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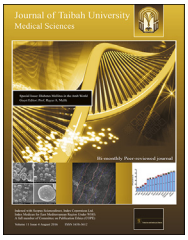

Review Article

The role of prophetic medicine in the management of diabetes mellitus: A review of literature

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ملخص

إن الطب النبوي هو مجموع ما ثبت وروده عن النبي صلى الله عليه وسلم مما له علاقة بالطب، سواء كان آيات قرآنية أو أحاديث نبوية شريفة، ويتضمن وصفات تداوى وداوى بها النبي صلى الله عليه وسلم، أو أنه دعا إلى التداوي بها، كما يتضمن توصيات تتعلق بصحة الإنسان في أحوال حياته من مأكل، ومشرب، ومسكن ومنكح، وتشمل تشريعات تتصل بأمور التداوي وأدب الطب في ممارسة المهنة وضمان المتطبب في منظار الشريعة الإسلامية. قال ابن القيم رحمه الله في كتابه زاد المعاد إلى هدي خير العباد: "وليس طبه صلى الله عليه وسلم كطب الأطباء، فإن طب النبي صلى الله عليه وسلم متيقن قطعي إلهي، صادر عن الوحي، ومشكاة النبوة وكمال العقل، وطب غيره أكثره حدس وظنون وتجارب". وفي المملكة العربية السعودية وحدها تم تسجيل ٣.٨ مليون حالة من حالات داء السكري، مما يستدعي زيادة الاهتمام الصحي العالمي بهذا المرض. وقد أبانت الأدلة العلمية ثبوت إيجابية بعض النباتات والعسل المذكورة في الطب النبوي في تحسين السيطرة على داء السكري. وإلى جانب تأثير المواد المذكورة على مستوى سكر الدم، فإن الدراسات تشير أيضا إلى أن مقتطفات من تلك النباتات والعسل تؤدي إلى تحسين في الخلل الأيضي المرتبط بداء السكري. في هذا الاستعراض، نقدم بعضا من أحدث النتائج التي تبين الفاعلية الحيوية لهذه النباتات والعسل في مراضة داء السكري وعلى مستوى إفراز الأنسولين.

الكلمات المفتاحية: داء السكري؛ المواد الكيميائية النباتية؛ الطب النبوي؛ الطب البديل؛ المنتجات الطبيعية

Abstract

Prophetic medicine is the total authentic Hadith narrated by the Prophet, peace be upon him, in relation to medicine, whether Qur'anic verses or honourable Prophetic Hadith. It includes remedy recipes, by which the Prophet, peace be upon him, was cured or he called people to be cured by. Furthermore, it includes recommendations relevant to human health in the conditions of life, including eating, drinking, housing, and marriage. It comprehends legislations related to medication, medicine in practicing the profession, and the guarantee of the patient in the perspective of Islamic Law. Ibn Al Qayyim, may Allah be merciful with him, in his book Zad Al Ma'ad Fe Haday Khair Al Abad, said: "The medicine of the Messenger, peace be upon him, is not similar to the medicine of physicians. The medicine of the Prophet, peace be upon him, is certain, categorical, and godly medicine; issued by the Revelation, Prophethood niche, and sagacity; while the medicine of others is inductive, assumptive, and experimental."

In KSA alone, 3.8 million cases of diabetes were recorded, thus warranting increased global health concern. Scientific evidence has accorded the claim of several plants and honey listed in prophetic medicine, which improve glycaemic control in diabetes mellitus. In addition to their hypoglycaemic effect, studies indicate that extracts from those plants and honey ameliorate other associated metabolic derangements. In this review, we present several of the latest findings linking the bioefficacy of these plants and honey with the pathogenesis of diabetes and insulin secretion in diabetes mellitus subjects.

