Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2930-2963

THE POTENTIAL ANTIDIABETIC ACTIVITY OF PHYTOCONSTITUENTS AGAINST TYPE 2 DIABETES MELLITUS- A REVIEW ON *IN-VITRO* AND *IN-VIVO* STUDIES

Mohd Arif
Department of Pharmacy, MJP Rohilkhand University, Bareilly, Uttar Pradesh, India- 243006

Rubi Parveen
Department of Pharmacy, MJP Rohilkhand University, Bareilly, Uttar Pradesh, India- 243006

S B Tiwari
Department of Pharmacy, MJP Rohilkhand University, Bareilly, Uttar Pradesh, India- 243006

Shiv Dev Singh
Department of Pharmacy, MJP Rohilkhand University, Bareilly, Uttar Pradesh, India- 243006

***Corresponding Author:** Dr. Shiv Dev Singh
*Associate Professor, Department of Pharmacy, M J P Rohilkhand University, Bareilly, Uttar Pradesh, India– 243006, E-mail id: shivdev.singh@mjpru.ac.in

Abstract
Type 2 Diabetes Mellitus has been one of the most common types of diabetes, affecting more than 90% of the population. High blood sugar levels can lead to stiffness, kidney failure, hypertrophy, strokes, or heart attack. Other than these serve consequences,some major secondary symptoms include loss of eyesight, hearing and cognitive ability. Conventional drugs for the treatment of T2DM such as biguanides like metformin, glucosidase inhibitors like acarbose, miglitol, sulphonyl urea like glibenclamides have shown severe side effects on the body such as insulin resistance, brain atrophy, fatty liver, etc. So these adverse effect can be minimize by using the natural bioactive constituents isolated from the plants. Medicinal herbs have long been utilised as diabetes treatments all throughout the world. They create a wide range of chemical substances with biological activity and antidiabetic characteristics. The management of many diseases as well as the overall enhancement of human well-being rely heavily on phytoconstituents. The goal of the present study is to provide a comprehensive account of the current state of antidiabetic herbal medicine research and development, with a focus on phytoconstituents and their potential anti-diabetic effects.

Keywords: Diabetes mellitus, antidiabetic, medicinal herbs, insulin, phytochemical constituents, blood glucose.

Abbreviations:
CDC: Centres of Diseases Control and Prevention; T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; GDM: Gastational Diabetes Mellitus; IDDM: Insulin-Dependent Diabetes

Mellitus; NIDDM: Non-Insulin Dependent Diabetes Mellitus; SLNs: Solid liquid Nanoparticles; DPP4: dipeptidyl-peptidase-4; AMPK: AMP-activated protein kinase; PTP1B: protein tyrosine phosphatase1B; SGLT2: sodium-glucose transporter-2; PPAR: Peroxisome Proliferator-Activated Receptor; TZDs: Thiazolidinediones; HPLC: high-performance liquid chromatography; FBG: fasting blood glucose; IPGTT: intraperitoneal glucose tolerance test; ITT: insulin tolerance test; SI: serum insulin; TC: total cholesterol; DPPH: 2, 2-diphenyl-1-picrylhydrazyl

INTRODUCTION

Diabetes has become a major public health challenge, with constraint evidence affecting millions of people, including children and adolescents. National Diabetes Statistics Reports by the Centres of Diseases Control and Prevention (CDC) confirm that the number of diabetes cases globally has reached 37.3 million. In contrast, ninety-six million people under age of 18 years have been diagnosed as prediabetic, and this data is expected to quadruple by 2025 (Malathi et al., 2010). Diabetes mellitus (DM) is a chronic disease which occurs due to the inability of beta (β-cells) cells to produce insulin or inadequate insulin production from the pancreatic cells. T1DM is formerly called Insulin-Dependent Diabetes Mellitus (IDDM). It's a type of autoimmune illness associated with loss of β-cells in the pancreatic islets of Langerhans, which produce insulin, whereas T2DM is commonly known as Non-Insulin Dependent Diabetes Mellitus (NIDDM), caused by the body's insulin inefficiency **Figure 1**(Baynest, 2015). T2DM has been one of the most common types of diabetes, affecting more than 90% of the population. High blood sugar levels can lead to stiffness, kidney failure, hypertrophy, strokes, or heart attack. Other than these serve consequences,some major secondary symptoms include loss of eyesight, hearing and cognitive ability(Bermúdez-Pirela et al., 2007). The number of patients who are affected by type 2 DM was expanded from 0.108 billion in 1980 to 0.422 billion in 2014; according to WHO estimates diabetes afflicted 8.5 per cent of young people aged 18 and above in 2014. With 1.5 million fatalities linked to the condition during 2000 and 2016, diabetes mellitus was the ninth leading cause of death in 2019, Premature mortality, or the rate of passing away before age 70, rose about 5% (WHO reports on diabetes 2021).

Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2930-2963

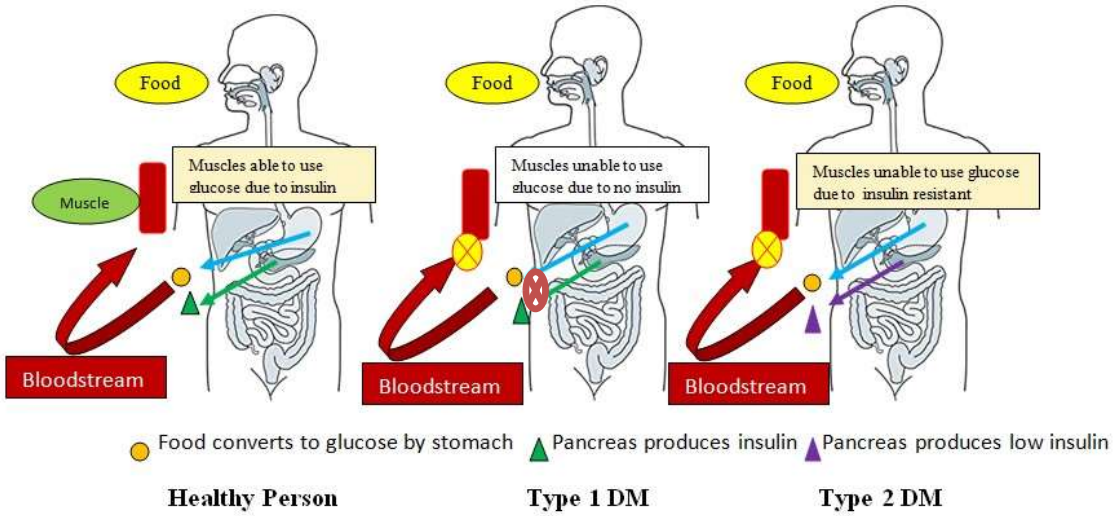


Fig 1. Pathophysiology of type 1 and type 2 Diabetes mellitus (Baynest, 2015)

Conventional drugs for the treatment of T2DM such as biguanides like metformin, glucosidase inhibitors like acarbose, miglitol, sulphonyl urea like glibenclamides have shown severe side effects on the body such as insulin resistance, brain atrophy, fatty liver, etc. So these adverse effect can be minimize by using the natural bioactive constituents isolated from the plants. Several targets are involved in T2DM management and treatment, including α-amylase, α-glucosidase, dipeptidyl-peptidase-4(DPP-4), PPRA, protein tyrosine phosphatase1B (PTP1B), AMP-activated protein kinase(AMPK), sodium-glucose transporter-2 (SGLT-2). The important therapeutic targets for the treatment of diabetes, according to Tolmie *et al.*, (2021) are α-amylase and α-glucosidase. α-amylase and α-glucosidase convert the starch or oligosaccharides into the monosaccharides or glucose which is absorbed into the small intestine which results increase the postprandial hyperglycemia. Postprandial hyperglycemia is reduced when these enzymes are inhibited. The capacity of substances discovered available condiments and spices to prohibit these two enzymes were investigated like eriodi-ctyol, myrcene, rosmarinic acid, cinnamic acid, and acetyleugenol were studied. Now times the inhibition of α-glucosidase and α-amylase is very effective therapy for the cure or treatment of type 2 diabetes(Tolmie et al., 2021). DPP4 (dipeptidyl peptidase-4) is a type II transmembrane glycoprotein found in a variety of organs and cells. It can also be found in a soluble form in body fluids. DPP4 regulates energy metabolism, inflammation, and immunological function, and so it is play a very crucial role in a variety of pathological or physiological processes(T. Zhang et al., 2021). DPP-4 is an enzyme that degrades the hormone incretin GLP-1. Incretin (GLP-1) assists the body in producing more insulin only when it is required and decreases the amount of glucose generated by the liver. Inhibition of target DPP-4 is a novel therapeutic and management strategy for type 2 diabetes mellitus. DPP-4 inhibitors work regardless of body weight and have been demonstrated to be cardiovascular safe. Patients with impaired renal function, the majority of drugs can be used(Gallwitz, 2019). SGLT2 is a sodium-glucose co-transporter that is mostly found in renal proximal tubule (S1) and is liable for roughly

Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2930-2963

reuptake of 90% of total glucose in kidney. SGLT2 inhibition is a novel pharmaceutical method for lowering glucose level in diabetic patients by blocking reabsorption of tubular glucose. This class of medicines has shown considerable cardiovascular and renal protective effects in addition to reducing glucose. In persons having type 1 or type 2 DM, competitive inhibition of SGLT2 indicate a different curative option for the treatment of hyperglycemia and/or obesity. SGLT2 reabsorbed the 90% of filtered glucose, with remaining SGLT1 reabsorbed the 10% of filtered glucose in the S3 region (late proximal straight tubule)(Idris & Donnelly, 2009). A possible strategy for managing type 2 diabetes (T2DM) is to target the transcription factor that is Peroxisome Proliferator-Activated Receptor (PPAR), which regulates the protein production crucial for Type 2DM. This process will be a huge step for the treatment of Type 2DM in the future(Frkic et al., 2021). The nuclear hormone receptor superfamily includes ligand-activated transcription factors such as peroxisome proliferator-activated receptors (PPARs). The activation of PPAR-gamma, a subtype of PPARs, can increase or decrease target gene transcription(Guo & Tabrizchi, 2006). The major enzyme involved in insulin receptor desensitization, Protein Tyrosine Phosphatase (PTP1b), has become a therapeutic target for the treatment of T2DM(Eleftheriou et al., 2019). PTP1B (protein tyrosine phosphatase 1B) is a novel therapeutic method for the treatment of type 2 diabetes that play a crucial significance in the insulin signaling transduction pathways negative control. PTP1B inhibitors improve insulin receptor sensitivity and they have a suited cure impact for diseases caused by insulin resistance. PTP1B inhibitors have been produced and studied for their capacity to enhance insulin signaling, whether synthetic or isolated as bioactive molecules from natural sources (Tamrakar et al., 2014).

Various medicinal herbs with their phytoconstituents have an Anti-diabetic effect

The World Health Organization (WHO) claims that 80 percent population in underdeveloped nations relies on the usage of medicinal herbs to treat diabetes(Panday V.N., Rajagopalan S.S., 1995). Herbals are a type of food that can be used to treat sickness or ailments. Ayush-82 is an anti-diabetic herbal medication made up of four different herbs such as Mangifera indica, Syzygium cumini, Memordica charantia, and Gymnema sylvestra. In clinical trials, it has been proven to be effective in Type 2DM when taken with shilajit. Natural substances are play a crucial role for the management or cure of diseases.

Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2930-2963

Allium cepa (Liliaceae)

Allium cepa also known as onion and belongs to the family liliaceae. They found that *Allium cepa* aqueous extracts decreased blood glucose levels in diabetic animals (rats) and also discovered that a chemical compound Kaempferol-3-O-β-D-6 (P-coumaroyl) glucopyranoside, ($C_{30}H_{26}O_{13}$) that was extracted by a fraction of *Allium cepa* plant extracts at diminished blood glucose (sugar) levels in diabetic rats group. Aqueous extracts of *Allium cepa* reduced blood sugar levels in diabetic animal (rats) in a dose-dependent way, with maximum reductions of 77.31 percent, 77.75 percent, 78.5 percent, and 81.28 percent for 100mg/kg, 300mg/kg, 600mg/kg, and glibenclamide 2mg/kg, respectively. They extracted a chemical compound isolated from a fraction of *Allium cepa* extracts at 25 mg/kg reduced blood sugar levels in diabetic rats with 60.69 percent in 24 hours, compared to 44.19 percent for glibenclamide (2mg/kg). The antidiabetic effects of isolated chemical compound $C_{30}H_{26}O_{13}$ from fraction at 25 mg/kg were higher than those of glibenclamide at 2 mg/kg(Ikechukwu & Ifeanyi, 2016).

