Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 7, Issue 6, 2015

Review Article

SOME NATURAL PRODUCTS AND THEIR SECONDARY METABOLITES ATTRIBUTED TOWARDS DIABETIC CURE: A REVIEW

MUHAMMAD ABDURRAZAK[1], MAHADEVA U. S. RAO*[2], AHMAD BASHIR ADO[1], KHAMSAH SURYATI MOHD[3], THANT ZIN[2]

[1]Masters students, Faculty of Medicine, Universiti Sultan ZainalAbidin (UniSZA) Malaysia, [2]University Medical Lecturer, Faculty of Medicine, UniSZA, Malaysia, [3]University Lecturer, Faculty of Bioresources and Food Industry, UniSZA, Malaysia
Email: raousm@gmail.com

Received: 25 Jan 2015 Revised and Accepted: 20 Feb 2015

ABSTRACT

Diabetes is one of the major health and development challenges of the 21st century. According to the International Diabetes Federation, there are currently more than 371 million people living with diabetes and another 28 million are at risk of developing the disease. Aside from conventional allopathic medicines, traditional/alternative therapy plays a substantial part in treating diabetes mellitus. In the final few decades eco-friendly, bio-friendly, cost effective and relatively safe plant-based medicines have gone from the periphery to the mainstream with the increased research in the area of traditional medication. Plant-based medications are preferable as mainly non-toxic, having typically fewer side effects, better compatibility with physiological flora, and availability at low-costs. However, secondary metabolites isolated from these plants (Diosmin, Tangeritin, Lycopene, Syringin etc.,) possess this antidiabetic property. The power of the herb/active compound to enhance glucose utilization and lower plasma glucose level in rats suffering from insulin deficiency suggests that these plant extracts/phytochemicals may be useful in the discussion of human diabetes.

Keywords: Diabetes, Disease, Allopathic Drugs, Secondary metabolites.

INTRODUCTION

Diabetes mellitus (DM) is one of the most challenging healthproblems of our time. As one of the most common non-communicable diseases globally, it is the fourth or fifth leading reason of death in high-income countries and is rapidly becoming an epidemic in many developing and newly industrialized nations. It is a syndrome, initially characterized by a deprivation of glucose homeostasis resulting from defects in insulin secretion and/or insulin action, which consequently brings about impaired metabolism of glucose and other energy yielding fuels such as lipids and proteins [1]. Despite theintroduction of hypoglycaemic agents from natural and synthetic sources, diabetes and its secondary complications continue to be a major problem in the world population. Diabetes is a leading cause of morbidity and mortality in the world's growing population. The International Diabetes Federation has fore cast a world wide increase from 8.3 % to 9.9 % by the year 2030, with China and India predicted to receive the greatest number of diabetic cases.

Human type 2 diabetes (T2DM) is a metabolic disorder which comes up from the comparative inability of the endocrine pancreas to meet increasing metabolic demands and to compensate for insulin resistance. Insulin resistance is a state of reduced responsiveness of insulin target tissues to normal circulating levels of insulin. The level to which glucose tolerance deteriorates in insulin-resistant individuals vary as a occasion of both the magnitude of insulin resistance and the capability of the pancreas to adequately pay for this short coming. If insulin secretion fails to recover fully, a condition of hyperglycemia despite hyperinsulinemia occurs. Hence, the worsening of insulin resistance together with abnormalities in compensatory insulin secretion and finally a failure of beta-cell function may eventually contribute to the development of T2DM [2] despite the keen interest in the evolution of novel drugs to prevent the burden of complications associated with this diseaseand the heightened interest in the scientific community to evaluate either raw or isolated natural products in experimental studies [3].

As of 2010, an estimated 280 million peoplehave diabetes, with type 2 making up about 90 % of thecases globally [4]. The incidence of this disease is increasing quickly and at the end of 2030, the number of cases will double, as a result of increasing longevity and obesity. Diabetes is more prevalent in developed nations; even though there is an increment in the prevalence rate in Asia and Africa. Environmental and genetic elements playsa significant part in the evolution of diabetes in varying populations [5]. The incidence of insulin-dependent diabetes mellitus (IDDM) ranged from 1.8 to 7.0/100 000 per year in Africa, 0.14 to 10/100 000 per year in Asia, approximately 3.4 to 36/100 000 per year in Europe, 2.61 to 20.18/100 000 per year in the Middle East and 7.60 to 25.6/100 000 per year in North America andthat ofnon-insulin dependent diabetes mellitus (NIDDM) ranged from 0.4 % to 17.9 % in Africa, 1.2 % to 14.6 % in Asia, 0.7 % to 11.6 % in Europe, 5.6 % to 40 % in the Middle East and 7 % to 28.2 % in North America [6].

Natural plant products

In the final few decades eco-friendly, bio-friendly, cost-effective and relatively safe plant-based medicines have gone from the periphery to the main stream with the increased research in the area of traditional medicine [7]. Plant-based medicine, which uses medicinal plants as the first medicine is a general phenomenon. Every civilization on earth, through written or oral tradition, has relied on the vast variety of healing plants for their healing attributes. The majority of medicinal plant products available today, originated from the same traditional recipe or ingredients.

The benefit of plant-based cures is that they are cheap and readily obtainable. They can be obtained straight from nature. Plant-based medicinal drugs are preferable as they are chiefly non-toxic, having fewer side effects typically, better compatibility with physiological flora and availability at affordable prices. The limitations of plant-based medicines are usually involved with the treatment of more dangerous ailments like broken arms. These websites need constant medical supervision and utilization of more advanced medications and many patients are allergic to some plant-based medicines, making matters worse once they take them in whatsoever form. Treatments are longerwhen a natural method is chosen [7]. The World Health Organization (WHO) estimates that 4 billion people, i.e., 80 % of the world's population, presently use plant-established medical specialty for some aspect of their primary health concern [2]. WHO has listed 21, 000 plants, which are used for medicinal purposes around the world. Among these 2500 species are in India, out of which 150 species are used commercially on a relatively large scale. India is the largest producer of medicinal herbs and is called the botanical garden of the world [8].

