PLANT SCIENCE TODAY
ISSN 2348-1900 (online)
Vol x(x): xx–xx
https://doi.org/10.14719/pst.2021

HORIZON
e-Publishing Group
HePG

REVIEW ARTICLE

Phytotherapy for diabetes: An overview of Indian traditional plants with saponins as a phytoconstituent

Avijit Mazumder*, Sanjana, Bhavani Pentela & Vikas Gupta

Noida Institute of Engineering and Technology (Pharmacy Institute), 19, Knowledge Park II, Institutional Area, Greater Noida, Uttar Pradesh 201306 , India

*Email: avijitmazum@yahoo.com

OPEN ACCESS

ARTICLE HISTORY

Received: 23 July 2022
Accepted: 08 January 2023

Available online
Version 1.0 : 11 June 2023

Check for updates

Additional information

Peer review: Publisher thanks Sectional Editor and the other anonymous reviewers for their contribution to the peer review of this work.

Reprints & permissions information is available at https://horizonepublishing.com/journals/index.php/PST/open_access_policy

Publisher's Note: Horizon e-Publishing Group remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Indexing: Plant Science Today, published by Horizon e-Publishing Group, is covered by Scopus, Web of Science, BIOSIS Previews, Clarivate Analytics, NAAS, UGC Care, etc
See https://horizonepublishing.com/journals/index.php/PST/indexing_abstracting

CITE THIS ARTICLE

Mazumder A, Sanjana, Pentela B, Gupta V , Phytotherapy for diabetes: An overview of Indian traditional plants with saponins as a phytoconstituent. Plant Science Today (Early Access). https://doi.org/10.14719/pst.2021

Abstract

The present article consists of the basic knowledge about diabetes with its classification as Type 1, Type 2, gestational diabetes as well as other types of diabetes mellitus (DM). Diabetes mellitus is a long-term metabolic disorder defined by increased blood glucose levels. Insulin secretion and action are defective in diabetic patients. Diabetes leads to irreversible damage and failure of many organs because of chronic hyperglycemia. They have a complex etiology that arises when the equilibrium of offensive and protective components is altered. The limited effectiveness and severe adverse effects of the currently available medications make treatment extremely difficult. In experimental models of anti-diabetic preparations, natural items such as herbal plants and their extracted components have been frequently used. Saponins, a glycosidic molecule, is proven to have therapeutic potential and they are used as an alternative treatment for insulin in diabetic patients. Saponin-induced dyslipidemia will aid diabetic people in lowering their risk of cardiovascular disease and atherosclerosis. This review aims to explain the antidiabetic function of saponins as well as its potential in the management of diabetes

Keywords

Diabetes mellitus, saponin, anti-diabetic, glucose

Introduction

Diabetes mellitus is a metabolic disorder and it affects carbohydrates, fats, and proteins in the body. Diabetes is characterized by a defective or insufficient insulin secretory response, leading to reduced glucose tolerance, inability of the body to make use of carbohydrate (glucose) and hyperglycemia (1). Diabetes mellitus is the most common type of endocrine disease, and it happens due to shortage of insulin (2).According to International Diabetes Federation (IDF), the overall country's population (age category of 20–79 years) living with diabetes is 463 million as of 2019, and it may rise to 578 million by the year 2030 (3). Diabetes kills one person every 6 seconds, which is more than the combined death rates of tuberculosis (1.5 million), HIV (1.5 million), and malaria (0.6 million) (4–6). The pancreas makes both glucose and insulin hormones. The β-cell secretes insulin and α-cell secretes glucagon hormone. Both are present in the islets of Langerhans.

The insulin decreases blood sugar levels and prevents the transportation of glucose inside the liver, muscles, and fatty tissue which also inhibits its gluconeogenesis. By generating glucagon, α-cell plays a crucial part in blood glucose regulation and enhances blood sugar levels accelerating gly-

cogenolysis. Red cells, as well as neural tissue, do not require insulin for utilization of glucose, while α-cells play an important part in regulation of blood sugar levels including glucagon production. If blood sugar level increases, the enzymes phosphorylase kinase and glycogen phosphorylase breaks down glycogen into glucose-1-phosphate and glucose (7, 8).

Causes of Diabetes Mellitus

ß-cell glucose-receptor irregularities lead to a reaction to increased glucose concentrations or relative ß-cell reduction (9). The effects of diabetes on the metabolism of neurons are the basic premise of microvascular illness that leads to neural hypoxia (10).

Insulin sensitivity in peripheral tissues is decreased as an outcome of a reduction in the different types of insulin receptors and insulin receptor 'down-regulation'. So majority of individuals are suffering from hypersensitiveness and hyperinsulinemia, but sugar level in the blood is normal. They also have dyslipidemia, abdominal obesity, hyperuricemia and abdominal obesity. As an output, there is relative insulin resistance, especially in the hepatic, fat, and muscles. Hyperinsulinemia has been connected to the generation of angiopathy (11).

Obesity and excess hyperglycemia hormone (glucagon) create insufficiency of relative insulin, the ß-cells fall behind. Two models are established in the metabolism of nitric oxide, as an outcome of changed perineural blood circulation and nerve injury (9).

Various uncommon kinds of hyperglycemia include "Maturity Diabetic Onset of the Young" (MODY), other endocrine illnesses, gestational diabetes mellitus, pancreatectomy and those that are caused by genetic flaws (type 3) (GDM) (11).

Diabetes mellitus can be brought on by an imbalance of certain receptors eg., glucagon-like peptide-1 (GLP -1) receptor, (30 or -31 amino acid peptide hormone), Peroxisomes Proliferator Activated Receptor (PPAR), gloxazone reverse insulin resistance,beta-3 adrenergic receptor (ADRB3),and enzymes such as Dipeptidyl peptidase-4 (DPP -4) glycosidase and others (11).

Classification of Diabetes Mellitus

Diabetes mellitus was introduced by World Health Organization in 1980 and as per the classification system, 4 types of diabetes mellitus are established: Type 1, Type 2, gestational diabetes, and "other types" (WHO Expert Committee 1999). In 1991, the International Nomenclature of Diseases (IND) was revised (13). As an output, diabetes mellitus is categorized as follows-

Insulin Dependent Diabetes Mellitus: IDDM (Type1)

Insulin dependent diabetes mellitus (IDDM) is called as Type1diabetes andalso as autoimmune diabetes. Along with genetic factors, non-genetic factors also play a major role in the expression of the type 1 diabetes (12). Other immunological disease conditions that the person may seek include Hashimoto's thyroiditis, Graves' disease and Addison's disease (13). Type I diabetes affects both men and women. Its onset is usually abrupt, and it has the potential to be lethal (7). Acid decarboxylase, anti-glutamic islet cells, or insulin antibodies are commonly present in Type1 diabetes, indicating autoimmune mechanisms that contribute to β-cell death (14). The β-cell breakdown frequency is varied in Type1 diabetes; sometimes it happens very quickly in some people while taking a very long time in others (15). As the pancreatic β-cells are killed, there will be a big shortage or insufficient secretion of insulin. The treatment necessitates insulin shots (7). When overnight diabetic glucose is first discovered, immunological markers damage, such as Glutamic Acid Decarboxylase auto antibodies (GAD) and islet cell auto antibodies are found in 85-90 percent of people having insulin-dependent diabetes mellitus (type 1) (15). An automatic process of the immune system that involves auto antibodies that damage β-islet cells exist in most people , the exact cause of which is unknown (7).