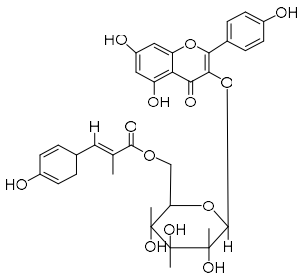


Fig 2. Kaempferol-3-O-β-D-6 (P-coumaroyl)-glucopyranoside ($C_{30}H_{26}O_{13}$)(Ikechukwu & Ifeanyi, 2016).

The researcher's conducted an *in-vitro* assay of all extracted compounds 1-15 as shown in Fig 3. from *Allium cepa* and found that compounds 1–3 and 8–15 inhibited PTP1B in a dose-dependent way. Inhibition of PTP1B was particularly strong in compounds 15, 14, and 13, which were more powerful than both positive controls (Ursolic acid and sodium orthovanadate). PTP1B inhibitory activity was also seen in compounds 10 and 12. There was two molecules 4 and 6 had no effect against α-glucosidase, whereas the other molecules had an IC50 0.89–74.44μM, that was significantly greater than positive control acarbose. Another pair of powerful PTP1B inhibitors, 14 and 15, were discovered to be 100 and 250 times more effective at inhibiting α-glucosidase than the positive control acarbose(Vu et al., 2020).

Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2930-2963

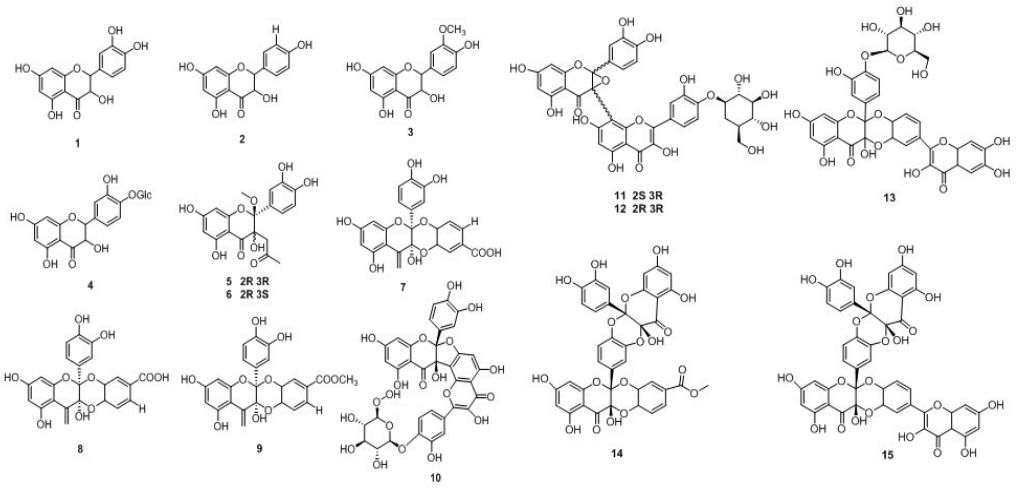


Fig 3. Different isolated compounds from fraction of *Allium cepa* have antidiabetic activity(Vu et al., 2020)

Amomum tsao ko (Zingiberaceae)

Amomum tsao ko comes under ginger-like family. The ethyl acetate fraction of amomum tsao-ko was showing antidiabetic activity(He et al., 2021)**.** They used the dried powdered fruits of *Amomum tsao-ko* and extracted with ethyl alcohol-water (50:50 percent). To remove the ethyl alcohol, the mixed extraction was concentrated at decreased pressure, and the water solution was extracted with ethyl acetate. The ethyl acetate fraction was separated into seven fractions using column chromatography (CC) and a gradient elution with Methanol-Chlorofom. Silica gel Column Chromatography (CC), Sephadex LH-20 CC, and HPLC on Agilent XDB-C18 columns were used to purify substances 13, 14, 17, and 18 from Fraction A-6. Compounds 9, 10, 11, 12, 15, and 16 were identified using HPLC, as well as Sephadex LH-20 CC, silica gel CC, and Sephadex LH-20 CC which are represents in **Fig 4.** Compounds 5, 6, 7, 8, 1, 2, 3, and 4 were discovered as new compounds that were isolated using column chromatography and HPLC (High-performance liquid chromatography). From Amomum tsao-ko, eight unusual flavanol-menthane conjugates, amomutsaokins (1-8), as well as ten known polyphenolic compounds (9-18), were separated. The chemical structure of these various isolated chemical compounds were studied using 1D or 2D NMR, HRESIMS, IR, and also by using UV data. Extensive spectral data and ECD computations revealed their structures, including absolute configurations. Their anti-diabetic effectiveness was tested against three proteins or enzymes associated with diabetes (PTP1B, α-glucosidase, and TCPTP). Some of the chemical compounds such as 2, 3, 6, 14, and 16 showed selective inhibition of PTP1B target, whereas compounds 1-3, 5-8, 10, and 16-18 shown inhibitory effects of α-glucosidase. It was discovered that chemical compounds 1 and 6 are mixed-type α-glucosidase inhibitors. For the isolation of novel chemical compounds and *in-vitro* biological experiments, Zhang *et al*., (2021) employed the dried mature fruits of *Amomum tsao ko*. The powders of Amomum tsao-ko were cleaned for 24 hours with carbon tetrachloride, filtered, and dried. Methanol and ethanol solvents were used to extract the defatted powders for 24 hours at room temperature, respectively. A rotary evaporator was used to mix and concentrated the filtrates

Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2930-2963

produced by using extracted defatted powders. *In-vitro* and *in-vivo* experiments (Antioxidant antidiabetic effect) were investigated of identified compounds i.e. flavonoid from *Amomum tsao-ko*. *Amomum tsao-ko* methanol extracts had more flavonoid compounds, and 29 flavonoids compounds were identified by using UPLC-MS or Mass Spectroscopy**.** *Amomum tsao-ko* demonstrated antioxidant activity *in-vitro* together with inhibitory effect against α-amylase and α-glucosidase. In rats, type 2 diabetes was developed *in-vivo* by a high-fat diet paired with a streptozotocin infusion. Treatment with the *Amomum tsao-ko* extract for six weeks enhanced impaired glucose tolerance, decreased insulin, fasting blood glucose, and malondialdehyde (MDA), and elevated superoxide dismutase (SOD) concentrations. *In-vitro* and *in-vivo* assay found that the flavonoid content of *Amomum tsao* ko exhibits outstanding antioxidant and anti-diabetic effect. *Amomum tsao-ko* may be a novel natural plant that can be used to create functional foods or medications for people with Type 2DM(X. Zhang et al., 2022).

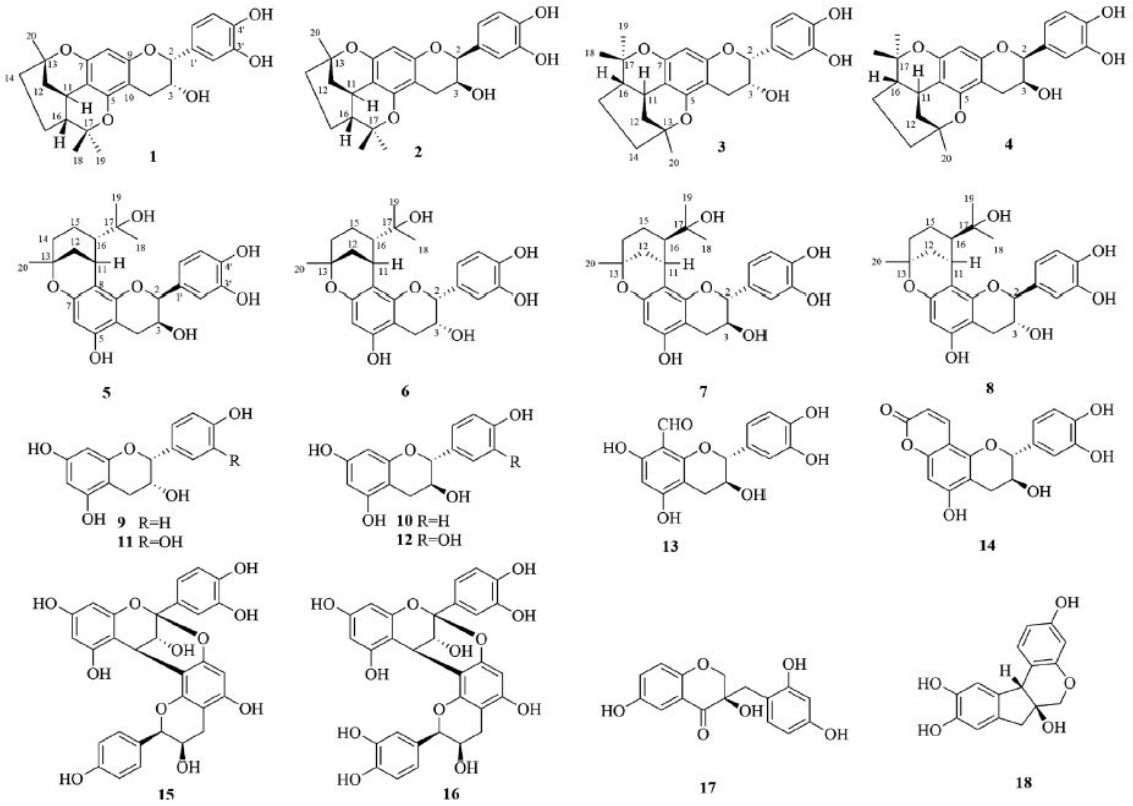


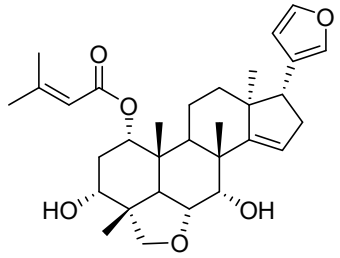
Fig 4. The chemical structures of various constituents 1-18 isolated from Amomum tsao-ko (He et al., 2021)

Azadirecta indica (Myractaceae)

Khosla *et al*., (2000) discovered that treating rabbits an aqueous extracts of neem leaves over 4 weeks lowered blood sugar levels after alloxan-induced type 2 diabetes mellitus substantially(Khosla et al., 2000). Giving *neem* root extract twice daily for 15 days resulted in significantly decreased blood sugar levels, according to research of Patil *et al*., (2013). This effect

was less significant and strong contrasted with glibenclamide. Patil *et al*., 2013 came to the conclusion that 70% alcoholic *neem* root extract had anti-diabetic properties (Patil et al., 2013). The actions of *Azadirecta indica* leaves extracts on the activation of insulin signalling markers and glucose metabolism in targeted site of high-fat and fructose-induced type 2 diabetic rats were investigated by Satyanarayana *et al*. in 2015. Rats with type 2 diabetes caused by a high-fat meal were given the orally optimal dose of *Azadirecta indica* leaves extract once every day for thirty days. Just at end of the experiments, the amounts of molecules that indicate insulin, the oxidation of glucose, and glycogen were measured, along with the serum lipid composition, fasting blood sugar, and oral glucose tolerance. The administration of A. indica leaves extract corrected the abnormal levels of GLUT4 protein, insulin levels, lipid levels, blood sugar, and insulin signaling markers. According to the results of the current investigation, *Azadirecta indica* could significantly contribute to the treatment of diabetes mellitus by enhancing insulin signaling marker's and skeletal muscle glucose uptake(Satyanarayana et al., 2015). Perez-Gutierrez *et al*., 2012 They utilized the dried aerial portion of the *Azadirecta indica* plant. Chloroform was used to extract plant material from ground powdered leaves. To form a dried residue, the plant extracts were blended and evaporated under reduced pressure. Different fractions were obtained after the extracts was put onto a chromatographic column and treated with chloroform/ethylic ether solvent. The hypoglycemia potential of these fractions was then evaluated. Thin layer chromatography analysis was used to classify active fractions together based on their common characteristics. One new tetranortriterpenoid was discovered after extensive chromatographic analysis of a chloroform extract. Based on spectrum data, the structure of the compound 24, 25, 26, 27-tetranor-apotirucalla-(apoeupha)-1-senecioyloxy-3,7-dihydroxy-14,20,22-trien-21,23-epoxy, which we named as meliacinolin, was determined as shown in **Fig 5.** The biochemical factors total cholesterol, lipid peroxidation, triglycerides, glucose level, liver and muscle glycogen, glutathione reductase, and glutathione peroxidase were examined after meliacinolin treatment of diabetic rats for 28 days. As indicators of the impact on glucose metabolism, *in-vitro* suppression of the enzyme activity of α-glucosidase and α-amylase have been used. As a results, we discovered that meliacinolin restored to normal levels of blood glucose level, reactive compounds of thiobarbituric acid, and insulin concentration in streptozotocin-induced diabetic mice. α-amylase and α-glucosidase both were suppressed by meliacinolin from A. indica. An efficient method for reducing postprandial hyperglycemia is to administer α-amylase and α-glucosidase inhibitors, which stop the digestion of carbohydrates or sugar molecules(Perez-Gutierrez & Damian-Guzman, 2012).

Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2930-2963

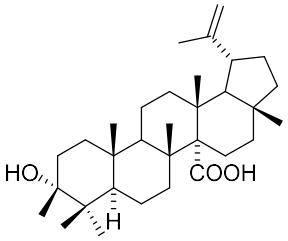


Meliacinolin

Fig 5. Structure of Meliacinolin(Perez-Gutierrez & Damian-Guzman, 2012)

Bacopa monnieri (Scrophulariaceae)

The researchers used the aerial portions of *Bacopa monnieri* for extraction and assessment of antihyperglycemic and antioxidant effects. The powdered material was separated from the mixture with petroleum ether before being extracted in a soxhlet device with 95 percent ethanol. Under decreasing pressure, the solvent was evaporated, leaving a greenish-black adhesive mess. The dried extract was kept in a desiccator until the study was completed. The extract, which is comparable to the common drug glibenclamide, significantly reduced blood glucose levels in alloxan-induced diabetic rats as compared to the control group in both single-dose and multiple-dose trials. The extract's antidiabetic effect might be explained by an increase in peripheral glucose uptake and oxidative damage resistance in alloxan-induced diabetes(Ghosh et al., 2008). In order to extract and isolate novel phytochemical components for the treatment of diabetes, Ghosh *et al*. (2010) collected fresh aerial sections of young and adult *Bacopa monnieri* plants. In a soxhlet system, the powdered plant material was separated from the mixture with petroleum ether and then extracted with 95 percent ethanol. The solvent was evaporated at a low pressure, leaving behind a greenish-black sticky residue. An ethyl acetate water system was used to separate the residue first, followed by n-butanol water system. Similar extraction techniques were used with the appropriate solvents at lower pressure, producing various types of fractions. They address the triterpene bacosine as shown in **Fig 6.** which was extracted from the fraction of ethyl acetate of the ethanolic extract of Bacopa monnieri, and its antihyperglycemic activity, in-vivo antioxidant capacity, and in-vitro peripheral glucose consumption. Bacosine significantly decreased blood glucose amounts comparative to the control group in all single administration and multiple administration experiments. Increased peripheral glucose uptake and resistance to oxidative damage may be responsible for bacosine's antihyperglycemic benefits in alloxanized diabetes. Bacosine may exhibit insulin-mimetic activity(Ghosh et al., 2011).



Bacosine

Fig 6. Structure of Bacosine (Ghosh et al., 2011)

Benincasa cerifera (Cucurbitaceae)

Ryu *et al*., (2022) explored about *Benincasae Exocarpium* is a fruits peel from the *Benincasa cerifera* tree which has been used to prevent or treat metabolic illnesses like diabetes, hyperlipidemia, and obesity. Because previous research have shown that *Benincasa cerifera* extracts were useful in treating type 2 diabetes, they investigated the inhibitory efficacy of *Benincasae Exocarpium* extracts and fractions towards α-glucosidase efficacy. Compounds 1–11 were identified from the plant *Benincasae Exocarpium* using bioassay-guided isolation based on this analysis as represents in **Table 1**. They also developed a high-performance liquid chromatography (HPLC) method that can evaluate all 11 compounds simultaneously. The pharmacological activity of the compounds was also tested, and eight of them exhibited high activity. Eight active chemical compounds (2, 5–11) were also subjected to a quantitative analysis. The most active of them were flavonoid compounds. They reach the conclusion that this research demonstrated the efficacy of *Benincasae Exocarpium* in the management of type 2 diabetes and its consequences. Compound 1 is known as p-hydroxybenzoic Acid with the molecular formulae $C_7H_6O_3$, Compound 2 is known as protocatechuic acid having molecular formulae $C_7H_6O_4$, Compound 3 is known as isovanillin with the molecular formulae $C_8H_8O_3$, Compound 4 is known as 5-hydroxymethylfurfural having molecular formulae $C_6H_6O_3$, Compound 5 is known as isovitexin with the molecular formulae $C_{21}H_{20}O_{10}$, Compound 6 is known as vitexin having molecular formulae $C_{21}H_{20}O_{10}$, Compound 7 is orientin with the molecular formulae $C_{21}H_{20}O_{11}$, Compound 8 is gallic acid with the molecular formulae $C_7H_6O_5$, Compound 9 is caffeic acid having molecular formulae $C_9H_8O_4$, Compound 10 is known as Vitexin-2"-*O*-Rhamnoside having molecular formulae $C_{27}H_{30}O_{14}$, Compound 11 is known as Vitexin-4"-*O*-Glucoside with the molecular formulae $C_{27}H_{30}O_{15}$ (Ryu et al., 2021).

Table 1. Various isolated compounds from *Benincasae Exocarpium* examined for antidiabetic activity (Ryu et al., 2021)

Compounds	Name of Compounds	Molecular formulae
1	p-Hydroxybenzoic Acid	$C_7H_6O_3$
2	Protocatechuic Acid	$C_7H_6O_4$
3	Isovanillin	$C_8H_8O_3$

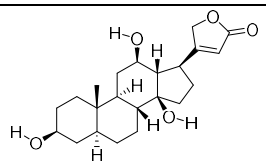
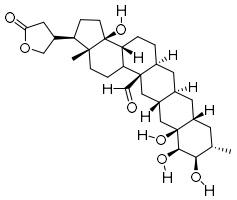
Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2930-2963

4	5-Hydroxymethylfurfural	$C_6H_6O_3$
5	Isovitexin	$C_{21}H_{20}O_{10}$
6	Vitexin	$C_{21}H_{20}O_{10}$
7	Orientin	$C_{21}H_{20}O_{11}$
8	Gallic Acid	$C_7H_6O_5$
9	Caffeic Acid	$C_9H_8O_4$
10	Vitexin-4"-*O*-Glucoside	$C_{27}H_{30}O_{15}$
11	Vitexin-2"-*O*-Rhamnoside	$C_{27}H_{30}O_{14}$

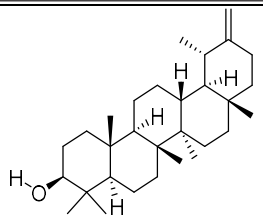
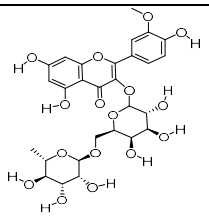
Calotropis procera (Apocynaceae)

Molecular docking and dynamics simulation methods utilized for screening compounds of *Calotropis procera* against with the receptor α-glucosidase. Extracts obtained from *Calotropis procera* have been widely employed in the management of type 2 diabetes mellitus, according to earlier research. Syriogenin, taraxasterol, calotoxin, and isorhamnetin-3-O-robinobioside, were found as innovative lead molecules as shown in **Table 2,** have reasonable α-glucosidase binding energies. Asp^{518}, Trp^{481}, Leu^{678}, Leu^{680}, and Leu^{677}were characterized as important binding residues, and these molecules were anticipated to be α-glucosidase inhibitors. Syriogenin, taraxerols, calotoxin, and isorhamnetin-3-O-robinobioside all have credible binding energies, biological activity, bond lengths, and hydrogen bond interactions. For molecular dynamic simulations, these substances were evaluated. These four molecules are novel therapeutic leads that will need to be evaluated in vivo and in vitro to see how they affect α-glucosidase action(Adinortey et al., 2022).

Table 2: List of isolated projected novel lead compounds from *Calotropis procera*, along with their IUPAC names and chemical structures(Adinortey et al., 2022).

Name of isolated compounds	**Structure of compounds**
Syriogenin	
Calotoxin	
Taraxasterol	

Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2930-2963

	
Isorhamnetin-3-Orobinobioside	

According to his research, the molecule taraxasterol has a variety of biological actions, including α-glucosidase inhibitor, anti-diabetic type 1, hydroxy-steroid de-hydrogenase inhibitor, and 17-beta-hydroxysterol de-hydrogenase inhibitor as represents in **Table 3**. Additionally, according to the study, calotoxin, syriogenin, and isorhamnetin-3-O-robinobioside may be capable of inhibiting the alpha-glucosidase enzyme(Adinortey et al., 2022).

Table 3: Various selected compounds from *Calotropis procera* with their biological activity(Adinortey et al., 2022).

Name of Compounds	**Biological Activity**
Syriogenin	α-Glucosidase inhibitor
Calotoxin	α-Glucosidase inhibitor
Taraxasterol	Protein tyrosine phosphate (PTP) inhibitor, α-glucosidase inhibitor, anti-diabetic type 1, hydroxysteroid dehydrogenase inhibitor
Isorhamnetin-3-Orobinobioside	α-Glucosidase inhibitor

Cinnamon (Lauraceae)

The *Cinnamon* extract may have a role in the regulation in blood sugar levels and lipids, as well as the blood glucose-reducing action via enhancing insulin sensitivity and decreasing sugar (carbohydrates) absorption in the intestinal tract(Kim et al., 2006). *Cinnamon* Oil was found to have a regulatory effect in blood glucose and cholesterol levels, as well as improved pancreatic islet function. *Cinnamon* oil may help with type 2 diabetes mellitus treatment(Ping et al., 2010). The hypoglycemic impacts of various procyanidin oligomer kinds were investigated by Chen *et al*., (2012). Two different cinnamon species were used to produce extracts that were high in procyanidin oligomers. *Cinnamon* have antidiabetic effect is assumed to be attributed to procyanidin oligomers. They discovered that the *Cinnamomum tamala* and *Cinnamomum cassia* extracts were rich in A-type and B-type procyanidin oligomers, respectively, utilising high-performance liquid chromatography (HPLC) and pure procyanidin oligomers as reference materials. They found that the *Cinnamomum tamala* extract and *Cinnamomum cassia* extract both

Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2930-2963

had anti-diabetic properties. They were also isolated the different compounds **(1-6)** from both Cinnamomum species as shown in **Figure 7.** They used the high-performance liquid chromatography to isolate the components from *Cinnamomum cassia* extract, and they discovered that several peaks such as 1, 2, 3, 4, 5, and 6 were produced. The findings demonstrated that peak 1 represents molecule 1, peak 2 represents molecule 2, peak 3 represents molecule 3, peak 4 represents molecule 4. Peak 5 was found to be a B-type procyanidin combination, suggesting that B-type procyanidins may be the major constituent in *Cinnamomum cassia* extract. They isolated the components from *Cinnamomum tamala* extract and discovered that multiple peaks were formed, including 1, 2, 3, 4, 5, and 6. The data revealed that peak 1 corresponds to molecule 5, peak 3 to molecule 6, and peak 4 to molecule 3. Peak 2 contained Molecule 1 and a different unidentified A-type tetramer procyanidin. *Cinnamomum tamala* extract have dominating peaks were 2, 3, and 4, which suggests that *Cinnamomum cassia* extract mostly contains A-type procyanidins (Chen et al., 2012).

