Glycosides: An Effect in the Treatment of Diabetes Mellitus

Mr. Josef Yakin
Faculty of Pharmaceutical Science,
Assam down town University, Panikhaiti,
Guwahati, 781026, Assam- India

Mr. Abdul Hadi Umam
Department of Pharmaceutics,
Rahman Institute of Pharmaceutical Sciences and Research,
Tepesia, Sonapur, 782402, Assam- India.

Mr. Kangkan Jyoti Saud
Arunachal University of Studies,
MH-52, Knowledge City, Namsai, 792103, Arunachal Pradesh- India.

Dr. Faruk Alam
Faculty of Pharmaceutical Science,
Assam down town University, Panikhaiti,
Guwahati, 781026, Assam- India

ABSTRACT

Diabetes is a medical condition that is among the leading causes of mortality in both industrialised and developing nations. For the treatment of diabetes, a great number of synthetic medicines are now being used. However, these medications have a wide range of negative side effects. In light of this, there is an urgent need for the development of novel medicines that have the potential to be helpful in improve diabetes control. Since the beginning of time, herbal medicines have been widely acknowledged for their medicinal potential in treating a variety of diseases and illnesses. Natural remedies that are derived from medicinal plants have the potential to be among the most effective treatments for a variety of ailments, including diabetes. Different secondary metabolites, such as terpenoids, saponins, tannins, flavonoids, anthraquinones, alkaloids, and glycosides, are produced by plants via the process of synthesis. Through the formation of a glycosidic bond, glycosides are composed of a sugar (glycone) moiety that is connected to a non-sugar moiety (aglycone). Numerous plant species produce glycosides, which may be digested by enzymes to produce glycone and aglycone. This process is known as glycolysis. Numerous glycosides and aglycones have been discovered to possess a wide range of biological actions according to their composition. It has been found that glycosides such as rutin, puerarin, gymnemic acid I, and stevioside have strong anti-diabetic efficacy. Numerous aglycones, including securigenin, strictinin, and christinin-A, have been documented for their ability to inhibit the development of diabetes. The antidiabetic effect of these substances is characterised by the stimulation of insulin secretion, as well as the inhibition of enzymes involved in glycemic regulation, including α-amylase, α-glucosidase, and tyrosine phosphatase 1B. The main topic of discussion in this chapter of the book is the impact that a variety of glycosides and aglycones generated from plants have on diabetes.

Keywords: Diabetes Mellitus, Glycosides, Natural Remedies, Antidiabetic Properties, Blood Sugar Levels.

1. INTRODUCTION

1.1 Overview of Diabetes Mellitus

The term "diabetes mellitus" (DM) encompasses a range of metabolic disorders characterized by elevated blood sugar levels. Diabetes can stem from irregularities in insulin production, action, or both, leading to altered carbohydrate, fat, and protein metabolism. Its ramifications extend to increased susceptibility to cardiovascular, cerebrovascular, and nonalcoholic fatty liver diseases, among others. Notably, individuals with diabetes face a heightened risk of infectious diseases like tuberculosis. Diagnostic symptoms include excessive thirst, increased hunger, polyuria, and weight loss, with severe cases potentially leading to ketoacidosis, a life-threatening condition. The classification of diabetes, as delineated by the World Health Organization (WHO), spans various types, including Type 1, Type 2, hybrid forms, specific types, and unclassified variants [30].

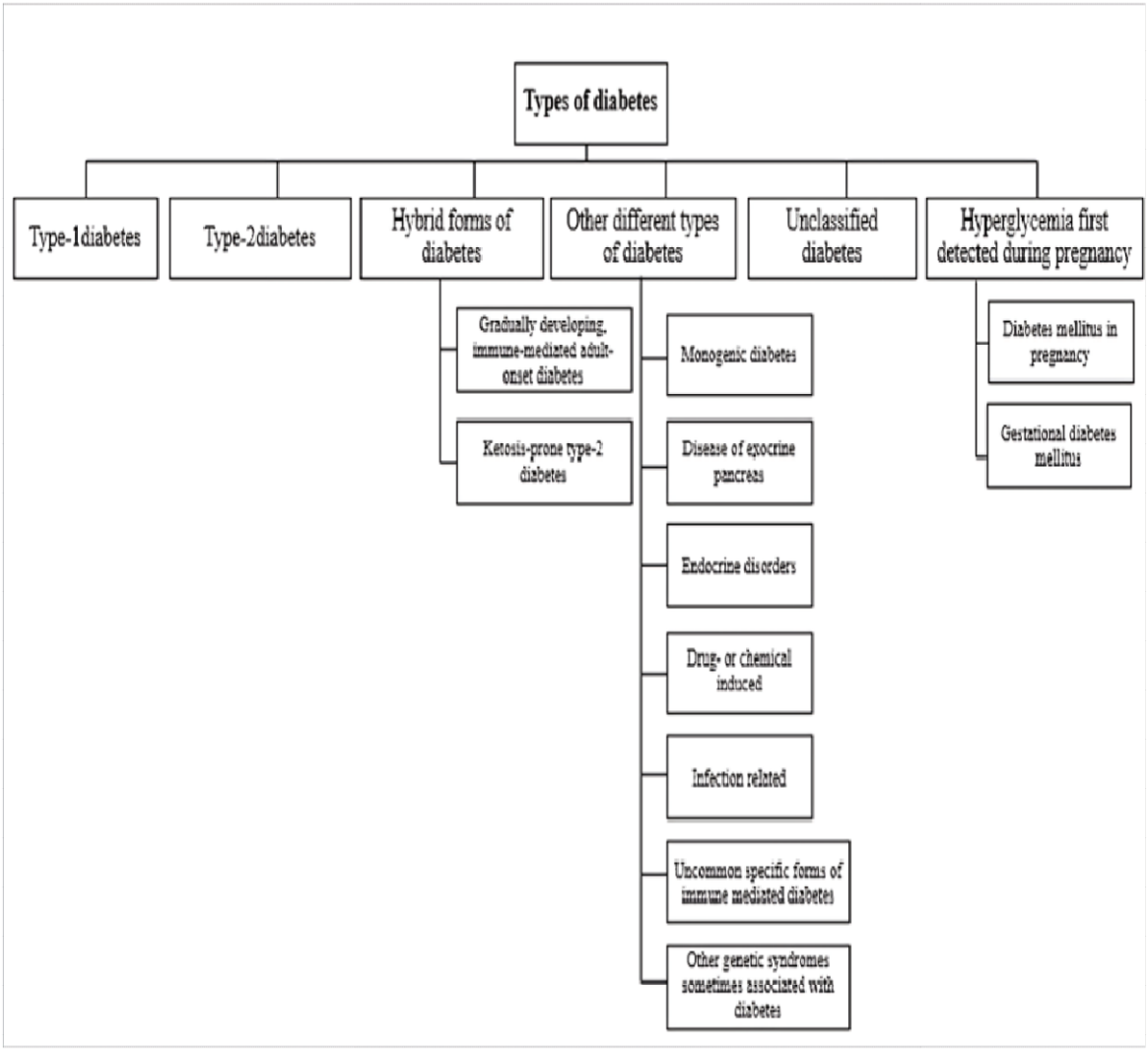

Figure 1. Classification of diabetes mellitus

1.2 Pathophysiological Underpinnings

At the core of all diabetes types lies the dysfunction or demise of pancreatic β-cells, a hallmark feature. Contributing factors encompass genetic predispositions, epigenetics, autoimmunity, insulin resistance, inflammation, and environmental influences [23,28].