Keywords: Alternative medicine; Diabetes; Natural products; Phytochemicals; Prophetic medicine

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Abbreviations: AF4, asymmetrical flow field-flow fractionation; AMPK, AMP-activated protein kinase; CHD, coronary heart disease; DPP, IV inhibitors of dipeptidyl peptidase 4; FBG, fasting blood glucose; FBS, fasting blood sugar; FPG, fasting plasma glucose; GI, glycaemic index; GII, insulinaemic response; GLP, glucagon-like peptide; HDL, high-density lipoprotein; HSCCC, high-speed counter-current chromatography; HUVECs, human umbilical vein endothelial cells; LDL, low-density lipoproteins; MALS, multi-angle light scattering; PPARγ, peroxisome proliferator-activated receptor gamma; PPBG, postprandial blood glucose; RI, refractive index; ROS, reactive oxidative species; TBARS, thiobarbituric acid reactive substances; VLDL, very low-density lipoproteins

Introduction

Diabetes mellitus is among the most important clinical risk factors involved in several disorders, including atherosclerosis, neuropathy, nephropathy, retinopathy and stroke.[1] Avicenna, a renowned physician of the golden ages, described diabetes in his book 'The Canon of Medicine' and mentioned gangrene among its complications.[2,3] Currently, it has been reported that approximately 387 million people live with diabetes globally, and it is projected to double by 2030.[4] In KSA alone, 3.8 million cases of diabetes were recorded in 2015.[5] Owing to this, global healthcare expenditures on the management of type 2 diabetes mellitus alone are anticipated to skyrocket from US $376 billion in 2010 to US $490 billion in 2030.[6] Thus, diabetes mellitus warrants the current increasing global health concern.

It is well accepted that insulin resistance plays a primary role in diabetes pathogenesis and that failure of pancreatic β-cells to secrete insulin is instrumental in the progression to hyperglycaemia. Pancreatic β-cells secrete insulin to regulate blood glucose homeostasis. The dysfunction and injury of these cells contribute to the pathogenesis of type 1 and type 2 diabetes.[7] Insulin secretion is subject to control by nutrients and by hormonal, neural, and pharmacological factors. Among these, glucose is by far the most important regulator of the machinery of insulin secretion.[8] In fact, chronic hyperglycaemia has been shown to be involved in β-cell dysfunction, a phenomenon described as glucotoxicity.[9]

Some of the current anti-diabetic drugs in use act mainly by inhibiting carbohydrate digestion and absorption. For example, Acarbose (BAY g 5421) was the first α-glucosidase inhibitor available for diabetes treatment. This drug inhibits the activities of α-amylase, sucrase and maltase, whereas voglibose is a newer α-glucosidase inhibitor of bacterial origin that inhibits the activities of isomaltase, sucrase and maltase. Although, the majority of these drugs is efficient in maintaining postprandial blood glucose levels in many patients, their administration is often associated with major gastrointestinal adverse effects. The looming concerns over possible health complications that arise as side effects of commercially available antihyperglycaemic compounds are partly responsible for the prevalence of nonadherence to medication that occurs in diabetic patients. This has become a driving force in the current momentum for seeking alternative therapies with less severe side effects. In this sense, herbal compounds appear to offer milder means of managing metabolic disorders. Therefore, the use of phytotherapy in the management of diabetes is well documented in traditional medicine systems, such as Chinese, Indian ayurveda and Arabic unani. A myriad of studies has substantiated the beneficial effects of medicinal herbs for controlling glycaemic status.[10–13] Among the phytotherapeutics are those listed in Islamic scholarly prophetic medicine, such as *Nigella sativa, Cymbopogon spp.,* and *Olea europaea*.

In this regard, this review aims to delineate the current research concerning the hypoglycaemic efficacy of several phytotherapeutic plants described in prophetic medicine, otherwise known as Tibb Al-Nabawi.