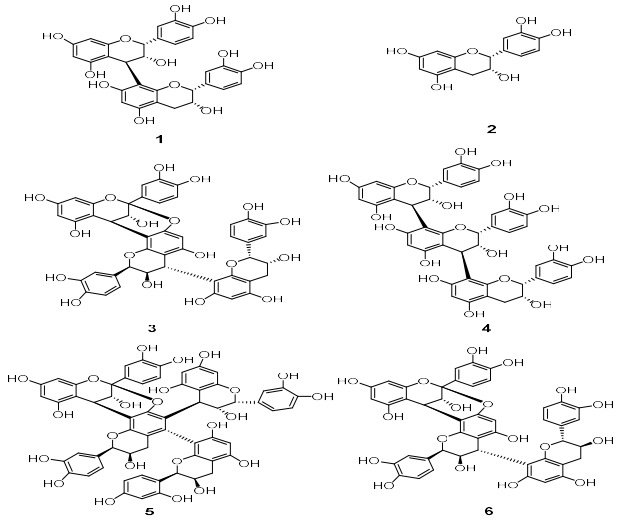


Fig 7. Various phytochemical compounds isolated from both *Cinnamomum* species (Chen et al., 2012)

Corni Fructus (Cornaceae)

They extracted dried *Cornus officinalis* fruit three times with aqueous acetone, and then concentrated the residue under vacuum. The concentrated extract was solubilized in water and then fractionated with CH_2Cl_2, n-hexane, and *n*-BuOH to yield 4 layers: H_2O, n-BuOH, CH_2Cl_2, and n-hexane. Following that, they employed column chromatogtraphy on a silica gel column to isolate compounds. *Cornus officinalis* have fruits is known as Corni fructus, the researcher discovered 12 new components, including 2 iridoid glycosides, 3 flavonoids, 2 triterpenoids and 3 phenolic compounds as well as 2-butoxybutanedioic acid (12) and cornuside (11) which are represents in **Figure 8**. HMBC, COSY, and ^{1}H, ^{13}C NMR spectral studies were used to identify the chemical structures of molecules. Within the presence of test organism, they were assessed for glucose absorption efficiency, phosphoenolpyruvate carboxykinase (PEPCK) messenger mRNA expression, and suppression of cytokine-mediated cytotoxicity. Compound 3 and 8, considerably decreased phosphoenolpyruvate carboxykinase mRNA expression, but the n-hexane layer and the

Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2930-2963

n-BuOH layer significantly boosted glucose absorption from muscle. Finally, compound 5 successfully inhibited β-cell death at concentrations of 50 and 100μM. They came to the conclusion that these molecules of *Corni fructus* may contribute to antihyperglycemic and β-cell-protective effects against diabetes mellitus. By using column chromatography, the researchers were able to distinguish 12 known components from *Corni fructus*, with loganin being the most important component. For the first time in this investigation, compounds 12 and 8 were isolated from plants. Depending on the isolated compounds, chemical compounds 2–12 displayed various degrees of insulin-like actions on dexamethasone as well as 8-bromo-cAMP–induced phosphoenolpyruvate carboxykinase expression. While compounds 3, 5, and 9 demonstrated anti-inflammatory characteristics as evaluated by NO generation, chemical compounds 5 and 6 reduced cytokine-mediated cells damage(Lin et al., 2011).

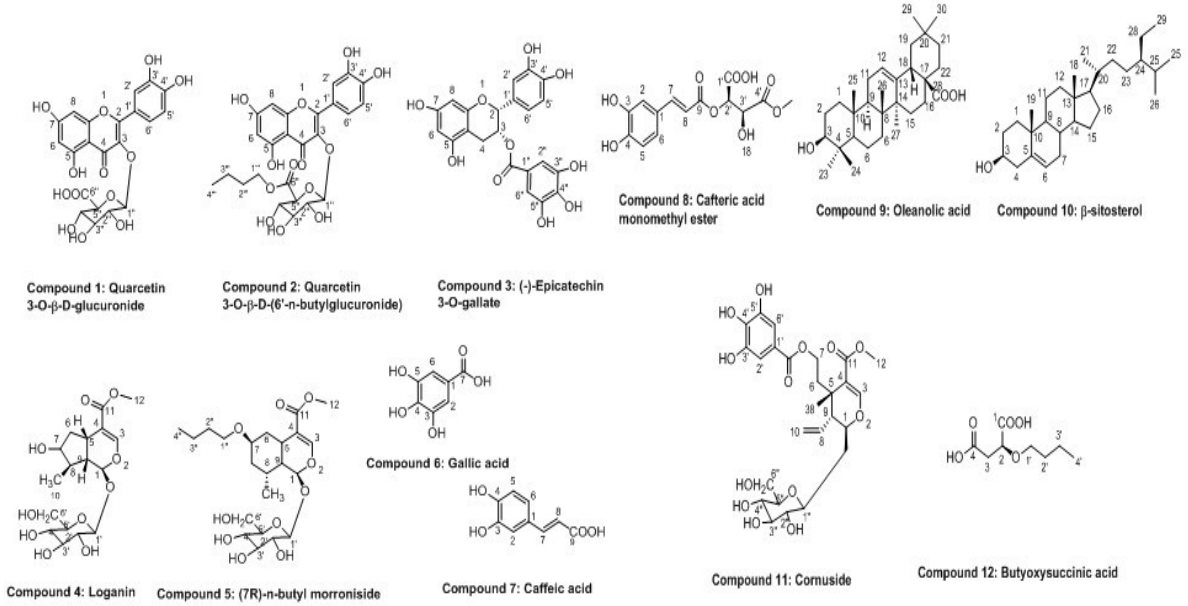


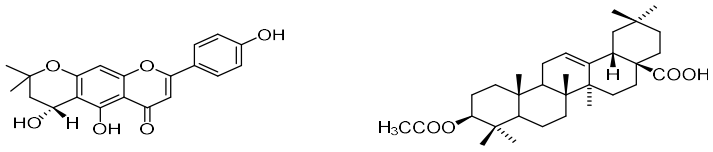
Fig 8. Phytochemical constituents isolated from *Corni Fructus* (Fruits of Cornus officinalis) having insulin-mimetic effect(Lin et al., 2011).

Eysenhardtia platycarpa (Fabaceae)

Narva´ez-Mastache *et al*., (2006) were utilized the bark, branches, and leaves of *Eysenhardtia platycarpa* for *in-vitro* biological evaluation of antihyperglycemic effect and for the isolation of a novel constituents. The air-dried of selected parts of this plant were extracted with the methanol solvent. To produce the appropriate dry extract residues, the solvent was evaporated using a rotary evaporator operating at low pressure. Dichloromethane (CH_2Cl_2) was used to suspend branches of *Eysenhardtia platycarpa* and separate the soluble and insoluble portions. Ten main fractions were produced by column chromatography (CC) partitioning the soluble fraction and washing it out with a mixture of n-hexane and ethyl acetate. They discovered that a one new flavones compound, together with the known many compounds were identified from the bracnches of *Eysenhardtia platycarpa*. They claimed that the main component of E. platycarpa's branches was 3-O-

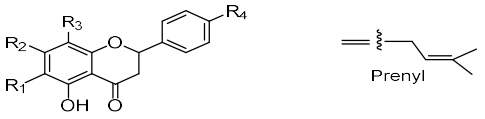
Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2930-2963

Acetyloleanolic acid. Furthermore, one another new flavanone compound were isolated as well as the identified compounds were isolated from leaves of *Eysenhardtia platycarpa* as shown in **Fig 9**. In the beginning, they discovered that the methanolic extracts of E. platycarpa's leaves and branches considerably lowered the blood glucose level in streptozotocin (STZ)-induced diabetic and healthy rats. After that they were performed the *in-vivo* antidiabetic evaluation of isolated constituents from various parts (Root, Bark, and leaves) of *Eysenhardtia platycarpa.* The major constituent of branches of *Eysenhardtia platycarpa* was 3-*O*-Acetyloleanolic acid showed a significant lowered in blood glucose concentration of the streptozotocin (STZ)-induced diabetic animal (rats)(Narváez-Mastache et al., 2006).



(1''R)-5,4',1''-trihydroxy-6,7 -(3'',3''-dimethylchroman)flavone

3-O-Acetyloleanolic acid



Prenyl

Compound Name	R1	R2	R3	R4
(2S)-4'-O-methyl-6-methyl-8-prenylnaringenin	CH3	OH	Prenyl	OCH3
5,7-dihydroxy-6-methyl-8-prenylflavanone	CH3	OH	Prenyl	H
5,7-dihydroxy-8-methyl-6-prenylflavanone	Prenyl	OH	CH3	H
5,7-dihydroxy-6-prenylflavanone	Prenyl	OH	H	H
5,7-dihydroxy-8-prenylflavanone	H	OH	Prenyl	H
4'-O-methyl-8-prenylnaringenin	H	OH	Prenyl	OCH3
5-hydroxy-7-methoxy-8-prenylflavanone	H	OCH3	Prenyl	H

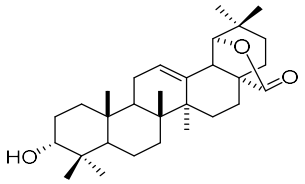
Fig 9. Various isolated phytochemical compounds with their chemical structure from *Eysenhardtia platycarpa* have potential to manage diabetes mellitus(Narváez-Mastache et al., 2006).

Ficus foveolata (Moraceae)

The stems of *Ficus foveolata* was extracted using 80 percent Methanol/H_2O. The crude extract was obtained after the evaporation of solvents from the extract under reduced pressure. The plant extracts were divided into polar and non-polar extracts. HPLC was used to isolate the compounds from DCM fraction, yielding Ficusonolide. The antidiabetic potential of a triterpene lactone is known as ficusonolide produced from F. foveolata was investigated utilising the *in-vitro* antidiabetic model involving L-6 cells as well as an *in-vivo* antidiabetic experiment against non insulin-dependent rats. Ficusonolide enhanced glucose consumption, as seen by the results of glucose uptake in the L-6 cell lines. Streptozotocin-induced hyperglycemia in diabetic rats was significantly reduced when the extract of Ficus foveolata was used. Ficusonolide as shown in **Fig 10**, a new chemical compound derived from ficus foveolata extracts, showed strong inhibitory effect in docking (molecular docking) tests with proteins including protein tyrosine phosphatase 1B, alpha-amylase, dipeptidyl peptidase-IV, alpha-glucosidase exposed to the molecular targeting.

Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2930-2963

With a probable method of interactions with DPP-4, PTP-1B, α-glucosidase, and α-amylase, the plant ficus foveolata and its isolated component ficusonolide exhibit strong antidiabetic effect(Din et al., 2021).



Ficusonolide

Fig 10. Structure of Ficusonolide

Mangifera indica (Anacardiaceae)

Mangifera indica leaves extract has hypoglycemic effects(Aderibigbe et al., 2001). Mangifera indica leaf methanolic extract was tested in vitro for DPPIV inhibitory activity in, and the IC50 value was 182.7 g/mL(Yogisha & Raveesha, 2010). They looked at the anti-diabetic properties of a chemical compound(s) or ingredient extracted from the *Mangifera indica* plant. The compounds were purified using solvent extraction method followed by thin layer (TLC) and column chromatographic methods. Purified substances such as compound 1, 2, 3A, 3B as shown in **Fig. 11,** were identified using 1H-NMR spectroscopy and may have antidiabetic properties. Based on the findings of this examination and the correlation of 1H NMR study, compound 1 has been identified as a semisolid off-white bulk with a preliminary chemical structure of 6-O-galloyl-5'-hydroxy mangiferin. Compound 2 was discovered as a white gum. A comparison of its 1H-NMR data with that of compound 1 revealed that both molecules include a sugar moiety. The structure of compound 2 was tentatively ascribed to mangiferin based on these results and NMR data. Compound 3 was identified as the combination of two molecules, methyl gallate (molecule 3B) and 5-hydroxy mangiferin (molecule 3A), by using 1H-NMR spectroscopy. The researcher found that the blood glucose concentration was lowered when a hexane extract of Mangifera indica kernel was given at different doses (2.5, 5.0, and 10.0 mg/kg). Additionally, alloxan-induced diabetic rats received larger doses of compounds 1, 2, and 3 relative to body weight. These compounds exhibited minor antidiabetic properties as compared to the hexane extract results(Amran et al., 2013).

Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2930-2963

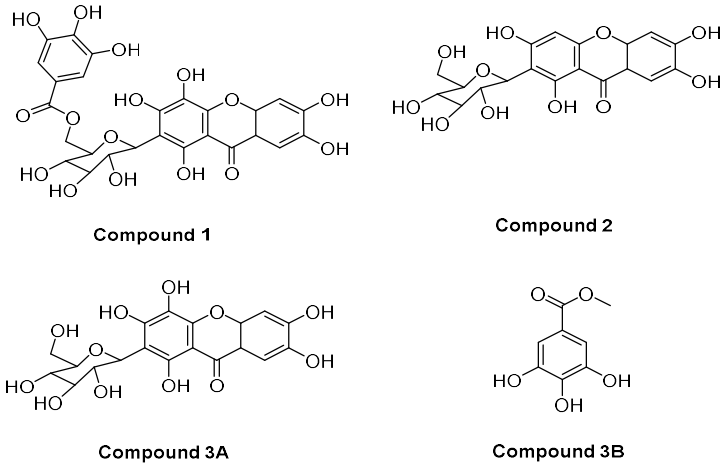


Fig 11. Various phytochemical compounds from *Mangifera indica* (Compound 1 - 6-*O*-galloyl-5'-hydroxy Mangiferin, compound 2 – Mangiferin, compound 3A - 5-hydroxy mangiferin, compound 3B - methyl gallate) have antidiabetic effect(Amran et al., 2013).

Sekar *et al*., (2017) examined and quantified the compound mangiferin concentration in the methanol extracts of ripe and unripe mango fruit using the Reverse Phase HPLC technique. Investigations were also conducted to determine how mangiferin affected the key regulators of serum glucose levels, α-glucosidase and α-amylase. The mangiferin's ability to inhibit enzymes was validated using in vitro α-glucosidase and α-amylase enzymatic assays and in silico docking studies with Autodock program. Mangiferin concentration was lower in unripe methanolic extract than in ripe, according to the conclusion of this research. In addition, mangiferin from M. indica inhibited α-glucosidase more effectively than α-amylase(Sekar et al., 2019). Isolated phytochemical constituents from *Mangifera indica* leaf extracts and tested their bioactivities, such as immunosuppressive antioxidant, α-glucosidase inhibitory effects, and immunosuppressive. Four benzophenone variants, including the new manindicins A and B, were discovered and characterised using ^{1}H and ^{13}C NMR spectroscopy. The amount of cellular ROS produced by H_2O_2-induced HepG2 cells was dramatically reduced by all four novel compounds. According to the spleen cell activation index, manindicins A and B showed good and equal immunosuppressive action, although mangiferin and norathyriol had less action. Norathyriol had the most potent inhibitory impact on α-glucosidase, while it was less potent than acarbose. Conversely, α-glucosidase inhibition was poor by manindicins A and B. Compound 1 - Manindicins A, compound 2 - Manindicins B, compound 3 - mangiferin, and compound 4 - norathyriol were isolated by NMR spectroscopy from Mangifera indica as shown in **Fig 12**(Gu et al., 2019).

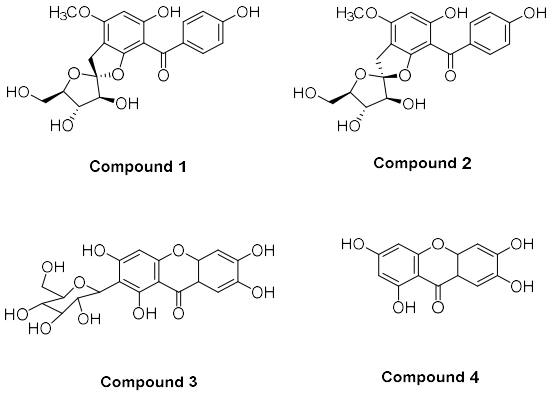


Fig 12. Various isolated phytoconstituents from leaves of *Mangifera indica* have antidiabetic potential(Gu et al., 2019).

Morus Alba (Moraceae)

Utilized branches of the plant *Morus Alba* taken from Yeongcheon, Andong, Republic of Korea. Hot methanol and reflux extraction were used to extract dried branches of Morus Alba. To obtain the methanol extract, the whole extract was concentrated by using rotary evaporator under a reduced pressure. After that, the extract was dissolved in distilled water and fractionated with dichloromethane, n-butanol and ethyl acetate, with the H_2O residue being kept. Additionally, they investigated whether the M. alba branch might inhibit the synthesis of AGEs, protein tyrosine phosphatase 1B (PTP1B), and -glucosidase. They employed column chromatography for identify new molecules, and in the end, they discovered eight novel compounds: one molecule of stilbene (5), one molecule of sterol (4), one molecule of Diels–Alder-type product (7), 4 flavonoids moety (1, 3, 6, and 8), and one molecule of arylbenzofuran (2) as represents in **Fig 13**. Molecules 5–7 and 1–3 were combined blockers of α-glucosidase, with acarbose-like catalytic regions and (Z)-3-bytylidenephthalide-like allosteric sites. Compounds oxyresveratrol (5) and Kuwanon C (1), which are linked to PTP1B allosteric site residues, indicating that they might be used as non-competitive blockers. Kuwanon G (7), a mixed-type inhibitor, either directly engaged the catalytic site or prevented the substrate from attaching to the active site. The inclusion of hydroxyl, resorcinol, and prenyl moieties was crucial in the prevention of diabetes' pathogenic mechanisms, according to the structure–activity relationship, and these findings were further validated by the research of molecular docking.

The prevention and treatment of development of diabetes will be aided by these experimental and computational findings(Kwon et al., 2022).

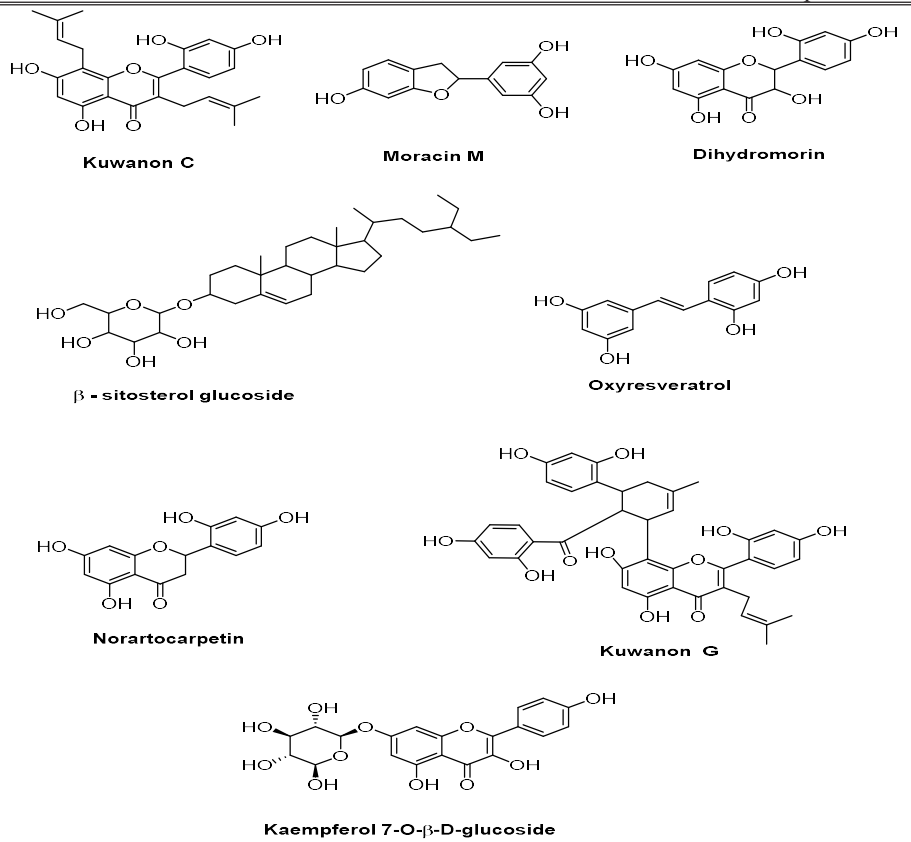


Fig 13. Phytochemical constituents isolated from the branches of *Morus Alba* posses the antidiabetic action(Kwon et al., 2022).

Murraya koenigii (Rutaceae)

Patel *et al*., (2015) employed *Murraya koenigii* leaves were percolated with aqueous ethyl alcohol for 24 hours, the extract was obtained, and the method was performed five times to made a an ethyl alcohol extract. To produce the n-hexane-soluble fraction, the concentrated ethyl alcohol extract was combined with n-hexane or petroleum ether and H2O. To get the ethyl acetate and H2O fractions, the H2O fraction was separated with ethyl acetate. Flash column chromatography was used to divide the main fraction, the ethyl acetate fraction. They used the percolation extraction and multiple liquid - liquid fractionation method to fractionate the aqueous ethyl alcohol extract, yielding five distinct fractions. Using diverse separation or isolation techniques such as thin layer chromatography, column chromatography, and flash chromatography, They extracted the six carbazole alkaloids components from *Murraya koenigii* leaves as shown in **Figure 14**. When tested in a mouse type 2 models, the researchers discovered koenidine (4) to be a metabolic robust antidiabetic drug that significantly reduced postprandial blood glucose concentration and improved insulin sensitivity. Initial *in-vitro* testing of extracted carbazole (1-6) alkaloid compounds on GLUT4 translocation in L6-GLUT4myc myotubes and glucose absorption, followed by an investigations of their action (compounds 2-5) in diabetic animals induced by streptozotocin. The action of compound Koenidine (4) on GLUT4 translocation in L6-GLUT4myc myotubes was communicated by a AKT-Mediated signaling pathway(Patel et al., 2016).

Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2930-2963

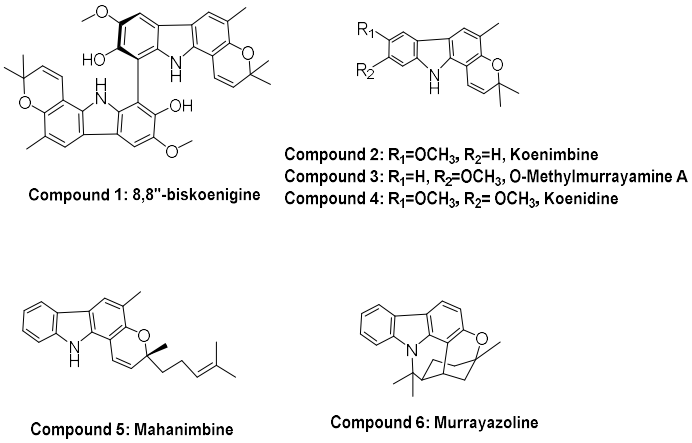


Fig 14. Various isolated phytochemical compounds from the branches of *Murraya koenigii* have potential to manage the diabetes mellitus(Patel et al., 2016)

Neuropeltis racemosa (Convolvulaceae)

They used the stem of *Neuropeltis racemosa* and extracted it. The plant components were washed and dried after being washed. Three times, the dried materials were macerated in n-hexane for 72 hours each time. The marc was separated from the filtrated. The marc was macerated again with ethyl acetate, ethanol, and filtrated water, following the same technique. Reduced pressure was used to evaporate each filtrated solvent. Until they were used, all extracts were maintained at a low temperature. To achieve 16 fractions, the ethanol crude extract was processed with a silica flash column chromatography using a gradient of n-hexane to ethyl alcohol (A1–A16) due to bioassay guided isolation. Using column chromatography, they were isolated molecule 1 from fractions A7 and A8. Using the silica column, the fractions A8 and A9 produce compound 2. Compounds 3 were recovered from fractions A13, A14, and compound 4, 5 were isolated from the A10 fraction , by utilizing silica column chromatography. Syringic acid, scopoletin, N-trans-feruloyltyramine, methyl 3-methyl-2-butenoate, and N-trans-coumaroyltyramine were found using spectroscopic techniques as a result of the bioassay-guided isolation as represents in **Figure 15**. The IC50 of compounds 1, 4, and 5 was 110.97, 29.87, and 0.92 g/mL, respectively, while the standard drug, acarbose, had an IC50 of 272.72 g/mL. Compound 1 exhibited a mixed-type inhibitory mechanism, while compounds 4 and 5 exhibited a non - competitive inhibition mechanism, according to a kinetic analysis(Sakulkeo et al., 2022).

Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2930-2963

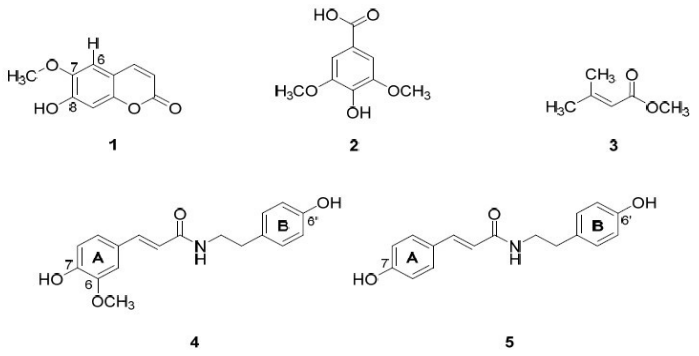
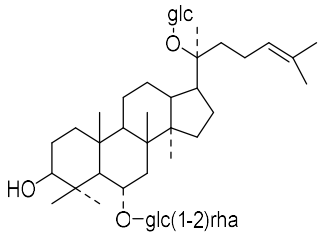


Fig 15. Phytoconstituents isolated from Neuropeltis racemosa having potential to manage the diabetes mellitus(Sakulkeo et al., 2022).

Panax zinsang (Araliaceae)

The roots of Zinseng were given orally and showed antihyperglycemic properties. The root of the *ginseng* plant is beneficial in the treatment of T2DM. In the management of type 2 diabetes, ginseng root is used as an adjuvant(Painter, 2009). In obese diabetic mice, They investigated the antiobese and antidiabetic action of berry extract of *Panax ginseng* as well as their main bioactive components, ginsenoside Re as represents in **figure 16**, and found that the total glucose trip during the two-h intra-peritoneal glucose tolerance or sufferance test lowered by 46% comparison to vehicle-treated mice. Lower serum insulin levels in fed or fasting mice were associated with the better level of blood glucose in the extract-treated ob/ob animals. On treated ob/ob mice, a hyperinsulinemic-euglycemic clamp study found a more than two-fold increase in insulin-stimulated sugar excretion. The extract-treated ob/ob mice also experienced significant weight loss, which was followed by a significant decrease in food intake and a significant rise in energy consumption and core body temperature. In ob/ob mice, treatment with the extract dramatically decreased plasma total cholesterol levels. Further investigation has revealed that ginsenoside Re has a significant anti-diabetic impact(Attele et al., 2002).



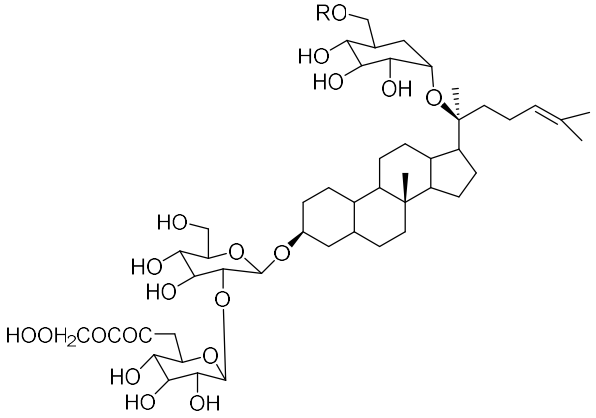
Ginsenoside Re

Fig 16. Structure of Ginsenoside Re (Attele et al., 2002).

Malonyl ginsenosides are naturally occurring ginsenosides that can be detected in both freshly harvested and air dried *ginseng* as shown in **Fig 17,** was utilized by Liu *et al*., (2012). They focus on how effective malonyl ginsenosides is at treating type 2 diabetes. Rats on a high-fat diet and those with diabetes induced by streptozotocin (STZ) administered 50 and 100 mg/kg/d of malonyl

Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2930-2963

ginsenosides or a vehicle for three weeks. Diabetic rats with type 2, having the consequences of malonyl ginsenosides were assessed on fasting blood glucose (FBG), serum insulin (SI), total cholesterol (TC), intraperitoneal glucose tolerance test (IPGTT), body mass, insulin tolerance test (ITT), and triglyceride (TG) levels. After 3 weeks of gentle therapy, administration of malonyl ginsenosides significantly reduced fasting blood glucose levels when compared to the diabetic control group. The findings of the intraperitoneal glucose tolerance test (IPGTT) revealed that both malonyl ginsenosides groups (50 and 100mg/kg) significantly increased sugar (Glucose) removal following a glucose concentration. The insulin tolerance test (IIT) also revealed that sensitivity of insulin improved after 120 minutes of insulin administration. Malonyl ginsenosides also lowered triglyceride and complete cholesterol levels in diabetic animal (rats) while having no effect on body weight. The findings of this study demonstrate that MGR can benefit individuals with type 2 diabetes who also have hyperlipidemia, hyperglycemia, and insulin resistance(Liu et al., 2013).



Compounds	R
Malonyl gensenoside Rb1	-glc
Malonyl gensenoside Rb2	-Ara(p)
Malonyl gensenoside Rc	-Ara(f)
Malonyl gensenosde Rd	-H

Fig 17. Natural malonyl ginsenosides phytochemical compounds isolated from freshly harvested and air dried Panax ginseng have antidiabetic effect (Liu et al., 2013)

Utilizing LC-MS-guided phytoconstituents separation to neutrally remove CO_2 and $C_3H_2O_3$ by negatively modes collision-induced desorption, they recovered 19 malonyl substituted (malonyl ginsenosides) triterpenoid saponins from *Panax ginseng* flower buds as represents in **Fig 18**. There are 15 new malonyl ginsenosides, as well as malonyl floral ginsenosides was characterized from *Panax ginseng*. Compound 11 is extracted by using the Panax genus which is the first di-malonyl saponin, while 2, 3, 4, 9, and 10 were five ginsenosides that have a single malonylation just at C-20 sugars terminal. The anti-diabetic effects of these five non-malonyl (Re, Rb_2, Rc, Rb_1, and Rd) ginsenosides and nine ginsenosides with a malonyl substitution (1, 3, 4, 8, 13, 16, 17, 18, and 19) were assessed using glucose intake and AMPKα2β1γ1 activation in L6 myotubes and in contrast, ginsenosides Rd, Rb2, and Rb1 and, as well as the malonyl ginsenosides 8, 4, 16, 13, 19, and 17, activated the AMPKα2β1γ1. They discovered that ginsenosides 1, 18, and Rb2 enhanced glucose consumption in differentiating L6 myotubes(Qiu et al., 2017).

Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2930-2963

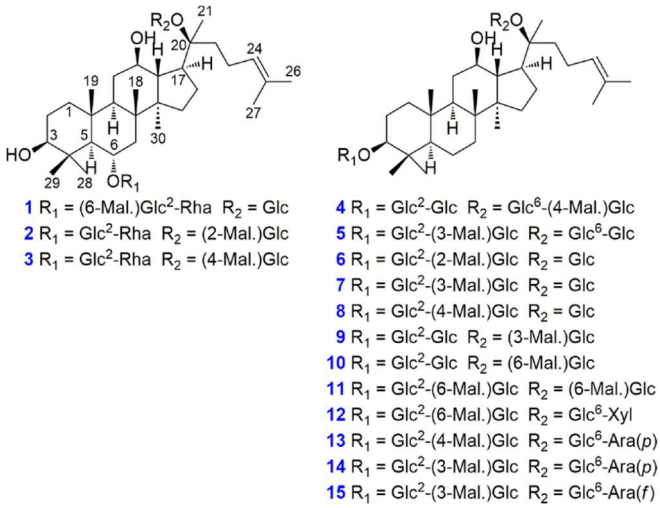


Fig 18. Different isolated malonyl substituted compound from flower buds of *Panax ginseng* (Qiu et al., 2017)

Pterocarpus marsupium (Leguminoceae)

They isolated three phytochemical components from the *Pterocarpus marsupium* heartwood, including Pterostilbene, Pterosupin, and Marsupsin as represents in **Figure 19**. Various spectroscopic techniques, such as ^{1}H- NMR and Mass spectroscopy, were used to identify the structure of these molecules. Glucose levels in rats were examined after being administered intraperitoneally (IP) to marsupsin (1), pterosupin (2), and pterostilbene (3) by the researcher, who utilised streptozotocin to induce hyperglycemia. These are the 3 major phenolic compounds or substances present in the heartwood of the plant *Pterocarpus marsupium*. Both pterostilbene and marsupsin pterostilbene effectively decreased the level of blood (sugar) glucose in diabetic animals(Manickam et al., 1997).

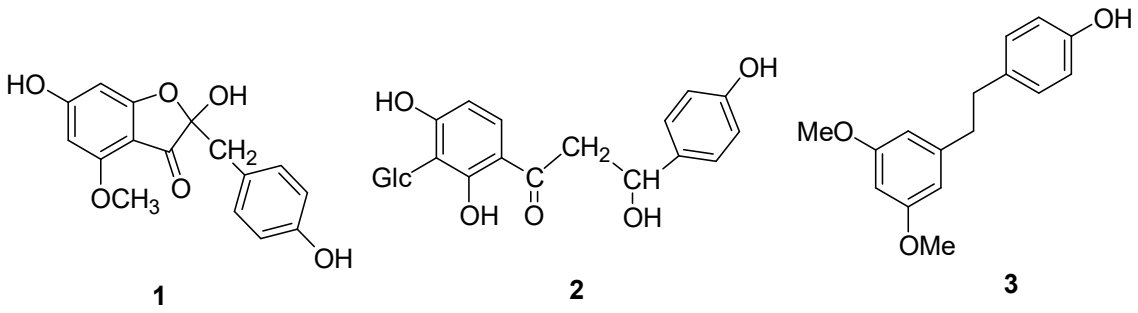


Fig 19. Chemical structure of Marsupuin (1), Pterosupin (2), and Prostilbene (3) phytoconstituents isolated from *Pterocarpus marsupium* have antidiabetic action(Manickam et al., 1997)

Trigonella stellata (Leguminosae)

Eldin *et al.,* (2017) collected the roots and aerial parts of *Trigonella stellata* were gathered by for the extraction and isolation of new chemical compounds using various separation techniques. The

Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2930-2963

plant material was ground into a coarse powder and extracted for 10 days at room temperature with 90% ethanol. To produce dry extract, the alcoholic extract was filtered and concentrated at a lower pressure. The alcoholic extract was fractionated using petroleum ether, dichloromethane, ethyl actetate, and n-BuOH in the order of polarity. The *in-vitro* antihyperlipidemic and antidiabetic effects of an ethanolic extract of plant Trigonella stellata were evaluated using the activation of PPARγ and PPARα in human hepatoma cells (HepG2). Three new isoflavans, (3R,4S)-4,2′,4′-trihydroxy-7-methoxy-4′-O—D-glucopyranosylisoflavan (2), (2S,3R,4R)-4,2′,4′-trihydroxy-7-dimethoxyisoflavan (3), and (3S,4R)-4,2′,4′-trihydroxy-7-methoxy-4′-O—D-glucopyranosylisoflavan (1), were isolated and identified along with the five another known molecules 7,4′-dihydroxyflavone (5), p-hydroxybenzoic acid (4), dihydromelilotoside (6), soyasaponin I (8), and quercetin-3,7-O-α-Ldirhamnoside (7) as shown in **Fig 20**. The chemical structures of compounds (1-3) were identified by using a variety of spectroscopic techniques, such as HRESIMS and NMR spectroscopy. The effects of the separated compounds on PPARα and PPARγ activation in HepG2 cells were investigated(Shams Eldin et al., 2018).

