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SGLT2 Inhibitors as Pioneering Solutions in Diabetes Care - A Comprehensive Review

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ABSTRACT

Plants play an important role in human existence; they are used as firewood, timber, fibres, fruitsand vegetables, and to make paper, cloth, rope, dyes, pesticides, etc. Besides as a source of food, they are an important source of medicine. Worldwide, the plants and their derived products are used for the treatment of health issues such as diabetes, cancer, hypertension, malaria, inflammation, and nervous disorders, etc. in different conventional as well as modern systems of medicine. Diabetes, a chronic metabolic disorder with elevated blood glucose levels, causes lasting damage to vital organs. Type-2 diabetes is prevalent worldwide, affecting 422 million individuals. Its global burden, causing 1.5 million deaths annually, has risen significantly. Several approaches are currently used to control and cure diabetes by using available anti-diabetic medications in modern medicine. α-Amylase inhibitors, α-glucosidase inhibitors, biguanides, sulphonylurea, GLP-1 receptor agonists, DPP-4 inhibitors, and thiazolidinediones are examples of anti-diabetic medicines, each targeting glucose regulation through distinct mechanisms. SGLT2 inhibitors, a novel class of drugs, effectively manage diabetes by impeding renal glucose reabsorption, reducing blood glucose levels. FDA-approved, these synthetic medications mark a significant advancement in diabetes care. Despite effective strategies, there's a need for safer, more efficient treatments, emphasizing the crucial role of medicinal plants in resource-limited settings. This study presents a comprehensive review of the SGLT2 inhibitors. It encapsulates the extensive research on SGLT2 inhibitors, unveiling their promising potential as a source of natural anti-diabetic medicine.

Keywords: Chronic metabolic disorder, FDA-approved medicine, Natural Products.

Introduction

The Ayurvedic medical system is remarkably ancient, with roots dating back approximately 5000 years B.C. Its Materia Medica encompasses resources in the form of medications, purportedly derived from plant, animal, and mineral sources, and their application has been recommended for a diverse range of clinical indications. Practitioners have adeptly transformed these medications into formulations of poly-herbal blends, herbs-mineral combinations, and metallic compounds. Their valuable clinical experiences have been documented in writing, ensuring the transmission of knowledge to future generations [1]. In addition to serving as a vital food source, plants are indispensable to human existence due to their provision of fibers used in crafting paper, cloth, rope, dyes, and lubricants. Moreover, plants frequently serve as therapeutic medications for various medical purposes [2]. The origin of natural products, particularly from plants, is a primary focus in the quest for promising lead candidates, playing a crucial role in upcoming drug evolution programs. Plant-based preparations emerge as key players in therapies due to their easy availability, cost-effectiveness, and minimal side effects, making them particularly pivotal in rural areas. Furthermore, numerous plants serve as rich sources of bioactive chemicals, devoid of undesirable side effects, and exhibit potent pharmacological actions [3]. Medicinal plants serve as commonly utilized starting materials for extracting the essential active components required in the production of various medications. Plant-based compounds contribute to the formulation of medications such as blood thinners, laxatives, antibiotics, antimalarial drugs, and a host of other treatments [4]. Recognizing the importance of medicinal plants, the World Health Organization (WHO) has developed methods to address their significance. These plants play a crucial role in maintaining the health of people in rural areas. Recent research has affirmed the effectiveness of Indian traditional medicinal systems, like Ayurveda. Overall, the development of such medicine requires a thorough understanding of the underlying processes, coupled with robust clinical investigations and a demonstrated efficacy in diverse populations [5]. Whether utilized in traditional or modern medicine, medicinal plants are harnessed to address specific illnesses, support health maintenance, or serve both purposes. Within plants, a diverse array of phytochemicals exhibit biological activity, with some well-known and others awaiting discovery. These plant-derived molecules, collectively known as phytochemicals, predominantly fall into four major biochemical classes: polyphenols, glycosides, alkaloids, and terpenes. Plant medicines are extensively used worldwide. In most of the developing countries, especially in the rural areas, local traditional medicines, such as herbalism, are the major source of health care for the people [6]. Over 90% of traditional medicines, utilized to address a range of illnesses through pastes, decoctions, crude extracts, or formulations, feature medicinal plants as their primary ingredient. Herbal therapy has become the preferred choice for patients today, especially those dealing with chronic conditions such as diabetes mellitus (DM) [7]. In India, numerous herbal traditional medicines have been documented for treating various skin disorders, including acne, bruises, and burns. Additionally, medicinal plants are frequently employed for conditions such as cuts, wounds, general skin diseases, ringworm, eczema, leprosy, scabies, stress, hypertension and diabetes etc. [8]. Medicinal plants have been utilized in traditional healing practices globally for an extensive duration to address diabetes. This is attributed to the hypoglycemic properties and other beneficial attributes inherent in such herbal plants [9]. Several plants species and their derived productsare reported in the previous study to have anti-diabetic potectial such as *Brassica juncea*, *Combretum micranthum*, *Gymnema sylvestre*, *Liriope spicata*, *Parinari excelsa*, *Ricinus communis*, *Sarcopoterium spinosum*, *Smallanthus sonchifolius*, *Swerti apunicea* etc. [10]. In the realm of pharmaceuticals and dietary supplements, natural products find widespread application in the treatment of various chronic diseases and the regulation of normal physiological parameters. Numerous research endeavors conducted thus far have demonstrated that extracts from natural products and/or their active

