Saponins and their potential role in diabetes mellitus

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ABSTRACT

Diabetes Mellitus (DM) is a chronic metabolic disorder characterized by an increase in the serum blood glucose levels. DM resulted from defects in insulin secretion, action, or both of them. The chronic hyperglycemia resulted from diabetes can lead to irreversible damage, dysfunction and failure of various organs. Glycosidic compounds namely, saponins, are shown to have potential therapeutic benefits and are theorized as an alternative medication in decreasing serum blood glucose level in patients they suffering from diabetes. This review article aimed to elucidate the antidiabetic activity of saponins as well as showed their merit that makes them ideal for antidiabetic remediation.

Introduction

Diabetes Mellitus (DM), represents a universal health issue that distinguished by hyperglycemia that stimulates oxidative stress to occur which cause a generation of free radicals [1]. It is the most predominant disease in the world in which the number of diabetic patients will reach 592 million by 2035 [2,3]. It gives rise to numerous complications, for instance, retinopathy, neuropathy and peripheral vascular disease [4]. Distinct pathogenic processes are implicated in the progression of diabetes. These vary from autoimmune destruction of the β-cells of the pancreas with resultant in insulin deficiency to abnormalities that result in resistance to insulin action. The basic role of the abnormalities in the metabolism of carbohydrate, fat, and protein in diabetes is due to the deficient action of insulin on target tissues [5]. Diabetes is classified into four categories: First category is Type I, also known as Insulin-dependent diabetes mellitus (IDDM), which is identified by absolute insulin deficiency. The main causes of type I diabetes are immune or idiopathic causes [6], whereas Type II diabetes the second category is known as Noninsulin-Dependent Diabetes Mellitus (NIDDM) which is recognized by tissue resistance to the action of insulin combined with a relative insufficiency in insulin secretion. Insulin is produced by the β cells in these patients, but, it is incompetent to conquer the resistance, which leads to increment of blood glucose level. The impaired insulin action also influences fat metabolism, give rise to increased free fatty acid, triacylglycerol and diminishes high-density lipoprotein level [6]. The third category, other specific types of diabetes such as (a) Genetic defects of the β-cell, they are pointed to diabetes in a young age which known as Maturity-Onset Diabetes of the Young (MODY) and they are distinguished by impaired insulin secretion with lower insulin action [7]. (b) Genetic defects in insulin action, there are uncommon causes of diabetes that result from genetic abnormalities of insulin action. The metabolic aberration may range from hyperinsulinemia and mild hyperglycemia to severe diabetes-related with the mutations of the insulin receptor [8]. (c) Diseases of the exocrine pancreas, acquired processes that contain pancreatitis, infection, pancreatectomy, and pancreatic carcinoma. damage to the pancreas must be prolonged for diabetes to occur, for example, adenocarcinomas that include a small part of the pancreas have been associated with diabetes [9]. (d) Endocrinopathies, there are

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KEYWORDS

- diabetes
- medicinal plants
- saponin
- hyperglycaemia
- sea cucumber

many several hormones that antagonize insulin action, for instance, growth hormone, cortisol, glucagon and epinephrine hormone. Excess amounts of these hormones can lead to diabetes. This mostly occurs in individuals with pre-existing defects in insulin secretion, and hyperglycemia [9]. (e) Drugs, there are many drugs that effect on insulin secretion. These drugs may promote diabetes in individuals with insulin resistance. For examples patients that receiving α-interferon has been more exposure to developing diabetes which associated with islet cell antibodies and in some cases, severe insulin deficiency [10]. (f) Infections, diabetes can occur in patients suffering from congenital rubella, coxsackievirus B, cytomegalovirus, adenovirus and mumps [7]. (g) Uncommon forms of immune-mediated diabetes, anti-insulin receptor antibodies can lead to diabetes via binding to the insulin receptor, herewith blocking the binding of insulin to its receptor in target tissues [11]. (h) Other genetic syndromes sometimes associated with diabetes, these include the chromosomal abnormalities of Down's syndrome, Klinefelter's syndrome, and Turner's syndrome. Wolfram's syndrome is an autosomal disorder that characterized by insulin deficiency and the absence of β-cells at autopsy [12]. The fourth and last category is gestational diabetes mellitus (GDM), which known as any degree of glucose intolerance with first estimated during pregnancy [9] **(FIGURE 1)**. Regardless of the presence of anti-diabetic medicines, screening for new anti-diabetic sources from natural products is still attractive as they contain substances that have a safe effect on diabetes mellitus. Natural compounds supposedly to be suitable alternatives for diabetes therapy. They may minimize the risk of the disease. Large amounts can be consumed in daily, which is a positive aspect [13]. Saponins are amphipathic glycosides secondary metabolites which synthesized by many different plant species, have high molecular weight, consisting of a sugar moiety united to a triterpenoid or steroid sapogenins. Saponin has received numerous attention due to their various biological activities that including hepatoprotective, antitumor, antimicrobial, and anti-inflammatory activities. Marine organisms such as starfish, sponges and sea cucumbers are now considered a rich source of saponin [14,15]. Saponins have been known to possess the anti-diabetic property and are promising compounds with potential to be developed into new drugs for anti-diabetes [16,17]. So, the aim of this article review is to show some available data on saponin which isolated from some medicinal plant and marine animals with an anti-diabetic effect. It is hoped that the information will provide the reader with information regarding the anti-diabetic potential of saponins and stimulate further research into these compounds.