Table 1: List of some plants with Antidiabetic property

S. No.	Plant name	Family	Parts of the plant USED	Reference
1	*Acacia Arabia*	Leguminosae	Bark	[9]
2	*Acacia catechu wild*	Leguminosae	Bark	[10]
3	*Aloe vera*	Liliceae	Leaf	[11]
4	*Aeglemarmelos*	Rutaceae	Leaf	[12]
5	*Aervalanatalin*	Amarantheceae	Aerial parts	[13]
6	*Alpiniacaalcarata*	Zingiberaceae	Rhizome	[14]
7	*Azadirachtaindica*	Meliaceae	Root bark	[15]
8	*Allium sativum*	Liliaceae	Bulb	[16]
9	*Annonasquamosa*	Annonaceae	Leaves	[17]
10	*Albizzialebbek*	Mimosaceae	Bark	[18]
11	*Acacia tortolis*	Fabaceae	Seed	[19]
12	*Aconitum napellus*	Leguminoseae	Bark	[20]
13	*Andrographispaniculata*	Acantheceae	Root	[21]
14	*Asparagus racemosus*	Asparagaceae	Root	[22]
15	*Allium sepa*	Liliaceae	Bulb	[23]
16	*Benincasahispida*	Cucurbitaceous	Stem	[24]
17	*Banbusa vulgaris*	Poaceae	Leaves	[25]
18	*Brassica juncea*	Cruciferae	Seed	[26]
19	*Boerhaaviadiffusa*	Nyctaginaceae	Leaves	[27]
20	*Capsicum annuum*	Solanaceae	Fruit	[28]
21	*Catharanthusroscus*	Apocynaceae	Flower, roots and stem	[29]
22	*Centellaasiatica*	Umbelliferare	Leaves	[30]
23	*Cocciniaindica*	Cucurbitaceae	Leaves and fruits	[31]
24	*Emblicaofficinalis*	Euphorbiaceae	Fruit	[32]
25	*Eugenia jambolana*	Myrtaceae	Seed	[33]
26	*Ficusreliginosa*	Moroceae	Fruit and leaves	[34]
27	*Grewiaassiatica*	Tilliaceae	Fruits, stem bark, leaves.	[35]
28	*Gymnemasylvestre*	Ascelpidaceae	Leaves	[36]
29	*Hyptissuaveolens*	Lamiaceae	Leaves	[37]
30	*Jutrophacurcas*	Euphorbbiaceae	Leaves	[38]
31	*Mimosa pudica*	Fabaceae	Leaves	[39]
32	*Moringaolefeira*	Moringaceae	Leaves	[40]
33	*Terminaliacatappa*	Combritaceae	Leaves	[41]
34	*Tinosporacordifolia*	Menispermaceae	Roots	[42]
35	*Tragia involucrate*	Euphorbiaceae	Entire plant	[43]

Some natural products (secondary metabolites) as a source of antidiabetes

Diosmin $C_{28}H_{32}O_{15}$

Diosmin (DS) (diosmetin 7-O-rutinoside), a natural flavone glycoside, is readily obtained by dehydrogenation of the corresponding flavanone glycoside hesperidin, which is abundant in the pericarp of various citrus fruits. According to Sanjay *et al.,* DS has been reported to induce the pancreas β-cells, which playa essential part in the production and secretion of insulin [44]. Theadministration of the DS to diabetic rats decreases the blood glucose concentration to near normal, which is an essential trigger for the liver and kidney to revert back to its normal homeostasis during experimental diabetes. The mechanism of antihyperglycemic action of DS may be through its scavenging ability to protectthe pancreatic islets from free radical-induced damage by streptozotocin (STZ) in experimentalrats. DS possesses blood lipid lowering and anticarcinogenic activities [45].

Beta carotene $C_{40}H_{56}$

Carotenoids are natural lipid-soluble antioxidants. β-carotene, β-cryptoxanthine, lutein, and lycopene are the most abundant carotenoid components of the human diet. β-carotene is a strongly colored red-orange pigment abundant in plants and fruits. It is an organic compound and is chemically classified as a hydrocarbon and specifically as a sharpened (isoprenoid), reflecting its derivation from isoprene units. β-Caroteneis bio synthesized from geranyl pyrophosphate. It is a member of the carotenes, which are tetra terpenes, synthesized biochemically from eight isoprene units and thus having 40 carbons. Among this general class of carotenes, β-carotene is distinguished by having beta-rings at both ends of themolecule. Absorption of β-carotene is enhance difeaten with fats, as carotenes are fatsoluble. The β-carotene ameliorates the glucose level and isattributed to the hypoglycemic effect through the insulinogenic effect and subsequent improvement of the glycemic state. In general, carotenoids (beta-carotene, lycopene, lutein, and zeaxanthin) contribute to preventing degenerative diseases, such as diabetes and several characters of cancer [46].

Gamma sitosterol $C_{29}H_{50}O$

Itisfound in *Nigella sativa, Serenoa repens* (saw palmetto), *Pygeum africanum, sea-buckthorn, wolfberries, Mirabilis jalapa Cannabis sativa, Urtica dioica* and *Wrightiatinctoria.* Beta-Sitosterol-3-O-beta-D-glucopyranoside can be found in Acanthus hirsutus [47]. It is likewise found in pecans, avocados, Cucurbita pepo (pumpkin seeds), cashew fruit, rice bran, wheat seed, corn oils, soya beans and dandelion coffee.

The γ-sitosterol isolated from *Lippia nodiflora* was screened for its antidiabetic property in STZ induceddiabeticrats. Insulin secretion in response to glucose was assessed in isolated rat islets. Oral administration of γ-sitosterol (20 mg/kg B.w.) oncedaily for 21 days in STZ induced diabetic rats resulted in a substantial reduction ($P<0.05$) in blood glucose and glycosylated hemoglobin with an increment in plasma insulin level, body weight and nutrient uptake. Furthermore γ-sitosterol showed antihyperlipidemic activity as shown by a substantial decrease ($P<0.05$) in serum total cholesterol, triglycerides and very low-density lipoprotein-cholesterol levels coupled with an elevation of high-density lipoprotein-cholesterol levels in treated rats. A reduction in the natural processes of liver marker enzymes in γ-sitosterol treated rats when compared to diabetic control rats indicated its protective role against liver damage.γ-Sitosterol increased insulin secretion in response to glucose. Immuno histochemical study of the pancreas also confirmed the biochemical findings. These results showed that γ-sitosterol, possesses antidiabetic activity [48].