phytochemicals exhibit various anti-diabetic characteristics. These include the activation of Peroxisome Proliferator-activated Receptor γ (PPARγ), activation of the AMP-activated Protein Kinase (AMPK) pathway, inhibition of α-glucosidase, regulation of Gglucose Transporter 4 (GLUT4) expression and translocation, inhibition of Protein Tyrosine Phosphatase 1B (PTP1B), and SGLT2 inhibition, all achieved with lower associated side effects [11]. The twenty-first century has witnessed one of the most significant worldwide epidemics – diabetes mellitus [12]. It represents a perilous metabolic disease impacting hormonal regulation in the body, marked by improper hyperglycemia and disturbed metabolism as two primary symptoms [13]. It is a multifactorial metabolic illness characterized by persistent hyperglycemia and disruptions in carbohydrate, fat, and protein metabolism. Abnormalities in insulin secretion, insulin action, or both contribute to these disruptions, leading to long-term organ damage and malfunction [14]. Currently afflicting over 350 million people globally, with an additional one billion individuals at risk due to pre-diabetes, diabetes mellitus poses a substantial burden with an estimated cost of $1,200 billion USD for diagnosis, treatment, and care [15]. The prevalence of diabetes has been steadily rising, with a projected global prevalence of 5.4% by 2025, compared to 4% in 1995 [16]. Access to affordable treatment, including insulin, is deemed critical for the survival of those living with diabetes, as emphasized by the World Health Organization (WHO). A global initiative, the Global Diabetes Compact, was announced in April 2021, aiming to support low- and middle-income nations in achieving lasting improvements in diabetes prevention and care. With 422 million people worldwide diagnosed with diabetes and 1.5 million deaths attributed directly to the condition annually, WHO established five global goals for diabetes treatment and coverage in May 2022. The objective is to achieve these goals by 2030, with a focus on halting the rise in diabetes and obesity [17]. Diabetic patients find themselves navigating a complex regimen involving prolonged use of hypoglycemic medications, strict adherence to dietary norms, engagement in regular physical exercise, and efforts to shed excessive weight—all aimed at maintaining healthy blood sugar levels and averting potential complications [18]. Diabetes mellitus (DM) is categorized into two classes: Class I and Class II. Type 1 diabetes, owing to its polygenic and heterogeneous nature, is influenced by several non-HLA (human leukocyte antigen) loci determining an individual's susceptibility to the disease. This type further divides into idiopathic diabetes with β-cell blockage (Type 1B) and autoimmune/immune-mediated diabetes (Type 1A). In contrast, type 2 diabetes results from a combination of deficiencies in insulin action and secretion, with either factor potentially predominating [19]. In specific forms of Type 1 diabetes, the pathogenesis hinges on the autoimmune destruction of β-cells, leading to absolute insulin deficiency. On the other hand, Type 2 diabetes is characterized by a progressive loss of β-cell insulin secretion, often against a backdrop of insulin resistance [20].The escalation in diabetes rates is widely ascribed to global environmental factors fostering unhealthy behaviors, obesity, and overweight conditions [21]. Presently, conventional anti-diabetic medications encompass a spectrum of pharmaceuticals, including Carbohydrate hydrolyzing enzyme inhibitors (α-amylase and α-glucosidase), Dipeptidyl peptidase 4 (DPP-4) Inhibitors, Protein phosphate inhibitors, GLUT-4, glitazones, glinides, biguanides, and sulfonylureas. However, it is noteworthy that these pharmaceutical interventions are not without significant adverse effects, such as edema, weight gain, intestinal issues, and particularly hypoglycemic disorders; Table No. 1 shows the available class of synthetic anti-diabetic medication [22].

Table No. 1: Examples of Synthetic Anti-diabetic Drugs and Their Adverse Effects [23]

S.No.	Anti-diabetic Class	Examples	Adverse effects
1.	Carbohydrates-hydrolyzing enzyme inhibitors	Acarbose	Gastrointestinal effects and hepatitis.
2.	Biguanides	Metformin	Gastrointestinal effects and Lactic acidosis.
3.	DPP-4 inhibitors	Saxagliptin	Pancreatitis, risk for cancer, acute hepatitis, and kidney impairment.
4.	Protein tyrosine phosphatase 1B inhibitors	Arsenate	Diarrhea, Stomach cramps and Poor appetite
5.	Sulphonylureas	Glibenclamide	Hypoglycemia, Weight gain, Cardiovascular risk, rash, Cholestatic jaundice, Bone marrow damage and Photosensitivity.
6.	AMPK activators	Metformin	Weight loss, Headache, Stomach ache and Constipation.
7.	Glucagon-like peptide 1 (GLP-1) agonists	Exenatide	Gastrointestinal effects, Pancreatitis, risk for cancer and cardiovascular events.
8.	Dual PPAR agonists	Saroglitazar	Gastritis, asthenia and pyrexia.
9.	GLUT-4	Metformin	Weight loss, Headache, Stomach ache and Constipation.
10.	Meglitinides	Repaglinide	Hypoglycemia and Sensitivity reaction.
11.	Insulin and analogues	Regular insulin	Hypoglycemia, Weight gain, Insulin allergy and Lipodystrophy at the injection site.
12	Phenylaniline analogues	Rapaglinide	Loss of voice, Pain in joints, Body pain and Muscle stiffness.
13.	Sodium-Glucose co-transporters (SGLT2 inhibitors	Canagliflozin	Glycosuria and Cardiovascular concern

SGLT2 inhibitors represent the latest class of FDA-approved anti-hyperglycemic agents. Operating through a unique mechanism that involves the reduction of renal tubular glucose reabsorption, these inhibitors induce a decrease in blood glucose levels without triggering insulin release [24]. Notably, their impact on glucose regulation is attributed to the kidneys' pivotal role in maintaining glucose homeostasis [25]. Offering a distinctive approach in treating type 2 diabetes (T2DM), SGLT2 inhibitors stand out for not targeting the two primary pathophysiological abnormalities in T2DM—insulin resistance and decreased insulin secretion [26]. Beyond their glucose-lowering effects, SGLT2 inhibitors enhance glucose-insulin metabolism, improve lipid profiles, and modulate serum uric acid levels. Their action includes osmotic diuresis, natriuresis, volume contraction, hemoconcentration, and weight reduction by impeding proximal tubular glucose/Na^+ reabsorption. Additionally, glycosuria leads to a significant calorie reduction, aiding in weight loss. These inhibitors also play a role in blood pressure regulation, restoration of impaired renal function measures, and reduction of pro-inflammatory indicators [27]. The

high-capacity, low-affinity transporter SGLT2, primarily situated on the luminal surface of the kidney's proximal convoluted tubule epithelial cells, facilitates around 90% of renal glucose reabsorption [28]. SGLT2 inhibitors are versatile and compatible with various comorbid conditions, such as heart failure, chronic disease, atherosclerotic cardiovascular disease, and different estimated glomerular filtration rates [29].

Currently, four oral agents- canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin, are approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency for treating T2DM either as monotherapy or in combination with other glucose-lowering drug classes [30]. These inhibitors are rapidly absorbed into the bloodstream after oral administration, primarily binding to SGLT2, resulting in a 50% to 60% reduction in glucose reabsorption, leading to decreased plasma glucose and glycosylated hemoglobin levels [31].

Empagliflozin, among the SGLT2 inhibitors, has been associated with improved β-cell function in patients with type 2 diabetes and the preservation of β-cell mass in patients with type 1 diabetes. Conversely, canagliflozin enhances β-cell activity in people with type 2 diabetes [32]. Since the discovery of the first natural SGLT2 inhibitor, Phlorizin, several synthetic glucoside analogues have been developed and introduced to the market. Ongoing research aims to identify novel active ingredients from natural sources that inhibit SGLT2 [11]. The mechanism of SGLT2 inhibitors is shown in Figure 1 [33].