1.3 Global Burden and Epidemiology

Diabetes represents one of the most rapidly escalating health concerns worldwide in the twenty-first century, affecting diverse demographics across the globe, including less developed regions. Statistics from the International Diabetes Federation (IDF) project a continuous rise in diabetes prevalence, with estimations reaching 700 million affected individuals by 2045. Besides individual health impacts, diabetes exerts substantial socioeconomic repercussions and influences national productivity and economies [11,17].

1.4 Plant-Derived Therapies in Diabetes Management

Since ancient times, plants have served as therapeutic agents for various ailments, including diabetes. Plant secondary metabolites, encompassing a diverse array of compounds like terpenoids, alkaloids, flavonoids, and glycosides, exhibit significant physiological effects [12].

1.5 Glycosides: Structures and Functions

Glycosides, among the pivotal secondary metabolites in plants, undergo post-synthetic modifications catalyzed by enzymes like glycosyltransferases. These compounds play essential roles in plant growth, signaling, defense mechanisms, and response to stressors [5]. Glycosides are composed of a glycone (R1C) and an aglycone (R2C) component, both of which are chemically and functionally distinct components that are connected to one another by a glycosidic bond (Fig. 2).

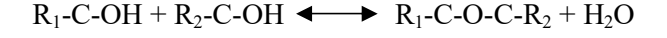

Figure. 2 Formation of glycosidic linkage between glycone (R1C) and aglycone (R2C)

1.6 Classification and Characteristics of Glycosides

Glycosides, characterized by glycone and aglycone components linked via glycosidic bonds, exhibit diverse structural and functional properties. Their categorization includes O-glycosides, C-glycosides, S-glycosides, and N-glycosides, each with distinct biochemical features and occurrences in nature [2, 4].

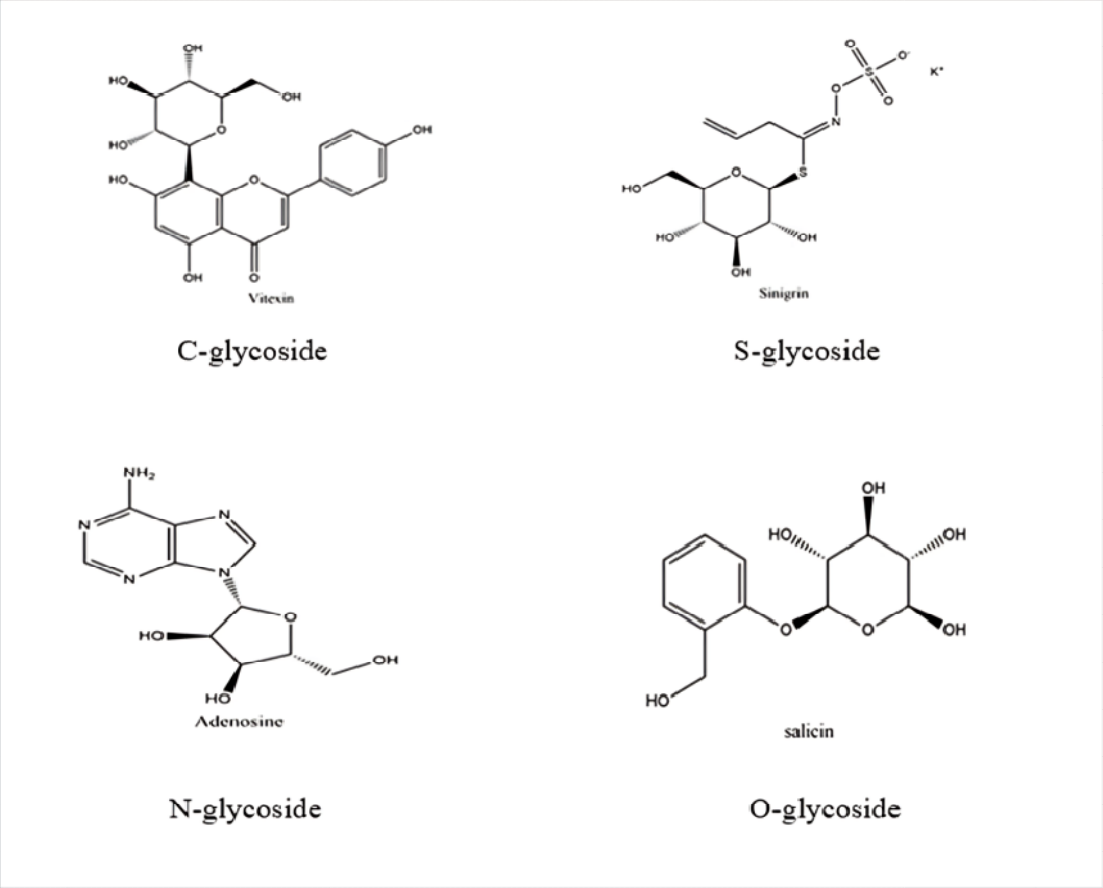

Figure. 3 Types of glycosides depending on the type of glycosidic linkage

2. GLYCOSIDES IN DIABETES

There is evidence in the scientific literature that a number of glycosides and aglycones have shown considerable efficacy in the treatment of diabetes. These plant glycosides exert their effects via a variety of methods [21].

2.1 Rutin

The compound known as rutin (2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2S,3R,4S,5S, 6R)-3,4,5-trihy-droxy-6-[[(2R,3R,4R,5R,6S)1842 was the year when the compound known as -3,4,5-trihydroxy-6-methyloxan-2-yl] oxymethyl] oxan2-yl] oxychromen-4-one) was discovered. As seen in Figure 4, rutin, also known as quercetin-3-O-rutinoside, is a flavonol glycoside. Also known as vitamin P, rutoside, sophorin, and quercetin-3-rutinoside, it is also known by these other names. Rutin is a chemical compound that is composed of flavonol aglycone, also known as quercetin, and disaccharide, also known as rutinose. There are a number of plants that contain it, including Fagopyrum esculentum, Vitis vinifera, Amaranthus cruentus, Guiera senegalensis, Capparis spinosa, Allium cepa, Asparagus officinalis, Malus pumila, and Ruta graveolens [8]. It was the plant Ruta graveolens that gave rise to the term "rutin." Buckwheat and grapes have been shown to have the greatest quantities of rutin, according to these studies. A significant amount of rutin may be found in many plant components, including roots, leaves, flowers, and fruit skins. This substance has a wide range of beneficial properties, including antioxidant, anti-inflammatory, anti-cancer, neuroprotective, and cardioprotective properties [9].