Non-Insulin Dependent Diabetes Mellitus: NIDDM (Type2)

A progressive insulin secretary breakdown is the setting of insulin sensitivity (16). Insulin sensitivity is more frequent in various individuals suffering from type-2 diabetes (17). Both kinds of diabetes have chronic problems in the eyes, nerves, kidneys, and blood vessels. All of these are the most prominent causes of morbidity and mortality (1).

Obesity, sedentary way of life, increasing age (affects middle-aged and old persons) and hereditary factors, all these are predisposing factors, and such patients are at an elevated possibility of getting into macro and microvascular problems (18, 19).

Gestational Diabetes Mellitus: GDM

GDM stands for gestational diabetes mellitus, which is a type of glucose intolerance that occurs during pregnancy (2). GDM is a disease in which women develop diabetes mellitus during pregnancy or find undetected asymptomatic type-2 diabetes mellitus during pregnancy (20). GDM can occur during infertility and be cured after delivery. Children born to mothers with GDM are more prone to acquire overweight as well astype-2 diabetes mellitus in life, a situation linked to complications of intrauterine-hyperglycemia (21).

Other Specific Type

This type of diabetes is caused by mutations on chromosome 12. It is also known as a β-cell genetic disorder. These kinds of diabetes mellitus are often marked by the beginning of hyperglycemia at a young age. People with diseases of the exocrine pancreas; people with pancreatic dysfunction caused by medicines, chemicals or viruses and caused by other endocrinopathies (acromegaly) are example to this (20). Some medicines used in AIDS treatment or in collaboration with organ transplantation also can cause this type of diabetes. In some families, genetic anomalies that lead to the failure to transform proinsulin into insulin has been found, and this can be transmitted to the next generation in a dominant autosomal pattern (22).

Management of Diabetes Mellitus

Studying diabetes pathophysiology is critical for effective

therapy. Glycaemic control is defined as a blood glucose level during bedtime which is between 100 to 140 mg/dL (5.6 to 7.8 mmol/L) a pre-prandial blood glucose level of 80 to 120 mg/dL (4.4 to 6.7 mmol/L), and an HbA1c level of less than 7% are all required as per American Diabetes Association (23–25).

Physical activity, a healthy diet, and weight management are at the heart of every diabetes mellitus treatment plan (26). Such activities and exercise programs not only decrease blood glucose levels but also reduce the risk of various cardiovascular diseases and aid weight loss. Moreover, because most patients are unable to live a healthy lifestyle (27), they must rely on both traditional and modern medicines to reduce glucose levels in the blood by interfering with β-cells to release maximum insulin from the pancreatic islet, raising the level of glucose by inhibiting the action of hormones, increasing the sensitivity of the insulin receptor sites, inhibiting the hydrolysis of glycogen in the liver and enhancing the usage of glucose in organs and tissue (28, 29).

There are currently six primary classes of contemporary pharmaceuticals used worldwide to regulate glucose levels in the blood, as well as two classes of injections (26). Thiazolidinediones (glitazones), biguanides (metformin), sulfonylurea's, meglitinides (glinides), DPP-4 inhibitors, and alpha-glucosidase inhibitors are some of the names of the tablets commonly used (30–33). The mechanisms of action of these medications have been published. Most modern pharmaceuticals have several side effects and unfavourable consequences, which may result in major medical complications during administration. Metformin is a biguanide drug that enhances insulin sensitivity by preventing glucose molecules forming in the liver. Metformin, on the other hand, has several major side effects, including nausea, dyspepsia, and diarrhoea in its first condition. Metformin should be avoided if you have substantially impaired renal function, severe liver disease, decompensated heart failure, or other serious medical conditions. Thiazolidinediones have been proven to increase the sensitivity of insulin, decrease insulin resistance, and lower cardiovascular risks in people with diabetes. Fluid retention and weight-gain are the most prevalent negative effects of thiazolidinediones, which can lead to peripheral edema and heart failure (citation needed). The individual with similar conditions like heart failure and serious liver problems were advised against using the medications. Heart attacks and cardiovascular issues have been related to Rosiglitazone (30).

The classifications of anti-diabetic drugs are explained in Fig. 1 with their mechanism of action.

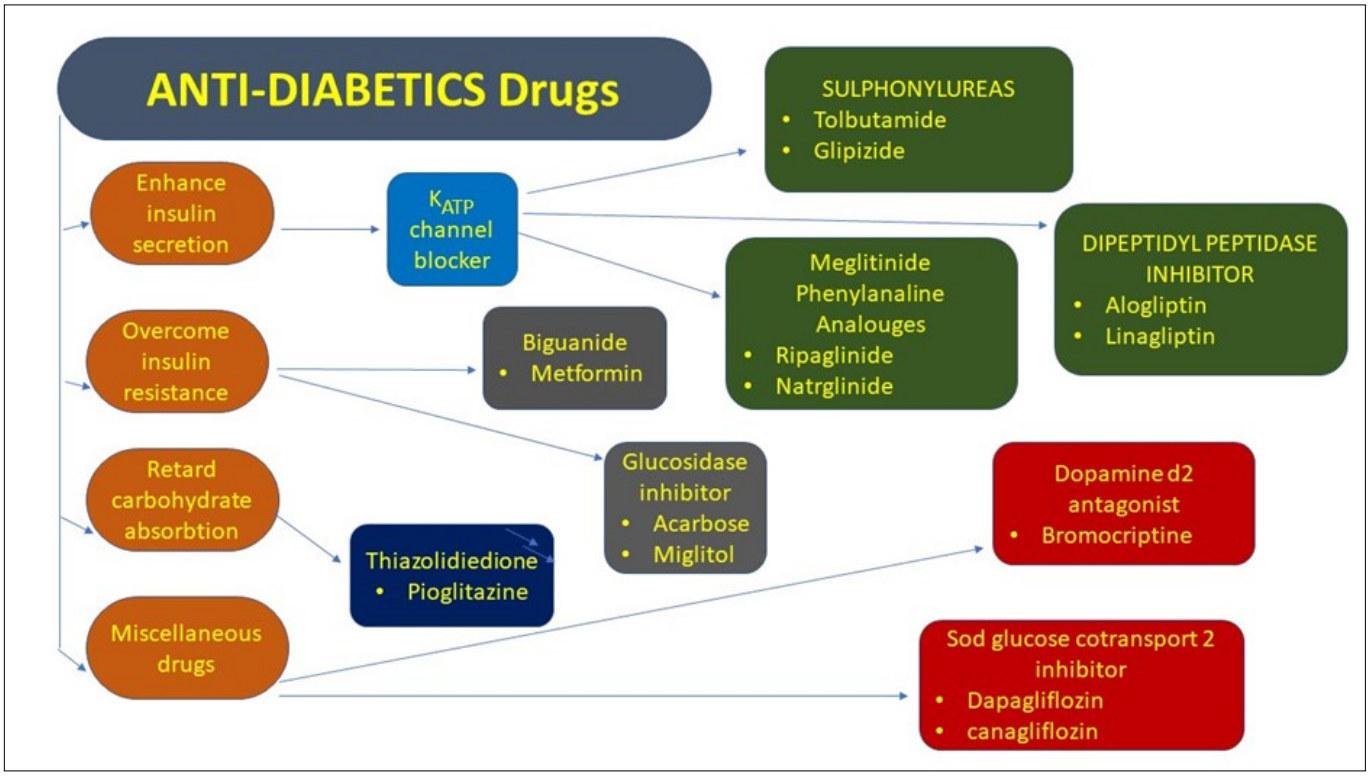

Fig. 1. Classification of anti-diabetic drugs.