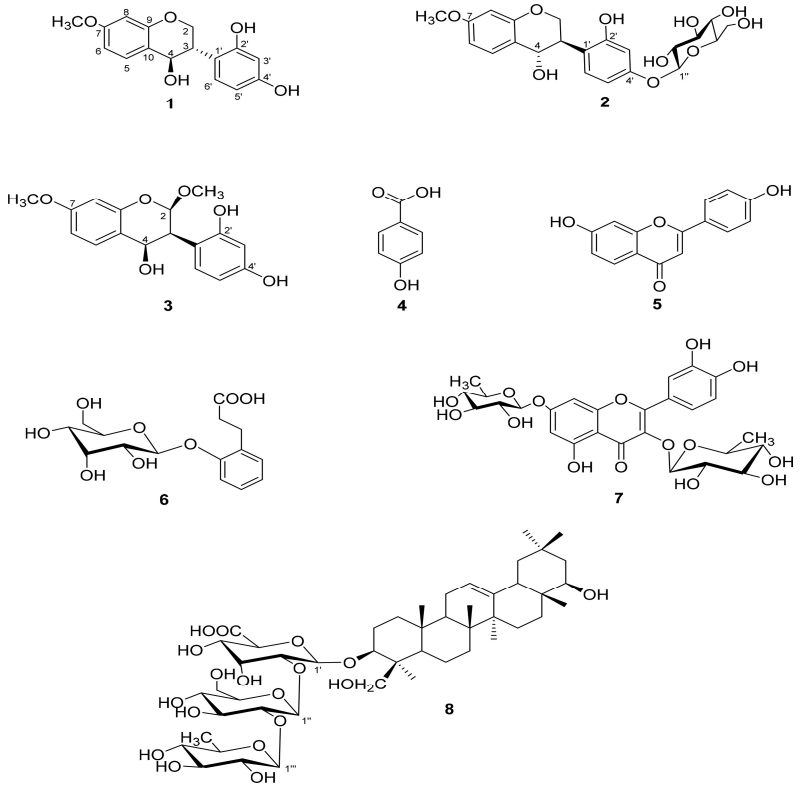


Fig 20. Different structure of compounds that were isolated from *Trigonella stellata* (Shams Eldin et al., 2018)

Table 4: Various medicinal plants of their parts have Antidiabetic activity found in worldwide

S. No.	Biological source	Family	Location	Parts Used	Isolated Constituents	Biological Activity	References
1.		Liliaceae	Europe, North		($C_{30}H_{26}O_{13}$) Kaempferol-3-	Antidiabetic	

	Allium cepa		America, Asia, and Africa	Entire plant	O-β-D-6-(P-coumaroyl) glucopyranoside		(Ikechukwu & Ifeanyi, 2016)
2.	*Amomum tsao ko*	Zingiberaceae	North Vietnam South-west China, and some other parts of Asia	Dried fruits	Hydroxykaempferol 3-β-rutinoside, Procyanidin B1, Nobiletin, Procyanidin B2, 6″-O-Acetylgenistin, Morin, Ephedrannin A, Dihydromyricetin, Taxifolin, Reynoutrin, Quercetin 3-O-sophoroside-7-Orhamnoside, Liquiritigenin,	α-glucosidase inhibitor and α-amylase inhibitor	(X. Zhang et al., 2022)
3.	*Azadirecta indica*	Myrataceae	India, Africa, Pakistan, Sri lanka	Leaves	-	Antidiabetic	(Patil et al., 2013)
4.	*Bacopa monnirei*	Scrophulariaceae	India	Aerial parts	Bacosine	lowered blood glucose level	(Ghosh et al., 2008)
5.	*Benincasa cerifera*	Cucurbitaceae	Southern China, Southeast Asia, Korea, and India	Fruit peel	Vitexin-2”-*O*-Rhamnoside, p-Hydroxybenzoic Acid, Protocatechuic Acid, Gallic acid, Isovanillin, 5-Hydroxymethylf	α-glucosidase inhibitor	(Ryu et al., 2021)

					urfural, Isovitexin, Vitexin, Orientin, Caffeic Acid, Vitexin-4”-*O*-Glucoside		
6.	*Calotropis Procera*	Apocynaceae	Africa, Arabian Peninsula, Western Asia, India, and China	Entire plant	Syriogenin	α-glucosidase inhibitor	(Adinortey et al., 2022)
					Calotoxin	α-glucosidase inhibitor	(Adinortey et al., 2022)
					Taraxasterol	α-glucosidase inhibitor, protein tyrosine phosphate (PTP1B) inhibitor	(Adinortey et al., 2022)
					Isorhamnetin-3-Orobinobioside	α-glucosidase inhibitor	(Adinortey et al., 2022)
7.	*Cinnamon*	Lauraceae	India, Sri lanka, Myanmar, South America, and West Indies	Entire plant	-	Regulation of blood sugar and cholesterol level	(Kim et al., 2006)
				Cinnamon oil	-	Antidiabetic	(Ping et al., 2010)
				Cinnamomum tamala extract and	Procyanidin oligomer	Hypoglycemic	(Chen et al., 2012)

Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2930-2963

				Cinnamomum cassia extract			
8.	*Corni fructus*	Cornaceae	Korea, China, and Japan	Fruits	Quarcetin 3-O-β-D-glucuronide, Cafteric acid monomethyl ester, Oleanolic acid, β-sitosterol, Cornuside, Butyoxysuccinic acid, Quarcetin (-)-Epicatechin 3-O-gallate, Loganin, (7R)-n-butyl morroniside, Caffeic acid, 3-O-β-D-(6'-n-butylglucuronide)	Insulin mimetic effect and Anti-inflammatory effect	(Lin et al., 2011)
9.	*Eysenhardtia platycarpa*	Fabaceae	Maxico	Leaves, Branches, and Bark	(1"*R*)-5,4',1"-trihydroxy- 6,7-(3",3"-dimethylchroman) flavones, oleanolic acid, lupeol, betulinic acid, *β*-sitosteryl *β*-D-glucopyranoside, 3-*O*-methyl-*myo*-inositol, 3-*O*-acetyloleanolic acid, (2*S*)-4'-*O*-	lowered blood glucose concentration of the streptozotocin (STZ)-induced diabetic rats (*In-vivo*)	(Narváez-Mastache et al., 2006)

					methyl-6-methyl-8-prenylnaringenin, 4'-*O*-methyl-8-prenylnaringenin, *β*-sitosterol 5,7-dihydroxy-6-prenylflavanone, 3-*O*-Acetyloleanolic acid, 5,7-dihydroxy-8-methyl-6-prenylflavanone,		
10.	*Ficus foveolata*	Moraceae	Northern parts of Pakistan, China	Entire plant	Ficusonolide	PTP1B (Protein tyrosine phosphatase 1B), α-amylase, DPP-4 (dipeptidyl peptidase-4), α-glucosidase Inhibitor	(Din et al., 2021)
12.	*Mangifera Indica*	Anacardiaceae	India, Myanmar, Bangladesh	Leaves	-	Hypoglycemic effect	(Aderibigbe et al., 2001)
				Leaves	-	DPP-4 Inhibitor	(Yogisha & Raveesha, 2010)
				Entire plant	Mixture of 5-Hydroxy mangiferin and methyl gallate, Mangiferin, 6-	Minor Antidiabetic	

					O-galloyl-5'-hydroxy-mangiferin,		(Amran et al., 2013)
				Fruits	Mangiferin	α-glucosidase inhibitor	(Sekar et al., 2019)
				Leaves	Manindicins A, Manindicins B, Mangiferin, Norathyriol	α-glucosidase inhibitor	(Gu et al., 2019)
13.	*Morus alba*	Moraceae	China, United States, Canada, South America, and South Africa	Branches	Kuwanon C, oxyresveratrol, kuwanon G, Moracin M, Dihydromorin, b-sitosterol glucoside, Norartocarpetin, Kaempferol 7-O-β-D-glucoside	α-glucosidase, Protein tyrosine phosphatase 1B (PTP1B) inhibitor	(Kwon et al., 2022)
14.	*Murraya koenigii*	Rutaceae	Pakistan, Sri lanka, India, China, and Hainan	Leaves	8,8"-biskoenigine, Koenimbine, O-Methylmurrayamine A, Koenidine	Decrease postprandial blood sugar levels as well as an enhancement in insulin sensitivity	(Patel et al., 2016)
15.	*Neuropeltis racemosa*	Convolvulaceae	China, Malesia	Stem	Syringic acid, Scopoletin, N-trans-feruloyltyramine, N-trans-coumaroyltyramine and methyl 3-methyl-2-butenoate	Mixed-type and non-competitive inhibition	(Sakulkeo et al., 2022)
16.	*Panax ginseng*	Araliaceae	China, Russia,	Root	-	Antihyperglycemic	(Painter, 2009)

Catalyst Research Volume 23, Issue 2, October 2023 Pp. 2930-2963

			and Korea	Berry	Gensenoside Re	Antidiabetic	(Attele et al., 2002)
				Air dried ginseng	Malonyl ginsenosides (MGR)	Decrease fasting blood glucose level	(Liu et al., 2013)
				Flower buds	Malonyl substituted (malonyl ginsenosides) triterpenoid saponins	Activated AMPKα2β1γ1	(Qiu et al., 2017)
17.	*Pterocarpus marsupium*	Leguminosae	Various state of India	Heartwood	Marsupsin, Pterosupin, and Pterostilbene	significantly reduced diabetic rats' blood glucose levels	(Manickam et al., 1997)
18.	*Trigonella stellata*	Leguminosae	Europe, Africa, Asia	Aerial Parts	(3S,4R)-4,2′,4′-trihydroxy-7-methoxy-4′-O—D-glucopyranosylisoflavan, and (2S,3R,4R)-4,2′,4′-trihydroxy-7-dimethoxyisoflavan	PPARα and PPARγ activation	(Shams Eldin et al., 2018)

CONCLUSION

In conclusion, Several plants with various mechanisms of action and phytoconstituents are recognised to have anti-diabetic properties. An effort is being made to organise the phytoconstituents of a certain family with a particular mode of action to lower plasma glucose. Given the studies on their potential effectiveness against diabetes, it is expected that botanicals have a significant role to play in managing the disease. It would appear very appealing to treat diabetes mellitus with chemicals derived from plants that are available and do not require complicated pharmaceutical production. In order to discover based on evidence complementary

and alternative therapies to treat various types of diabetes in humans and animals, medical professionals, researchers, and scientists who work in the disciplines of pharmacology and therapeutics might discover the compilation of noted hypoglycemic trees from India as well as abroad beneficial. The improvement of the hypoglycemic impact can be significantly aided by the separation and recognition of the active ingredients from these plants, as well as the production of standardised doses and dosing guidelines. The preventive diabetology is ready to follow in the footsteps of traditional knowledge since it is equipped with an abundance of phytoconstituents and a stunning variety of genetic evidence. It is clear that due to their enzyme inhibitory capabilities, phytochemical components from herbal plants slow down the metabolism of glucose and may therefore be employed as a potential hypoglycemic medication. The results of numerous research indicate that a variety of natural extracts and bioactive component might exhibit positive outcomes in diabetes mellitus, raising the possibility of an entirely novel category of anti-diabetic medications. To understand the precise processes of the bioactive substances and extracts of herbs for their antidiabetic activity and to identify the bioactive constituents liable for these effects, an extensive biochemical and pharmacological study is needed. Additionally, these medications are all natural and quite affordable, which may make them accessible to the general public. Further research is needed to produce the medications and nutraceuticals from natural resources that are required for the effective management of diabetes mellitus.

FUNDING

Nil.

CONFLICT OF INTEREST

Authors have declared for ‘none conflict of interest’.