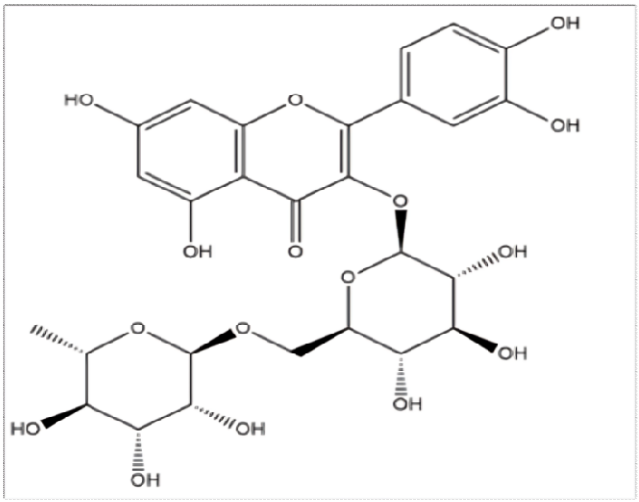

Figure . 4 Chemical structure of Rutin

A significant amount of rutin may be found in buckwheat. Flavonoids, carbohydrates, glycosides, and chemical compounds are all abundant in this crop, which is edible and contains a lot of them. Countries such as Europe, China, North America, Japan, and Korea are among those that have a significant presence of this species in their temperate regions. Due to the high nutritious content of buckwheat, it has been extensively documented for its therapeutic properties in the treatment of a variety of ailments, including diabetes and cardiovascular disease. According to Figure 5, the anti-diabetic properties of buckwheat may be attributed to the presence of rutin. Buckwheat has a rutin concentration that ranges from around 0.8 to 1.7%. Buckwheat is now the subject of research by many experts due to its potential anti-diabetic and other nutraceutical properties [26].

Buckwheat stems, leaves, and flowers were used to extract rutin from the plant that was used. For the extraction, a solution consisting of sixty percent ethanol and five percent ammonia in water was used. By using capillary electrophoresis, the amount of rutin that was present in the extract was determined. A running buffer consisting of 50 mM borate with a pH of 9.3- and 100-mM sodium dodecyl sulphate was used in order to carry out capillary electrophoresis treatment. A measurement of absorbance was taken at 380 nm. Rutin was discovered to have a concentration ranging from 19–168 parts per million in flour fractions and from 131–476 parts per million in bran fractions. Rutin was found to be present in several regions of the plant at varying amounts, with the leaves containing around 300 parts per million (ppm), the stems containing 1000 ppm, and the blooms containing 46,000 ppm. According to the findings of the research, buckwheat acts as a significant source of rutin in terms of nutrition [22].

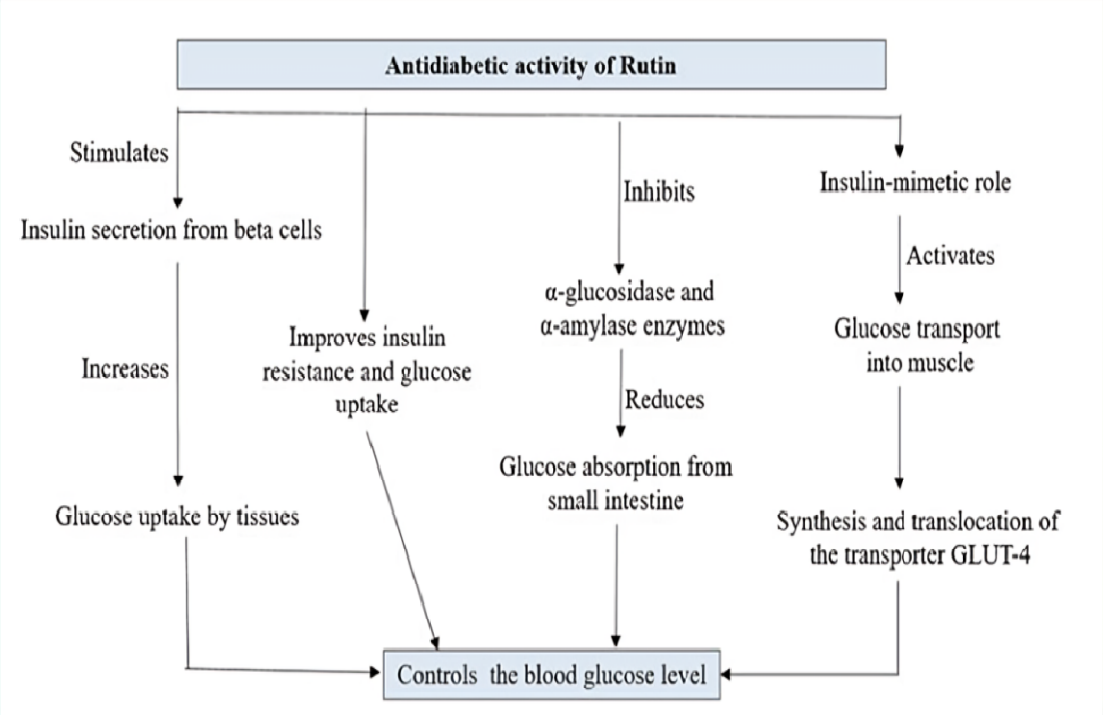

Figure. 5 Mechanism of antidiabetic activity of Rutin

Research conducted by Kamalakkannan and his colleagues has also investigated the antihyperglycemic action of rutin in diabetic rats that were induced with streptozotocin (STZ). The diabetic mice were given rutin orally at a dose of 100 mg/kg for a period of forty-five days. Based on the findings of the research, the treatment of rutin resulted in an improvement in the antioxidant status, an increase in insulin levels, and a reduction in high plasma glucose levels in diabetic rats as compared to the conventional control group. In addition, the antioxidant activity of rutin has been shown to protect the liver, kidneys, and brain [20].

The abnormalities that occur in glucose metabolism are one of the most prevalent problems that are associated with diabetes. The antihyperglycemic action of rutin was investigated in male Wistar rats that had been stimulated with STZ to develop diabetes. The rats were given rutin at a dose of 50 mg/kg intraperitoneally for a period of forty-five days. Based on the findings of the research, rutin was able to reduce both the blood glucose levels and the lipid profile of diabetic rats. In addition, rutin has been shown to lower increased levels of glycogen and triacylglycerol in the tissue of the liver and the heart. The findings of the research demonstrated that the injection of rutin might influence the activities of the liver for the purpose of regulating hyperglycemia [7].