Traditional remedies, in addition to contemporary medication, have long been utilized and serve as an alternative method of treating diabetes (34–42). As per WHO, roughly 75–85 percent of people in the world believes in herbal or plant-based traditional systems of medicine, primarily in poor countries with rich biodiversity and plant wealth (43). Traditional medicines are more culturally acceptable and they have fewer adverse effects than allopathic medicine. Plant based medicines are often the first choice of treatment for primary healthcare in impoverished nations. Medicinal plants have been used as antidiabetic medicines in general and specifically against hyper-lipidemic conditions. Even though the literature contains over 400 plant species with hypoglycaemic activity (44), studying new anti-diabetic formulations from natural plants remains appealing because they are safe and the phytochemicals are having alternative effects on diabetes. The phytochemicals with therapeutic properties include bio-active com-

ponents with anti-diabetic properties such as saponins, flavonoids, alkaloids, phenolics, terpenoids and various others (45–47).

Amphiphilic glycosides are saponins that are produced by a variety of plant species, with a high molecular weight and a sugar moiety linked to a steroid or triterpenoid. Saponins (triterpene glycosides) have been a great attraction for researchers due to their diverse biological actions that include hepatoprotective, anti-cancer, antibacterial and anti-inflammatory properties. Saponins are abundant in various plants but reported only from a very few in animal kingdom that include certain marine groups such as sea-cucumbers, starfishes and sponges (48, 49). (Fig. 2)

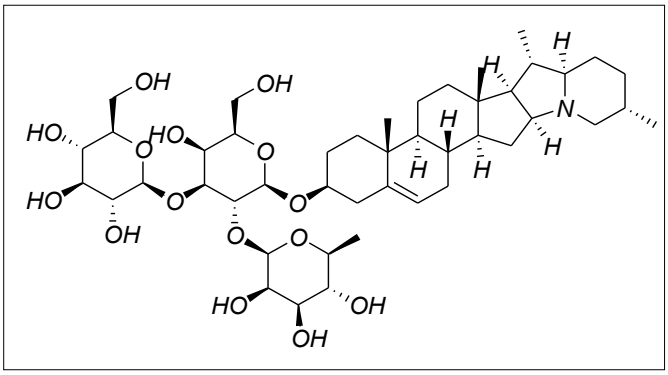

Fig. 2. Structure of Solanine.

Triterpene glycosides are interesting phytochemicals because of their potential for developing into new anti-diabetic drugs (50, 51). As an outcome, the objective of this review article is to present the known data about saponins that are extracted from medicinal plants and marine animals, which are having anti-diabetic properties. It is expected that the material provided will inform readers about saponins' anti-diabetic properties and encourage more study into these substances.

Plants with saponins having anti-diabetic activity

AstragalosideIV(AS- IV)

Astragaloside IV (AS- IV) found in the herb *Astragalus membranaceus* (Fisch.) Bge. is a molecular saponin which is frequently utilized in Chinese traditional medicine. Recent research has revealed that the molecule has anti-hypertensive, anti-diabetic, anti-inflammatory and cardiac protective characteristics (52). *Astragalus membranaceus* has a wide area of biological actions because of its high concentration of anti-diabetic substances including saponins (53). In a rat Streptozotocin (STZ)-induced diabetic nephropathy model, Wang *et al.,* intended to explore as to how ASIV altered the endoplasmic reticulum (ER) stress indicators expression (53). After overnight fast, healthy 1-month male Sprague–Dawley rats (150–200 g) were given 40 mg/kg body weight Streptozotocin (STZ) dissolved in citrate buffer (pH 4.6) intraperitoneally for five days. Following STZ induction for two weeks, ASIV (10 mg/kg/day) was given two times a day via oral gavage for eight weeks. They claimed that ASIV can reduce structural and functional defects in the STZ-induced rat model of diabetic nephropathy (DN), with reno-protective action mediated by endoplasmic reticulum stress reduction (53).

Berberis vulgaris

Berberis vulgaris L. also called barberry, is a member of the Berberidaceae family. *Berberis* is a genus with 190 species of prickly deciduous evergreen shrubs with yellow flowers and yellow wood. Saponins, alkaloids, tannins, sterols, and anthraquinones were found in the extracts investigated by phytochemical analyses (54). Meliani looked into the role of saponin, which was isolated from *Berberis vulgaris* root bark (54). The extract of saponin (25 mg/kg) treatment began after 10 days; the streptozotocin-induced diabetes Wistar rats (150-230 g) were injected for the last 21 days. The diabetic control group compared with, the diabetic group treated with extract of barberry saponin exhibited a maximum reduction of 73.1 percent on day 1 and 76.03 percent on day 21. These findings suggested that the hypoglycaemic effect was caused by saponins in the *Berberis vulgaris* L.*'s* root bark, which stimulate the remaining (β) cells. Extraction of saponin improved lipid profile in addition to hypoglycaemic action, suggesting that they may be useful in the treatment of diabetes (54).

Bitter gourd (*Momordica charantia*)

Momordica charantia L. known in Hindi as *karela* is a plant utilized to heal diabetes-related disorders among indigenous cultures in South America, Asia, India, East Africa, East Africa and the Caribbean (55). It gets its nickname Bitter gourd from the bitter taste, fruit/vegetable popular in many countries. Saponins such as *Momordicine*-II, 24-dien-19-al-73-hydroxycucurbita-5 and 23-di-O-glucopyranoside were isolated from *M.charantia.* Saponins from bitter gourd were used in a variety of clinical trials (56, 57).At concentrations of 10 and 25 g/mL, both substances showed considerable insulin-releasing action in MIN6-cells. Charantin isolated from *M. charantia* acts as a hypoglycaemic agent. Charantin is a characteristic cucurbitane type triterpenoid having anti-diabetic activities (58). Pitiphanpong (59) revealed that charantinis an anti-diabetic agent that can even substitute medication for diabetes. Furthermore, it was discovered that diabetic patients who consumed fresh bitter gourd juice had reduced glucose levels in their blood and improved their reaction to an oral glucose load test (60). The main component in *Momordica charantia* is saponin which is found in butanol fraction and is linked with antidiabetic activity (61). It works by blocking the enzymes that cause blood glucose to rise. Disaccharides must be broken down into monosaccharides (61). Its output is significant for the therapy of diabetic individuals with Type-II as well as Type-I diabetes. This helps to prevent blood sugar increases after meals. Saponin in bitter melon is also shown to induce glycogen accumulation in the liver and insulin release in the islets of Langerhans (62). Furthermore, the bitter melon saponin may be reduced. In erythrocytes and adipocytes, increasing peripheral glucose oxidation, hepatic glycogen production and hepatic gluconeogenesis (61).

Bitter kola (*Garcinia kola*)

Garcinia kola Heckel is a flowering plant belonging to Clusiaceae family, naturally found growing in subtropical or tropical moist lowland woods (63). There are a variety of non-timber forest products of high socio-economic value are derived from this plant (64). Smith and Adanlawo looked at how bitter kola saponin reduced oxidative stress in the tissue of diabetic Wistar albino rats (65). To induce diabetes, adult male albino rats (weighing 200 to 250 g) were given single intraperitonial injection of alloxan. Three days after receiving the injection, the hyperglycaemic rats were given saponin derived from the root of bitter kola at doses of 100, 200, and 400 mg/kg body weight daily for 7 days. Saponin has been shown to significantly reduce MDA generation and significantly increasing those enzymes that scavenge free radicals, such as catalase and superoxide dismutase (SOD). Saponin extract is has free radical scavenging activity and anti-oxidant activity, making *Garcinia kola* a potentially beneficial source of natural antioxidants which can be used for controlling or slowing down the progression of diabetes (65).