N. sativa

N. sativa (black cumin) is an important medicinal herb that finds application in a wide range of diseases. Its medical importance is documented in prophetic traditions. It has been reported on the authority of Aisha, may Allah be pleased with her, who narrated that she heard the Prophet, peace be upon him, saying, "This black cumin is healing for all diseases except As-Sam." Aisha, may Allah be pleased with her, asked 'What is As-Sam?' He (the Prophet peace be upon him) replied 'Death'.[14] Similarly Abu Huraira, may Allah be pleased with him, narrated, "I heard the Prophet, peace be upon him, saying, "There is healing in black cumin for all diseases except death."[14]

Scientifically, the biological activities of *N. sativa* are well studied.[15–20] Among the reported bioactive compounds of this plant are linoleic acid, melanthin, nigilline, thymoquinone, nigellone (dithymoquinone), damascenine, and tannins.[21,22] In particular, thymoquinone has been shown to induce mitochondria-mediated apoptosis,[23] anti-diabetic properties,[24] and antioxidative stress.[25] The hypoglycaemic effect of *N. sativa* has been reported in several studies.[26,27] One study illustrated that *N. sativa* significantly lowered glycated haemoglobin (HbA1c), fasting blood glucose (FBG) and postprandial blood glucose (PPBG) levels after 8 weeks. In fact, upon administering the *N. sativa* extract, the FBG was reported to be reduced by approximately 13% compared to the control (Table 1). In contrast, Adnyana et al.[28] reported a reduction in FBG of approximately 8% after 90 days of administering *N. sativa* (Table 1).

Likewise, treatment with *N. sativa* extract at a concentration of 5 mg/kg bw significantly reduced the FBG level when compared to the control, partially recovered hepatic glycogen content and protected a large amount of pancreatic islet cells.[29] Furthermore, studies have shown that supplementation with either *N. sativa* or its essential oils hold insulinotropic potential mediated by extra-pancreatic action.[17] This was in accordance with Kanter,[30] who observed that administering *N. sativa* or its bioactive compound thymoquinone at a dose of 400 and 50 mg/kg body weight/day, respectively, caused a marked decrease in glucose and increased serum insulin concentrations in streptozotocin-induced diabetic rats.

Similarly, *in vitro* studies have shown that *N. sativa* incurs increased insulin secretion in isolated rat pancreatic islets in the presence of 8.3 mmol/L glucose.[31] Additionally, it had

Table 1: Influence of *N. sativa* intervention on plasma glucose levels (adopted from Najmi et al.[26], Adnyana et al.[28]).

A	Parameters	Before intervention (Mean ± SD)	After intervention (Mean ± SD)
	FBG (Std)	144.2683 ± 21.6042	135.6951 ± 11.6414
	FBG (NS)	165.5823 ± 32.5772	144.3411 ± 12.9111

B	Group	Plasma glucose level (mg/dL)		
		0	60	90
	Control	125.60 ± 31.28	242.20 ± 56.95	186.00 ± 69.04
	NS1	129.60 ± 27.78	239.80 ± 39.54	180.80 ± 24.77
	NS2	128.20 ± 25.52	212.60 ± 32.18	171.00 ± 34.97

been proposed that *N. sativa* has the ability to restore the structural integrity of pancreatic islets in streptozotocin-induced diabetic rats.[30] This is in accordance with histopathological and immunohistochemical studies that revealed the morphological integrity of β-cells of pancreatic islets recovered after treatment with *N. sativa* or its seed oil.[32,33] A recent randomized double-blind, placebo-controlled trial demonstrated the efficacy of *N. sativa* oil on glucose metabolism and lipid concentrations in patients with type 2 diabetes.[34]

A previous study showed that the hypoglycaemic effect of *N. sativa* is due to decreased oxidative stress and preservation of pancreatic β-cell integrity,[35] and most of *N. sativa* antioxidant potency is associated with the presence of thymoquinone.[15] A previous study illustrated the antioxidant effects of *N. sativa* to be due to the inhibition of eicosanoid generation and membrane lipid peroxidation.[36] In another study, it was demonstrated that *N. sativa* seed ethanol extract (NSE) exhibits the remarkable ability to concomitantly increase insulin secretion, induce proliferation of pancreatic β-cells, and stimulate glucose uptake in skeletal muscle and fat cells *in vitro*.[37] Its oil extract was shown to repair damaged pancreatic tissue induced by diabetes.[38] Additionally, supplementation with *N. sativa* extract incurred insulin secretion, glucose absorption and hepatic gluconeogenesis.[39,40]

