effectively, and (iii) substances that slow down the absorption of sugar from the digestive system [23]. A major drawback of current diabetes

medications is that people with diabetes often need to take them for the rest of their lives. While applying antidiabetic drugs to DM patients, a good knowledge of the symptoms, efficacy, and potential side effects of these drugs must be handled with the utmost caution [24]. The primary drug categories used to treat diabetes today include insulin, sulfonylureas, thiazolidinediones, biguanides, meglitinides, 'alpha-glucosidase inhibitors, 'dipeptidyl peptidase-4 inhibitors, 'glucagon-like peptide-1 agonists', 'sodium-glucose cotransporter 2 inhibitors', and 'dopamine agonists' [25-36].

A. Insulin

The insulin-producing cells in the pancreas are the source of the hormone insulin. DM patients with type-1 sufferers suffer from complete insufficiency of insulin, whereas T2DM patients possess fall-off construction of endogenous insulin. Insulin lowers blood glucose levels by facilitating the uptake of peripheral glucose, particularly in skeletal muscle and fat, and by inhibiting hepatic glucose production. Individuals with Type 1 Diabetes Mellitus (T1DM) need insulin throughout their entire lives. DM patients with type-2 are administered insulin as a monotherapy or as a complement therapy to oral antidiabetic agents. Insulin is classified into long-acting, intermediate-acting, short-acting, and rapid-acting categories based on its pharmacokinetic and pharmacodynamic properties. Insulin is a short-acting hormone. Isophane insulin acts as an intermediate-acting. Glargine insulin, degludec insulin, and detemir insulin are examples of long-acting insulin while rapid-acting insulin includes aspart, Lispro, and glulisine [36]. Insulin primarily affects the liver, muscles, and fat tissues. Potential side effects of insulin treatment include allergic reactions, low blood potassium levels, dangerously low blood sugar, and discomfort or skin reactions at the injection site [37-39].

B. Sulfonylureas (SUs)

The earliest agent, sulfonylureas functions as an insulin secretagogue. Glibenclamide, tolazamide, tolbutamide, chlorpropamide, gliclazide, glipizide, glyburide, and glimepiride are the Sulfonylureas drugs for the treatment of T2DM, taking into account their protection, effectiveness, little expenditure of therapy, and pleiotropic advantages

[40]. SUs stimulate the pancreas to generate and discharge more insulin. The target organ for drugs is the β cells found in the islets of Langerhans within the pancreas. Hypoglycemia (low blood sugar), constipation, diarrhea, vomiting, and nausea, like gastrointestinal disorders, are the side effects of SUs therapy [41].