N-Trissacharide

In a study conductedto investigate the effect of N-Trisaccharide (a new compound isolated from the fruit of *C. prophetarum L.*)

onhyperglycemia in streptozotocin (STZ)–nicotinamide (NA) induced type 2 diabetic rats, different dosages of N-Trisaccharide (25 and 50 mg/kg B.w.) wereadministered once daily for 28 days to STZ-NA induced diabetic rats. It was found that N-Trisaccharide increased the plasma insulin and liver glycogen levels in diabetic rats, altered enzyme activities of carbohydrate metabolism in the liver and kidney of the diabetic rats were as well amended. Additionally, N-Trisaccharideincreased glycogen synthesis and decreased glycogen phosphorylase activity in diabetic rats. Histological studies confirmed an increase in insulin level, which is due to stimulation of injured pancreatic β-cells. The outcomes of the survey suggested that N-Trisaccharide possesses the propitious effect on STZ–NA induced type 2 diabetes, suggesting its usefulness in diabetes management [49].

Secoisolariciresinoldiglucoside (SDG) $C_{32}H_6O_{16}$

SDG can be isolated from de-fatted (hexane extraction) flax seed by extraction of the lignan polymer precursor with a water/acetone mixture, followed by acetone removal and alkaline hydrolysis. Or it can be pulled from the shell of whole flax through a cold-milled process without applying chemicals. According to Sadiq*et al.,* (2013), administration of SDG to the diabetic model causes moderate reduction in glucose levels, andthe lipidprofile, improved antioxidant status and ameliorated insulin and c-peptide levels which shows the regeneration of β-cells. The outcomes of the investigation indicated that diabetes is linked with an increase in oxidative stress as shown by the increment in serum malondialdehyde (MDA), diminished levels of catalase (CAT), superoxide dismutase (SOD), and glutathione (GSH). This SDG is effective in slowing the development of diabetic complications [50].

2-(4-[(2-hydroxybenzyl) amino]-phenyl amino-methyl)-phenol (HBPMP) $C_{33}H_{34}N_6O$

Oral administration of HBPMP (30 mg/kg) to STZ rats produced antidiabetic activity after 6 h of HBPMP administration. Treatment of the STZ rats with HBPMP (30 mg/kg/d) for 30 days resulted in a significant reduction ($P<0.05$) in their fasting blood glucose (FBG), serum total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), very low density lipoprotein-cholesterol (VLDL-C) and triglycerides (TG) along with an increment in serum high density lipoprotein-cholesterol (HDL-C) levels. Activities of serum aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) and levels of blood urea and creatinine were improved to approach normal levels in the treated STZ induced diabetic rats, indicating the protective function of the HBPMP against liver and kidney damage and its non-toxic property. Thus, HBPMP possesses antihyperglycemic and antihyper lipidemic activities [51].

Tangeritin $C_{20}H_{20}O_7$

Tangerine is an O-poly methoxylatedflavor that is found in tangerine and other citrus peels. Ramalingam*et al.,* (2014) evaluated the antihyperglycemic potential of tangeritin on the natural processes of key enzymes of carbohydrate and glycogen metabolism in control and STZ-induced diabetic rats and observed a significant diminution in the stages of plasma glucose, glycatedhemoglobin (HbA1c) and increase the levels of insulin and hemoglobin. The varied activities of the key enzymes of carbohydrate metabolism in the liver of diabetic rats were significantly reversed ($P<0.05$) to near normal levels by the administration of tangeritin. Furthermore, tangeritin administration to diabetic ratsimproved hepatic glycogen content, suggesting the antihyperglycemic potential of tangeritin in diabetic rats [52].

Lycopene $C_{40}H_{56}$

Lycopene (from the new Latin word*Lycopersicum*,referring to the tomatospecies) is a bright red carotene and carotenoidpigment. It is a phytochemicalfound in tomatoesandother red fruitsandvegetables, such as red carrots, water melons, and papayas (but not strawberries, red bell peppers, or cherries). Although lycopene is chemically a carotene, it has no vitamin Aactivity. Nutrients that are not red may contain lycopene as well. Lycopene's 11 conjugated double bonds givesit its dark red gloss and are responsible for its antioxidant action.

Mamdouh M. Ali andFatma G. Agha (2009) studiedtheeffects of variousdoses of lycopene in STZ-inducedhyperglycemicrats to evaluate its possible hypoglycaemic, hypolipidemicand antioxidant activity in diabetes. Exogenous administration of individual gradual doses of lycopene to hyperglycemia rats causes a social disease-dependent reduction in glucose level, an increase of insulin absorption, a decrease of hydrogen peroxide (H_2O_2) and thiobarbituric acid reactive substance (TBARS) levels, as well as increased total antioxidant status with increased antioxidant enzyme activities (CAT, SOD) and glutathione peroxidase (GPx) with improvement in serum lipid profile. It is obvious from this study that Lycopene acts as an antidiabetic agent through lowering the free radical and has an improving effect on a serum that turns over the average level [53].

Revasterol $C_{14}H_{12}O_3$

Revasterol (3, 5, 4'-trihydroxy-trans-stilbene) is produced in response to injury. It is a stilbenoid, a type of natural phenol, and a phytoalexin produced naturally by various plants when under attack by pathogens such as bacteria or fungi. Gyeong-Min Do (2012) investigated the effects of revasterol (RV) on diabetes-associated metabolic changes in a spontaneous model of type 2 diabetes, as well as activation of AMP-activated protein kinase (AMPK) and downstream targets and found that RV significantly decreased ($P<0.05$) blood glucose, plasma free fatty acid, triglyceride, APO B/APO AI levels and increased plasma adiponectin levels. RV activated AMPK and downstream targetsleadingto decreasedblood HbA1c levels, hepatic gluconeogenicenzymeactivity, and hepatic glycogen, while plasma insulin levels, pancreatic insulin protein, and skeletal muscle GLUT4 proteinwerehigher after RV supplementation. The high RV dose also increased hepatic glycolytic gene expression and enzyme action, along with skeletal muscle glycogen synthase protein expression. Furthermore, RV dose-dependently decreased hepatic triglyceride content and phosphorylated I kappa B kinase (p-IKK) proteinexpression, while hepatic uncoupling protein (UCP) and skeletal muscle UCP expression were increased. RV thus potentiates theimprovement of glycemiccontrol, glucose uptake, anddyslipidemia, as well as protection against pancreatic cell failure in a spontaneous type 2 diabetes models. Dietary RV has potential as an antidiabeticagent via activation of AMPK and its downstream targets [54].