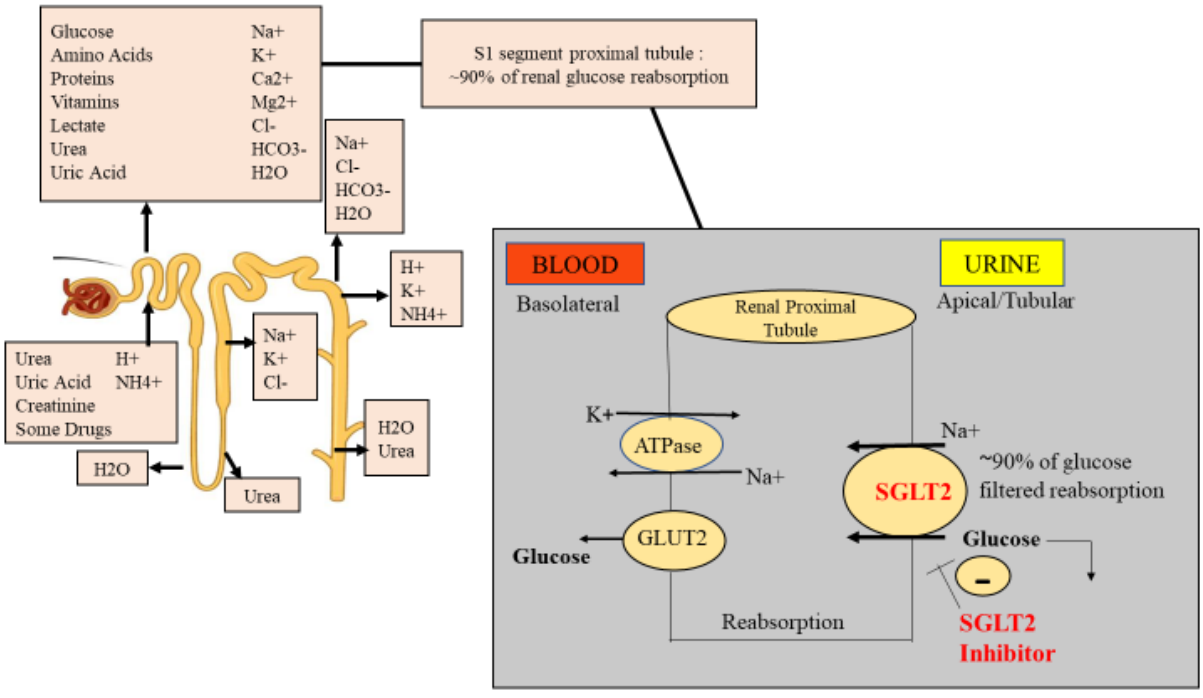

Figure: Mechanism of SGLT2 inhibitors [33]

Medicinal Plants with SGLT2 inhibitory activity.

***Malus domestica* (*Rosaceae*):** The impact of phlorizin treatment on tissue sensitivity to insulin in partially pancreatectomized rats has been examined. Phlorizin, primarily found in unripe Malus (apple), serves as a lead structure due to its inhibitory activity on SGLT1 and SGLT2 [43]. The flavonoid phlorizin, extracted from the bark of apple trees, was utilized in experimental animals, particularly in partially pancreatectomized rats. The study investigated the effects of phlorizin injection on insulin-sensitive tissue. Notably, insulin action remained unaffected by phenylephrine therapy, while insulin sensitivity was fully restored in diabetic rats. The findings of this study suggest that insulin-mediated glucose disposal returns to normal after correcting hyperglycemia with phlorizin, even in the absence of changes in fasting or glucose-stimulated insulin levels [44].

***Cynodon dactylon* (*Poaceae*):** *Cynodon dactylon*, traditionally employed for treating dysentery, urinary tract infections, and microbial illnesses, emerges as a potential source of metabolites like flavonoids, alkaloids, glycosides, and β-sitosterol. This experiment aims to evaluate the glycemic management potential of *C. dactylon* extracts. Utilizing HPLC–ESI MS analysis, aqueous extracts of *C. dactylon* revealed the presence of luteolin, apigenin, 6-C-pentosyl-8-C-hexosyl luteolin, and 6-C-hexosyl-8-C-pentosyl apigenin. These compounds were further investigated for their interactions with SGLT2 through an extensive in silico docking approach, evaluating hypoglycemic activity with Peroxisome Proliferator-Activated Receptor (PPAR), glucose transporter-4 (GLUT-4), and SGLT2. The results of the study indicate that luteolin, apigenin, 6-C-pentosyl-8-C-hexosyl luteolin, and 6-C-hexosyl-8-C-pentosyl apigenin interact with SGLT2. This finding suggests that the extract of *C. dactylon* has the potential to act as an SGLT2 inhibitor, offering promise for managing diabetic neuropathy. The exploration of these bioactive components opens avenues for further research and development in the realm of natural compounds for glycemic control [35].

***Tinospora cordifolia* (*Menispermaceae*):** The ethyl acetate extract from leaves exhibits significant hypoglycemic activity in a study. In the Kathmandu district and the far west of Nepal, the Newar community traditionally uses *T. cordifolia* in various forms, such as juice, powder, or liquid, for treating diabetes [Reference]. To scientifically evaluate its hypoglycemic potential, the leaf ethyl acetate extract was assessed using alloxan-induced diabetes on Wistar rats. Glibenclamide, a common anti-diabetic drug, served as the reference compound for comparison. The administration of leaf ethyl acetate extract, particularly at doses of 100 mg/kg and 200 mg/kg, led to a considerable increase in blood glucose levels. Interestingly, there was a sharp decrease in blood glucose levels observed between the second and sixth hours post-administration. Furthermore, between the sixth and eighth hours, a typical decline in percentage was noted, with the effect more pronounced at the higher dose of 200 mg/kg compared to 100 mg/kg. These findings support the traditional use of *Tinospora cordifolia* within the Newar community for managing diabetes. The observed hypoglycemic effects warrant further investigation into the specific bioactive compounds responsible for this activity and their potential applications in diabetes management [36]. SGLT2 ???