Chemical structure of saponin

Saponins chemically consist of two parts aglycone and glycone, the aglycone part is also known by sapogenin which classified to either triterpenoid (C-30), neutral or alkaloid steroids (C-27) [18]. The aglycone part covalently linked to one or more glycone (sugar) [19], which may be glucose, galactose, glucuronic acid, xylose or rhamnose, the oligosaccharide is attached at the C3 position but in some saponins, additional sugars are attached at C26 or C28 positions [20] **(FIGURE 2)**.

Sources of saponin for diabetic treatment

■ Anabasis articulata (Forssk) moq

Anabasis articulata locally named as 'ajrem' is a wild plant widely used in folk medicine to treat diabetes, kidney infections, fever, headache and skin diseases such as eczema [21-29]. It is taken orally after decoction in water as a single herb or with other medicinal plants. The phytochemical constituents of A. articulata revealed the presence of saponin. Segal [30] identified the type of saponin which has been isolated from A. articulata is triterpenoidsaponin. Metwally [31] administrated the saponin fractions of ethanolic extract which has been isolated from an A. articulate orally in a dose of 400 mg/kg B.W./day for 30 days to STZ-induced diabetes female Wistar albino rats weighing 180-200 g. The extract showed a beneficial glycemic control as well as it has principle role in preventing different metabolic disorders and liver damage caused by hyperglycemia. The antidiabetic activity is attributed to saponin components and its antihyperglycemic activity is through the release of insulin from the pancreas that is, it exerts a direct insulinotropic effect [31].

■ Astragaloside IV

Astragaloside IV (ASIV) is a small molecular saponin found in astragalusmembranaceus (Fisch) Bge, a herb widely used in traditional medicine in China. Recent studies have shown that the molecule has diverse pharmacological

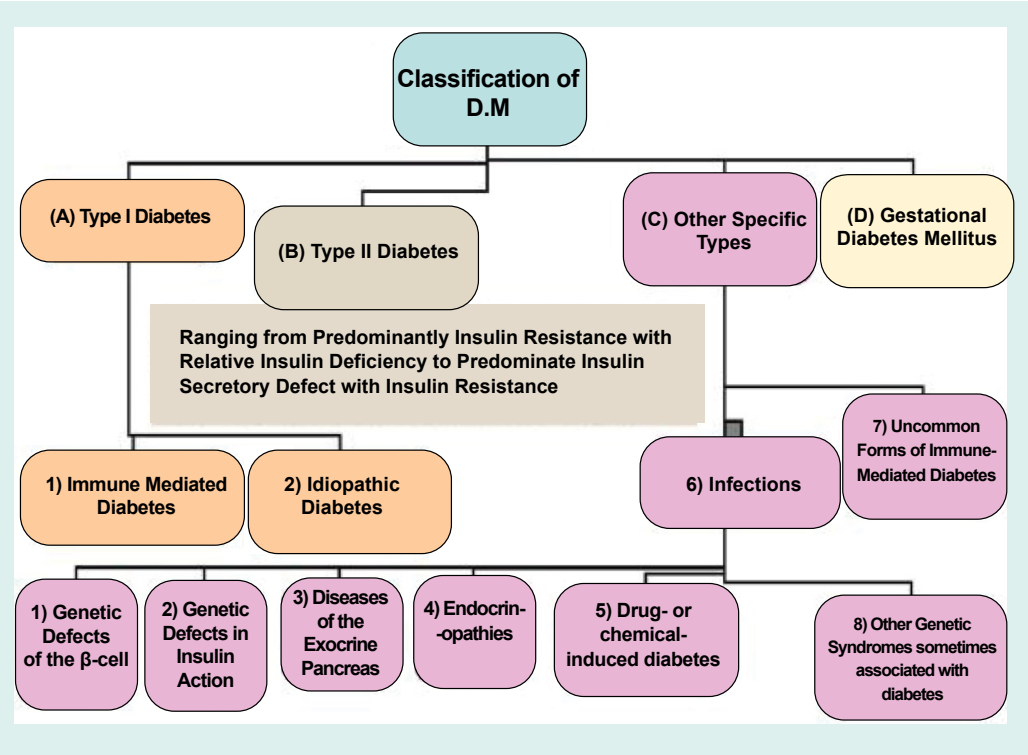

Figure 1: Classification of diabetes mellitus.