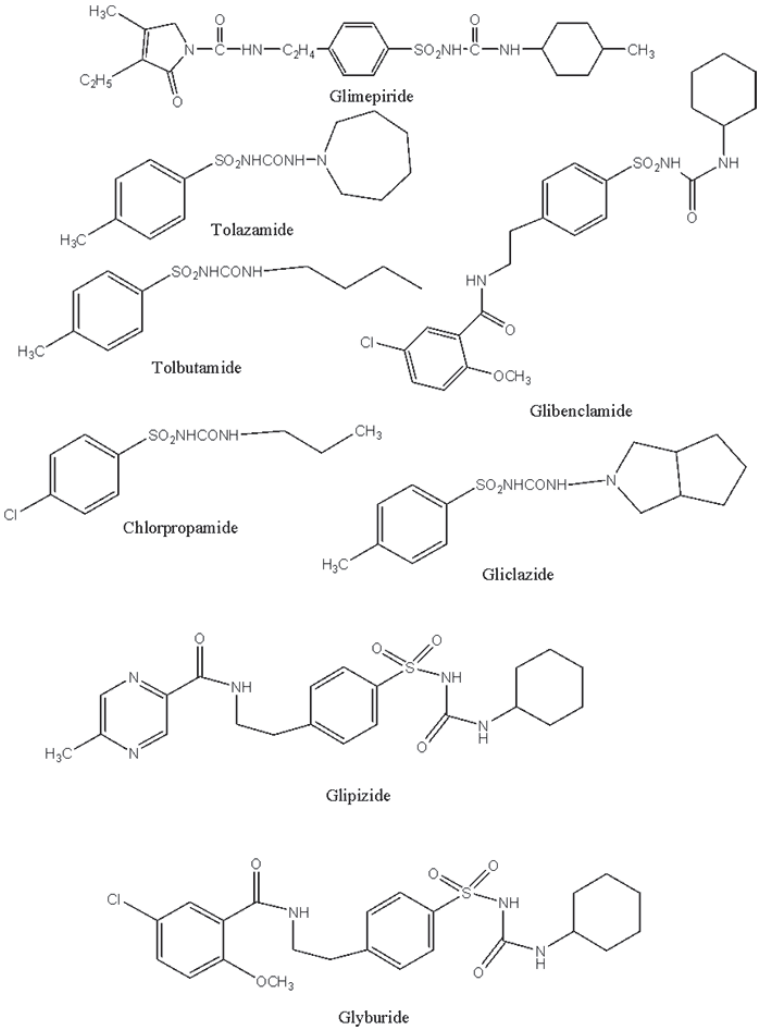


Fig.1. Structure of commonly used Sulfonylureas (SUs) drugs

C. Thiazolidinediones (TZDs)

Rosiglitazone, pioglitazone, lobeglitazone are the thiazolidinediones (TZDs) drugs which are considered as the precious curative

armamentarium of the T2DM. TZDs enhance the body's response to insulin and decrease the liver's sugar production. However, they can lead to weight gain and fluid retention. These drugs primarily affect fat tissues, liver, kidneys, central nervous system (CNS), and muscles. Rosiglitazone augmented the risk of a nonfatal heart attack. Pioglitazone causes an increased risk of bladder cancer [42-44].

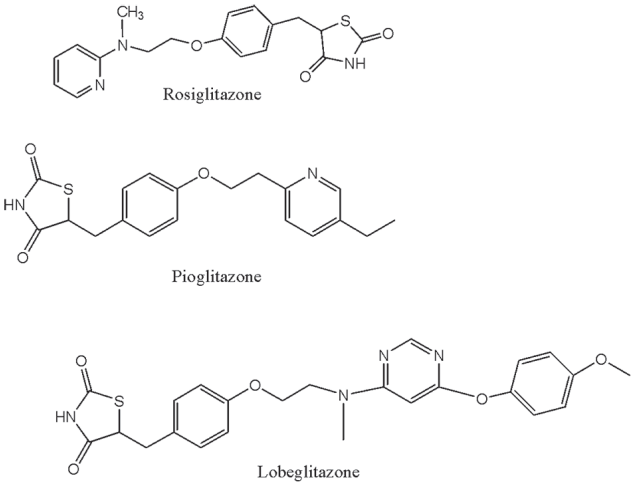


Fig.2. Structure of commonly used Thiazolidinediones (TZDs) drugs

D. Biguanides

The biguanides drugs metformin and phenformin lower the generation of glucose by the liver. Metformin is typically the first oral medication used to manage type 2 diabetes [45, 46] and is approved by the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists [47]. It lowers the glucose level chiefly by liver endogenous glucose production (EGP). The control of blood sugar is done by metformin with a slight reduction in weight, potentially contributing to a decrease in complications associated with diabetes. The liver and muscle are the target organs of biguanides. Diarrhea, nausea, and metallic aftertaste are the side effects of biguanides drugs [15].

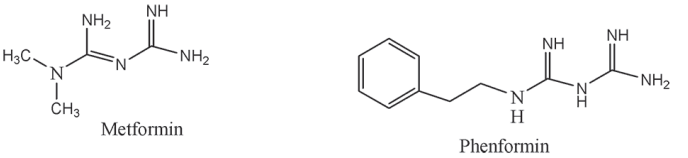


Fig.3. Structure of commonly used Biguanides drugs

E. Meglitinides

Nateglinide, repaglinide, and mitiglinide are the meglitinide drugs that stimulate the pancreas to produce more insulin to alleviate DM patients type-2. This drug functions in a glucose-dependent manner. The organ targeted is the β cells within the islets of Langerhans located in the pancreas. The most common adverse effect of this drug, particularly repaglinide is hypoglycemia [48, 49].