***Cissampelos pareira* (*Menispermaceae*):** *C. pareira*, has a rich history in Indian traditional medicine, where it has been utilized for various human ailments, including diabetes mellitus. In a recent study focusing on SGLT2 inhibition, the anti-diabetic potential of an aqueous-ethanolic extract of *C. pareira* roots was investigated in diabetic rats induced by streptozotocin-nicotinamide (STZ-NAM). The extract demonstrated inhibitory effects on α-amylase and α-glucosidase, with IC_{50} values of 18.0 ± 1.01 and 4.87 ± 0.54 mg/mL, respectively. Notably, the extract exhibited a significant impact on the expression of the

SGLT2 protein. In a 28-day *in vivo* investigation with a dose of 500 mg/kg body weight, the extract significantly ($p<0.05$) lowered blood glucose levels in the diabetic rats. Importantly, the study suggests that the extract may have the potential to reduce elevated blood glucose caused by STZ without adversely affecting liver or kidney function. These findings highlight the promising anti-diabetic properties of *C. pareira*, supporting its traditional use in Indian medicine. Further exploration of the specific bioactive compounds responsible for these effects and their underlying mechanisms could pave the way for the development of novel diabetes therapeutics [7]

5. *Gynuranepalensis (Asteraceae)*: Plant leaves are used in Bangladesh for the treatment of diabetes [45]. Examined the anti-hyperglycemic properties of *G.nepalensis* ethanol extracts, which have been traditionally employed in ethnomedicine to treat diabetes and a host of other illnesses.Oral administration of glucose (18 mmol/kg body weight) and ethanol extracts (250 mg/kg body weight) improved glucose tolerance.Furthermore, the extracts decreased food intake during the feeding test (250 mg/kg; $p << 0.05–0.001$) and enhanced gastrointestinal motility (250 mg/kg; $p << 0.05–0.001$).The plants' phytochemical screening revealed the presence of reducing sugars, flavonoids, alkaloids, tannins, saponins, and steroids.

6.Sophoraflavescens (Fabaceae): The root of *Sophora flavescens*, a plant in the *Fabaceae* family, has been traditionally used in China for the treatment of diabetes. A recent study aimed to evaluate the effects of nine chemicals extracted from the dried root of *S. flavescens* on SGLT2 inhibition [46]. The results revealed that the methanol extract from the plant demonstrated robust SGLT2 inhibitory action. This highlighted the impact of isoflavonoid glycosides derived from S. *flavescens* roots on SGLT2 inhibition. All nine isolated compounds in the study exhibited SGLT2 inhibitory action, with compound 7 [Name] demonstrating the most significant inhibition (IC_{50}: 2.6 ± 0.18 µM). Additionally, compound 8 [Name] showed moderate SGLT2 inhibition (IC50: 15.3 ± 1.44 µM). It's crucial to note that the study primarily focused on a screening evaluation, and the inhibitory efficacy was specifically demonstrated for SGLT2. These findings suggest the potential of *S. flavescens* as a source for developing SGLT2 inhibitors, contributing to the ongoing exploration of natural compounds for diabetes treatment. Further research may delve into the specific mechanisms and therapeutic applications of these compounds [11].

***7. Avicennia marina* (*Acanthaceae*):**The current study set out to investigate the possibility of improving diabetes-associated pathological changes through supplementation with the alcoholic extract of *A. marina* leaves.Animals in the DM group that received the alcoholic extract of *A. marina* leaves showed improved organ functions, decreased blood glucose levels, and improved blood picture.The findings of this study demonstrated that supplementing mice with the alcoholic extract of *A. marina* leaves alleviated the neurobehavioral changes linked to diabetes, preserved the liver, and decreased oxidative stress and blood sugar levels.Animal groups were given intraperitoneal injections of STZ (70 mg/kg) to induce diabetes. Within 5 days of STZ administration, rats injected with STZ showed severe glycosuria and hyperglycemia (200-250 mg·dL−1), in contrast to the control group (50-100 mg·dL−1). To assess the impact of oral supplementation with the alcoholic leaf extract of *A. marina*, liver and testis functioning were examined. The diabetic group (group C) had considerably higher blood levels of the liver functions indicator (55.6 ± 4.4 and 3.7 ± 0.1 U/l, respectively) [38].

8. *Rhizophora mucronate* (*Rhizophoraceae)*:This study evaluated the potential antidiabetic, antioxidant, and insulin-enhancing properties of the aqueous extracts of *A. marina* and *R. mucronata*, or both.On streptozotocin-induced diabetic rats, the effects of daily oral administration of an aqueous extract from the leaves of *R. mucronata*, *A. marina* (400 mg/kg BW for each), and a combination of both for six weeks were assessed taking intothe serum levels of insulin and blood glucose.When compared to the rats who were not treated, the effects of diabetes on serum glucose, insulin, and antioxidant status in the heart and muscles were lessened by the oral administration of plant extracts.Rats with STZ-induced diabetes showed a significantly lower serum insulin level ($p < 0.001$) when compared to the control group.When compared to untreated diabetic rats, the treatment of diabetic groups with *R. mucronata, A. marina*, or their mixture led to a substantial increase ($p < 0.001$; $p \leq 0.05$; $p \leq 0.001$) in the serum insulin levels.Serum insulin levels in the non-diabetic groups that received *R. mucronata, A. marina*, or their combination did not change significantly from those in the control group [39].

9. *Alstonia macrophylla* (*Apocynaceae*): *A. macrophylla,* a plant from the *Apocynaceae* family, is traditionally used as a tonic in Malaysia, Indonesia, and Thailand for the treatment of diabetes [47]. A study focused on this plant involved the extraction of twenty alkaloid components from *A. macrophylla* leaves. The capacity of these components to inhibit SGLT (sodium-glucose co-transporters) was then evaluated. Among the twenty compounds, five picraline-type alkaloids exhibited strong inhibition of both SGLT1 and SGLT2. The highest inhibitory effects were observed in 10-methoxy-N (1)-methylburnamine-17-O-veratrate (IC_{50} (µM) SGLT1: 4.0; SGLT2: 0.5) and alstiphyllanine D (IC_{50} (µM) SGLT1: 5.0; SGLT2: 2.0). Interestingly, the hydroxyl derivative of alstiphyllanine D demonstrated enhanced selectivity for SGLT2, despite a minor increase in the absolute IC_{50} value (IC_{50} (µM) SGLT1: 50.0; SGLT2: 7.0). This follow-up structure-activity relationship (SAR) investigation, utilizing eight derivatives, provided valuable insights into the potential of *A. macrophylla* alkaloids as SGLT inhibitors. The findings contribute to the exploration of natural compounds for diabetes treatment and highlight the importance of structure-activity relationships in understanding their pharmacological effects [11].