Cochlospermum vitifolium

The rusty pubescent tree *Cochlospermum vitifolium* (Willd.) Spreng. belongs to the Bixaceae family and is found in Maharashtra, Western Ghats and Indonesia. The bark and leaves of this tree are rich in saponins. It is traditionally used in the management of diabetes and as a poultice for itching and wound treatment. Padmaja *et al.,* reported that saponin extracted from *C. vitifolium* when administered orally at doses of 200, 400, and 600 mg/kg daily weight for 1 week caused a substantial drop (P0.05) (200 g to 250 g) (66).The extract of saponin lowered glucose levels in the blood by 35.98% comparison made to the metformin group after 4 to 8 days of therapy. The saponin extract's ability to lower the increased level of glucose to normal in the blood is important for the liver's recovery to normal homeostasis in rats having diabetes. This study shows that the anti-diabetic action of saponin from the leaves of *C. vitifolium* is in part due to the generation of insulin from the pancreatic cells in existence (66).

Diosgenin (DSG)

Diosgeninis a a steroid saponin found in fenugreek seeds (*Trigonella foenum-graecum* L.) and wild yam root tubers (*Dioscorea villosa* L.) (67). Wild yam tubers and fenugreek seeds are traditionally used as the preventative or therapeutic treatment of cancer, arthritis, diabetes, high cholesterol, gastro-intestinal issues and inflammation. According to data from several traditional medical practices (68). Diosgenin, when given orally to pregnant mice (C57BL/KsJdb/+ (db/+, heterozygous, 6–8-week-old, 18 g to 22 g) cured the gestational diabetes evidenced by the improvements in insulin tolerance, glucose level and increased level of liver glucose. Under conditions of gestational diabetes, diosgenin lowered TBARS levels, raised GSH levels and boosted the activity of antioxidant enzymes such as catalase and superoxide dismutase. Diosgenin could also impel aberrant changes in the pregnant mice's lipid profiles by inhibiting sterol-controlled binding protein-1, suggesting that lipid profile attenuation may contribute to anti-diabetic advantages of diosgenin in gestational diabetes in animals (69).

Entada phaseoloides

Entada phaseoloides (L.) Merr. is a species of the family Leguminosae found in Southern China. One subgroup of China's ethnic people, have been traditionally using the seeds of this plant as a medicine for the treatment of abdomen discomfort, edema, and diabetes, according to *Bencao Gangmu,* a material medica dating back to Ming dynasty, circa before 600 years (70). Seeds of *Entada phaseoloides* contain a group of metabolic compounds identified as saponins. (70). Zheng *et al.,* tried to explore the effect of total saponins extracted from *Entada phaseoloides* in the treatment of rats having type-2 diabetes (70). T2DM rats induced with a low-dose Streptozotocin and fat-rich diet were then given various oral dosages of *E. phaseoloides* extract *via* an intra-gastric tube, every day between 12:00 and 02:00 p.m., for 21 days. Sponin from *E. phaseoloides* enhanced the lipid profile as well as lowered serum glucose levels. Saponin's hypoglycaemic impact is achieved through reducing insulin resistance, preserving the islets, and increasing the production of insulin (70).

Fenugreek

Fenugreek (*Trigonella foenum-graecum* L.) is a leguminous herb grown widely in India, Pakistan, the Middle East and Egypt (71). Fenugreek seeds possess lysine, mucilaginous fiber, L-tryptophan-rich protein and other chemicals such as sapogenins, saponins, trigonelline and phytic acid which are known to be responsible for many of the predetermined therapeutic effects of the seeds of fenugreek.'. The saponin is suggested to be helping to reduce blood sugar levels by inhibiting cholesterol absorption (72). Fenugreek observed a novel alternative treatment for diabetic patients. Fenugreek ingestion can lower serum biochemical indicators such as urea, uric acid, blood glucose, serum lipid profile, and creatinine and elicit good result in liver function test. Fenugreek seeds are shown to be helping diabetic rats treated with alloxan to keep the normal histological state of their islet cells (73). Saponins contained in fenugreek seeds are responsible for this action of fenugreek seeds, according to another study also (74). Saponin has anti-diabetic properties because it slows down stomach emptying and in the mean time blocks the carbohydrate digesting enzymes (75) and boosts the production of insulin (76).

Momordica cymbalaria

Momordica cymbalaria (Hook, Fenzl) is a vine related to bitter gourd (*M. charantia*) that grows in Andhra Pradesh and Karnataka states in India (77). It is used as an abortifacient and to treat diabetes mellitus in traditional Chinese medicine. Koneri *et al*. (78) extracted saponin from the root of *M. cymbalaria* and tested it in male Swiss albino mice (25 g to 35 g) with STZ-induced diabetes. For one month, Per Peros, 100 mg/kg body weight of saponin was administered. Saponin, a constituent of *M. cymbalaria*, was proven to decrease glucose levels in the blood and increase the β-cell density, possibly due to β-cell regeneration and calcium channel modulation (78).

Red ginseng (*Panax ginseng*)

In India, Ginseng is grown commercially in Tripura, Himachal Pradesh, Uttarakhand and Maharashtra. Red Ginseng has several ginsenosides with various biological properties. Ginsenosides, in particular, have distinct components depending on how they are processed. Recent research has discovered that ginsenosides from Korean red ginseng, having polarity have actions on biological systems rendering them properties like anti-tumor actions (79). Choi *et al*. intended to explore whether saponin affected the development of diabetes in chronic ethanol-exposed mice (79). Male Otsuka Longer Evans Tokushima Fatty (OLETF) rats, 14 weeks old, were used to induce diabetes because these rats have symptoms like a long-term illness, hyperglycemia, modest obesity and pancreatic abnormalities. The rats were given saponin extract from steam-treated Korean red ginseng (200 mg/kg body weight) intraperitoneally every day. Therapy by the using of saponin acquired enhanced glucose metabolism, which had been hampered by log term ethanol intake, and led to a considerable reduction in weight of adipose tissue as well as lipids including cholesterol and triacylglycerol. They went on to say that saponin could help slowing down the progression of diabetes caused by chronic alcohol intake and that it could potentially be used by diabetic patients who intake alcohol regularly (80). Other plants containing saponins with anti-diabetic activity are summarised in Table 1.

Mechanism action of saponin in diabetes

Diabetes is a significant long-term disorder globally which causes death and it is frequently accompanied by various complications like neuropathy, retinopathy, nephropathy and cardiovascular problems (81). Diabetes mellitus is linked to long-term macro- and microvascular complications which considerably increases the chances of morbidity and death (82). The progression of diabetic mellitus is aided by oxidative stress as it promotes the creation of free radicals, which can aggravate the problems (83). Reactive Oxygen Species (ROS) are produced by oxidative stress, and can exert their harmful effects oncell generation, growth, and survival of the individual (84). The synthesis of Advanced Glycation End-Products (AGEP) can have can have a significant link to problems related to diabetes and can lead to oxidative stress (85). Free radicals produced by oxidative stress can facilitate and accelerate programmed cell death (86). By interacting with polyunsaturated fatty acids in the lipid membrane, oxidative stress also induces lipid peroxidation (87). Several workers have pointed out the wide variety of biological roles played by saponins (88). Their healing properties against diabetes seems, the most important (89, 90) (Fig. 3).