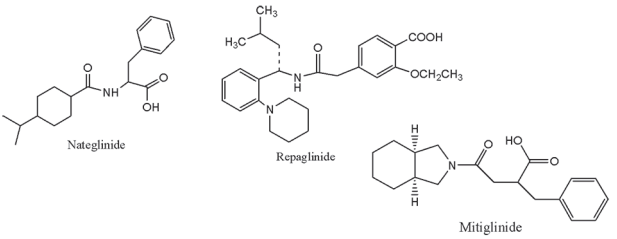


Fig.4. Structure of commonly used Meglitinides drugs

F. Alpha-glucosidase inhibitors (AGIs)

Acarbose, miglitol, and voglibose are alpha-glucosidase inhibitors (AGIs) drugs that slow the absorption of ingested carbohydrates (sugar), leading to plasma glucose reduction. This drug is used for T2DM patients and is recommended by the United States. Alpha-glucosidase inhibitors primarily affect the villi in the small intestine. The shortcomings of this drug are mainly gastrointestinal disorders such as flatulence and diarrhea [50-53].

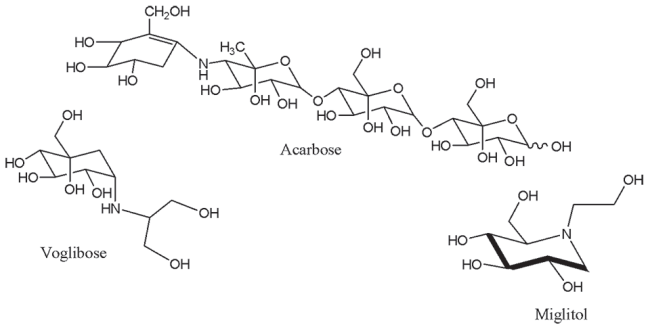


Fig.5. Structure of commonly used Alpha-glucosidase inhibitors (AGIs) dru

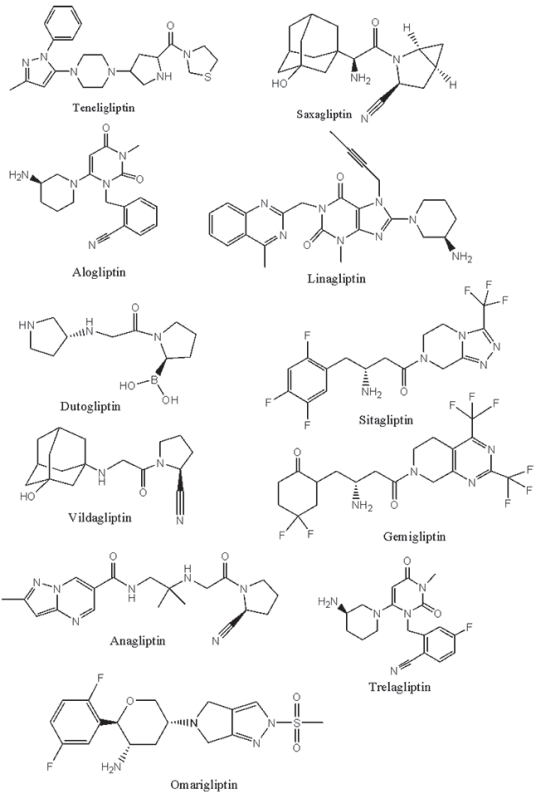


Fig.6. Structure of commonly used 'Dipeptidyl peptidase-4 (DPP-4) Inhibitors' drugs

G. Dipeptidyl peptidase-4 (DPP-4) inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a newer type of diabetes medication being studied as both a standalone treatment and an additional treatment alongside other diabetes drugs. Linagliptin saxagliptin, dutogliptin, alogliptin, sitagliptin, vildagliptin, gemigliptin, anagliptin, teneligliptin, trelagliptin, omarigliptin are comprised in this class. They function by enhancing the impact of intestinal hormones (incretins) that play a role in regulating blood sugar. DPP-4 inhibitors primarily affect the kidneys, intestines, lungs, and blood. Pharyngitis headaches are the common side effects of this drug [54-56].