10. *Gnetumgnemonoides (Gnetaceae):* Tropical lianas of the *G.gnemonoides* variety are extensively found throughout Southeast Asia-Pacific, including the Bismarck Archipelago, Malaysia, Indonesia, Philippines, and New Guinea. Despite the lack of scientific research on *G. gnemonoides's* potential as a medicine. However, stilbenes that have been isolated from the Gnetum species are known to have biological characteristics like actions that include hepatoprotective, antioxidant, antibacterial, and enzyme inhibitory. Two stilbene trimers, gneyulin A (18) and B (19), were identified by Shimokawa and comprised ofoxyresveratrol units from *G. gnemonoides's* dried bark and just tested their impact on the suppression of both SGLT1 and SGLT2. Both of these substances exhibited modest, non-selective inhibitingIC50 (µM) 18 SGLT1: 27.0, SGLT2: 25.0; 19 SGLT1: 37.0, SGLT2: 18.0] for each SGLT. Noidesol A and B, two recently identified dihydroflavonol-C-glucosides, did not exhibit any capacity to inhibit SGLT [11].

11. *Schisandra chinensis (Schisandraceae):* Used as a food supplement in China for the treatment of diabetes [48]. Native to Northern China and the Russian Far East, *S.chinensis* (also known as the "five-flavor berr") is used traditionally for its fruits' anti-aging, antitussive, sedative, and tonic properties. *S. chinensis* is a plant that includes a variety of phytochemicals, such as triterpenoids, lignans, and polyphenols. Its pharmacological effects on different organ systems have been well studied. In an effort to pinpoint certain SGLT2 inhibitory chemicals, *SchisandraeChinensis Fructus* (SCF) was recently

assessed for its SGLT inhibitory properties.During the initial screening process using both ethanol and aqueous SCF extracts at a cytotoxicity-free concentration of 1 mg/mL, the ethanol extract showed more significant inhibitory rates for both SGLTs. Nine fractions (F1–F9) in total underwent additional SGLT inhibition testing following the fractionation of the SCF ethanol extract. Only two fractions (F8 and F9), with an inhibition rate of 41.9% and 36.7% of the control, respectively, demonstrated significant SGLT2-selective patterns out of the six that showed inhibitory activity against SGLT1 and/or SGLT2. Finally, the effects on SGLT inhibition of three common lignan compounds isolated from F8, namely deoxyschisandrin, schisandrin B (γ-schisandrin), and schisandrin, were studied. None of them, however, exhibited inhibitory activity against either SGLT, indicating that these important lignans do not serve as the main building blocks for the SGLT inhibition of SCF [11].

12. ***Houttuynia cordata* (*Saururaceae*):** The plant is used as a medicinal salad in North Eastern part of India for diabetes [49]. The research determined which phytochemicals were present in *H. cordata*, screened them, and described their ADME/Tox characteristics. Following a conventional process, the powdered plant extract, which had been extracted for roughly 24 hours using water and methanol, was filtered, refluxed, and evaporated to dryness under reduced pressure before being analysed using High-Performance Thin Layer Chromatography and Gas Chromatography tandem mass spectrometry. The substances found in *H.cordata* were paired with sodium/glucose cotransporter 2 and dipeptidyl peptidase-IV, two antidiabetic targets. The compounds' potential as drug candidates is shown by their ADME/Tox characteristics and docking. The compounds' potential as drug candidates is shown by their ADME/Tox characteristics and docking. Certain *H.cordata* compounds have favourable pharmacokinetic characteristics and a strong binding affinity for both SGLT2 and DPP-IV. On the other hand, a deeper understanding and a new avenue for exploring the pharmacological efficacy of individual components will be provided by the isolation of these phytoconstituents and their in vivo action [40].

13. *Arbutus unedo* L., (*Ericaceae*):One of the most traditional herbs that is frequently used to cure diabetes in people is *A. unedo L*. The plant is used as a fruit in European countries for the treatment of diabetes [50]. In vitro, the electrogenic intestinal absorption of glucose was directly suppressed by an aqueous preparation of the roots bark of *A. unedo L*. Furthermore, long-term oral dosing in vivo, it reduced body weight and enhanced oral glucose tolerance in rats. A concentration-dependent reduction of sodium-dependent glucose transport across isolated mouse jejunum was caused by the aqueous extract of AU (10 µg/mL to 1 mg/mL). With an IC_{50} near 216 µg/mL, 1 mg/mL demonstrated over 80% of the Phloridzin inhibition, yielding the maximum inhibition. Oral glucose tolerance was enhanced equally effectively by a 6-week AU intake (2 g/(kg/day)) as by metformin (300 mg/(kg/day)). Metformin and *A. unedo L*. both decreased body weight. In vitro, the electrogenic intestinal absorption of glucose was directly suppressed by an aqueous preparation of the roots bark of *A. unedo L.* Furthermore, long-term oral dosing in vivo, reduced body weight and enhanced oral glucose tolerance in rats. The ethnopharmacological significance of using the roots bark of *A. unedo L*. to treat diabetes is further supported by these findings [41]**.**

14.*Lithocarpuspolystachyus* (*Fagaceae*): For a very long time, people have used *L.polystachyus* as a herbal tea to control and prevent diabetes in Southeast China [51].The effects of *L.polystachyus* leaf extract on type II diabetic mellitus (T2DM) and the components that are responsible for thiseffect.

Furthermore, utilizing long-term double high diet-fed and streptozotocin (STZ)-induced type II diabetic mice, the underlying molecular and pharmacological processes of the extracts on hyperglycemia for the first time. The leaf extract, phloridzin, and trilobatin were evaluated in experimental T2DM mice both in vivo (gavage) and in vitro (non-invasive micro-test technique, NMT). Hepatic glycogen, liver biochemical indices, blood lipid and glucose levels, and other biochemical parameters were examined. Additionally, the impact of leaf extracts on the physiological glucose flux in the liver tissue of mice with T2DM and control groups was examined. The experimental T2DM mice's body weight increased dramatically after the first week and then stabilised over the next three weeks. During the four weeks of the trial, the body weight of all other groups remained constant. All treatment groups showed a reduction in blood glucose after four weeks, and leaf extract treatment had many advantageous effects: promoted the liver's uptake of glucose, boosted the liver's production of glycogen, decreased oxidative stress, up-regulated the liver's expression of glucokinase (GK), sodium-glucoseco-transporter 2 (SGLT2), insulin receptor (IR), and insulin receptor substrate (IRS), down-regulated the liver's expression of glucose-6-phosphatase (G-6-P), and improved blood lipid levels. Following phloridzin therapy, liver tissue also showed enhanced expression of SGLT2, PEPCK, and G-6-P. According to findings, trilobatin or phloridzin alone do not have the same hypoglycemic effects as leaf extract from *L. polystachyus*. In T2DM mice, leaf extract dramatically lowered hepatic gluconeogenesis and oxidative stress while also increasing glucose absorption and hepatic glycogen production [42].