It has been reported that cellular energy homeostasis involves AMP-activated protein kinase (AMPK) as a major enzyme.[41] The AMPK pathway performs a primary function in the regulation of glucose and lipid metabolism. Thus, the activation of AMPK is thought to stimulate hepatic fatty acid oxidation and ketogenesis.[41] Furthermore, AMPK activation inhibits cholesterol synthesis, lipogenesis, and triglyceride synthesis; stimulates skeletal muscle fatty acid oxidation and muscle glucose uptake; and modulates insulin secretion by pancreatic β-cells.[42] Recently, six rare naturally occurring indazole-type alkaloids (Figure 1) isolated from *N. sativa* seeds were shown to exhibit antihyperglycaemic effects via AMPK activation *in vitro*.[43] Of these isolated compounds, 17-O-(β-D-glucopyranosyl)-4-O-methylnigellidine (Figure 1a) was described to increase glucose consumption by liver hepatocytes (HepG2 cells) through activation of AMP-activated protein kinase.[43] In a similar study, the *in vivo* anti-diabetic activity of *N. sativa* was described to be mediated through the activation of the AMPK pathway and increased muscle glucose transporter 'Glut4' content.[32]

Cymbopogon citratus

C. citratus (lemon grass) is a well known medicinal herb in tropical and subtropical countries, especially in Southeast Asia.[44] Cymbopogon essential oil is often used in aromatherapy. Its importance to the Arab and Islamic community has been documented for over a millennium. It is narrated that Prophet Muhammad, peace be upon him, said "… (It is not allowed to uproot its (the Holy city of Makkah) thorny shrubs, hunt its game, pick up its lost objects, except by announcing it, or to uproot its trees.) And Al-'Abbas, may Allah be pleased with him, said,

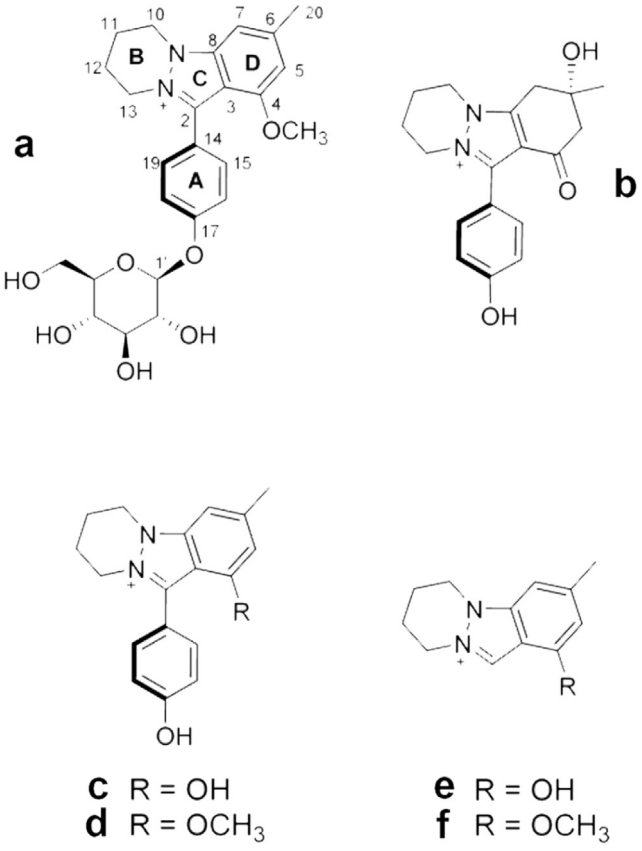

Figure 1: Isolated compounds from N. sativa seeds. Adopted from Yuan et al.[43] (a. 17-O-(β-D-glucopyranosyl)-4-O-methylnigellidine, b. nigelanoid, c. nigellidine, d. 4-O-methylnigellidine, e. nigeglanine and f. 4-O-methylnigeglanine).