H. Glucagon-like peptide-1 (GLP-1) agonists

The more sophisticated category of antihyperglycemic agents, GLP-1 receptor agonists, suppresses glucagon secretion, stimulates insulin secretion only when blood sugar is high, and slow down the emptying of the stomach. They help control blood sugar by mimicking the actions of natural gut hormones that regulate blood sugar levels. Semaglutide, exenatide, liraglutide, dulaglutide, taspoglutide, and lixisenatide belong to this category. For many years, GLP-1-based therapies are part of the treatment guiding principle provided by the 'American Diabetes Association (ADA)', 'The American Association of Clinical Endocrinologists' and the 'International Diabetes Federation'. GLP-1 agonists primarily affect the pancreas, brain, and insulin target tissues. Diarrhea, nausea, and vomiting are shortcomings of this drug [57-59].

I. Sodium-glucose cotransporter 2 (SGLT2) inhibitors

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are the potential therapy for T2DM patients. This remedy consists of empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, dapagliflozin, and canagliflozin. SGLT2 inhibitors act by regulating the majority of glucose reabsorption by the kidneys and assist in eliminating glucose in the urine. Kidneys are the target organs of SGLT2 inhibitors. Long-term use of SGLT2 inhibitors often leads to unwanted side effects such as increased urination and infections in the genital and urinary areas [60-62].

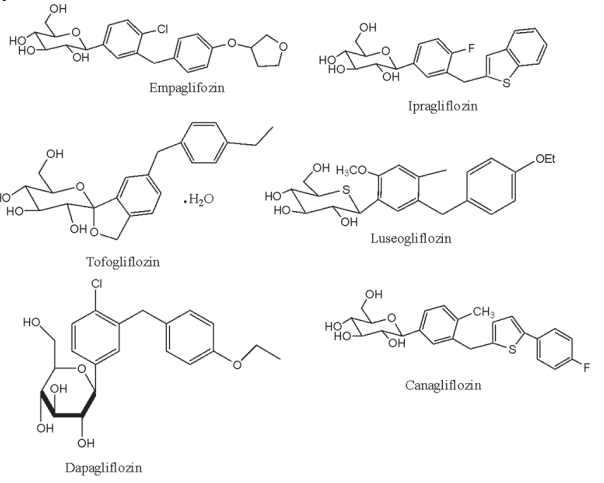
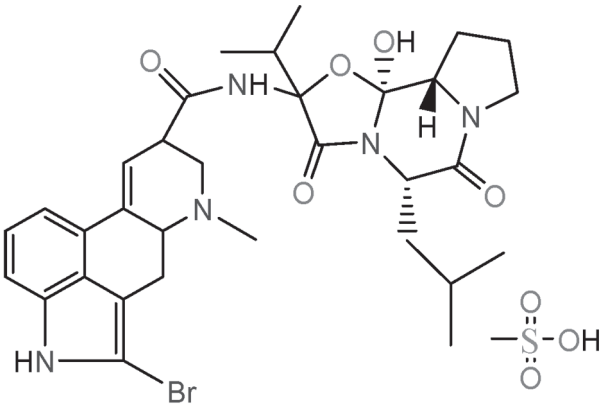


Fig. 7. Structure of commonly used 'Sodium-glucose cotransporter 2 (SGLT2) inhibitors'

J. 'Dopamine agonists'

Bromocriptine mesylate (bromocriptine), a central dopamine receptor agonist, has been licensed in the United States for the treatment of T2DM since 2009. The precise mechanism remains unclear. Bromocriptine might improve the body's response to insulin and blood sugar control by potentially changing the body's internal clock in the 'hypothalamus.' It suppresses hepatic glucose production. Bromocriptine has been employed as monotherapy and combination therapy with SUs, metformin, and insulin with medical efficiency. The brain is the target organ of dopamine agonists. Hypotension, nausea, and/or orthostatic hypotension are the adverse effects of this drug [63-65].



Bromocriptine mesylate

Fig.8. Structure of Dopamine agonists drug

Novel antidiabetic compounds from the plant kingdom

As the recently used synthetic antidiabetic drugs contain severe side effects, toxic and moreover toxic, researchers are engaged to find out the novel, safer, less toxic, inexpensive, more effective, new class of therapeutic antidiabetic compounds with fewer side effects from the natural source. In this context, phyto-constituents isolated from medicinal plants play a crucial role in controlling diabetes, showing higher potential than synthetic drugs during the past few years. Inspired by this, a great deal of scientific interest has been drawn towards the use of traditional antihyperglycemic medicinal plants in daily food supplements [66-86].