S. No.	Common Name	Scientific Name (Family)	Medicinal Use in Diabetes	Scientific Validation/ Pharmacological Study	Reference
1.	Apple tree	*Malus domestica*	Fruit juice of the plant is used in the Haute Moulouya area for the treatment of diabetes.	In experimental animals, the impact of phlorizin injection on insulin-sensitive tissue in partly pancreatectomized rats was investigated. Insulin action was unaffected by phenylephrine therapy, while insulin sensitivity was fully restored in diabetic rats.	[34]

2.	Bermuda grass	*Cynodondactylon* (Poaceae)	The juice of leaves or powder of leaves is used in the treatment of diabetes.	Using HPLC–ESI MS analysis, aqueous extracts of *C. dactylon* were found to contain luteolin, apigenin, 6-C-pentosyl-8-C-hexosyl luteolin, and 6-C-hexosyl-8-C-pentosyl apigenin by in silico docking.	[35]
3.	Malabar Gulbel	*Tnosporasinesis (Menispermaceae)*	Plant juice of leaves is used in the Kathmandu district of Nepal for the treatment of diabetes.	Using an alloxan-induced technique, the hypoglycemic activity of the ethyl acetateleaf extract was assessed against Wistar rats, with glibenclamide serving as the reference compound. The glucose level has shown a typical percentage decline, with the dose of 200 mg/kg being larger than the dose of 100 mg/kg.	[36]

4.	Velvet leaf	*Cissampelospareira* (*Menispermaceae*)	This plant has a rich history of its traditional uses, and is widely employed to cure various ailments in Ayurveda, Traditional Chinese Medicine, and Western Herbalism	The aqueous-ethanolic extract of *C. pareira* roots in diabetic rats induced by streptozotocin-nicotinamide (STZ-NAM). At a dose of 500 mg/kg, b.w., the extract considerably ($p<0.05$) lowered the rats' blood glucose levels during the course of a 28-day in vivo investigation.	[7]
5.	Purple velvet plant	*Gynuranepalensis (Ateraceae)*	Plant leaves are used in Bangladesh for the treatment of diabetes.	Oral administration of glucose (18 mmol/kg body weight) and ethanol extracts (250 mg/kg body weight) improved glucose tolerance. Furthermore, the extracts decreased food intake during the feeding testand enhanced gastrointestinal motility.	[37]
6.	Kushen	*Sophoraflavescens (Fabaceae)*	The root is used in China for the treatment of diabetes.	*S. flavescens* methanol extract has a significant SGLT inhibitory activity. Nine chemicals extracted from the dried root of S. flavescens were evaluated for their effects on SGLT. All nine of the isolated compounds in the study showed SGLT2 inhibitory action; compound 7 had the greatest SGLT2 inhibition (IC_{50} (µM): 2.6 ± 0.18)	[11]

7.	Grey mangrove	*Avicennia marina (Acanthaceae)*	The plant leaves in New Zealand for the treatment of diabetes.	The alcoholic extract of *A. marina* leaves showed improved organ functions, decreased blood glucose levels, and improved blood picture. rats injected with STZ showed severe glycosuria and hyperglycemia (200-250 mg·dL−1), in contrast to the control group (50-100 mg·dL−1).	[38]
8.	Loop root mangrove	*Rihizophora mucronate (Rhizophoraceae)*	This plant leaves has been used in traditional medicine to treat conditions like diabetes in the coastal parts of the Asian subcontinent.	Aqueous extract Compared to control rats, STZ-induced diabetic rats had higher serum glucose levels; however, when *R. mucronata*orwere given to STZ-induced diabetic rats, either alone or in combination, the serum glucose levels significantly decreased.	[39]
9.	Batino Devil-tree	*Alstonia macrophylla (Apocynaceae)*	Plant leaves used as a tonic in Malaysia, Indonesia and Thailand for the treatment of diabetes	Five picraline-type alkaloids out of twenty compounds showed strong inhibition of SGLT1 and SGLT2; the highest was observed in 10-methoxy-N(1)-methylburnamine-17-O-veratrate [15, IC_{50} (µM) SGLT1: 4.0; SGLT2: 0.5]. and [16, IC_{50} (µM) SGLT1: 5.0; SGLT2: 2.0] alstiphyllanine D.	[11]

10.	Belinjau	*Gnetumgnemonoides (Gnetaceae)*	The bark of the plant used in East Northern India for the treatment of diabetes.	*G. gnemonoides's* dried bark, and just tested their impact on the suppression of both SGLT1 and SGLT2. Both of these substances exhibited modest, non-selective inhibitingIC_{50} (µM) 18 SGLT1: 27.0, SGLT2: 25.0; 19 SGLT1: 37.0, SGLT2: 18.0] for each SGLT.	[11]
11.	Magloni a vine	*Schisandra chinensis (Schisandraceae)*	The fruit is used as a food supplement in China for the treatment of diabetes	During the initial screening process using both ethanol and aqueous SCF extracts at a cytotoxicity-free concentration of 1 mg/mL, the ethanol extract showed more significant inhibitory rates for both SGLTs.	[11]
12.	Fishwort	*Houttuynia cordata* (Saururaceae)	The plantleaves areused as a medicinal salad in North Eastern part of India for diabetes.	Aqueous- methanol Certain *H. cordata* compounds have favourable pharmacokinetic characteristics and a strong binding affinity for both SGLT2 and DPP-IV. On the other hand, a deeper understanding and a new avenue for exploring the pharmacological efficacy of individual components will be provided by the isolation of these phytoconstituents and their in vivo action.	[40]

13.	Strawberry tree	*Arbutus unedo* L., (Ericaceae)	The plant is used as a fruit in European countries for the treatment of diabetes,	In vitro, the electrogenic intestinal absorption of glucose was directly suppressed by an aqueous preparation of the roots bark of Arbutus unedo L. Furthermore, upon long-term oral dosing in vivo, it reduced body weight and enhanced oral glucose tolerance in rats.	[41]
14.	Stone oaks	*Lithocarpuspolystachyus* (Fagaceae)	For a very long time, people have used *Lithocarpuspolystachyus*leaves asa herbal tea to control and prevent diabetes in Southest China.	All treatment groups showed a reduction in blood glucose after four weeks, and leaf extract treatment had many advantageous effects.	[42]

Discussion: Large rises in the prevalence of diabetes have been observed in almost every part of the world in recent decades. Due in large part to a higher prevalence of complications unique to diabetes, such as renal failure and peripheral vascular disease, the number of persons with diabetes or those who have had the condition for a longer period of time is expected to change the disease profile in many populations worldwide.There are few non-CVD-related causes of death, diabetes retinopathy and neuropathy, and "emerging" problems in these populations [52].When compared to the control group, therapy of the diabetic rat reversed the atrophy of the islets of Langerhans in the pancreas caused by STZ, and positive staining of b-cells with aldehyde fuchsin was verified. In the control group, there were fewer islets and a lower ratio of total islet tissue to pancreatic tissue [53].