In STZ-diabetic rats, saponin, extracted from the sea cucumber *Holothuria thomasi*, exhibits a significant hypoglycaemic impact (1), as it promotes releases, insulin action, β-cell reformation, and glucose utilization enzyme activation (58). Beta-sitosterol-beta-D-glucoside and 5.25 stigmadien-3-beta-ol glycoside make up charantin, a mix of steroidal saponin (59). Hypoglycaemic extract enhances

Table 1. Saponins with anti-diabetic activity

S. No.	Plant	Family	Diabetes inducing agent	Mechanism of action	References
1	Astragaloside IV	Fabaceae	Streptozotocin- induced	Inhibition of endoplasmic reticulum stress.	53
2	*Berberis vulgaris*	Berberidaceae	Streptozotocin- induced	Effect of stimulation on the remaining β cells	54
3	Bitter gourd (*Momordicacharantia*)	Cucurbitaceae	-	Stop the enzymes from converting disaccharides into monosaccharides to lower the rise in blood sugar.	60
4	Bitter kola (*Garcinia kola*)	Clusiaceae	Alloxan induced	decrease in the generation of MDA and a considerable increase in the activity of free radical-scavenging enzymes like SOD and catalase	63
5	*Cochlospermumvitifolium*	Cochlospermaceae	Alloxan induced	reduce high blood sugar levels, mostly as a result of the pancreas's existing cells releasing insulin.	66
6	*Entadaphaseoloides*	Fabaceae	Streptozotocin- induced	By reducing insulin resistance, safeguarding islet -cells, and increasing insulin secretion	70
7	Fenugreek (*Trigonellafoenum-graecum*)	Papilionaceae	Alloxan induced	Slow stomach emptying, suppression of the enzymes that break down carbohydrates, and stimulation of the insulin secretion	71
8	*Momordicacymbalaria*	Berberidaceae.	Streptozotocin- induced	Lower blood glucose level	78
9	Red ginseng (*Panax ginseng*)	Araliaceae	Streptozotocin- induced	Enhancement of glucose metabolism	79
10	Sea cucumber saponin (Holothurians)		Streptozotocin- induced	Hexadecanoic acid, octadecanoic acid, and eicosanoic acid all possess insulin secretion, insulin stimulation, and -glucosidase inhibitors, which have already been used to demonstrate their anti -diabetic efficacy.	91
11	*Solanumanguivi* Fruit	Solanaceae	Alloxan induced	Through increasing the activity of antioxidant enzymes like CAT and SOD	85

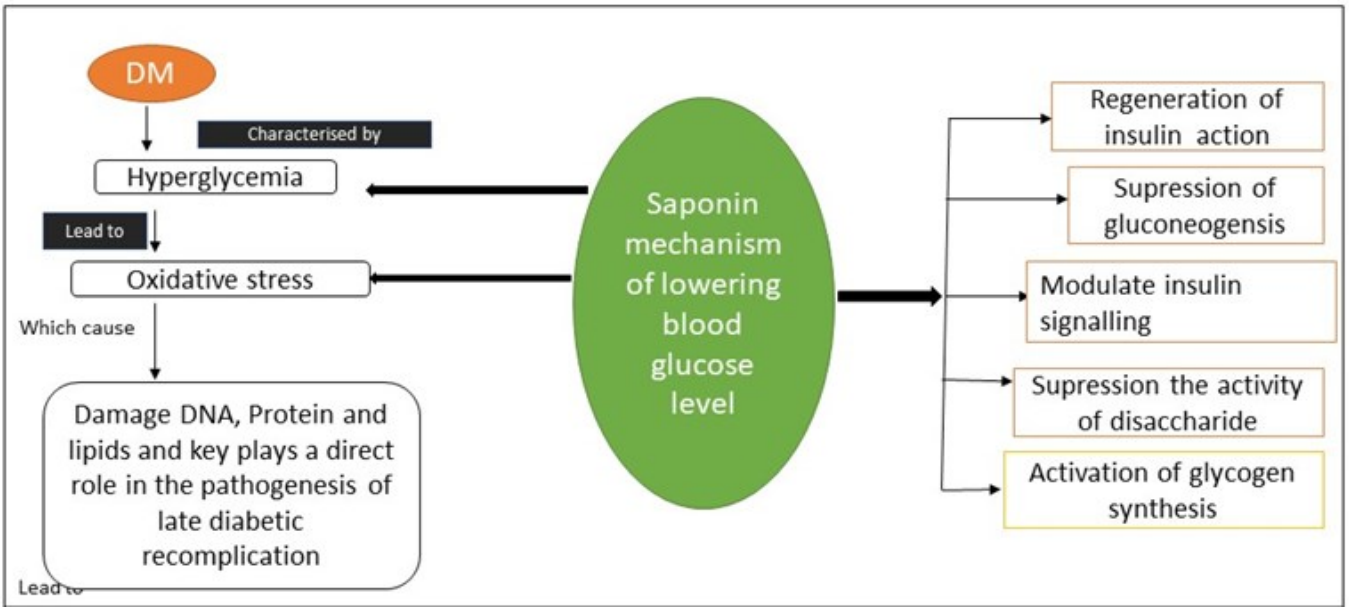

Fig. 3. Mechanism of saponin as anti-diabetic activity.

the islet of Langerhans in production of insulin, glucose intake and serum protein levels. Hypoglycaemic saponin enhances the oxidation of glucose by interfering with glucose-6-phosphate dehydrogenase through the shunting route while inhibiting glucose-6-phosphate and fructose-1,6 bisphosphates. Charantin boosts insulin production from β-cells in pancreatic islets by promoting insulin growth-secreting β cells (59). The anti-diabetic activity of this chemical is an increase in plasma insulin levels and a reduction in blood glucose. Saponin is a useful antioxidant in diabetes mellitus therapy because of its ability to reduce blood glucose levels. The hypoglycaemic impact of saponin is mediated *via* insulin rejuvenation, insulin signalling alteration insulin release from β-cell islets (55), glycogen synthesis activation, inhibition of disaccharide activity, inhibition of glucosidase activity, inhibition of gluconeogenesis, inhibition of glucose 6-phosphatasemRNA expression, up-regulation and stopping of glycogen phosphorylase.

Conclusion

This article reviews the fundamental functions of saponin as an anti-diabetic drug. Hypoglycaemic action has been reported in saponins from diverse plants and marine animals. The antioxidant activity of saponins allows it to regulate blood glucose level and to prevent complications in diabetic patients. Saponin-induced dyslipidemia will help diabetic people in lowering their risk of cardiovascular disease and atherosclerosis. However, more study is required to assess the relevance of saponins in the treatment of diabetes and for the better understanding of their pharmacology.

Acknowledgements

The authors gratefully acknowledge the Management of Noida Institute of Engineering and Technology (Pharmacy Institute), Greater Noida for their cooperation to complete the screening work.

Authors contributions

All the authors contributed equally to this paper.

Compliance with ethical standards

Conflict of interest: All authors declare that they have no conflict of interest.

Ethical issues: None.