It has been shown that rutin has the capability to increase the phosphorylation of insulin-dependent receptor kinase as well as glucose transporter type 4 (GLUT4). An investigation into the mechanism by which rutin reduces hyperglycemia was carried out using insulin-dependent receptor kinase activity. The mechanism of rutin's anti-diabetic effect was investigated in mouse muscle myoblast cells and insulin-resistant mice, respectively, in both in vitro and in vivo settings. A process known as insulin receptor kinase auto-phosphorylation was initiated in differentiated mouse muscle myoblast cells by the administration of insulin. Mouse muscle myoblast cells (C2C12) and mouse muscle myoblast cells (L6) were subjected

to an incubation period of 90 minutes with rutin at a concentration of 100 μM. Western blot, insulin receptor test, glucose uptake capacity, GLUT4 translocation assay, and glucose uptake assay were the methods that were used to examine these cells. The phosphorylation of the insulin receptor kinase was also further enhanced by the presence of rutin. The inhibition of insulin-dependent translocation of GLUT4 was decreased when cells were co-treated with rutin to minimise the inhibition. Rutin was administered orally to C57BL/6 mice at a dose of 25 mg/kg for a period of four days. This group of mice with insulin resistance was used for the purpose of determining the effectiveness of glucose tolerance. When compared to normal animals, the in vivo administration of rutin demonstrated the capacity to reduce blood glucose levels, hence exhibiting anti-diabetic effects. Based on the findings of the research, it was determined that the antihyperglycemic action of rutin may be attributed to the increase of the insulin signalling pathway via the induction of glucose uptake and GLUT4 translocation [15].

Amylin and insulin are both hormones that are secreted by β-cells in the pancreas. The formation of amyloid aggregates is a consequence of any structural changes that occur in human amylase throughout time. Specifically, these amyloid aggregates possess the capability to trigger apoptosis in cultured β-cells and to kill the β-cell in islets that are isolated from the body. It has been observed that mice that have been transgenic for human amylin express human amylase in their β-cells in a selective manner. When β-cells undergo apoptosis and the islet undergoes increasing destruction, it results in diabetes that is comparable to the condition that is seen in people who have type 2 diabetes. Because of this, the accumulation of human amylase is regarded as one of the risk factors that contribute to the development of diabetes. In addition to its role in the disaggregation of human amylase, rutin has been shown to be an inhibitor of misfolding by many researchers. Research conducted by Aitken and his colleagues has investigated the anti-diabetic properties of rutin in human amylin-transgenic mice. Rutin at a concentration of 0.5 mg/ml was given to hemizygous human amylase-transgenic mice via the drinking water for a period of sixty days for oral administration. The control group consisted of male mice that were hemizygous and did not have any transgenic gene. Animals in the control group were given water that was free of any contaminants. The ion-mobility mass spectrometry and time-dependent thioflavin-T spectroscopy techniques were used in order to determine the amount of misfolding that occurred in human amylase. Following the findings of the investigation, it was shown that rutin had the capability to prevent the misfolding and disaggregation of human amylase in transgenic mice. Additionally, the research demonstrated that rutin had the capability to alter the conformation of human amylase that has been misfolded in order to shift it towards the normal physiological human amylase. Administration of rutin resulted in a reduction of high blood glucose. Based on the findings of the investigation, it was determined that the administration of rutin has the ability to inhibit the aggregation of human amylase and to extend the lifetime of diabetic human amylase-transgenic mice [1].

2.2 Puerarin

The primary bioactive chemical that was isolated from the root of the Pueraria lobata plant is called puerarin (7-hydroxy-3-(4-hydroxyphenyl)-8-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy6-hydroxymethyl) oxan-2-yl] chromen-4-one. The chemical formula for puerarin is daidzein's 8-C-glucoside, as shown in Figure 6. Over the course of the late 1950s, puerarin was separated from Ohwi for the very first time. The compound known as puerarin may be found in plants such as Pueraria phaseoloides and Ziziphus jujuba. Several studies have shown its considerable benefits in a variety of conditions, including cerebrovascular and cardiovascular

disorders, Parkinson's disease, Alzheimer's disease, cancer, diabetes, and problems associated with diabetes [10].

In addition, puerarin may be synthesised from the Kudzu plant. South East Asia is the natural habitat of this plant, which is a perennial, semi-woody, and legumeous plant. In the practice of traditional Chinese medicine, it is commonly used. It has been claimed that kudzu root contains more than seventy different phytoconstituents, some of which include triterpenoids, glycosides, and isoflavonoides. Puerarin is the greatest phytoconstituent found in Kudzu root, which contains seventy different phytoconstituents. For the treatment of a variety of conditions, including fever, diarrhoea, acute dysentery, diabetes, and cardiovascular illnesses, kudzu root has been used. [29]

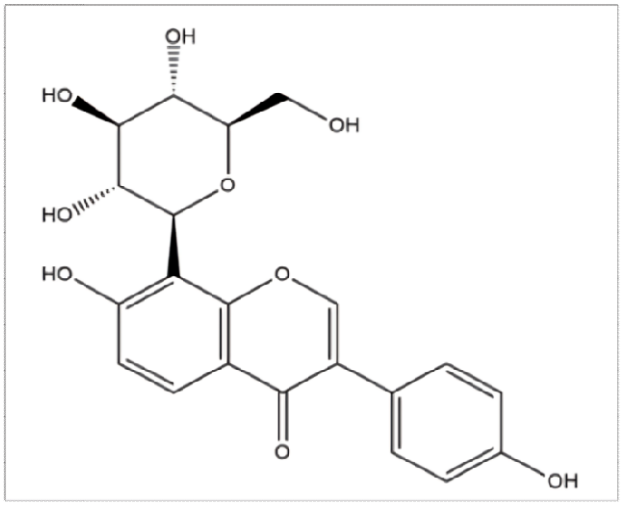

Figure. 6 Chemical structure of Puerarin

Kudzu roots that had been dried were put through a milling process and then sieved using a mesh size ranging from 20 to 40. One hundred grammes of the sample was combined with one thousand millilitres of n-butanol and water at a volume-to-volume ratio of one to one. An extraction sample was stored at 25 degrees Celsius for sixty minutes. In addition, the extract was filtered before being added to the mixture. In order to achieve full phase separation, the filtrate was stored. After that, the water phase was used in order to yield puerarin. According to the findings of the research, puerarin may be extracted from both hydrophilic and hydrophobic contaminants using a process known as double solvent extraction. The extraction of puerarin is dependent on pH. Using a magnetic stirrer operating at 300 revolutions per minute, the first solvent extraction was carried out in a beaker. The extract was dissolved in an equal amount of n-butanol, and the resulting aqueous solution was agitated for at least one hour. By using a solution of sodium hydroxide or hydrochloric acid at a concentration of one mole per litre, the pH of the mixture was maintained between 2 and 8. At a pH greater than 8, it was discovered that puerarin was unstable. A funnel was used to store the mixture so that it could undergo full phase separation. HPLC was used in order to determine the amount of puerarin present in both aqueous and n-butanol solutions. Bringing the pH down was the method that was used in the purification of puerarin. During the course of one hour, the combination that was produced was swirled with an equal amount of distilled water. Using high-performance liquid chromatography (HPLC), the pure form of puerarin was measured. High-performance liquid chromatography (HPLC) was performed with the assistance of HPLC grade methanol and an Agilent system. This system included a

quaternary pump, a Waters column with dimensions of 150 mm × 3.9 mm and a particle size of 5 m, a column thermostat, a degasser unit, an auto sampler, and a UV detector [32].