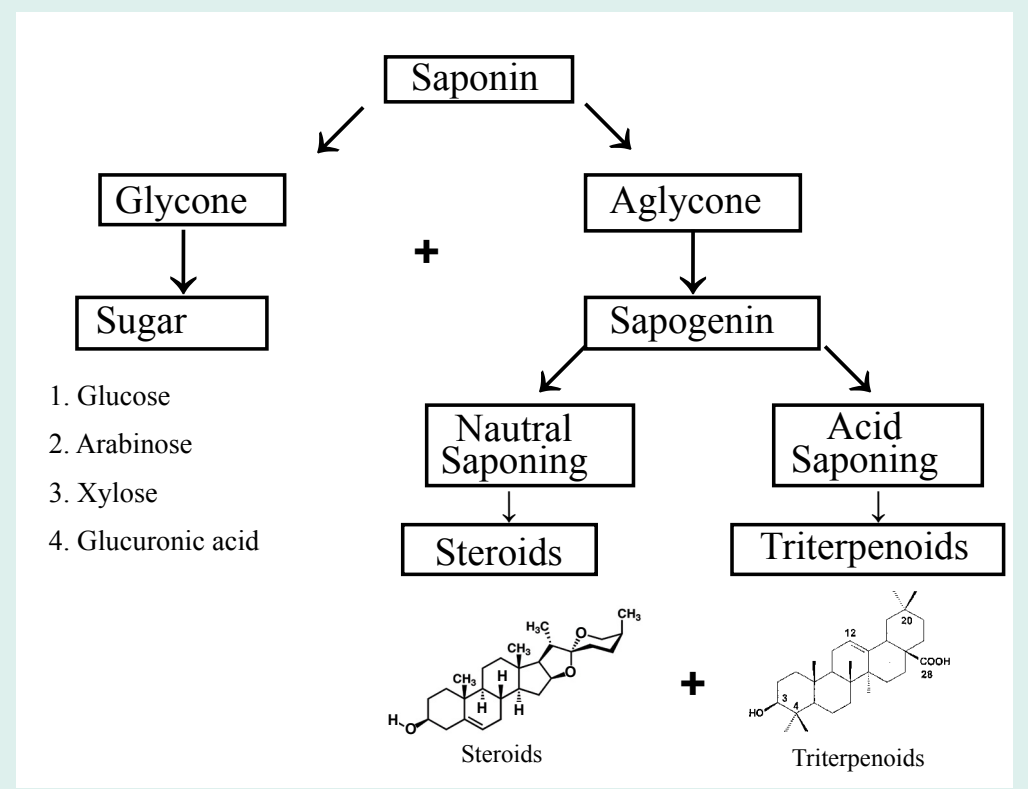

Figure 2: Saponin structure [21].

activities including anti-inflammatory, antihypertensive, antidiabetes and myocardial protective properties [32]. The various biological activities of astragalusmembranaceus, is due to their rich in anti-diabetic compounds such as saponins [33]. In a study by Wang [34] they aimed to investigate the effect of ASIV on the expression of endoplasmic reticulum (ER) stress signals in a rat streptozotocin (STZ) induced model of diabetic nephropathy (DN). Healthy male 6-week old sprague–dawley (SD) rats (180–200 g) were injected intraperitoneally with 40 mg/kg body weight STZ which has been dissolved in citrate buffer (pH 4.6) for 5 consecutive days after an overnight fast. After 2 weeks from STZ induction, ASIV (10 mg/kg/day) were administered via oral gavage daily and lasted for 8 weeks. They concluded that treatment with ASIV can ameliorate the structural and functional abnormalities present in STZ-induced rat model of diabetic nephropathy (DN), with the renoprotective activity mediated through the inhibition endoplasmic reticulum stress. This novel finding provides support for alternative therapies for the treatment of DN based on targeting the regulation of the ER stress response [34].

■ *Berberis vulgaris* linn

Berberis vulgaris (*B. vulgaris*) Linn which is commonly known as barberry belongs to the family Berberidaceae. Berberis is the genus of spiny deciduous evergreen shrubs, with yellow wood and yellow flowers, and comprises 190 species. The phytochemical tests for the extracts studied revealed the presence of tannins, alkaloids, saponins, sterols and anthraquinones [35].