References

1. Kumar CR. Basic pathology. 5th ed. Bangalore: Prism PVT. Limited; 1992. p. 569-87.
2. Ross JS, Wilson KJ, Waugh A. Anatomy and physiology in health and illness. 9th ed. Churchill Livingstone; 1996.Federation ID. IDF diabetes atlas.
3. Medagama AB, Bandara R. The use of complementary and alternative medicines (CAMs) in the treatment of diabetes mellitus: is continued use safe and effective? Nutr J. 2014 Dec;13(1):102. https://doi.org/10.1186/1475-2891-13-102
4. Alqathama A, Alluhiabi G, Baghdadi H, Aljahani L, Khan O, Jabal S *et al*. Herbal medicine from the perspective of type II diabetic patients and physicians: what is the relationship? BMC Complement Med Ther. 2020 Dec;20(1):65. https://doi.org/10.1186/s12906-020-2854-4
5. Kesavadev J, Saboo B, Sadikot S, Das AK, Joshi S, Chawla R *et al*. Unproven therapies for diabetes and their implications. Adv Ther. 2017 Jan;34(1):60-77. https://doi.org/10.1007/s12325-016-0439-x
6. Wandstrat A, Wakeland E. The genetics of complex autoimmune diseases: non-MHC susceptibility genes. Nat Immunol. 2001 Sep;2(9):802-9. https://doi.org/10.1038/ni0901-802
7. Atkinson MA, Eisenbarth GS. Type 1 diabetes: new perspectives on disease pathogenesis and treatment. Lancet. 2001 Jul 21;358 (9277):221-9. https://doi.org/10.1016/S0140-6736(01)05415-0
8. Alemu S, Dessie A, Seid E, Bard E, Lee PT, Trimble ER *et al*. Insulin-requiring diabetes in rural Ethiopia: should we reopen the case for malnutrition-related diabetes? Diabetologia. 2009

Sep;52(9):1842-5. https://doi.org/10.1007/s00125-009-1433-5

9. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004 May 1;27(5):1047-53. https://doi.org/10.2337/diacare.27.5.1047
10. Gupta OP, Joshi MH, Dave SK. Prevalence of diabetes in India. Adv Metab Disord. 1978;9:147-65. https://doi.org/10.1016/b978-0-12-027309-6.50013-6
11. De Fronzo RA, Bonadonna RC, Ferrannini E. Pathogenesis of NIDDM, International Textbook of diabetes mellitus. Alberti K, Zimmet P, DeFronzo. Rev 1997.
12. Jun H-S, Yoon J-W. A new look at viruses in type 1 diabetes. ILAR J. 2004 Jan 1;45(3):349-74. https://doi.org/10.1093/ilar.45.3.349
13. WHO? Study Group Diabetes Mellitus, Technical report series no. 727. Geneva: World Health Organization; 1985.
14. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics. 2005 Mar;115(3):e290-6. https://doi.org/10.1542/peds.2004-1808
15. Leonardo Jacob S. Pharmacology. The national medical series from Williams and Wilkins Bart arco, Hong Kong, London. 3rd ed; 1987. p. 221-5.
16. Bloom A, Hayes TM, Gamble DR. Register of newly diagnosed diabetic children. Br Med J. 1975 Sep 6;3(5983):580-3. https://doi.org/10.1136/bmj.3.5983.580
17. Tripathi KD. Essentials of medical pharmacology. JP Medical Ltd; 2013 Sep 30.
18. Dyck PJ, Kratz KM, Karnes JL, Litchy WJ, Klein R, Pach JM *et al*. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. Neurology. 1993 Apr 1;43(4):817-24. https://doi.org/10.1212/wnl.43.4.817, PMID 8469345
19. Harris MI. Undiagnosed NIDDM: clinical and public health issues. Diabetes Care. 1993 Apr 1;16(4):642-52. https://doi.org/10.2337/diacare.16.4.642
20. Jun HS, Yoon JW. A new look at viruses in Type 1 diabetes. Diabetes Metab Res Rev. 2003;19(1):8-31. https://doi.org/10.1002/dmrr.337
21. Verge CF, Gianani R, Kawasaki E, Yu L, Pietropaolo M, Jackson RA *et al*. Predicting type I diabetes in first-degree relatives using a combination of insulin, GAD, and ICA512bdc/IA-2autoantibodiesDiabetes. Diabetes. 1996;45(7):926-33. https://doi.org/10.2337/diab.45.7.926
22. Mohan V, Pradeepan R. Epidemiology of diabetes in different regions of India. 2009;22:1-18.
23. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of Medical Care in Diabetes–2019. Diabetes Care. 2019;42;Suppl 1;Suppl 1:S13-28:S13-28. https://doi.org/10.2337/dc19-S002
24. Knight K, Badamgarav E, Henning JM, Hasselblad V, Gano Jr AD, Ofman JJ *et al*. A systematic review of diabetes disease management programs. Am J Manag Care. 2005 Apr 1;11(4):242-50
25. Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC *et al*. Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. Diabetes Care. 2016 Nov 1;39(11):2065-79. https://doi.org/10.2337/dc16-1728
26. Khan MU. Lifestyle modification in the prevention of type II diabetes mellitus. Oman Med J. 2012;27(2):170-1. https://doi.org/10.5001/omj.2012.36
27. Bhoyar PK, Tripathi AK, Baheti JR, Biyani D. Herbal antidiabetics: a review. Int J Res Pharm Sci. 2011;2:30-7.
28. Thulé PM. Mechanisms of current therapies for diabetes mellitus type 2. Adv Physiol Educ. 2012;36(4):275-83. https://doi.org/10.1152/advan.00094.2012
29. DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. Ann Intern Med. 1999;131(4):281-303. https://doi.org/10.7326/0003-4819-131-4-199908170-00008
30. Goldberg RB, Kendall DM, Deeg MA, Buse JB, Zagar AJ, Pinaire JA *et al*. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. Diabetes Care. 2005 Jul 1;28(7):1547-54. https://doi.org/10.2337/diacare.28.7.1547
31. Jovanovic L, Dailey G III, Huang WC, Strange P, Goldstein BJ. Repaglinide in type 2 diabetes: A 24-week, fixed-dose efficacy and safety study. J Clin Pharmacol. 2000;40(1):49-57. https://doi.org/10.1177/00912700022008694
32. Yakubu OE, Imo C, Shaibu C, Akighir J, Ameh DS. Effects of ethanolic Leaf and Stem-bark Extracts of Adansonia digitate in alloxan-induced Diabetic Wistar rats. J Pharmacol Toxicol. 2019;15(1):1-7. https://doi.org/10.3923/jpt.2020.1.7
33. Chan CH, Ngoh GC, Yusoff R. A brief review on antidiabetic plants: global distribution, active ingredients, extraction techniques, and acting mechanisms. Pharmacogn Rev. 2012;6(11):22-8. https://doi.org/10.4103/0973-7847.95854
34. Evans M. A guide to herbal remedies; ISBN-10: 8122201628. Delhi, India: Orient Paperbacks; 1994.
35. Patel DK, Prasad SK, Kumar R, Hemalatha S. An overview on antidiabetic medicinal plants having insulin mimetic property. Asian Pac J Trop Biomed. 2012;2(4):320-30. https://doi.org/10.1016/S2221-1691(12)60032-X
36. Malviya N, Jain S, Malviya S. Antidiabetic potential of medicinal plants. Acta Pol Pharm. 2010;67(2):113-8. PMID 20369787
37. Grover JK, Yadav S, Vats V. Medicinal plants of India with antidiabetic potential. J Ethnopharmacol. 2002;81(1):81-100. https://doi.org/10.1016/s0378-8741(02)00059-4
38. Aggarwal N, Aggarwal S. A review of recent investigations on medicinal herbs possessing AntiDiabetic properties. J Nutr Disord Ther. 2011. https://doi.org/10.4172/jndt.1000102
39. Kayarohanam S, Kavimani S. Current trends of plants having antidiabetic activity: a review. J Bioanal Biomed. 2015;7:55-65. https://doi.org/10.4172/1948-593X.1000124
40. Sharma V, Paliwal R. Isolation and characterization of saponin from *Moringa oleifera* (Moringaeceae) pods. Int J Pharm Pharm Sci. 2013;5(1):179-83.
41. Moghimipour E, Kooshapour H, Parkhideh S, Handali S. In-vitro evaluation of complex forming affinity of total saponins extracted from *Ziziphus spina-christi* and Quillajasaponaria with cholesterol. Res J Pharm Biol Chem Sci. 2015 Sep 1;6(5):619-24.
42. Kim SH, Hyun SH, Choung SY. Anti-diabetic effect of cinnamon extract on blood glucose in db/db mice. J Ethnopharmacol. 2006 Mar 8;104(1-2):119-23. https://doi.org/10.1016/j.jep.2005.08.059
43. Saliu JA, Fapohunda O. The antihyperglycemic, hepatoprotective and renoprotective potentials of the aqueous extract of *Costus lucanusianus* on streptozotocin-induced diabetic rats. JALSI. 2016;4(2):1-10. https://doi.org/10.9734/JALSI/2016/20781
44. Das TK, Banerjee D, Chakraborty D, Pakhira MC, Shrivastava B, Kuhad RC. Saponin: role in animal system. Vet World. 2012 Apr 1;5(4):248. https://doi.org/10.5455/vetworld.2012.248-254
45. Yingzi L, Haoran L, Jiansong Z. Total saponins of CornusofficinalisSieb. ameliorates the endothelium-dependent relaxation of mesenteric artery by regulating nitric oxide release in streptozotocin-induced diabetic rats. J Cent S Univ. 2012;37(8):757-64. https://doi.org/10.3969/j.issn.1672-7347.2012.08.001
46. Elekofehinti OO, Adanlawo IG, Saliu JA, Sodehinde SA. Saponins