Carvone $C_{10}H_{14}O$

Carvone is a member of a family of phyto chemicals called terpenoids [55]. Carvone is found naturally in many essential oils, but is most abundant in the oils from seeds of caraway (*Carumcarvi*) and dill. UdaiyarMuruganathan (2013) looked into the effect of carvone on derangement in glycoprotein levels in the STZ-induced diabetic model. Oral administration of carvone (40 mg/kg b. w) for 30 d dose dependently improved the glycemic status in STZ-induced diabetic rats. The points of plasma glucose decreased with a comparable growth in plasma insulin level. The varied levels of plasma and tissue glycoprotein components were repaired to near normal. It indicates that carvone can potentially ameliorate glycoprotein components abnormalities in addition to its antihyperglycemic effect in experimental diabetes. In brightness of these advantageous results, it is advisable to extend the scale of carvone in a trial to alleviate the adverse outcome of diabetes [56].

Fraxetin $C_{10}H_8O_5$

Fraxetin is an O-methylated coumarin (7, 8-dihydroxy-6-methoxychromen-2-one). It can be found in *Fraxinusrhynchophylla*. Fraxin is a glucoside of fraxetin. De Carvalho*et al.,* (2006) evaluated the antihyperglycemic potential of fraxetin by determining the activities of key enzymes of carbohydrate metabolism in STZ induced diabetic rats. Thedose 80 mg/kg b. w, reducedthe levels of blood glucose and HbA1c andincreased plasma insulin level. The varied activities of the key enzymes of carbohydrate metabolism and hepatic enzymes in the liver tissues of diabetic rats were reverted to near normal level upon the administration of fraxetin. Further fraxetin administration to diabetic rats improved body weight and hepatic glycogen content, which in turndemonstrated its antihyperglycemic potential [57].

Diosgenin $C_{27}H_{42}O_3$

Diosgenin, a steroid sapogenin (3β, 25R)-spirost-5-en-3-ol), is the product of hydrolysis by acids, strong alkalis, or enzymes of saponins, extracted from the tubers of Dioscorea wild yam, such as the Kokoro. The sugar-free (Aglycone), diosgenin is used for the commercial synthesis of cortisone, Pregnenolone, progesterone, andother steroid products. Leelavinothan*et al.,* (2012) investigated the beneficial role of diosgenin on oxidative stress markers and histopathological alterations in the aorta of STZ-induced diabetic rats. At the final stage of the experimental periods, diabetic rats exhibited an increase in the levels of plasma glucose, glycosylatedhe moglobin with a decrease in insulin and total hemoglobin. Theactivities of antioxidant enzymes such as SOD, CAT, GPx, and GSH were decreased while an increase in the levels of lipid peroxidation (LPO) markerswas observed in aortic tissues of diabeticrats. These findings suggest that diosgenin could have a beneficial role against aortic damage induced by oxidative stress in diabetic state, which was demonstrated by the propensity of diosgenin to modulate the antioxidant defense and to decrease the lipid peroxidation in aortic [58].

D-saccharic acid-1, 4-lactone (DSL) $C_6H_8O_7.H_2O$

Oxidative stressplays a vitalrole in diabetic complications. To inhibit the oxidative stress-mediated damage in diabetes pathophysiology, a special focus has been devoted to naturally occurring antioxidants present in a sizable diet. D-saccharic acid 1, 4-lactone (DSL), a derivative of D-glucaric acid, is present in many dietary plants and is experienced for its detoxifying and antioxidant properties. Semantic Bhattacharya *et al.*, (2011) evaluated the beneficial use of DSL against alloxan-induced diabetes in the pancreas tissue of rats. Alloxan exposure, elevated the blood glucose, HbA1c, decreased the plasma insulin and disturbed the intracellular antioxidant machineries whereas oral administration of DSL (80 mg/kg b.w.) restored these alterations close to normal. On looking into the mechanism of the protective activity of DSL, it was discovered that it prevented the pancreatic β-cell programmed cell death via a mitochondria-dependent pathway. Resultsshoweddecreased mitochondrial membrane potential, enhanced cytochrome Crelease in the cytosol and reciprocalregulation of Bcl-2 familyproteins in the diabetic rats. These results were likewise found to be linked with increased levels of Apaf-1, caspase 9, and caspase 3 that ultimately led to pancreatic β-cell programmed cell death. DSL treatment, however, counteractedthesechanges. In conclusion, DSL possesses the capability of ameliorating the oxidative stress in diabetes and hence could be a promising approach in lessening diabetic complications [59].

Ecdysterone $C_{27}H_{44}O_7$

Hydroxyecdysone (20E), (2β, 3β, 5β, 22R-2, 3, 14, 20, 22, 25-Hexahydroxycholest-7-en-6-one) is a naturallyoccurringecdysteroid hormone which controls theecdysis (moulting) andmetamorphosis of arthropods. It is thus one of the most common moulting hormones in insects, crabs, etc. It is also a phytoecdysteroid produced by various plants, including *Cyanotisvaga*, where its function is presumably to disrupt the development and breeding of insect pests. In arthropods, 20E acts through theecdysone receptor. Although mammals lack this receptor, 20E may affect mammalian (including human) biological systems *in vitro*, but there is uncertainty whether any *in vivo* or physiological effects take place. Ramalingam Sundaram *et al.,* (2012) assessed the anti-diabetic activity of 20E on glucose metabolic key enzymes in control and STZ induced diabetic rats. On oral administration of 20E at a dosage of 5 mg/kg B.w./d to diabetic rats for 30 d resulted in a reduction in the levels of plasma glucose, HbA1c and an increase in the levels of insulin and hemoglobin. Administration of 20E showed a significant increase ($P<0.05$) in the levels of glycolyticenzyme (hexokinase) and hepatic shunt enzyme (glucose-6-phosphate dehydrogenase) whereasthe significant decrease in the levels of gluconeogenicenzymes (glucose-6-phosphatase and fructose-1, 6-bisphosphatase) in diabetic treatedrats. Furthermore, protection against body weight, loss of diabetic animals was noted. This work shows that the administration of 20E to diabetic rats resulted in alterations in the metabolism of glucose with the subsequent decrease in plasma glucose levels [60].