Meliani [35] evaluated the role of saponin which has been extracted from the root bark of Berberis vulgaris linn. Treatment with saponins extract (25 mg/kg) was started ten days after STZ-induced diabetes male Wistar rats (190 -230 g) injection and lasted for 3 weeks. The diabetic group that treated with barberry saponin extract showed a maximum fall of 73.1% and 76.03% at day 1 and day 21 as compared to the diabetics control group. These results indicated that the hypoglycemic effect was due to the presence of saponins in the root bark of Berberis vulgaris linn which may have a stimulating effect on the remnant beta cells. In addition to hypoglycemic effect, saponins extracts showed an improvement of lipid profile and so it might be of value in diabetes treatment [35].

■ Bitter gourd (*Momordica charantia*)

Momordica charantia (*M. charantia*), also known as bitter melon, karela, balsam pear, or bitter gourd, is a popular plant used for the treating of diabetes-related conditions amongst the indigenous populations of Asia, South America, India, the Caribbean and East Africa [36], Its fruit has a distinguishing bitter taste, which is more pronounced as it ripens, hence the name bitter melon or bitter gourd. A number of reported clinical studies have shown that bitter melon extract from the fruit, seeds, and leaves contain several bioactive compounds that have hypoglycemic activity in both diabetic animals and humans [37,38], For instance, Momordicine II and 3-hydroxycucurbita-5, 24-dien-19-al-7, 23-di-O-β-glucopyranoside (4), were isolated as saponins from *M. charantia*. Both compounds showed significant insulin releasing activity in MIN6 β-cells at a concentration of 10 and 25 μg/mL [39]. The major compounds that have been isolated from bitter melon and identified as hypoglycemic agents ischarantin. Charantin is a typical cucurbitane-type triterpenoid in *M. charantia* and is a potential substance with antidiabeticproperties [40]. Pitiphanpong [41] demonstrated that charantin could be used to treat diabetes and can potentially replace diabetes treatment. Moreover, Diabetic patient that consumed fresh bitter gourd juice was shown to significantly diminish their blood glucose level and ameliorate their response to an oral glucose load test [42]. The main active ingredient of *Momordicacharantia* which present in the butanol fraction and related to the anti-diabetic effect is saponin [43]. Saponin can reduce the increment of blood glucose by inhibiting the enzymes that break down disaccharides into monosaccharides [43]. This effect is remarkable for the treatment of both Type I and Type II diabetic patients and helps to prevent high blood sugar levels postprandial. Also, bitter melon saponin has shown to prompt glycogen storage by liver and insulin secretion by islets of Langerhans [44]. In addition, saponin of bitter melon may diminish the hepatic gluconeogenesis, raise hepatic glycogen synthesis, and increase peripheral glucose oxidation in erythrocytes and adipocytes [45].

■ Bitter kola (*Garcinia kola*)

Garcinia kola is a species of flowering plant in the Clusiaceae or Guttiferae family. Its natural habitat is subtropical or tropical moist lowland forests [46]. It has been proved to be one of the

many non-timber forest products that are of high socio-economic importance [47]. The effect of saponin from the root of bitterkola in reducing oxidative stress was evaluated in diabetic Wistar albino rat's tissues in a study by Smith and Adanlawo [48]. Diabetes was induced in adult male albino rats (200 g to 250 g) by a single intraperitoneal injection of alloxan, three days after alloxan injection, the hyperglycemic rats were treated orally with saponin which has been extracted from the root of Garcinia kola at the dose of 100, 200 and 400 mg/kg body weight daily for 7 days. Saponin has beendisplayed a significant decrease of MDA production and cause a significant elevation of free radical scavenging enzyme activities such as SOD and catalase. Saponin extract has antioxidant and free radical scavenging ability and as such could be a potential source of natural antioxidant that could have a great importance as therapeutic agents in preventing or slowing the progress of diabetes [48].

■ Cochlosperumvitifolium

*Cochlosperumvitifolium*a rusty pubescent tree with white flowers belonging to family Cochlospermaceae is distributed in the Western ghats, Maharashtra and Indomalaysia. The leaves and bark of this tree rich in saponin, they are used in traditional medicine, for instance, poultice against itching, treat wounds and treatment of diabetes. In a study by Padmaja [49] they stated that a significant decrease ($P<0.05$) was observed in alloxan- induced diabetic male Wistar albino rat (200 g to 250 g), after administration of saponin which has been extractedfrom*Cochlosperumvitifolium* orally at a dose of 200, 400 and 600 mg/kg body weight daily for 7 days. Thesaponin extract led to decrease blood glucose level by 35.98% as compared to the metformin group after 3 and 7 days treatment. The capacity of the saponin extract to decrease elevated blood glucose levels to normal levels is an essential for the liver to return to its normal homeostasis in experimental diabetic rats. Furthermore, this fact indirectly indicates that the anti-diabetic effect of saponin from the leaves of *Cochlosperumviti folium*is partly due to insulin release from the existing cells of the pancreas [49].