from Solanum anguivi fruits exhibit hypolipidemic potential in Rattusnovergicus. Pharm Lett. 2012;4(3):811-4.

47. Adiukwu PC, Kayanja FIB, Nambatya G, Adzu B, Twinomujuni S, Twikirize O *et al*. Anti–inflammatory and antipyretic activity of the Leaf, root and saponin fraction from *Vernonia amygdalina*. Br J Pharmacol Toxicol. 2013;4(2):33-40. https://doi.org/10.19026/bjpt.4.5375

48. Perumal PS, Anaswara PV, Muthuraman A, Krishan S. Therapeutic potency of saponin rich aqueous extract of Scoparia dulcis L. In alloxan-induced diabetes in rats. Ayu. 2014;35(2):211-7. https://doi.org/10.4103/0974-8520.146261

49. Xiao F, Hu YG, Wu SN, Shou QY, Cai YQ, Wang HM *et al*. Protective effect of astragalus saponin extracts on kidneys of diabetic rats. [Zhongguo Zhong yao za zhi= Zhongguozhongyaozazhi=]. China J Chin Mater Med. 2015 May 1;40(10):2014-8.PMID26390666.

50. Benmehdi H, Azzi R, Djaziri R, Lahfa F, Benariba N, Tabti B. Effect of saponosides crude extract isolated from *Citrullus colocynthis* (L.) seeds on blood glucose level in normal and streptozotocin induced diabetic rats. J Med Plants Res. 2011 Dec 16;5(31):6864-8. https://doi.org/10.5897/JMPR11.1369

51. Patel SB, Santani D, Shah MB, Patel VS. Anti-hyperglycemic and anti-hyperlipidemic effects of *Bryonia laciniosa* seed extract and its saponin fraction in streptozotocin-induced diabetes in rats. J Young Pharm. 2012 Jul 1;4(3):171-6. https://doi.org/10.4103/0975-1483.100024

52. Zhang K, Pugliese M, Pugliese A, Passantino A. Biological active ingredients of traditional Chinese herb *Astragalus membranaceus* on treatment of diabetes: a systematic review. Mini Rev Med Chem. 2015 Apr 1;15(4):315-29. https://doi.org/10.2174/1389557515666150227113431

53. Wang ZS, Xiong F, Xie XH, Chen D, Pan JH, Cheng L. Astragaloside IV attenuates proteinuria in streptozotocin-induced diabetic nephropathy via the inhibition of endoplasmic reticulum stress. BMC Nephrol. 2015 Dec;16(1):44. https://doi.org/10.1186/s12882-015-0031-7

54. Meliani N, Dib A, Allali H, Tabti B. Hypoglycaemic effect of Berberis vulgaris L. in normal and streptozotocin–induced diabetic rats. Asian Pac J Trop Biomed. 2011;1(6):468-71. https://doi.org/10.1016/S2221-1691(11)60102-0

55. Joseph B, Jini D. Antidiabetic effects of *Momordica charantia* (bitter melon) and its medicinal potency. Asian Pacific Journal of Tropical Disease. 2013 Apr; 3(2): 93–102. https://doi.org/10.1016/S2222-1808(13)60052-3

56. Evandro FF, Tzi N. Bitter Gourd (*Momordica charantia*) Oils. Essential Oils in Food Preservation, Flavor and Safety on Science Direct. 2016, Pages 253-257. https://doi.org/10.1016/B978-0-12-416641-7.00028-6

57. Keller AC, Ma J, Kavalier A, He K, Brillantes AM, Kennelly EJ. Saponins from the traditional medicinal plant Momordica charantia stimulate insulin secretion in vitro. Phytomedicine. 2011 Dec 15;19(1):32-7. https://doi.org/10.1016/j.phymed.2011.06.019

58. Patel T, Parmar K, Bhatt Y, Patel Y, Patel NM. Isolation, characterization and antimicrobial activity of charantin from *Momordica charantialinn*. Fruit. Int J Drug Dev Res. 2010;2(3):0-.

59. Pitipanapong J, Chitprasert S, Goto M, Jiratchariyakul W, Sasaki M, Shotipruk A. New approach for extraction of charantin from *Momordica charantia* with pressurized liquid extraction. Sep Purif Technol. 2007 Jan 1;52(3):416-22. https://doi.org/10.1016/j.seppur.2005.11.037

60. Oishi Y, Sakamoto T, Udagawa H, Taniguchi H, Kobayashi-Hattori K, Ozawa Y *et al*. Inhibition of increases in blood glucose and serum neutral fat by *Momordica charantia* saponin fraction. Biosci Biotechnol Biochem. 2007 Mar 23;71(3):735-40. https://doi.org/10.1271/bbb.60570

61. Hamissou M, Smith AC, Carter Jr RE, Triplett II JK. Antioxidative properties of bitter gourd (*Momordica charantia*) and zucchini (Cucurbita pepo). Emirates J Food Agric. 2013 Mar 2:641-7. https://doi.org/10.9755/ejfa.v25i9.15978

62. Zhu Y, Dong Y, Qian X, Cui F, Guo Q, Zhou X *et al*. Effect of superfine grinding on antidiabetic activity of bitter melon powder. Int J Mol Sci. 2012 Nov 2;13(11):14203-18. https://doi.org/10.3390/ijms131114203

63. Richards AJ. Studies in Garcinia, dioecious tropical forest trees: agamospermy. Bot J Linn Soc. 1990 Jul 1;103(3):233-50. https://doi.org/10.1111/j.1095-8339.1990.tb00186.x

64. Adebisi AA. A Case Study of Garcinia kola nut Production- to–Consumption System in J4 area of Omo Forest Reserve, South–West Nigeria; 1991.