REFERENCES

1. Aderibigbe, A. O., Emudianughe, T. S., & Lawal, B. A. S. (2001). Evaluation of the antidiabetic action of Mangifera indica in mice. *Phytotherapy Research*, *15*(5), 456–458.
2. Adinortey, C., Kwarko, G., Koranteng, R., Boison, D., Obuaba, I., Wilson, M., & Kwofie, S. (2022). Molecular Structure-Based Screening of the Constituents of Calotropis procera Identifies Potential Inhibitors of Diabetes Mellitus Target Alpha Glucosidase. *Current Issue in Molecular Biology*, *44*(2), 963–987.
3. Amran, M., Sultan, M., Rahman, A., & Rashid, M. (2013). Antidiabetic activity of compounds isolated from the kernel of Mangifera indica in alloxan induced diabetic rats. *Dhaka University Journal of Pharmaceutical Science*, *12*(1), 77–81.
4. Attele, A. S., Zhou, Y.-P., Xie, J.-T., Wu, J. A., Zhang, L., Dey, L., Pugh, W., Rue, P. A., Polonsky, K. S., & Yuan, C.-S. (2002). Antidiabetic Effects of Panax ginseng Berry Extract and the Identification of an Effective Component. *Am Diabetes Assoc*, *51*, 1851–1858.
5. Baynest, H. W. (2015). Classification, Pathophysiology, Diagnosis and Management of Diabetes Mellitus. *Journal of Diabetes & Metabolism*, *06*(05).
6. Bermúdez-Pirela, V. J., Cano, C., Medina, M. T., Souki, A., Lemus, M. A., Leal, E. M., Seyfi, H. A., Cano, R., Ciscek, A., Bermúdez-Arias, F., Contreras, F., Israili, Z. H., Hernández-Hernández, R., & Valasco, M. (2007). Metformin plus low-dose glimeperide significantly

improves homeostasis model assessment for insulin resistance (HOMAIR) and β-cell function (HOMAβ-cell) without hyperinsulinemia in patients with type 2 diabetes mellitus. *American Journal of Therapeutics*, *14*(2), 194–202.
7. Chen, L., Sun, P., Wang, T., Chen, K., Jia, Q., Wang, H., & Li, Y. (2012). Diverse mechanisms of antidiabetic effects of the different procyanidin oligomer types of two different cinnamon species on db/db mice. *Journal of Agricultural and Food Chemistry*, *60*(36), 9144–9150.
8. Din, A. U., Khan, M., Shah, M. Z., Rauf, A., Rashid, U., Khalil, A. A., Zaman, K., Al-Awthan, Y. S., Al-Duais, M. A., Bahattab, O., Mujawah, A. A. H., & Muhammad, N. (2021). Antidiabetic Activity of Ficusonolide, a Triterpene Lactone from Ficus foveolata (Wall. ex Miq.): In Vitro, in Vivo, and in Silico Approaches. *ACS Omega*, *6*(41), 27351–27357.
9. Eleftheriou, P., Geronikaki, A., & Petrou, A. (2019). PTP1b inhibition, a promising approach for the treatment of diabetes type II. *Current Topics in Medicinal Chemistry*, *19*(18), 246–263.
10. Frkic, R., Richter, K., & Bruning, J. (2021). The therapeutic potential of inhibiting PPARγ phosphorylation to treat type 2 diabetes. *Journal of Biological Chemistry*, *297*(3), 1–9.
11. Gallwitz, B. (2019). Clinical use of DPP-4 inhibitors. *Frontiers in Endocrinology*, *10*(JUN), 389.
12. Ghosh, T., Kumar Maity, T., Sengupta, P., Dash, D. K., & Bose, A. (2008). *Antidiabetic and in vivo antioxidant activity of ethanolic extract of Bacopa monnieri Linn. aerial parts: a possible mechanism of action*.
13. Ghosh, T., Maity, T. K., & Singh, J. (2011). Antihyperglycemic activity of bacosine, a triterpene from bacopa monnieri, in alloxan-induced diabetic rats. *Planta Medica*, *77*(8), 804–808.
14. Gu, C., Yang, M., Zhou, Z., Khan, A., Cao, J., & Cheng, G. (2019). Purification and characterization of four benzophenone derivatives from Mangifera indica L. leaves and their antioxidant, immunosuppressive and α-glucosidase. *Journal of Functional Food*, *52*, 709–714.
15. Guo, L., & Tabrizchi, R. (2006). Peroxisome proliferator-activated receptor gamma as a drug target in the pathogenesis of insulin resistance. *Pharmacology and Therapeutics*, *111*(1), 145–173.
16. He, X., Chen, J., Huang, X., Hu, J., Zhang, X., Guo, Y., Zhang, X., & Geng, C. (2021). The antidiabetic potency of Amomum tsao-ko and its active flavanols, as PTP1B selective and α-glucosidase dual inhibitors. *Industrial Crops and Products*, *160*, 1–11.
17. Idris, I., & Donnelly, R. (2009). Sodium-glucose co-transporter-2 inhibitors: An emerging new class of oral antidiabetic drug. *Diabetes, Obesity and Metabolism*, *11*(2), 79–88.
18. Ikechukwu, O., & Ifeanyi, O. (2016). The antidiabetic effects of the bioactive flavonoid (kaempferol-3-O-β-D-6 {P-Coumaroyl} glucopyranoside) isolated from Allium cepa. *Recent Patents on Anti-Infective Drug Discovery*, *11*(9), 44–52.
19. Khosla, P., Bhanwra, S., Singh, J., Seth, S., & Srivastava, R. (2000). A study of hypoglycaemic effects of Azadirachta indica (Neem) in normal and alloxan diabetic rabbits.

Indian Journal of Physiology and Pharmacology, *44*(1), 69–74.

20. Kim, S., Hyun, S., & Choung, S. (2006). Anti-diabetic effect of cinnamon extract on blood glucose in db/db mice. *Journal of Ethnopharmacology*, *104*(1–2), 119–123.
21. Kwon, R., Thaku, N., Timalsina, B., Park, S., Choi, J., & Jung, H. (2022). Inhibition Mechanism of Components Isolated from Morus alba Branches on Diabetes and Diabetic Complications via Experimental and Molecular Docking Analyses. *Antioxidants*, *11*(2), 383.
22. Lin, M. H., Liu, H. K., Huang, W. J., Huang, C. C., Wu, T. H., & Hsu, F. L. (2011). Evaluation of the potential hypoglycemic and beta-cell protective constituents isolated from corni fructus to tackle insulin-dependent diabetes mellitus. *Journal of Agricultural and Food Chemistry*, *59*(14), 7743–7751.
23. Liu, Z., Li, W., Li, X., Zhang, M., Chen, L., Zheng, Y., Sun, G., & Ruan, C. (2013). Antidiabetic effects of malonyl ginsenosides from Panax ginseng on type 2 diabetic rats induced by high-fat diet and streptozotocin. *Journal of Ethnopharmacology*, *145*(1), 233–240.
24. Malathi, V., Sathana, S., And, D., & Revathi, K. (2010). Anti diabetic activity by the in vitro alpha amylase and alpha-glucosidase inhibitory activity of Catharanthus roseus. *Save Nature to Survive*, *5*(4), 655–659.
25. Manickam, M., Ramanathan, M., Farboodniay Jahromi, M. A., Chansouria, J. P. N., & Ray, A. B. (1997). Antihyperglycemic activity of phenolics from Pterocarpus marsupium. *Journal of Natural Products*, *60*(6), 609–610.
26. Narváez-Mastache, J. M., Luisa Garduño-Ramírez, M., Alvarez, L., & Delgado, G. (2006). Antihyperglycemic Activity and Chemical Constituents of Eysenhardtia platycarpa. *ACS Publications*, *69*(12), 1687–1691.
27. Painter, F. M. (2009). Panax ginseng Monograph. *Alternative Medicine Review*, *14*(2), 172–176.
28. Panday V.N., Rajagopalan S.S., C. D. P. (1995). *An effective ayurvedic hypoglycemic formulation*. J. Res. Ayurveda Siddha.
29. Patel, O. P. S., Mishra, A., Maurya, R., Saini, D., Pandey, J., Taneja, I., Raju, K. S. R., Kanojiya, S., Shukla, S. K., Srivastava, M. N., Wahajuddin, M., Tamrakar, A. K., Srivastava, A. K., & Yadav, P. P. (2016). Naturally Occurring Carbazole Alkaloids from Murraya koenigii as Potential Antidiabetic Agents. *Journal of Natural Products*, *79*(5), 1276–1284.
30. Patil, P., Patil, S., Mane, A., & Verma, S. (2013). Antidiabetic activity of alcoholic extract of neem (Azadirachta indica) root bark. *National Journal of Physiology, Pharmacy and Pharmacology*, *3*(2), 142–146.
31. Perez-Gutierrez, R., & Damian-Guzman, M. (2012). Meliacinolin: a potent α-glucosidase and α-amylase inhibitor isolated from Azadirachta indica leaves and in vivo antidiabetic property in streptozotocin-nicotinamide. *Biological and Pharmaceutical Bulletin*, *35*(9), 1516–1524.
32. Ping, H., Zhang, G., & Ren, G. (2010). Antidiabetic effects of cinnamon oil in diabetic KK-Ay mice. *Food and Chemical Toxicology*, *48*(8–9), 2344–2349.
33. Qiu, S., Yang, W. Z., Yao, C. L., Shi, X. J., Li, J. Y., Lou, Y., Duan, Y. N., Wu, W. Y., & Guo, D. A. (2017). Malonylginsenosides with Potential Antidiabetic Activities from the

Flower Buds of Panax ginseng. *Journal of Natural Products*, *80*(4), 899–908.
34. Ryu, H., Lee, S., & Whang, W. (2021). Isolation of Anti-Diabetic Active Compounds from Benincasae Exocarpium and Development of Simultaneous Analysis by HPLC-PDA. *Molecules*, *27*(1), 9.
35. Sakulkeo, O., Wattanapiromsakul, C., Pitakbut, T., & Dej-adisai, S. (2022). Alpha-Glucosidase Inhibition and Molecular Docking of Isolated Compounds from Traditional Thai Medicinal Plant, Neuropeltis racemosa Wall. *Molecules*, *27*(3), 639.
36. Satyanarayana, K., Sravanthi, K., Shaker, I., & Ponnulakshmi, R. (2015). Molecular approach to identify antidiabetic potential of Azadirachta indica. *Journal of Ayurveda*, *6*(3), 165–174.
37. Sekar, V., Chakraborty, S., Mani, S., Sali, V., & Vasanthi, H. (2019). Mangiferin from Mangifera indica fruits reduces post-prandial glucose level by inhibiting α-glucosidase and α-amylase activity. *South African Journal of Botany*, *120*, 129–134.
38. Shams Eldin, S. M., Radwan, M. M., Wanas, A. S., Habib, A. A. M., Kassem, F. F., Hammoda, H. M., Khan, S. I., Klein, M. L., Elokely, K. M., & Elsohly, M. A. (2018). Bioactivity-Guided Isolation of Potential Antidiabetic and Antihyperlipidemic Compounds from Trigonella stellata. *Journal of Natural Products*, *81*(5), 1154–1161.
39. Tamrakar, A. K., Maurya, C. K., & Rai, A. K. (2014). PTP1B inhibitors for type 2 diabetes treatment: A patent review (2011-2014). *Expert Opinion on Therapeutic Patents*, *24*(10), 1101–1115.
40. Tolmie, M., Bester, M. J., & Apostolides, Z. (2021). Inhibition of α-glucosidase and α-amylase by herbal compounds for the treatment of type 2 diabetes: A validation of in silico reverse docking with in vitro enzyme assays. *Journal of Diabetes*, *13*(10), 779–791.
41. Vu, N. K., Kim, C. S., Ha, M. T., Ngo, Q. M. T., Park, S. E., Kwon, H., Lee, D., Choi, J. S., Kim, J. A., & Min, B. S. (2020). Antioxidant and Antidiabetic Activities of Flavonoid Derivatives from the Outer Skins of Allium cepa L. *Journal of Agricultural and Food Chemistry*, *68*(33), 8797–8811.
42. Yogisha, S., & Raveesha, K. (2010). Dipeptidyl Peptidase IV inhibitory activity of Mangifera indica. *Journal of Natural Products*, *3*, 76–79.
43. Zhang, T., Tong, X., Zhang, S., Wang, D., Wang, L., Wang, Q., & Fan, H. (2021). The Roles of Dipeptidyl Peptidase 4 (DPP4) and DPP4 Inhibitors in Different Lung Diseases: New Evidence. *Frontiers in Pharmacology*, *12*.
44. Zhang, X., Tang, Y., Guan, X., Lu, X., Li, J., Chen, X., Deng, J., & Fan, J. (2022). Flavonoid constituents of Amomum tsao-ko Crevost et Lemarie and their antioxidant and antidiabetic effects in diabetic rats–in vitro and in vivo studies. *Food and Function*, *13*, 437–450.