■ Diosgenin (DSG)

Diosgenin is a major bioactive constituent of various edible pulses and roots, well characterized in the seeds of fenugreek (*Trigonella foenumgraecum* Linn) as well as in the root tubers of wild yams (*Dioscorea villosa* Linn) [50]. Data available from various traditional medical practices indicate that fenugreek seeds and wild yam tubers have been purported to be used as a preventive or therapeutic medicine against several ailments including arthritis, cancer, diabetes, gastrointestinal disorders, high cholesterol, and inflammation suggesting a variety in its use [51]. Diosgenin which is a steroid saponin, was evaluated in gestational diabetes mellitus in a study by [52], it has been administered orally at a dose of (10 and 20 mg/kg b.w.) to pregnant C57BL/KsJdb/+ (db/+, heterozygous) mice (6–8 week old, 18 g to 22 g) it showed that it could improve gestational diabetes in the pregnant mice as reflected by the improvement of glucose, insulin intolerance and increase hepatic glycogen content. Also, DSG displayed antioxidant activities as it can ameliorate oxidative stress under GD condition by decreasing TBARS content, increase GSH level, and SOD and CAT antioxidant enzymes activities. Furthermore, DSG could ameliorate the abnormal changes of lipid profiles in pregnant mice through inhibition of sterol regulatory element binding protein-1 which indicated that attenuation of abnormal changes of lipid profiles may participate in the anti-diabetic effects of DSG in GD mice [52].

■ *Entada phaseoloides* (L.) merr

Entada phaseoloides (L.) Merrcan be commonly found in southern China and belongs to the genus of Entada (family Leguminosae). It had been documented in an earlier material medica "BencaoGangmu" (Ming dynasty, about 600 years ago) that its seeds have been long used as a folk medicine by dai people, one of the ethnic minorities in China, for the treatment of stomachache, edema and diabetes mellitus [53]. Saponin is the numerous type of secondary metabolic products in the seed of entadaphaseoloides [53]. In a study by Zheng et al. [53], they aimed to evaluate the potential therapeutic effects of total saponins which have been extracted from Entadaphaseoloides in experimental type 2 diabetes mellitus rats. T2DM rats were induced by high-fat diet and low-dose streptozotocin, then different oral doses of saponin of entadaphaseoloides extract were administrated at a dose of (25, 50 and 100 mg/kg) to T2DM rats daily between 12:00 and 02:00 p.m. using an intragastric tube once a day continuously for 21 days. Entadaphaseoloidessaponin showed a significant decrease not only in serum glucose but also in the lipid profile of. Saponin exhibits its hypoglycemic

effect through ameliorating insulin resistance, protecting β-cells islets and stimulating insulin secretion [53].

■ Fenugreek (*Trigonella foenum-graecum* L. Leguminosae)

Fenugreek is an annual herb that belongs to the family Leguminosae widely grown in Pakistan, India, Egypt and Middle Eastern countries [54]. The seeds of fenugreek contain lysine, L-tryptophan rich proteins, mucilaginous fiber and other rare chemical constituents such as saponins, coumarin, fenugreekine, nicotinic acid, sapogenins, phytic acid, scopoletin and trigonelline, which are thought to account for many of its presumed therapeutic effects. Saponin of fenugreek may inhibit cholesterol absorption and thought to help lower sugar levels [55]. Fenugreek may be considered a new alternative medication for the diabetic patient. The consumption of fenugreek can decrease serum biochemical parameters like blood glucose level, urea, creatinine, uric acid, liver function test and serum lipid profile. Also, fenugreek can preserve the normal histological architecture of the islets cells of pancreatic tissues of diabetic rats that treated with alloxan [56]. The activity of fenugreek has been attributed to saponins [57]. Saponin has anti-diabetic activity as it could slow gastric emptying, inhibiting of carbohydrate digestive enzymes [58] and stimulating of insulin secretion [59].

■ Momordicacymbalariafenzel

MomordicacymbalariaFenzl is a vine of the Momordica genus found in the Indian states of Andhra Pradesh, Karnataka [60]. It is used in the local folk medicine as an abortifacient and for the treatment of diabetes mellitus. It is a relative of the bitter melon plant. In a study by Koneri [61], they have been isolated saponin from the root of *Momordicacymbalaria*and evaluated their role in STZ-induced diabetes in male Swiss albino mice (25 g to 35 g). Saponin was administrated at a dose of (100 mg/kg B.Wt.) daily Peros for one month. Saponin which is the ingredient part of *Momordicacymbalaria* possesses a potential role in diabetes as it could lower blood glucose level and have shown to improve beta cell density which may be attributed to modulation of calcium channel, and beta-cell regeneration [61].