Through the use of STZ-induced diabetic mice, puerarin's antihyperglycemic actions were discovered and investigated. Puerarin at doses of 20, 40, and 80 mg/kg was administered orally to diabetic mice for a period of fourteen days. Following therapy, investigations of plasma glucose levels, insulin levels, and lipid profiles were carried out. It was shown that therapy with puerarin dramatically boosted serum insulin levels while simultaneously lowering blood glucose levels. An improvement in the lipid profile was also seen in diabetic mice. Furthermore, puerarin was shown to protect the pancreas against diabetic lesions, as demonstrated by histological examinations of the pancreas. Through the use of Western blot analysis, it was discovered that the levels of insulin-like growth factor-1 and insulin receptor substrate-1 were elevated in pancreatic tissues. In addition, a real-time polymerase chain reaction demonstrated that puerarin induced an increase in the expression of the peroxisome proliferators-activated receptor as well as the skeletal muscle insulin receptor. Through the maintenance of metabolic homoeostasis and the elevation of insulin levels, puerarin was shown to exhibit hypoglycemic and hypolipidemic action in STZ-induced diabetic mice [31]. A significant part in the development of diabetes is played by the glucagon-like peptide 1 receptor, often known as GLP-1R. A study was conducted on db/db mice to investigate the effects of puerarin. For a period of twelve weeks, the db/db mice were maintained on a diet that was heavy in fat. Oral administration of puerarin at a dose of 150 mg/kg was administered to the animals for a period of 55 days after 12 weeks. Following therapy with puerarin, diabetic db/db mice exhibited an increase in body weight, greater glucose tolerance, and better management of their blood glucose levels. Immunostaining investigations of pancreatic sections revealed that further puerarin administration resulted in a reduction in the amount of cell death. In order to investigate the mechanism behind puerarin's anti-diabetic action, the GLP-1R signalling pathway was the focus of the research undertaken. GLP-1R expression was found to be elevated, and protein kinase B was shown to be activated, according to the western blot study [33].

After being extracted and refined from Pueraria lobata, puerarin was obtained. An investigation on the anti-diabetic properties of puerarin was carried out on male Wistar rats. In order to induce diabetes, an intravenous injection of STZ at a dose of 60 mg/kg was administered. Rats with diabetes were given puerarin at a dosage of 20 milligrammes per kilogramme for a period of three days. In order to determine the impact of puerarin, we measured the levels of glucose in the plasma, performed an intravenous glucose challenge test, measured the amount of glucose that was absorbed by the soleus muscle, and analysed the expression of genes using both northern and western blot analysis. The findings demonstrated that a bolus injection of puerarin administered intravenously resulted in a reduction in the plasma glucose levels in diabetic rats at a dose of 20 mg/kg. The elevated levels of plasma glucose that were seen in diabetic rats during the glucose challenge test were dramatically lowered by the administration of puerarin. Puerarin promoted an increase in the absorption of radio-labeled glucose in the soleus muscle of diabetic rats that was isolated. This improvement was dependent on the concentration of the substance. GLUT4 was shown to be upregulated in soleus muscle, according to a research that examined gene expression at both the mRNA and protein levels (Fig.7) [16].