Two antidiabetic compounds, namely oleanolic acid (OA) and quercetin-3-rutinoside, have been extracted from the aqueous extract from the stem bark of *Abutilon indicum* (L.) Sw. which is locally known as ghantiphool or Indian mallow. It is generally found in all the districts of Kerala, Maharashtra, Tamil Nadu, Karnataka, Odisha, and Goa. A typical dose involves consuming 25 to 50 milliliters of a decoction made from the stem bark twice daily after meals for a month-long treatment. OA strengthens the body's insulin sensitivity and promotes insulin release from pancreatic beta cells. OA also protects the performance and durability of pancreatic β-cells and thereby shows hypoglycemic activity [69, 87, 88]. Umbelliferone β-D-galactopyranoside is isolated from aqueous and alcoholic extract of *Aegle marmelos (L.) Correa,* which is locally known as bael. The location of this plant is generally seen in eastern and southern parts of India, such as West Bengal, Assam, Bihar, Andhra Pradesh, Kerala, and Gujrat. Umbelliferone β-D-galactopyranoside has the potential to treat diabetes by increasing the amount of insulin produced by the pancreas [89-92]. Two antidiabetic compounds, namely Aloresin A and 'Aloe emodin-8-O-glycoside' are isolated from the *Aloe vera* (L.) Burm. f. The local name of the plant is ghew kumari. It is generally found in Maharashtra, Rajasthan, Gujrat, and Madhya Pradesh. Its fresh leaf pulp (40-50g) is generally taken on an empty stomach for a period of 10-12 weeks. These two compounds retards α-glucosidase and hold back insulin resistance. They also enhance glucose transport and glycogen storage [93, 94]. Nimbidiol is found in the chloroform extract of *Azadirachta indica A. Juss,* locally known as neem or Indian liliac leaves, and it shows hypoglycemic activity by retarding the mammalian and fungal α-glucosidase.

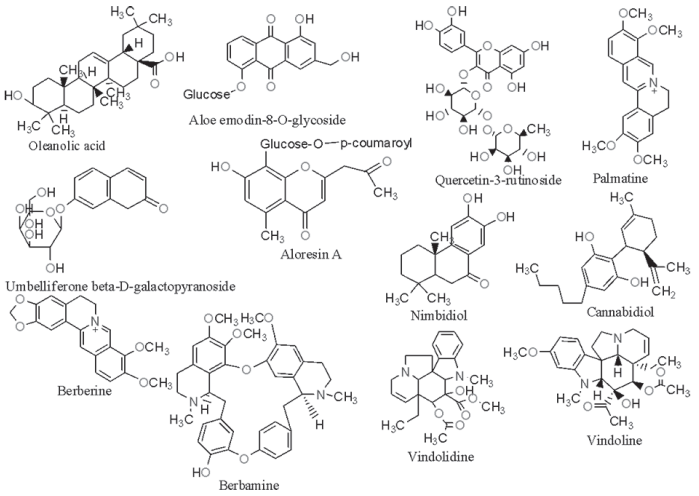


Fig. 9. Structure of some selected natural anti-diabetic compounds (Part-I)

Neem tree is found from south India to the Himalayan region. [95, 96]. The methanolic decoction of the root and bark stem of Berberis aristata DC, locally known as Indian Barberry or Dāruhaldi or Chitra, provides three antidiabetic compounds, namely Berberine, Berbamine, and Palmatine. Berbamine and berberine stimulate a process called glycolysis by activating a protein called AMP kinase. On the other hand, palmatine works by influencing the insulin system. The location of this plant is in the sub-Himalayan region and Nilgiri hills of south India [97-99]. The leaf extracts of *Cannabis sativa* L, locally known as Indian hemp bhang or marijuana, contains Cannabidiol, which shows hypoglycemic activity by reducing the harmful effects of diabetes, such as oxidative stress, inflammation, and cell damage [100].