■ Red ginseng (*Panax ginseng*)

Ginseng (*Panax ginseng* C. A. Meyer) has been well known to have a variety of ginsenosides that show diverse biological activities. Especially, the components of ginsenosides are quite different depending on the processing method. Recently, there have been several reports showing that less polar ginsenosides from Korean red ginseng (steam-treated Panax ginseng) have potent biological activities such as radical scavenging, vasodilating and anti-tumor activities [62]. Choi et al. [63] aimed to identify if saponin affects the development of diabetes in chronic ethanol-exposed rats, they induced diabetes using fourteen-week-old male OtsukaLonge Evans Tokushima fatty (OLETF) rats, as these types of rats exhibit features such as hyperglycemia, a chronic course of disease, abnormalities of the pancreas, and mild obesity, they have been commonly used as an animal model to investigate T2DM and obesity [64]. The rats received daily intraperitoneal injections of saponin (200 mg/kg B.W). Chronic treatment with saponin which has been produced from steam-treated Korean red ginseng was purchased from Vitallink Inc. causing an enhancement of glucose metabolism which impaired by chronic ethanol consumption and causes a significant decrease in fat tissue weights and lipids, including cholesterol and triacylglycerol. Moreover, saponin inhibits the reduction in islet cell mass and the decrease insulin expression which worst by chronic ethanol consumption. They added saponin may be helpful in relieving the rapid progress of diabetes due to chronic alcohol consumption and also showed a potential role as an antidiabetic drug for diabetic patients who chronically consume alcohol [63].

■ Rhizoma anemarrhenaesaponin

Rhizoma anemarrhenae (family Asparagaceae), is a well-known Chinese materiamedica and has multiple pharmacological actions including antipyretic, anti-inflammatory, antidiabetic, anti-platelet aggregation and anti-superoxide formation effects in modern medicine [65]. *Rhizoma anemarrhenae* primarily contains steroidal saponins. On a study by Yun-peng [66] they aimed to investigate the effects of total saponins from *Rhizoma anemarrhenae* (TS) on acetylcholinesterase (AChE) activity in the hippocampus of streptozotocin-induced diabeticmale Sprague Dawley rat (10 weeks of age) and their possible mechanisms. The TS group rats were treated with TS (200 $mg{\cdot}kg^{-1}$) intragastric for 8 weeks. Total saponins from *Rhizoma anemarrhenae* have an inhibitory action on the enhanced cerebralacetylcholinesterase (AChE) activity in the hippocampus diabetic conditionwhich may be partly due to its

antioxidant and anti-diabetes efficacy. In addition, the improvement effect of TS on AChE activity as well as the antioxidant action affords a support for TS application in brain disorderssuch as cognitive dysfunction. TS could ameliorate cognitive functions of diabetic rats [67]. These reports suggested that TS could enhance the learning and memory abilities of animals and the inhibitory effect on AChE activity is one of the action mechanisms [66].

■ Sea cucumber saponin (Holothurians)

Saponin (Table 1) is the most important secondary metabolite and bioactive composition of marine invertebrates sea cucumber, which has been proven to display numerous biological activities [68]. In a study by EL barky [1] they reported that saponin which has been extracted from the Egyptian Holothuriathomasi, sea cucumber was dissolved in distilled water and administrated orally at 7:30 a.m. daily with a dose of 300 mg/kg B.wt. after 35 days of STZ-induced diabetic female albino Wistar rats (3–4 months old and average body weight 180–220 g) and lasted for six weeks. Saponin of Holothuriathomasi may be effective in controlling the glycemic state as illustrated by diminished blood glucose level and increased serum insulin level. Furthermore, Holothuriathomasisaponin extract ameliorated dyslipidemia of diabetic rats as well as diminishing diabetic cardiovascular complications which related to diabetes. Also, Holothuriathomasisaponin has a potential role in decrease the pro-inflammatory marker as reflected by the amelioration of both serum TNF-α and IL-6 and it displayed an antioxidant activity as it can ameliorate oxidative stress under diabetic condition by decreasing liver L-MDA and increase the activity of liver. Saponins have been reported to lower blood glucose level via rejuvenation of insulin action, increased plasma insulin level and released insulin from the pancreas [31]. Also, saponin can block the formation of glucose in the bloodstream [69]. Moreover, EL Barky [1] reported that the results pertaining to GC-MS analysis of the saponin extract showed that the aglycone part of saponin was methyl ester of octadecanoic acid which had the biggest abundance of 48.4% and 18.85%, respectively. This result indicated that the aglycone part from sea cucumber, Holothuriathomasi is from triterpenoid type. The octadecanoic acid may be the cause of lowering blood glucose level in STZ-induced diabetic rats [1], this results in accordance [70] they concluded that 9,12,15-octadecatrienoic acid methyl ester and 9,12-octadecadienoic acid methyl ester have the potential effect to protect pancreas from up normality changes which induced in diabetic disease. Also, Wuttke [71] reported that hexadecanoic acid, octadecanoic acid and eicosanoic acid have already proved as antidiabetic activity by possessing insulin secretion, insulin stimulation, α- glucosidase inhibitors.