Syringin $C_{17}H_{24}O_9$

Syringin, 4-[(1E)-3-Hydroxyprop-1-ene-1-yl]-2, 6-dimethoxyphenyl β-D-glucopyranoside, a phenylpropanoid glycoside belongs to eleutheroside derivative (B). This bioactive compound was identified in several plantsincluding*Musa paradisiaca, Jasminummesnyi, Edgeworthiachrysantha, Acanthopanaxsenticosus,* etc. Shanmuga*et al.,* isolated and characterized syringin from *Musa paradisiaca* tepal extract (MPTE) and evaluated its antidiabetic efficacy in STZ-induced diabeticrats. Syringin was isolated from MPTE and characterized using spectral studies. Diabetic rats were administered 50 mg/kg/d. Of syringing orally for 30 days. Elevated blood glucose and HbA1c levels, the reduced plasma insulin and hemoglobin levels in diabetic rats were significantly reversed ($P<0.05$) to nearnormal after oral administration of syringin. Plasma protein, blood urea, serum creatinine and uric acid levels werealso normalized after treatment. The altered activities of serum trans aminases and alkaline phosphatases were normalized upon syring intreatmen tindicating it's non-toxic and hepatoprotective nature. The ability of syringin to enhance glucose utilization andlower plasma glucose level in rats suffering from insulin deficiency suggest that this phytochemical may be useful in the treatment of human diabetes [61].

Quercetin $C_{15}H_{10}O_7$

Quercetin is a flavonoid widelydistributed in nature. The epithet has been used since 1857, and is derived from *quercetum* (oak forest), after *Quercus*. It is a naturally occurring polar auxin transport inhibitor. It is primarily found in red onions, higher concentrations of quercetin occur in the outermost rings and in the office closest to the root, the latter being the portion of the plant with the highest concentration. One survey found that organically grown tomatoes had 79 % more quercetin than chemically grown fruit. Quercetin is present in several sorts of honey from different plant roots [62].

According to Vessal*et al.,* (2003), the effects of the intraperitoneal injection of quercetin in streptozocin-induced diabetic and normal rats were investigated and compared. Although quercetin had no effect on plasma glucose level of normalanimals, it significantly and dose-dependently decreasedthe plasma glucose level of STZ-induced diabetic rats. Glucose tolerancetests of the diabetic animals approached those of normal rats, their plasma cholesterol and triglycerides were reduced significantly ($p<0.05$), while their hepatic glucokinase activity was significantly increased upon quercetin treatment. In normal rats, quercetin did not move the glucose tolerance test, but resulted in an addition of plasma cholesterol and triglycerides and a reduction in hepatic glucokinase activity. No significant pathologic changes were observed in hepatocytes or kidney tubules and glomeruli, while the number of pancreatic islets increased in both treated normal and diabetic groups. It is concluded that quercetin, a flavonoid with antioxidant properties brings about the regeneration ofthe pancreatic islets and probablyincreases insulin release in STZ-induced diabetic rats; thus exerting its beneficial antidiabetic effects. Nevertheless, it may be of trivial value in normoglycemic animals [63].

Garlic acid $C_7H_6O_5$

Garlic acid is a trihydroxy benzoic acid, a type of phenolic acid, alsoknown as 3, 4, 5-trihydroxybenzoic acid, found in gallnuts, sumac, witch hazel, tealeaves, oakbark, andotherplants. The chemical formula is $C_6H_2(OH)_3COOH$. Garlic acid is found both free and equally part of hydrolyzable tannins. Garlic acid is usually employed in the pharmaceutical industry and has many pharmacological applications [64]. It is likewise set up in the aquatic plant *Myriophyllumspicatum* and shows an allelopathic effect on the ontogeny of the bluish-green algae *Microcystisaeruginosa*.

In a survey carried out by Punithavati*et al.,* (2011) to evaluate the antihyperglycemic, anti lipidperoxidative and antioxidant effects of garlic acid on STZ-induced diabetic male Wistar rats, it was found that STZ-induced diabetic rats showed significant ($P<0.05$) increase in the degrees of blood glucose, glycosylatedhemoglobin and significant ($P<0.05$) reduction in the levels of plasma insulin, body weight and total hemoglobin. Diabetic rats also exhibited significant

(P<0.05) reduction in the action of hepatic hexokinase and significant (P<0.05) increase in the natural processes of glucose-6-phosphatase and fructose-1, 6-bisphosphatase. The pancreatic thiobarbituric acid reactive substances and lipid hydroperoxides were significantly (P<0.05) increasedandtheactivities of pancreatic superoxide dismutase, catalase and glutathione peroxidase were significantly (P<0.05) decreased in diabeticrats. Oraltreatment with garlicacid (10 and20 mg/kg) dailyfor a period of 21 days showed significant (P<0.05) protective effects on all the biochemical parameters studied. Histopathology of pancreas confirmed the protective effects of garlicacid in diabeticrats. *In vitro* study also revealed the potent antioxidant effect of garlicacid. Thus, the study shows the antihyperglycemic, anti lipidperoxidative and antioxidant effects of garlic acid on STZ-induced diabetic rats. Theeffectexerted by 20 mg/kg bodyweight of garlic acid was more effective than 10 mg/kg body weight of garlic acid [65].