65. Smith AYR, Adanlawo IG. *In vitro* and *in vivo* antioxidant activity of saponin extracted from the root of *Garcinia kola* (bitter kola) on alloxan–induced diabetic rats. WJPPS. 2014;3(7):08-26.

66. Padmaja V, Eshwar MC, Naik AS. In vivo screening of hypoglycaemic activity of *Cochlospermum vitifolium* on alloxan–induced diabetic rats. IJPR Jour. 2014;4(1):55-8.

67. Taylor WG, Elder JL, Chang PR, Richards KW. Microdetermination of diosgenin from fenugreek (*Trigonella foenum-graecum*) seeds [*Trigonella foenum*—graecum]. J Agric Food Chem. 2000; Nov 20;48(11):5206-10. https://doi.org/10.1021/jf000467t

68. Hua S, Li Y, Su L, Liu X. Diosgenin ameliorates gestational diabetes through inhibition of sterol regulatory element-binding protein-1. Biomedicine & Pharmacotherapy. 2016 Dec 1;84:1460-5. https://doi.org/10.1016/j.biopha.2016.10.049

69. Hua S, Li Y, Su L, Liu X. Diosgenin ameliorates gestational diabetes through inhibition of sterol regulatory element-binding protein-1. Biomed Pharmacother. 2016 Dec 1;84:1460-5. https://doi.org/10.1016/j.biopha.2016.10.049

70. Zheng T, Shu G, Yang Z, Mo S, Zhao Y, Mei Z. Antidiabetic effect of total saponins from *Entada phaseoloides* (L.) Merr. in type 2 diabetic rats. J Ethnopharmacol. 2012 Feb 15;139(3):814-21. https://doi.org/10.1016/j.jep.2011.12.025

71. Alarcon-Aguilara FJ, Roman-Ramos R, Perez-Gutierrez S, Aguilar -Contreras A, Contreras-Weber CC, Flores-Saenz JL. Study of the anti-hyperglycemic effect of plants used as antidiabetics. J Ethnopharmacol. 1998 Jun 1;61(2):101-10. https://doi.org/10.1016/s0378-8741(98)00020-8

72. Billaud C, Adrian J. Fenugreek: composition, nutritional value and physiological properties. Sci Ailment. 2001;21(1):3-26.

73. Ramesh BK, Yogesh RH, Kantikar SM, Prakash KB. Antidiabetic and histopathological analysis of fenugreek extract on alloxan induced diabetic rats. Int J Drug Dev Res. 2010;2(20):356-64.

74. Petit PR, Sauvaire YD, Hillaire-Buys DM, Leconte OM, Baissac YG, Ponsin GR *et al*. Steroid saponins from fenugreek seeds: extraction, purification, and pharmacological investigation on feeding behavior and plasma cholesterol. Steroids. 1995 Oct 1;60 (10):674-80. https://doi.org/10.1016/0039-128x(95)00090-d

75. Ali L, Azad Khan AK, Hassan Z, Mosihuzzaman M, Nahar N, Nasreen T *et al*. Characterization of the hypoglycemic effects of *Trigonella foenumgraecum* seed. Planta Med. 1995 Aug;61 (4):358-60. https://doi.org/10.1055/s-2006-958100

76. Sauvaire Y, Petit P, Broca C, Manteghetti M, Baissac Y, Fernandez -Alvarez J *et al*. 4-Hydroxyisoleucine: a novel amino acid potentiator of insulin secretion. Diabetes. 1998 Feb 1;47(2):206-10. https://doi.org/10.2337/diab.47.2.206

77. Parvathi S, Kumar VJF. Studies on chemical composition and utilization of the wild edible vegetable athalakkai (*Momordica tuberosa*). Plant Foods Hum Nutr. 2002;57(3-4):215-22. https://doi.org/10.1023/a:1021884406024

78. Koneri RB, Samaddar S, Simi SM, Rao ST. Neuroprotective effect of a triterpenoid saponin isolated from Momordica cymbalariaFenzl in diabetic peripheral neuropathy. Indian J Pharmacol. 2014 Jan;46(1):76-81. https://doi.org/10.4103/0253-7613.125179

79. Ha YW, Lim SS, Ha IJ, Na YC, Seo JJ, Shin H *et al*. Preparative isolation of four ginsenosides from Korean red ginseng (steam-treated *Panax ginseng* CA Meyer), by high-speed counter-current chromatography coupled with evaporative light scattering detection. J Chromatogr A. 2007 Jun 1;1151(1-2):37-44. https://doi.org/10.1016/j.chroma.2007.01.038

80. Choi MR, Kwak SM, Bang SH, Jeong JE, Kim DJ. Chronic saponin treatment attenuates damage to the pancreas in chronic alcohol-treated diabetic rats. J Ginseng Res. 2017 Oct 1;41(4):503-12. https://doi.org/10.1016/j.jgr.2016.09.002

81. Jung KI, Ju A, Lee HM, Lee SS, Song CH, Won WY *et al*. Chronic ethanol ingestion, type 2 diabetes mellitus, and brain– derived neurotrophic factor (BDNF) in rats. Neurosci Lett. 2011;487 (2):149-52. https://doi.org/10.1016/j.neulet.2010.10.011

82. Ebrahimi E, Shirali S, Talaei R. The protective effect of marigold hydroalcoholic extract in STZ–induced diabetic rats: evaluation of cardiac and pancreatic biomarkers in the serum. J Bot. 2016;2016:1-6. https://doi.org/10.1155/2016/9803928

83. Xi Y, Bu S. Stem cells therapy in diabetes mellitus. J Stem Cell Res Ther. 2014;4:1-6.

84. Karasu C. Glycoxidative stress and cardiovascular complications in experimentally– induced diabetes: effects of antioxidant treatment. Open Cardiovasc Med J. 2010;4:240-56. https://doi.org/10.2174/1874192401004010240

85. Deavall DG, Martin EA, Horner JM, Roberts R. Drug-induced oxidative stress and toxicity. J Toxicol. 2012 Oct;2012:645460. https://doi.org/10.1155/2012/645460

86. Villeneuve LM, Natarajan R. The role of epigenetics in the pathology of diabetic complications. Am J Physiol Ren Physiol. 2010;299(1):F14-25. https://doi.org/10.1152/ajprenal.00200.2010

87. Rother KI. Diabetes treatment–bridging divide. N Engl J Med. 2007;356(15):1499-501–14501. https://doi.org/10.1056/NEJMp078030

88. Barrera G. Oxidative stress and lipid peroxidation products in cancer progression and therapy. ISRN Oncol. 2012;2012:137289. https://doi.org/10.5402/2012/137289

89. Smith YA, Adanlawo IG, Oni OS. Hypoglycaemic effect of saponin from the root of *Garcinia kola* (bitter kola) on alloxan–induced diabetic rats. J Drug Delivery Ther. 2012;2(6):9-12. https://doi.org/10.22270/jddt.v2i6.338

90. Kumar DS, Sharathnath KV, Yogeswaran P, Harani A, Sudhakar K, Sudha P *et al*. Medicinal potency of *Momordica charantia*. Int J Pharm Sci Rev Res. 2010;1(2):18.

91. El Barky AR, Hussein SA, Alm-Eldeen AA, Hafez YA, Mohamed TM. Anti-diabetic activity of *Holothuria thomasi* saponin. Biomed Pharmacother. 2016 Dec 1;84:1472-87. https://doi.org/10.1016/j.biopha.2016.10.002