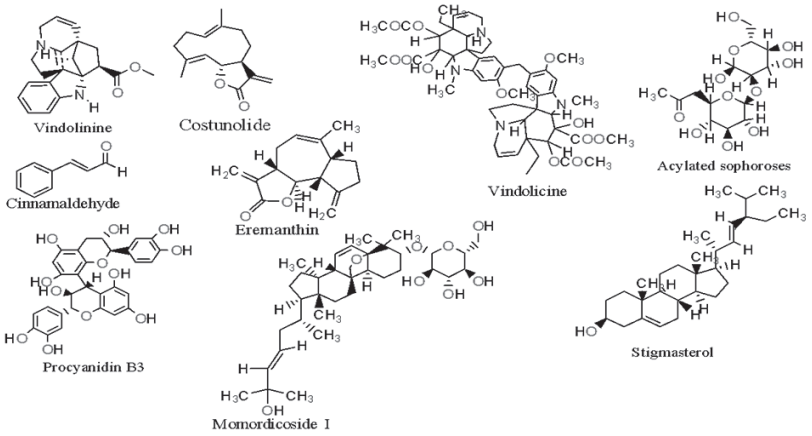


Fig. 10. Structure of some selected natural anti-diabetic compounds

This plant is found in the western part of the Himalayan region. The four anti-diabetic compounds, namely Vindoline, Vindolidine, Vindolicine, and Vindolinine, were isolated from leaf and root decoction of *Catharanthus roseus* (L.) G. Don, which is locally known as Nayantara. These compounds stimulate pancreatic beta cells or muscle precursor cells to significantly absorb more glucose. Location of this plant is commonly seen in Uttar Pradesh, Andhra Pradesh, Bihar, Assam, Gujrat, and Madhya Pradesh [101]. The leaf extract of *Cinnamomum tamala* (Buch.-Ham.) T. Nees & Eberm contains two antidiabetic compounds, Cinnamaldehyde and Procyanidin B3 oligomers. These two compounds work by immune-suppressive mechanisms and instigate the release of insulin from the β-cells within the islets of Langerhans. The availability of this plant is in the two northwest parts of Himalaya, Assam, Sikkim, Mizoram, and also in Meghalaya [102-104]. Costunolide and Eremanthin, the two antidiabetic compounds which are isolated from *Hellenia speciose* (J. Koening) S.R.Dutta Costunolide which is known as crepe ginger, boost the release of insulin from β-cells and upgrades insulin sensitivity.

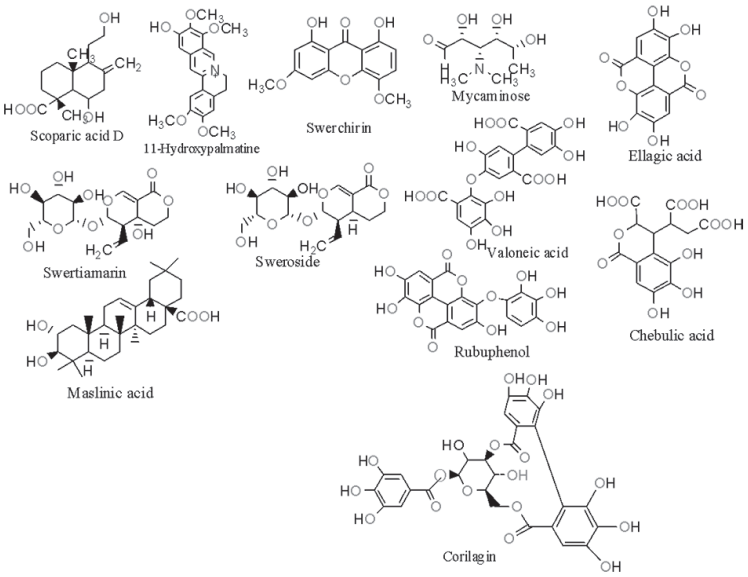


Fig. 11. Structure of some selected natural anti-diabetic compounds (Part-III)