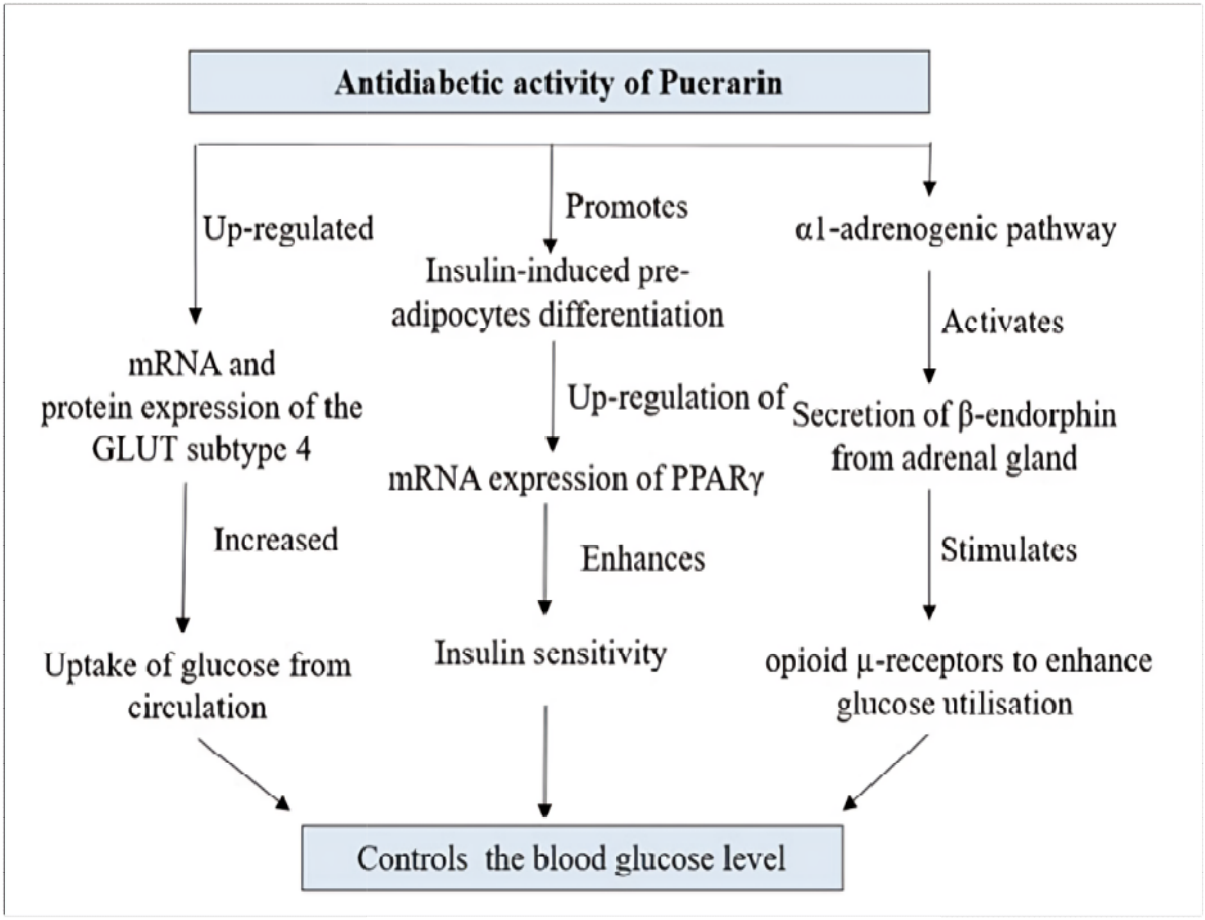

Figure. 7 Mechanism of antidiabetic activity of puerarin

In type 2 diabetic mice, it was recently shown that puerarin and pumpkin polysaccharides exhibited synergistic anti-diabetic efficacy. During the course of three consecutive days, a meal heavy in fat and an intraperitoneal injection of STZ at a dose of 35 mg/kg were used to induce type 2 diabetes. Oral administration of pumpkin polysaccharides (400 mg/kg) and puerarin (200 mg/kg) was administered to diabetic mice daily for a period of eight weeks. The findings demonstrated that the combination of pumpkin polysaccharides and puerarin reduced the high plasma glucose level, decreased the lipid profile, and decreased the amount of oxidative stress in diabetic mice. Due to the elevated production of nuclear factor E2 related factor 2, phosphoinositide-3-kinase, and heme oxygenase-1 in the Nrf2 and PI3K signalling pathway, it was proven that the combination of pumpkin polysaccharides and puerarin exhibited additional hypoglycemic action [6].

2.3 Gymnemic Acid I

The element gymnemic acid I ((2S,3S,4S,5R,6R))(-3S, 4R, 4aR, 6aR, 6bS, 8S, 8aR, 9R, 10R, 12aS, 14aR, 14bR)The -8a-(acetyloxymethyl) typeThe compound -8,9-dihydroxy-4-(hydroxymethyl)-4,6a,6b,11,11,14b-hexamethyl-10-[(E)-2-methylbut-2-enoyl]oxy1,2,3,4a,5, 6,7,8,9,10,12,12a,14,14a-tetradecahydropicen-3-yl]oxy] Atriterpenoid glycoside is represented by the formula -3,4,5-trihydroxyoxane-2-carboxylic acid (Fig. 8). A significant amount of gymnemic acid may be discovered in *Gymnema sylvestre*. Gymnemic acid was also discovered in a wide range of plants, such as those belonging to the species Hovenia

dulcis, Ziziphus jujuba, Gymnema alterniflorum, Stephanotis *lutchuensis*, and *Styrax japonicus*. In India and Japan, the plant *Gymnema sylvestre* has been historically used for the treatment of diabetes as well as the management of unhealthy weight [18].

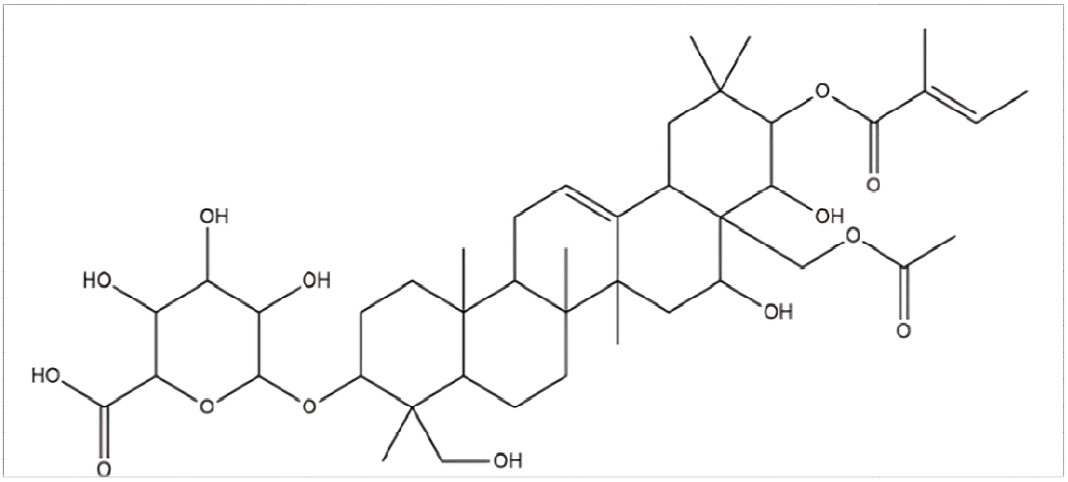

Figure.8 Chemical structure of Gymnemic acid I

Gymnema sylvestre is a woody plant that takes a long time to grow and is used for therapeutic purposes. One may find it in the southern and central regions of India as well as in tropical Africa. Asthma, inflammation, eye problems, inflammation, and snakebite are among of the conditions that have been treated with it since ancient times. Extract of the leaf is used as a cough suppressant, laxative, and diuretic of the organism. There is a high concentration of glycosides, saponins, and anthraquinones in the plant. Leaves contain a significant amount of the glycoside gymnemic acid I, which is the main glycoside. One of the active components that was shown to be responsible for the antidiabetic effect of *Gymnema sylvestre* was *gymnemic* acid [27].

The process of extracting gymnemic acid These actions were carried out by Hiroshimin and his squad. Gymnema sylvestre leaves were washed and dried in an oven with hot air at a temperature of fifty degrees Celsius. After being crushed, the dry leaves were then put through a sieve with a mesh size of forty. Once again, the powdered sample was dried at a temperature of fifty degrees Celsius. The powder was extracted using the Soxhlet apparatus under heated conditions with 95% ethanol. The extraction process was carried out. A hoover dryer was used to dry the ethanol that had been extracted. The amount of gymnemic acid that I could acquire was 6.15 percent. By blocking the binding of sweets to the sweet receptors on the tongue, gymnemic acid I has the capacity to decrease sweetness in humans. This is accomplished by preventing the binding of sweets. The acyl group of gymnemic acid I has the ability to lessen the activity that is associated with the antisweet effect. Aspartame and thaumatin are two examples of natural and artificial sweeteners that are both affected by the presence of gymnemic acid, which has the ability to lower their sweetness [24].