Table 2: List of some secondary metabolites with antidiabetic property

Name	Source	Molecular formula	Reference
Diosmin	*Citrus orentifolia*	$C_{28}H_{32}O_{15}$	[45]
Beta-Carotene		$C_{40}H_{56}$	[46]
Gamma-Sitosterol	*Nigella sativa*	$C_{29}H_{50}O$	[47, 48]
N-Trissacharide	*Cucumisprophetarum*		[49]
Secoisolariciresinoldiglucoside (SDG)		$C_{32}H_6O_{16}$	[50]
2-(4-[(2-hydroxybenzyl) amino]-phenyl amino-methyl)-phenol(HBPMP)	*Eugenia jambolana*	$C_{33}H_{34}N_6O$	[51]
Tangeritin	*Poncirus trifoliate*	$C_{20}H_{20}O_7$	[52]
Lycopene	*Lycopersicumesculentum*	$C_{40}H_{56}$	[53]
Revasterol		$C_{14}H_{12}O_3$	[54]
Carvone	*Carumcarvi*	$C_{10}H_{14}O$	[55, 56]
Fraxetin	*Fraxinusrhyncophylla*	$C_{10}H_8O_5$	[57]
Diosgenin	*Dioscoreaspp*	$C_{27}H_{42}O_3$	[58]
D-saccharic acid-1, 4-Lactone	*Eleutherococcusspp*	$C_6H_8O_7.H_2O$	[59]
20-OH-Ecdysone	*CyanotisVaga*	$C_{27}H_{44}O_7$	[60]
Syringin	*Musa paradisiaca*	$C_{17}H_{24}O_9$	[61]
Quercetin	*Lycopersicumesculentum*	$C_{10}H_{15}O_7$	[62, 63]
Gallic acid	*Toonasinensis*	$C_7H_6O_5$	[64]

From the above review of literature, it is clear to state that the various biochemical parameters and other variables that were used as indices to imply diabetes condition, e.g., fasting blood glucose were all improved upon treatment with each of those secondary metabolites. Treatment of diabetic rats with herbal extracts/secondary metabolites significantly reversed the anomaly caused by diabetes in both liver and kidney. Regarding the antioxidant status, a significant depletion in the activities of enzymatic antioxidants in STZ treated rats were observed. Treatment of herbal extracts/secondary metabolites also increased the levels of enzymatic antioxidants in the liver and kidney.

Mankind uses herbal extracts and their active compounds for alleviating ailments and for the maintenance of general health. For example Diosmin, (DS) is a common constituent in many citrus species [66]. DS has been reported to stimulate the pancreatic β-cells, which play a crucial role in the production and secretion of insulin [67]. Similar actions are noted with other a for ementioned herbal/secondary metabolites (Table 1 and 2). Apart from conventional allopathic medicines, traditional/alternative therapy plays a significant role in treating diabetes mellitus due to their perceived effectiveness, minimal side effects in clinical experience and relatively small costs. Herbal drugs are prescribed widely even when their biologically active compounds are unknown. One of the major problems with this herbal formulation is that the active ingredients are not well defined. It is important to know the active component and their molecular interaction, which will help to analyse therapeutic efficacy of the product and also to standardize the product. Efforts are now being made to investigate the mechanism of action of some of these plant products using*in vitro* model systems.

CONCLUSION

Diabetes mellitus and particularly non-insulin-dependent diabetes (type 2 diabetes) is an increasingly prevalent condition worldwide with serious consequences of multi organ involvement and in particular cardiovascular and renal disease.According to the International Diabetes Federation, there are currently more than 371 million people with diabetes and another 28 million are at risk of developing the disease. Secondary metabolites widely used in traditional medicine have been proven to combat and cure various ailments through exerting their pharmacological actions. Exploitation of these pharmacological properties involves further investigation of these active ingredients by implementing the techniques of their extraction, purification, separation, crystallization and identification.

CONFLICT OF INTERESTS

The authors wish to declare that there are no conflicts of interest

REFERENCES

1. Scheen AJ. Drug treatment of non-insulin dependent diabetes mellitus in the 1990s. Achievements and future developments. Drugs 1997;54:355-68.
2. CW Spellman. Pathophysiology of type 2 diabetes: targeting islet cell dysfunction. J Am Osteopath Assoc 2010;110:S2-7.
3. TS Fr¨ode, YS Medeiros. Animal models to test drugs with potential antidiabetic activity. JEthnopharmacol 2008;115:173-83.
4. Melmed S, Polonsky KS, Larsen PR, Kronenberg HM. Williams textbook of endocrinology. 12th ed. Amsterdam: Elsevier; 2012. p.1371-435.
5. 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;27:1047-53.
6. Adeqhate E, Schattner P, Dunn E. An update on the etiology and epidemiology of diabetes mellitus. Ann N Y Acad Sci2006;1084:1-29.
7. Sen S, Chakraborty R, Biplab D. Challenges and opportunities in the advancement of herbal medicine. India's position and role in a global context.J Herb Med2011;1:67-75.
8. Modak M, Dixit P, Londhe J. Devasagayam. Indian herbs and herbal drugs used for the treatment of diabetes. J ClinBiochem Nutr 2007;40:163-73.
9. Yasir M, Prateek Jain D, Kharya MD. Hypoglycemic and antihyperglycemic effect of different extracts of *Acacia arabica* bark in normal and alloxan induced diabetic rats. Int J Phytomed2010;2:133-8.
10. Jarald E, Joshi SB, Jain DC. Biochemical study on the hypoglycaemic effects of extract and fraction of *Acacia catechu*willd in alloxan-induced diabetic rats. Int J Diabetes Metab2009;17:63-9.
11. Rajasekaran R, Satishsekar D. Therapeutic evaluation of aloe vera leaf gel extract on glycoprotein components in rats with streptozotocin diabetes. J Pharmacol Toxicol 2007;2:380-5.