Conclusion: Diabetes has emerged as the metabolic disease with the fastest rate of growth in the world in recent years. Many synthetic medications are on the market to control or treat diabetes and associated complications, but they come with a high price tag and a high risk of adverse effects. Natural product therapy is safe and regarded as an alternative method that has been practised since ancient times in many

medical systems across the world. In this review, the SGLT2 plants are considered also their pharmacological activity. In future, more scientific studies are needed for plants which have activity against SGLT2 inhibitors.

REFERENCE

1. Barve, Mayur, et al. "Therapeutics potentials of metals in ancient India: A review through Charaka Samhita." Journal of Ayurveda and Integrative Medicine 2.2 (2011): 55.
2. Hamada, Fatma A. "Ethno-botanical Uses of Some Plants in the Ha'ilian Traditional, Northern Saudi Arabia" *International Journal of Ecotoxicology and Ecobiology* 2018; 3(1):1.
3. Salehi, Bahare, et al. "Antidiabetic potential of medicinal plants and their active components." *Biomolecules* 9.10 (2019): 551.
4. Rasool Hassan, B.A. "Medicinal plants (importance and uses)"*Pharmaceut Anal Acta* 3.10(2012):2153-0435.
5. Agrawal, Ushakiran. "A Brief Overview of the Role of Herbal Medicine in Daily Life." *Int. J. Phar. &Biomedi. Rese* 10.2 (2023): 5-10.
6. Awuchi, Chinaza Godswill. "Medicinal plants: the medical, food, and nutritional biochemistry and uses." *International Journal of Advanced Academic Research* 5.11 (2019): 220-241.
7. Kumar, Ankit, et al. "Evaluation of antidiabetic effect of Cissampelospareira L. (Menispermaceae) root extract in streptozotocin-nicotinamide-induced diabetic rats via targeting SGLT2 inhibition." *Phytomedicine Plus* 2.4 (2022): 100374.
8. Anand, Uttpal, et al. "Ethanodermatological use of medicinal plants in India: From ayurvedic formulations to clinical perspectives- A review." Journal of ethnopharmacology 284 (2022): 114744.
9. Kavishankar, G. B., et al. "Diabetes and medicinal plants-A review." *Int J Pharm Biomed Sci* 2.3 (2011): 65-80.
10. Arumugam, G., P. Manjula, and N. Paari. "A review: Anti-diabetic medicinal plants used for diabetes mellitus." *Journal of Acute Disease* 2.3 (2013): 196-200.
11. Choi, Chang-Ik. "Sodium-glucose cotransporter 2 (SGLT2) inhibitors from natural products: discovery of next-generation antihyperglycemic agents." *Molecules* 21.9 (2016): 1136.
12. Vieira, Raquel, et al. "Sugar-lowering drugs for type 2 diabetes mellitus and metabolic syndrome-Review of classical and new compounds: Part-1*." Pharmaceuticals 12.4 (2019): 152.*
13. Osadebe, Patience O., Estella U. Odoh, and Philip F. Uzor. "Natural products as potential sources of antidiabetic drugs." *British Journal of Pharmaceutical Research* 4.17 (2014): 2075-2095
14. Praveena, S., Pasula, S., & Sameera, K.(2013).Trace elements in diabetes mellitus. *Journal of clinical and diagnostic research: JCDR, 7(9), 1863*.
15. , Mohamed, et al. "Chronic complications of diabetes mellitus: a mini review." *Current diabetes reviews* 13.1(2017): 3-10].
16. Lofty Wee, H.L.,Ho, H.K., & Li, S. C. (2002). Public awareness of diabetes mellitus in Singapore. *Singapore mediacl journal*, 43(3), 128-134.
17. World Health Organisation 2023]. World Health Organisation (WHO). 2023. Diabetes, News-room. Fact Sheet. Retrieved from https://www.who.int/news-room/fact-sheets/detail/diabetes on 11 November, 2023.
18. Kumar, Praveen, and Manu Krishna. "Quality of life in diabetes mellitus*." Science Journal of Public Health* 3.3(2015): 310-313.