2.4 Stevioside

[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl] are the chemical formulas for stevioside. 1R, 4S, 5R, 09S, 10R, and 13S[(2S,3R,4S,5S,6R)] -13-[dihydroxy-6 hydroxymethyl -4,5-dihydroxy-6-The number 3-[(2S,3R,4S,5S,6R)The chemical formula for

-3,4,5-trihydroxy-6-(hydroxymethyl)oxan2ylpolyoxyoxan2yl]oxy5,9 dimethyl14 methylidenetetracyclo[11.2.1.01,10.04,9]hexadecane-5-carboxylate) is made up of three glucose molecules that have been fused together with an aglycone-steviol; this is seen in Figure 10. The majority of stevioside may be found in the leaves of the Stevia rebaudiana plant. 1931 was the year when Bridel and Lavielle made the discovery of stevioside. In addition to South America, the Stevia rebaudiana plant may be found in a number of Asian nations. In both Brazil and Paraguay, stevia is used as a sweetener in the preparation of food and drinks. According to [19, 3], stevioside is mostly used in the production of vegetable goods, soft drinks, fruit products, seafood, confectionary, and as a sweetener for tabletop beverages. It has been discovered that stevioside is between 150 and 400 times sweeter than saccharose. This is the reason why it is used as a sweetener in the treatment of heart disorders and weight reduction. Using a technology that Lopez devised that is environmentally friendly, it is possible to extract stevioside in an effective manner. A factorial design was used in order to develop an environmentally friendly approach for the extraction of steviol. When designing the Box–Behnken surface, there are five factors that are taken into consideration for the effective extraction of stevioside. These variables are temperature, time, agitation, sample–solvent ratio, and grinding time. In this particular extraction, the solvent that was used was hot water. An extraction period of twenty minutes, a leaf water ratio of two hundred grammes per litre, a temperature of seventy-five degrees Celsius, and interim grinding were necessary in order to achieve the optimal approach for the highest recovery of stevioside from the leaves of Stevia rebaudiana. By using this approach, the highest possible yield of stevioside was measured at 188.64 mg/L. Because this technique was shown to be inexpensive, simple, and kind to the environment, it has the potential to be used for the extraction of stevioside at an industrial level [25].

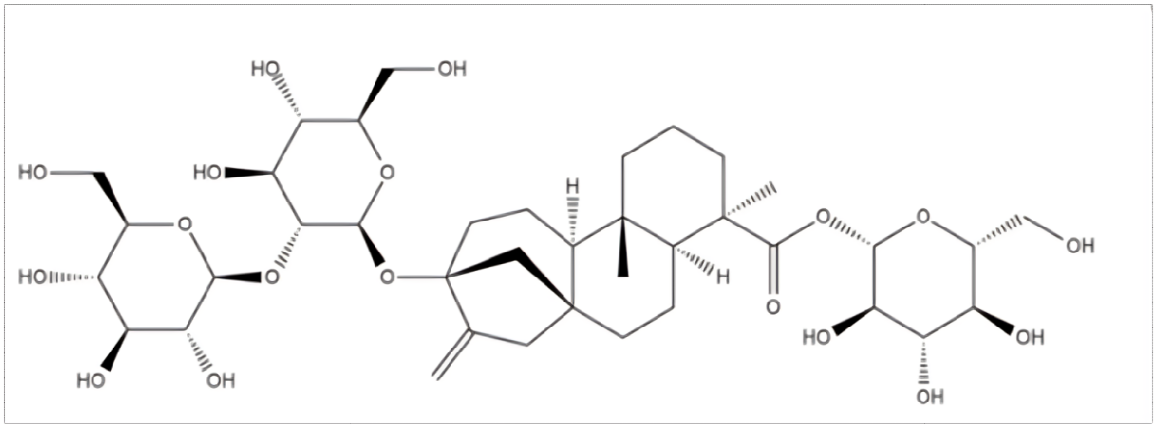

Figure. 10 Chemical structure of Stevioside

2.5 Securigenin

The aglycone component of securidaside is referred to as securigenin. A significant amount of securigenin may be found in the seeds of the Securigera securidaca plant. An unsaturated lactone ring and an aldehyde group are both present in the aglycone securigenin component. Securigenin glycosides are used in traditional Persian medicine for the purpose of lowering blood sugar levels [14].

Throughout addition to Africa, Europe, and West Asia, the annual plant known as Securigera securidaca may be found throughout Africa. Beginning in ancient times, it has

been regarded a kind of Iranian traditional medicine. It has been claimed that Securigera securidaca may be used to treat a variety of conditions, including diabetes, epilepsy, hyperlipidemia, hypertension, diuretic, gastrointestinal disturbances, and hypokalemic diseases. This particular plant is known to contain a variety of phytochemical substances, including tannins, phenols, alkaloids, flavonoids, and saponins. Both the ethanolic and aqueous extracts of Securigera securidaca have been found to exhibit a variety of pharmacological properties [13].

Hydroalcoholic extract was used by Hadjzadeh and the group in order to accomplish the process of isolating securigenin. The seeds of Securigera securidaca were ground into a powder and macerated with an ethanol solution that contained seventy percent. The powder was submerged in 3.2 litres of water for a period of 72 hours. Following filtration, the extract was concentrated at a temperature of 40–45 degrees Celsius for a period of 72 hours. After the extraction was completed, it was purified. In addition, the purified extract was used for the purpose of determining the antihyperglycemic activity levels in diabetic female Wistar rats that had been induced with STZ. Animals with diabetes were given pure hydroalcoholic extract in drinking water at doses of 100 and 200 mg/kg per day for a period of four weeks. In comparison to diabetic control rats, the administration of Securigera securidaca seed extract resulted in a substantial decrease in the levels of blood glucose and total cholesterol when administered at a dosage of 200 mg/kg. [34].

3. SUMMERY

Diabetes mellitus (DM) encompasses a spectrum of metabolic disorders marked by elevated blood sugar levels, stemming from irregularities in insulin production or action. This condition poses significant health risks, including cardiovascular, cerebrovascular, and liver diseases, as well as increased susceptibility to infections like tuberculosis. The World Health Organization (WHO) classifies diabetes into various types, including Type 1, Type 2, and hybrid forms. Plant-derived therapies have a long history in managing diabetes, with compounds like glycosides showing promise. Glycosides, such as rutin, puerarin, gymnemic acid I, stevioside, and securigenin, have exhibited considerable efficacy in diabetes treatment through mechanisms like insulin level regulation, antioxidant effects, and modulation of glucose metabolism. Rutin, found in various plants like buckwheat, has demonstrated antidiabetic properties by improving insulin levels and reducing hyperglycemia. Puerarin, isolated from the Kudzu plant, has shown hypoglycemic and hypolipidemic effects in diabetic mice. Gymnemic acid I, primarily derived from Gymnema sylvestre, has been studied for its potential to reduce sweetness perception and manage blood glucose levels. Stevioside, extracted from Stevia rebaudiana, is a potent sweetener with potential applications in diabetes management. Securigenin, found in the seeds of Securigera securidaca, has shown antihyperglycemic effects in diabetic rats. These plant-derived compounds offer promising avenues for diabetes management, highlighting the therapeutic potential of natural remedies in combating this global health concern.

REFERENCES

[1] Aitken JF, Loomes KM, Riba-Garcia I et al (2017) Rutin suppresses human-amylin/hIAPP misfolding and oligomer formation in-vitro, and ameliorates diabetes and its impacts in humanamylin/hIAPP transgenic mice. Biochem Biophys Res Commun 482:625–631. https://doi.org/10.1016/j.bbrc.2016.11.083

[2] Bartnik M, Facey PC (2017) Glycosides. In: Pharmacognosy: fundamentals, applications and strategy.