12. Arumugam S, Kavimani S, Kadalmanic B, Ahmed AB, Akbarsha MA, Rao MV, *et al.* Antidiabetic activity ofleaf and callus extracts of *Aegle marmelos*in rabbit. Sci Asia 2008;34:317-21.
13. Appia Krishnan G, Rai VK, Nandy BC, Meena KC, Dey S, Tyagi PK, *et al.* Hypoglycemic and antihyperlipidaemic effect of ethanolic extract of aerial parts of *Aerva lanata*Linn. in normal and alloxan induced diabetic rats. Int J Pharm Sci Drug Res 2009;1:191-4.
14. Raj N, Nadeem S, Jain S, Raj C, PrithwishNandi KC. Ameliorative effects of *Alpinia calcarata*in alloxan-induced diabetic rats. Digest J Nanomater Biostructures2011;6:991-7.
15. Patil P, Patil S, Mane A, Verma S. Antidiabetic activity of alcoholic extract of neem (*Azadirachta indica*) root bark. Natl J Physiol Pharm Pharmacol2013;3:142-6.
16. Eidi A, Eidi M, Esmaeili E. Antidiabetic effect of garlic (*Allium sativumL.*) in normal and streptozotocin-induced diabetic rats. Phytomed 2006;13:624-9.
17. Tomar RS, Sisodia S. Antidiabetic activity of *Annona squamosaL.*in experimental induced diabetic rats. Int J Pharm Biol Arch 2012;3:1492-5.
18. Syiem D, Khup PZ, Syiem AB. Evaluation of anti-diabetic potential of *Albizzia lebbek*bark in normal and alloxan-induced diabetic mice. Pharmacol Online 2008;3:563-73.
19. Agrawal NK, Gupta U. Evaluation of hypoglycemic and antihyperglycemic effects of *Acacia tortilis*seed extract in normal and diabetic rats. Int J PharmTech Res2013;5:330-6.
20. Chhetree RR, Dash GK, Mondal S, Acharyya S. Studies on the hypoglycaemic activity of *Aconitum napellusL.*roots. DrugInvention Today 2010;2:343-6.
21. Rao NK. Anti-hyperglycemic and renal protective activities of *Andrographis paniculata*roots chloroform extract. Iran J PharmacolTher2006;5:47-50.
22. Vadivelan R, Dipanjan M, Umasankar P, Dhanabal SP, Satishkumar MN, Antony S, *et al.* Hypoglycemic, antioxidant and hypolipidemic activity of *Asparagus racemosus*on streptozotocin-induced diabetic in rats. Adv Appl Sci Res 2011;2:179-85.
23. El-Demerdash FM, Yousef MI, Abou El-Naga NI. Biochemical study on the hypoglycemic effects of onion and garlic in alloxan-induced diabetic rats. Food Chem Toxicol 2005;43:57-63.
24. Mohana Rupa L, Mohan K. Hypoglycaemic effect of aqueous extract of *Benincasa hispida*in rabbits. J Ayurveda Integrative Med2013;1:1-5.
25. Senthilkumar MK, Sivakumar P, Changanakkattil F, Rajesh V, Perumal P. Evaluation of anti-diabetic activity of *Bambusavulgaris*leaves in streptozotocin induced diabetic rats. Int J Pharm Sci Drug Res2011;3:208-10.
26. Thirumalai T, Therasa SV, Elumalai E, David E. Hypoglycemic effect of *Brassica juncea*(seeds) on streptozotocin induced diabetic male albino rat. Asian Pac J Trop Biomed2011;1:323-5.
27. Nalamolu RK, Boini KM, Nammi S. Effect of chronic administration of *Boerhaavia diffusaLinn*. leafextract on experimental diabetes in rats. Trop J Pharm Res 2004;3:305-9.
28. Kwon Y, Apostolidis E, Shetty K. Evaluation of pepper (*Capsicum annuum*) for management of diabetes and hypertension. J Food Biochem2007;31:370-85.
29. Vega-Avila E, Cano-Velasco JL, Alarcon-Aguilar FJ, Fajardo Ortíz MC, Almanza-Perez JC, *et al.* Hypoglycemic activity of aqueous extracts from *Catharanthus roseus*. Evidence-Based Complementary Altern Med2012;5:35-40.
30. Chauhan PK, Pandey IP, Dhatwalia VK. Evaluation of the antidiabetic effect of ethanolic and methanolic extracts of *Centellaasiatica*leaves extract on alloxan induced diabetic rats. Adv BiolRes 2010;4:27-30.
31. Gunjan M, Jana GK, Jha AK, Mishra U. Pharmacognostic and antihyperglycemic study of *Coccinia indica*. Int J Phytomed 2010;2:36-40.
32. Tirgar PR, Shah KV, Patel VP, Desai TR, Goyal RK. Investigation into mechanism of action of anti-diabetic activity of*Emblicaofficinalis*on streptozotocin induced type I diabetic rat. Res JPharm Biol Chem Sci 2010;1:672-82.
33. Sridhar SB, Sheetal UD, Pai MR, Shastri MS. Preclinical evaluation of the antidiabetic effect of *Eugenia jambolana*seed powder in streptozotocin-diabetic rats. BrazJ Med Biol Res 2005;38:463-8.
34. Choudhary S, Pathak AK, Khare S, Kushwah S. Evaluation of antidiabetic activity of leaves and fruits of *Ficus religiosaLinn*. Int J Pharm Life Sci 2011;2:1325-7.
35. Parveen A, Irfan M, Mohammad F. Antihyperglycemic activity in *Grewia asiatica*, a comparative investigation. Int J PharmPharm Sci 2012;4:210-3.
36. Verma N, Shakya VK, Saxena RC. Antidiabetic activity of glycoside isolated from *Gymnema sylvestre*instreptozotocin induced diabetic rats. Asian J Chem 2008;20:5033-6.
37. Danmalam UH, Abdullahi LM, Agunu A, Musa KY. Acute toxicity studies and hypoglycemic activity of the methanol extract of the leaves of *Hyptis suaveolens*Poit. (lamiaceae). Niger J Pharm Sci 2009;8:87-92.
38. Mishra SB, Vijayakumar M, Ojha SK, Verma A. Antidiabetic effect of *Jatropha curcasL*. leaves extract in normal and alloxan-induced diabetic rats. Int J Pharm Sci 2010;2:482-7.
39. Sutar NG, Sutar UN, Behera BC. Antidiabetic activity of the leaves of*Mimosa pudicaLinn*. in albino rats. J Herbal MedToxicol 2009;3:123-6.
40. Jaiswal D, Kumar Rai P, Kumar A, Mehta S, Watal G. Effect of *Moringa oleiferaLam.*leaves aqueous extract therapy on hyperglycemic rats. J Ethnopharmacol2009;123:392-6.
41. Ahmed SM, Vrushabendra Swamy BM, Gopkumar P, Dhanapal R, Chandrashekara VM. Anti-diabetic activity of *Terminaliacatappa Linn*. leaf extracts in alloxan-induced diabetic rats. Iran J PharmacolTher2005;4:36-9.
42. Stanely P, Prince M, Menon VP. Hypoglycaemic and other related actions of *Tinospora cordifolia*roots in alloxan-induced diabeticrats. J Ethnopharmacol2000;70:9-15.
43. Farook SM, Atlee CW. Antidiabetic and hypolipidemic potential of *Tragia involucrata linn*. In streptozotocin-induced type II diabetic rats. Int J Pharm Pharm Sci 2011;3:103-9.
44. MA Campanero, M Escolar, E Perez, Garcia-Quetglas, B Sadaba, JR Azanza, *et al.*
45. Simultaneous determination of diosmin and diosmetin in human plasma by ion trapliquid chromatography-atmospheric pressure chemical ionization tandem mass spectrometry. J Pharm Biomed Anal2010;51:875-81.
46. Le Marchand, SP Murphy, JH Hankin, LR Wilkens, LN Kolonel. Intake offlavonoids and lung cancer. J Nat Cancer Inst 2000;92:154-60.
47. Maughan, Barbara, Iervolino, Alessandra C, Collishaw, Stephan. Time trends in child and adolescent mental disorders. Curr Opinion Psychiatry 2005;18(4):381–5.
48. Capanlar S, Böke N, Yaşa I, KirmizigülS. A novel glycoside from *Acanthus hirsutus* (Acanthaceae). Nat Prod Commun 2010;5:563-6.
49. Rangachari Balamurugan, Veeramuthu Duraipandiyan, Savarimuthu Ignacimuthu. Antidiabetic activity of γ-sitosterol isolated from *Lippia nodiflora L*. instreptozotocininduced diabetic rats. Eur J Pharmacol 2011;66:410-8.
50. GB Kavishankara, N Lakshmidevia.Anti-diabetic effect of a novel N-Trisaccharide isolated from *Cucumis prophetarum* on streptozotocin–nicotinamide induced type 2 diabetic rats. Phytomed2014;21:624-30.
51. Sadiq S, Moreea GB, Kavishankarb J, Rajeshaa. Antidiabetic effect of secoisolariciresinol diglucoside in streptozotocin-induced diabetic rats. Phytomed 2013;20:237-45.
52. Swapna Sirasanagandla, RameshBabuKasetti, AbdulNabiShaik, Rajesh Natava, VenkataPrasadSurtineni, SureshReddyCirradur, *et al.* Antihyperglycemic and antihyperlipidemic activities of 2-(4-[(2-hydroxybenzyl) amino]-phenyl amino-methyl)-phenol in STZ induced diabetic rats. Eur J Med Chem 2013;66:400-6.
53. Ramalingam Sundarama, Palanivelu Shanthib, Panchanatham Sachdanandam. Effect of tangeretin, a polymethoxylated flavone on glucose metabolism in streptozotocin-induced diabetic rats. Phytomed2014;21:793-9.
54. MamdouhMAli, FatmaGAgha.Amelioration of streptozotocin-induced diabetes mellitus, oxidative stress and dyslipidemia in rats by tomato extract lycopene. Scand J Clin Lab Invest2009;69:371-9.
55. Gyeong-Min Do, Un Ju Jung, Hae-Jin Park, Eun-Young Kwon, Seon-Min Jeon,
56. RobinA McGregor, *et al.* Resveratrol ameliorates diabetes-relatedmetabolic changes via activation of AMP-activated protein kinase and its downstreamtargets in db/db mice. Mol Nutr Food Res2012;56(8):1282-91.
57. De Carvalho, C C C R D, FonsecaM M R. "Carvone: Why and how should one bother to produce this terpene".Food Chem2006;95:413-22.