On the contrary, Eremanthin acts by stimulating the secretion of insulin and normalizing disrupted levels of plasma enzymes like acid phosphatase, alkaline phosphatase, and aspartate aminotransferase [105]. Acylated sophoroses from the leaf extract of the *Ipomoea batatas* (L.) Lamk, which is locally known as sweet potato or Shakarkanda, shows hypoglycemic activity by inhibiting maltase. It is generally cultivated in Kerala. [106]. The ethanolic root and leaf extract of *Justicia adhatoda* L., locally known as Vasaka or Malabar nut, contains the hypoglycemic agent Stigmasterol, which exerts insulin-resembling action by ameliorating glucose transfer coupled with cholesterol-lowering efficiency. This plant is found in the lower part of the Himalayan region [107]. Momordicoside I, a triterpenoids, from the boiling water extraction of *Momordica charantia* L., which is locally known as Karela, shows antidiabetic potential. It restores pancreatic cell and insulin secretion by stimulating glucose transporter 4 translocation and AMP kinase. This plant is cultivated in the southern part of India, especially in Andhra Pradesh [106]. The water and ethanolic extract of *Scoparia dulcis* L, which is locally known as Mithi Patti, contains a blood glucose lowering agent, namely Scoparic acid D interferes with the digestive process of starch and sugar by

inhibiting the α-glucosidase enzyme. This plant is widely found in the Madhya Pradesh and Kerala [108, 109]. 11-Hydroxypalmatine from the ethanolic extract of *Stephania glabra* (Roxb.) Miers, which is known as Barkuli Lhara, shows anti hyperglycemic activity by lowering blood glucose levels. It is generally seen in Jharkhand, West Bengal, Madhya Pradesh, Uttarakhand, Mizoram, Meghalaya, Assam, and Arunachal Pradesh [110]. The aqueous extract of *Swertia chirayita* (Roxb. Ex Flem.) Karst, which is locally known Chirata, shows promising hypoglycemic activity. The location of this plant is at the lower altitude of the Sikkim Himalayan region. The hypoglycemic agents present in it are Swerchirin, Swertiamarin, and Sweroside.

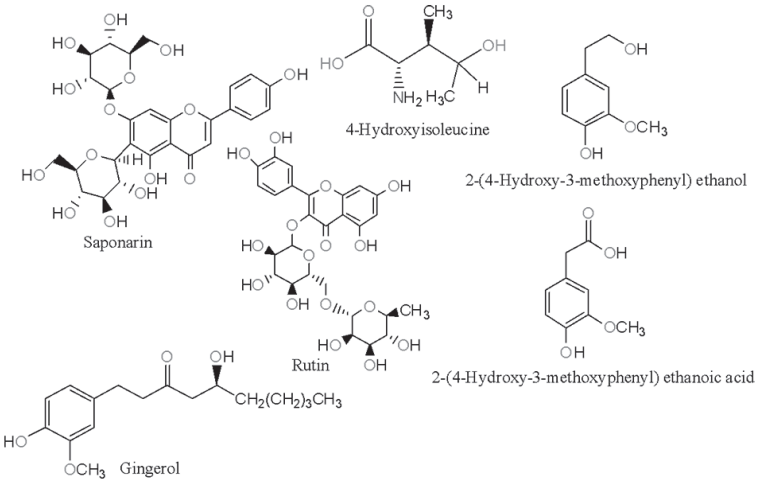


Fig. 12. Structure of some selected natural anti-diabetic compounds (Part-IV)

They reduce blood glucose by restoring insulin discharge from islets of Langerhans and also by up-regulating peroxisome-proliferater-activated receptor gene expression [69, 111]. The fruits, stem bark, and seeds of *Syzygium cumini* (L.) Skeels locally known as Indian blackberry or jamun, show significant antidiabetic activity. It is generally found in the subtropical and tropical regions of India and also the lower part of the Himalayan region and Kumaon hills. It contains mainly five hypoglycemic agents, and they are Mycaminose, Maslinic acid, Valoneic acid, Rubuphenol, Ellagic acid. These hypoglycaemic agents work by the activation through inhibiting insulin secretion from pancreatic β-cells and slowing down the activity of aldose reductase