Elsevier Inc., London, pp 101–161
[3] Bassoli A, Merlini L (2003) Sweetners | intensive. In: Encyclopedia of food sciences and nutrition. Academic Press, Cambridge, pp 5688–5695
[4] Bone K, Mills S (2012) Principles and practice of phytotherapy: modern herbal medicine. Elsevier Ltd, London
[5] Brunetton J (2008) Pharmacognosy, phytochemistry, medicinal plants (2nd ed. - retirage broch). Lavoisier, Paris
[6] Chen X, Qian L, Wang B et al (2019) Synergistic hypoglycemic effects of pumpkin polysaccharides and puerarin on type II diabetes mellitus mice. Molecules 24:955. https://doi.org/ 10.3390/molecules24050955
[7] Fernandes AAH, Novelli ELB, Okoshi K et al (2010) Influence of rutin treatment on biochemical alterations in experimental diabetes. Biomed Pharmacother 64:214–219. https://doi.org/10. 1016/j.biopha.2009.08.007
[8] Frutos MJ, Rincón-Frutos L, Valero-Cases E (2018) Rutin. In: Nonvitamin and nonmineral nutritional supplements. Elsevier, London, pp 111–117
[9] Ganeshpurkar A, Saluja AK (2017) The pharmacological potential of rutin. Saudi Pharm J 25:149–164
[10] Ghorbani A (2017) Mechanisms of antidiabetic effects of flavonoid rutin. Biomed Pharmacother 96:305–312
[11] Global Report On Diabetes (2016) The World Health Organization Library. Cataloguing-in-publication data global report on diabetes
[12] Guerriero G, Berni R, Muñoz-Sanchez JA et al (2018) Production of plant secondary metabolites: examples, tips and suggestions for biotechnologists. Genes (Basel) 9:309
[13] Hadjzadeh M-A-R, Moradi R, Ghorbani A et al (2015) Antihyperglycemic and antihyperlipidemic effects of hydroalcoholic extract of Securigera securidaca seeds in streptozotocin-induced diabetic rats. Adv Biomed Res 4:33. https://doi.org/10.4103/2277- 9175.150427
[14] Hosseinzadeh H, Ramezani M, Danaei AR (2002) Antihyperglycaemic effect and acute toxicity of Securigera securidaca L. seed extracts in mice. Phyther Res 16:745–747. https://doi.org/10. 1002/ptr.1020
[15] Hsu CY, Shih HY, Chia YC et al (2014) Rutin potentiates insulin receptor kinase to enhance insulin-dependent glucose transporter 4 translocation. Mol Nutr Food Res 58:1168–1176. https://doi.org/10.1002/mnfr.201300691
[16] Hsu FL, Liu IM, Kuo DH et al (2003) Antihyperglycemic effect of puerarin in streptozotocininduced diabetic rats. J Nat Prod 66:788–792. https://doi.org/10.1021/np0203887
[17] International Diabetes Federation Diabetes Atlas (2019) 9th edition
[18] Izawa K, Amino Y, Kohmura M et al (2010) Human-environment interactions - taste. In: Comprehensive natural products II: chemistry and biology. Elsevier Ltd, London, pp 631–671
[19] Jorge K (2003) Soft drinks | chemical composition. In: Encycl food Sci Nutr, 2nd edn. Elsevier Ltd, London, pp 5346–5352. https://doi.org/10.1016/B0-12-227055-X/01101-9
[20] Kamalakkannan N, Prince PSM (2006) Rutin improves the antioxidant status in streptozotocininduced diabetic rat tissues. Mol Cell Biochem 293:211–219. https://doi.org/10.1007/s11010- 006-9244-1
[21] Khattak S, Khan H (2016) Phyto-glycosides as therapeutic target in the treatment of diabetes. mini-reviews. Med Chem 18:208–215. https://doi.org/10.2174/1389557516666160909112751
[22] Kreft S, Knapp M, Kreft I (1999) Extraction of rutin from buckwheat (Fagopyrum esculentum moench) seeds and determination by capillary electrophoresis. J Agric Food Chem 47:4649–4652. https://doi.org/10.1021/jf990186p
[23] Leslie RD, Palmer J, Schloot NC, Lernmark A (2016) Diabetes at the crossroads: relevance of disease classification to pathophysiology and treatment. Diabetologia 59:13–20
[24] Liu HM, Kiuchi T (1992) Isolation and structure elucidation of Gymnemic acids, Antisweet principles of Gymnema sylvestre. Chem Pharm Bull (Tokyo) 40:1366–1375. https://doi.org/10. 1248/cpb.40.1366
[25] Lopez-Carbon V, Sayago A, Gonzalez-Domínguez R, Fernandez-Recamales A (2019) Simple and efficient green extraction of steviol glycosides from stevia rebaudiana leaves. Foods 8:402. https://doi.org/10.3390/foods8090402
[26] Lu CL, Zheng Q, Shen Q et al (2017) Uncovering the relationship and mechanisms of Tartary buckwheat (Fagopyrum tataricum) and type II diabetes, hypertension, and hyperlipidemia using a network pharmacology approach. Peer J 2017:e4042. https://doi.org/10.7717/peerj. 4042
[27] Pothuraju R, Sharma RK, Chagalamarri J et al (2014) A systematic review of Gymnema sylvestre in obesity and diabetes management. J Sci Food Agric 94:834–840
[28] Skyler JS, Bakris GL, Bonifacio E et al (2017) Differentiation of diabetes by pathophysiology, natural history, and prognosis. Diabetes 66:241–255

[29] Wong KH, Li GQ, Li KM et al (2011) Kudzu root: traditional uses and potential medicinal benefits in diabetes and cardiovascular diseases. J Ethnopharmacol 134:584–607
[30] World Health Organization (2019) In: Classif. diabetes. https://apps.who.int/iris/handle/10665/ 325182. Accessed 5 Sept 2019
[31] Wu K, Liang T, Duan X et al (2013) Anti-diabetic effects of puerarin, isolated from Pueraria lobata (Willd.), on streptozotocin-diabetogenic mice through promoting insulin expression and ameliorating metabolic function. Food Chem Toxicol 60:341–347. https://doi.org/10.1016/j.fct. 2013.07.077
[32] Xu HN, He CH (2007) Separation and purification of puerarin with solvent extraction. Sep Purif Technol 56:397–400. https://doi.org/10.1016/j.seppur.2007.06.003
[33] Yang L, Yao D, Yang H et al (2016) Puerarin protects pancreatic β-cells in obese diabetic mice via activation of GLP-1R signaling. Mol Endocrinol 30:361–371. https://doi.org/10.1210/me. 2015-1213
[34] Zhou YX, Zhang H, Peng C (2014) Puerarin: a review of pharmacological effects. Phyther Res 28:961–975