58. Udaiyar Muruganathan, Subramani Srinivasan, Dhananjayan Indumathi. Antihyperglycemic effect of carvone on the levels of glycoprotein components in streptozotocin-induced diabetic rats.J Acupuncture Dis 2013;4:310-5.
59. Raju Murali, Subramani Srinivasan, Natarajan Ashokkumar. Antihyperglycemic effect of fraxetin on hepatic key enzymes of carbohydrate metabolism in streptozotocin-induced diabetic rats. Biochim2013;95:1848-54.
60. Leelavinothan Parin, Pandurangan Monisha, Abdul Mohamed Jalaludeen.Beneficial role of diosgenin on oxidative stress in aorta of streptozotocin induced diabetic rats. Eur J Pharmacol2012;691:143-50.
61. SemanteeBhattacharya, Prasenjit Manna, RatanGachhui, Parames C.D-saccharic acid-1, 4-lactone ameliorates alloxan-induced diabetes mellitus and oxidative stress in rats through inhibiting pancreatic beta-cells from apoptosis via mitochondrial dependent pathway. ToxicolApplPharmacol2011;257:272-83.
62. Ramalingam Sundaram, Rajendran Naresh, Palanivelu Shanthi, Panchanatham Sachdanandam.Efficacy of 20-OH-ecdysone on hepatic key enzymes of carbohydrate metabolism in streptozotocin induced diabetic rats. Phytomed 2012;19:725-72.
63. Shanmuga Sundaram, Chinna Krishnan, Iyyam Pillai Subramanian, Sorimuthu Pillai Subramanian. Isolation, characterization of syringin, phenylpropanoid glycoside from *Musa paradisiaca* tepal extract and evaluation of its antidiabetic effect in streptozotocin-induced diabetic rats. Biomed Prev Nutr 2014;4:105-11.
64. Mitchell AE, Hong YJ, Koh E, Barrett DM, Bryant DE, Denison RF, *et al*. "Ten-year comparison of the influence of organic and conventional crop management practices on the content of flavonoids in tomatoes". JAgricFood Chem2007;55:6154–9.
65. Vessal, Mahmood, Mina Hemmati, Mohammad Vasei. "Antidiabetic effects of quercetin in streptozocin-induced diabetic rats." Comp BiochemPhysiol Part C: ToxicolPharmacol 2003;135:357-64.
66. Fiuza SM. "Phenolic acid derivatives with potential anticancer properties–a structure–activity relationship study. Part 1:Methyl, propyl and octyl esters of caffeic and gallic acids." Bioorg Med Chem 2004;12:3581-9.
67. Punithavathi, Vilapakkam Ranganathan. "Antihyperglycaemic, antilipid peroxidative and antioxidant effects of gallic acid on streptozotocin induced diabetic Wistar rats." Eur JPharmacol 2011;650:465-71.
68. E Tripoli, MLa Guardia, S Giammanco, DDi Majo, MGiammanco. Citrus flavonoids: molecular structure, biological activity and nutritional properties, a review. Food Chem2007;104:466-79.
69. L Pari, S Srinivasan. Antihyperglycemic effect of diosmin on hepatic key enzymes of carbohydrate metabolism in streptozotocin-nicotinamide-induced diabetic rats. Biomed Pharmacother2010;64:477-81.