Table 1: Sources and dosage of saponin from some plants and marine animals.

Source	Dosage and time	Experimental models of diabetes	Route of administration	Degree off blood sugar reduction	Reference
***Cornus officinalis* sieb.**	60 and 120 mg/kg B.W. for 28 days	Sprague Dawley rats (200 g)	per os	11.11 and 22.22% respectively	[22]
***Solanum anguivi* fruits**	20, 40, 60, 80 and 100 mg/kg b.w. daily for 21 days	Wistar albino rats (125 ± 12 g)	Oral	-	[23]
Vernonia amygdalina	100 and 200 mg/kg	Wistar rats of both sexes (120-200 g)	Oral	-	[24]
Sea cucumber	300 mg/kg body weight after 35 days of STZ-induction and lasted for 6 weeks	Female albino Wistar rats (3–4 months old and average body weight 180–220 g)	Oral	54.31 and 77.53% respectively	[1]
***Scoparia dulcis* L.**	10, 20 and 30 mg/kg	Male Wistar rats (200–220 g)	Oral		[25]
Astragalus	50 and 200 mg/kg b.w for 6 weeks.	-	Oral		[26]
***Citrullus colocynthis* (L.) seeds**	20 mg/kg b.w. at days 28 and 63	Wistar rats (150-200 g)	Intraperitoneal route		[27]
***Bryonia laciniosa* seed**	100 and 200 mg/kg B.W. for 28 days.	Female albino Wistar rats (200–250 g)	Oral	32.12 and 48.19%	[28]

■ *Solanum anguivi* lam. Fruit

Solanum anguivi Lam. (Table 1) is a non-tuberous and widely distributed plant that possesses various medicinal properties. Mostly, the plant prefers to grow in humid temperature and commonly found as a weed in gardens. It is a rare ethnomedicinal herb belonging to the family Solanaceae. The plant is used as a therapeutic agent for various diseases. *S. anguivi* fruit is the most edible source of saponin in the south-western and south-eastern parts of Nigeria because of the traditional belief that it can cure hypertension and diabetes. Saponins have been reported as plant phytochemical having insulin sensitization and antihyperlipidemic effects in the diabetic state [72]. Elekofehinti [73] aimed to evaluate the hypoglycemic, antiperoxidative and antihyperlipidemic activities of saponins which have been extracted from Solanumanguivi fruits in alloxan induced diabetes albino rats (125 g ± 39 g). Diabetic rats were treated orally with doses of saponin extract (20 mg/kg to 100 mg/kg) for 21 days. Results obtained [73] indicated that administration of saponins which have been extracted from solanumanguivi fruits (SAGU) can scavenge free radical, possess reducing power and iron chelating ability which making it an excellent in the treatment of diseases in which ROS has been implicated. SAGU also displayed antioxidant activities by raising the level of antioxidant enzymes such as CAT and SOD in alloxan-induced diabetes. So, SAGU has an ability to hinder diabetic complications. Hence, saponins can be employed in the management of diabetes [73].

■ Mechanism action of saponin in diabetes

Diabetes mellitus (DM) is a serious chronic endocrine disturbance that is a main source of malady worldwide, it is commonly accompanied by distinct complications for instance retinopathy, neuropathy, nephropathy and cardiovascular disease [74]. Diabetes is associated with severe long-term micro and macrovascular and significantly raises the number of morbidity and mortality [75]. Oxidative stress plays a fundamental role in the development of DM which increases complications with increased free radical formation [76]. Oxidative stress also produces reactive oxygen species, which resultant toxic effect on cell development, growth and survival [77]. Oxidative stress is created with the formation of advanced glycation end product which has a strong association with the diabetic complications [78]. Free radicals which resulted from oxidative stress stress-mediated