and protein tyrosine phosphatase [112, 113]. The fruit extract of *Terminalia chebula* Retz, locally known as Black Myrobalan or Hard or Haritaki, shows anti-diabetic activity in a dose-dependent manner and promotes insulin sensitivity. This plant is mostly found in North India, such as Uttarakhand West Bengal, and Assam. Chebulic acid and Corilagin are the antidiabetic agents present in this fruit. These agents have α-glucosidase inhibitory activity and show protective efficiency in preventing the development of advanced glycation end products and dysfunction of endothelial cells [114-117]. The methanolic extract of *Tinospora cordifolia* (Willd.) Hook f. & Thoms, locally known as guduchi, is found in the tropical areas of India, and it contains two antidiabetic agents, Saponarin and Palmatine, which retards the functions of α-glucosidase and sucrose. They also show successful expression of glucose transporter 4 [118, 119]. The seed powder of *Trigonella foenum-graecum* L., locally known as methi, is generally found in Punjab, Haryana, Rajasthan, and Gujrat. This seed contains the hypoglycemic agent 4-Hydroxyisoleucine. This agent works by enhancing insulin sensitivity and lowering the elevated levels of lipids and uric acid [120]. The aqueous and ethanolic leaf extract of *Urtica dioica* L., locally known as stinging nettle or Bichhua pattee' or 'Bicchu Buti' which is generally seen in the Himalayan region of India, and the antidiabetic compound Rutin is present in this substance, which stimulates the pancreas to release more insulin and contribute a vital role in the metabolism of carbohydrates [121]. The ethyl acetate extract of *Zingiber officinale* Roscoe, locally known as ginger Orissa, Karnataka, Gujrat, Arunachal Pradesh, Meghalaya, Assam and it contains three hypoglycemic agents Gingerol, 2-(4-Hydroxy-3-methoxyphenyl) ethanoic acid, 2-(4-Hydroxy-3-methoxyphenyl) ethanol. These substances act as potent inhibitors of aldose reductase and function by enhancing impaired insulin signaling [69, 122, 123].

Mechanism of action

It has already been reported that the plant kingdom supplies numerous phytochemicals and pharmacologically active compounds, which is employed as a potential management for patients with both type 1 and type 2 diabetes. Ayurvedic and herbal treatments employ these compounds to create both single and combination

herbal formulas. Although the resolution of the actual dosage is difficult and is associated with allergic responses, the treatment is lengthy. Addressing the limitations of herbal management involves comprehensive studies of active principles, including the precise determination of dosage [69]. These bioactive compounds act upon the different organs of the human body to control blood glucose. Some of them retard the glucose assimilation from the intestine. Some of them elevate insulin secretion in the pancreas. Some compounds lower the glucose building in the liver. Some agents increase the absorption capacity of glucose by the adipose. Other agents escalate the peripheral intake of glucose from blood to muscle/ tissue. The therapeutic evaluations of these promising bioactive compounds in vitro are antioxidant activity, α-amylase inhibitory activity, α-glucosidase activity, and antimicrobial activity. On the other hand, the in vivo therapeutic models are insulin secretion tests, glucose tolerance tests, streptozotocin/high fat diet induced diabetes models [66].

Conclusion

The application of safe and less toxic herbal medicines in the treatment of diabetes patients are rising day by day because of the toxic and undesirable side effects of the available synthetic drugs. The hypoglycemic activities of medicinal plants are attributed to the single or mixture of phytochemicals present in them. These anti-diabetic phytochemicals are flavonoids, alkaloids, phenolic acids, saponins, stilbenes, glycosides, polysaccharides, and tannins. A number of endogenous and exogenous factors, such as utilized plant organs, genetic qualities, and growing, drying, and storing environment, control the phytochemical compositions. WHO advocates natural plant-derived antidiabetic agents in conventional medicine. Mainly, the hypoglycemic therapeutics from medicinal plants are attributed to the recovery of the activity of pancreatic tissues by enhancing the secretion of insulin. Besides this, other factors which are related to the antidiabetic potential of phytochemicals are the regulation of glucose and lipid metabolism, ROS protective action, inhibition of gluconeogenic enzymes, and NF-kB signaling pathway. In this connection, the research of antihyperglycemic phytochemicals has advanced in the preceding few decades. The added advantage

of phytochemicals is widely available without any lengthy pharmaceutical synthesis, which greatly attracts pharmacologists and researchers to search for a novel natural antidiabetic agent. Moreover fruits, vegetables, and spices contain natural antioxidants like flavonoids, phenolic compounds, which can control our diabetes and its complications. Rigorous medical studies are needed to identify the hypoglycemic leads from the antidiabetic plants. Furthermore, this study has a future prospect to design new functional foods having antidiabetic activity and also keep away from simple carbohydrate enriched foods having hyperglycemic activity.

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Conflict of Interest

The authors hereby declare no potential conflicts of interest with respect to the research, funding, authorship, and/or publication of this article

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