19. Tripathi, Brajendra Kumar, and Arvind Kumar Srivastava. "Diabetes mellitus: complications and therapeutics." *Med Sci Monit* 12.7 (2006): 130-47.
20. Gliozzi, Micaela, et al. "From diabetes care to heart failure management: a potential therapeutic approach combining SGLT2 inhibitors and plant extracts." *Nutrients* 14.18 (2022): 3737.
21. Lontchi- Yimagou, Eric, et al. "Diabetes mellitus and inflammation." Current Diabetes Reports 13.3 (2013): 435-444.
22. Abbas, Ghulam, et al. "The management of diabetes mellitus-imperative role of natural products against dipeptidyl peptidase-4, α-glucosidase and sodium-dependent glucose co-transporter 2 (SGLT2)." *Bioorganic Chemistry* 86 (2019): 305-315.
23. Osadebe, Patience O., Estella U. Odoh, and Philip F. Uzor. "Natural products as potential sources of antidiabetic drugs." *British Journal of Pharmaceutical Research* 4.17 (2014): 2075-2095.
24. Hasia,Daniel S., Owen Grove, and William T. Cefalu. "An update on SGLT2 inhibitors for the treatment of diabetes mellitus." *Current opinion in endocrinology, diabetes, and obesity 24.1 (2017): 73.*
25. Mosley, Jaun F., et al. "Sodium-glucose linked transporter 2 (SGLT2) inhibitors in the management of type_2 diabetes: a drug class overview." *Pharmacy and Therapeutics 40.7 (2015): 451.*
26. Chao, Edward C., and Robert R. Henry. "SGLT2 inhibition—a novel strategy for diabetes treatment." *Nature reviews drug discovery* 9.7 (2010): 551-559.
27. Berbari, Adel E. "Sodium- Glucose Cotransporter (SGLT2) inhibitors: A new Era in renovascular protection." *International Journal of Cardiology Hypertension 7 (2020):100058.*
28. Kong, Young Kyu, et al. "Discovery of GCC5694A: A potent and selective sodium glucose co-transporter 2 inhibitor for the treatment of type 2 diabetes." *Bioorganic & Medicinal Chemistry Letters* 56 (2022): 128466
29. Nelinson, Donald S., Jose M. Sosa, and Robert J. Chilton. "SGLT2 inhibitors: a narrative review of efficacy and safety*." Journal of osteopathic medicine 121.2 (2021): 229-239*
30. van Baar, Michael JB,et al."SGLT2 inhibitors in combination therapy: from mechanisms of clinical considerations in type 2 diabetes management." *Diabetes care 41.8 (2018): 1543-1556*]
31. Wright, Ernest M. "SGLT2 inhibitors: physiology and pharmacology." *Kidney360* 2.12 (2021): 2027.
32. Bhardwaj, Gurprit, et al. "Swertisin, a novel SGLT2inhibitor, with improved glucose homeostasis for effective diabetes therapy." *Archives of Biochemistry and Biophysics 710 (2021): 10899.*
33. Youssef, Mahmoud E., et al. "Unlocking the Full Potential of SGLT2 Inhibitors: Expanding Applications beyond Glycemic Control." International Journal of Molecular Sciences 24.7 (2023): 6039]
34. Rossetti, Luciano, et al. "Correction of hyperglycemia with phlorizin normalizes tissue sensitivity to insulin in diabetic rats." *The Journal of Clinical Investigation* 79.5 (1987): 1510-1515.
35. Annapurna, Hasthi V., et al. "Isolation and in silico evaluation of antidiabetic molecules of Cynodondactylon (L.)." *Journal of Molecular Graphics and Modelling* 39 (2013): 87-97
36. Hegde, Sachet, and M. Jayaraj. "A Review of the Medicinal Properties, Phytochemical and Biological Active Compounds of Tinosporasinensis (Lour.) Merr." *Journal of Biologically Active Products from Nature* 6.2 (2016): 84-94.
37. Hannan, J. M. A., et al. "Acute Anti-Hyperglycaemic Activity of Five Traditional Medicinal Plants in High Fat Diet Induced Obese Rats." *Frontiers in Bioscience-Scholar* 15.2 (2023): 5.
38. Okla, Mohammad K., et al. "Antioxidant, hypoglycemic, and neurobehavioral effects of a leaf extract of Avicennia marina on autoimmune diabetic mice." *Evidence-Based Complementary and Alternative Medicine* 2019 (2019).
39. Zeid, I. E. M. E. A., Obidallah Hamdan Ali Al-Jaghthmi, and Hassan Mohammad Heba. "Augmentation of Insulin Secretion Induced by Rhizophora Mucronata and Avicennia Marina Extracts in Streptozotocin-Induced Diabetic Rats." *Int. J. Pharm. Res. Allied Sci* 8 (2019): 14-22.

40. Pakyntein, Careen Liza, et al. "Validation of phytochemicals from Houttuynia cordata for their effect on dipeptidyl peptidase IV and sodium/glucose cotransporter 2: an in silico study." (2023)
41. Mrabti, HanaeNaceiri, et al. "Arbutus unedo L., (Ericaceae) inhibits intestinal glucose absorption and improves glucose tolerance in rodents." *Journal of ethnopharmacology* 235 (2019): 385-391.
42. Wang, Jinfei, et al. "Leaf extract from LithocarpuspolystachyusRehd. promote glycogen synthesis in T2DM mice." *PLoS One* 11.11 (2016): e0166557.
43. Makarova, Elina; Górnaś, Paweł; Konrade, Ilze; Tirzite, Dace; Cirule, Helena; Gulbe, Anita; Pugajeva, Iveta; et al. (2015). "Acute anti-hyperglycaemic effects of an unripe apple preparation containing phlorizin in healthy volunteers: A preliminary study". Journal of the Science of Food and Agriculture. 95 (3): 560–568. doi:10.1002/jsfa.6779. PMID 24917557.
44. Moradi-Marjaneh, Reyhaneh, Maryam Paseban, and Amirhossein Sahebkar. "Natural products with SGLT2 inhibitory activity: Possibilities of application for the treatment of diabetes." *Phytotherapy Research* 33.10 (2019): 2518-2530.
45. Aktar, Anzuman, et al. "Further phytochemical screening; non-clinical evaluation of toxic and anti-inflammatory effects of crude aqueous extract of Gynuranepalensis." *Pharmacologyonline* 1 (2019): 136-153.
46. Yang, Xinzhou, et al. "Antidiabetic effects of flavonoids from SophoraflavescensEtOAc extract in type 2 diabetic KK-ay mice." *Journal of Ethnopharmacology* 171 (2015): 161-170.]
47. Khyade, Mahendra S., Deepak M. Kasote, and Nityanand P. Vaikos. "Alstoniascholaris (L.) R. Br. and Alstonia macrophylla Wall. ex G. Don: A comparative review on traditional uses, phytochemistry and pharmacology." *Journal of Ethnopharmacology* 153.1 (2014): 1-18.
48. Fang, Linlin, et al. "Protein tyrosine phosphatase 1B (PTP1B) and α-glucosidase inhibitory activities of Schisandra chinensis (Turcz.) Baill." *Journal of functional foods* 9 (2014): 264-270.
49. Kumar, Manish, et al. "Antihyperglycemic activity of Houttuynia cordataThunb. in streptozotocin-induced diabetic rats." *Advances in Pharmacological and Pharmaceutical Sciences* 2014 (2014)
50. Morgado, Sandra, et al. "Arbutus unedo L.: From traditional medicine to potential uses in modern pharmacotherapy." *Journal of Ethnopharmacology* 225 (2018): 90-102.
51. Shang, Ao, et al. "Sweet tea (Lithocarpuspolystachyusrehd.) as a new natural source of bioactive dihydrochalcones with multiple health benefits." *Critical Reviews in Food Science and Nutrition* 62.4 (2022): 917-934
52. Harding, Jessica L., et al. "Global trends in diabetes complications: a review of current evidence." *Diabetologia* 62 (2019): 3-16.
53. Kumar, Ankit, et al. "Role of plant-derived alkaloids against diabetes and diabetes-related complications: a mechanism-based approach." *Phytochemistry Reviews* 18 (2019): 1277-1298.