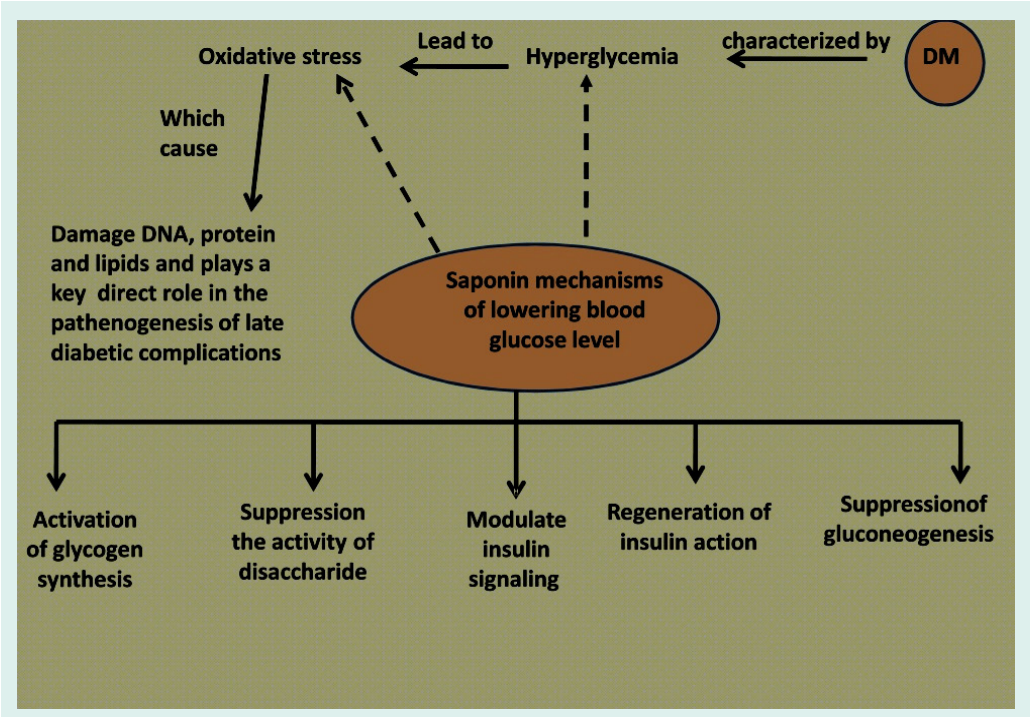

Figure 3: Mechanism action of saponin in diabetes.

and promoted programmed β-cell death [79]. Oxidative stress also, reacts with polyunsaturated Fatty Acids of lipid membrane and cause lipid peroxidation [80]. Saponins have been reported to possess a wide range of biological activities [81]. For instance, saponins were known to be bioactive against diabetes [82,83]. Saponin which has been extracted from*Holothuriathomasi,* sea cucumber, has a potent hypoglycemic effect in STZ-diabetic rats [1] as it stimulates secretion, the action of insulin, regeneration of beta cells islets and activate the enzymes which are responsible for glucose utilization [84]. Charantin which is a steroidal saponin is composed of a mixture of beta-sitosterol-beta-D-glucoside and 5.25 stigmadien-3-beta-ol glycoside, utmost quantity of charantin is found in the fruit of bitter melon which characteristic by hypoglycemic effect [85]. *Momordicacharantia* extract enhances liver glycogen storage, supports healthy insulin secretion by the islets of Langerhans, promotes peripheral glucose utilization, and healthy serum protein levels. Saponin of *Momordicacharantia* increase glucose utilization by the liver, decrease gluconeogenesis via inhibition the two key enzyme glucose-6-phasphat and fructose-1,6 bisphosphatase and improve glucose oxidation by activating glucose-6-phasphate dehydrogenase via the shunt pathway [86]. Charantin also upgrades insulin release from beta cells pancreatic islets and promote a new growth of insulin-secreting beta cells [87]. The antidiabetic mechanism of this compound is a diminish blood glucose and an increase plasma insulin levels [88]. The ability of saponin to decrease blood glucose level makes saponin an excellent efficient antioxidant in the remediation of diabetes mellitus. The hypoglycemic action of saponin is via rejuvenation of insulin [73], amendment insulin signaling [89], release insulin from the beta cell islets [31], inhibition the activity of disaccharide [90], activation of glycogen synthesis [91], Inhibition of gluconeogenesis [92], inhibition the activity of α-glucosidase [93], inhibition of mRNA expression of glycogen phosphorylase and glucose 6-phosphatase [94] and increase the expression of Glut4 [95] (**FIGURE 3**).

Conclusion

This article review has abbreviated the fundamental role of saponin as an antidiabetic agent. Saponins from various plants and marine animals have been reported to have a hypoglycemic activity. These activities of saponin regulate blood glucose level and prevent diabetic complications due to their antioxidant activity. Dyslipidemia which is attributed to saponin will help to decrease the risk of atherosclerosis and cardiovascular disease in diabetic patients. More research is needed to evaluate the role of saponins and understand their pharmacology in the treatment of diabetes.

Acknowledgement

I wish to express my sincere thanks and deepest to Prof. Dr. Ehab Mostafa Mohamed Ali Professor of Biochemistry, faculty of science Tanta University, Egypt for his continuous help and cooperation.

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