'Except the lemon grass, O Allah's Messenger, as they use it in their houses and graves.' And the Prophet, peace be upon him, said: Except lemongrass."

Medically, the plant is known to contain bioactive compounds, such as citral α, citral β, nerol geraniol, citronellal, terpinolene, geranyl acetate, myrecene and terpinol methylheptenone.[22] The plant also contains reported phytoconstituents, such as flavonoids and phenolic compounds, which consist of luteolin, isoorientin 2′-O-rhamnoside, quercetin, kaempferol and apiginin.[45] Studies have indicated that *C. citratus* possesses various pharmacological activities, such as anti-amoebic, anti-bacterial, anti-diarrheal, anti-filarial, anti-fungal and hypoglycaemic properties.[46–48]

The hypoglycaemic and hypolipidaemic effects of aqueous extracts of *C. citratus* in experimental diabetic rats were evaluated.[49] The research evaluated blood samples from rats for fasting plasma glucose (FPG), total cholesterol, triglycerides, low-density lipoproteins (LDL-c), very low-density lipoprotein (VLDL-c) and high-density lipoprotein (HDL-c) assays through cardiac puncture under halothane anaesthesia. The results obtained from their analysis indicated that *C. citratus* treatment significantly and dose-dependently lowered the FPG and lipid parameters while raising plasma HDL-c levels.[49] It has been proposed that the observed hypoglycaemic activity associated with *C. citratus* extract could be due to increased insulin synthesis and secretion (hyperinsulinaemia) or increased peripheral glucose utilization.[49] In a similar study, Campos et al.[50] showed that *C. citratus* bioactive compounds (chlorogenic acid, isoorientin and swertiajaponin) displayed 60% inhibition of reactive oxidative species (ROS) production in human umbilical vein endothelial cells (HUVECs) challenged with high D-glucose. Additionally, the extract was able to inhibit vasoconstriction induced by the thromboxane A2 receptor agonist U46619, thus suggesting a NO-independent vasodilator effect on blood vessels.[50] These studies on *C. citratus* hypoglycaemic bioactivity were found to be at variance with that of Leite et al.[51] in humans; they reported that tea made from the dried leaves of *C. citratus* induced no glycaemic changes in patients treated with the tea for 2 weeks. The observed contrast between these studies could be attributed to the fact that variations may occur in bioactive compounds of different parts of the same plant and even in the same parts found in different environments[52] or due to differences in plant materials used, dosage and duration of drug exposure.[49]

Similarly, Bharti et al.[53] evaluated the anti-diabetic activities of *C. citratus* essential oil obtained by steam distillation of the leaf sheath in poloxamer-407-induced type 2 diabetic Wister rats. GCMS analysis of the extracted essential oil revealed the presence of 23 compounds, of which geranial (42.4%), neral (29.8%), myrcene (8.9%) and geraniol (8.5%) were the major compounds.[53] Post-treatment analyses indicated that diabetic rats presented significant amelioration of glycaemia, insulinaemia, lipid dysmetabolism, accompanied by increased GLP-1 content in caecum and a remarkable reduction of oxidative markers.[53] It has been documented that GLP-1 plays a key role in insulin secretion, glucagon and somatostatin inhibition, pancreatic β-cell mass development, maintenance, and expansion.[54] Furthermore, *in silico* molecular HYBRID and FRED docking have shown that *C. citratus* bioactive compounds, such as myrcenol, linalool, α-elemol and β-eudesmol, showed significant interactions with the proteins PPAR-γ and DPP-IV, which are known to be key anti-diabetic pathways.[53] Aldose reductase is a known rate-limiting enzyme in the hazardous polyol pathway of glucose metabolism, which becomes active when intracellular glucose levels are elevated. This enzyme reduces glucose to sorbitol using NADPH as a co-factor; sorbitol is then metabolized to fructose by sorbitol dehydrogenase that uses NAD^+ as a cofactor. As in previous studies, molecular docking was used to analyse the effect of essential phytochemicals obtained from *C. citratus* on aldose reductase activity.[55] *C. citratus* essential bioactive compounds, such as myrcene, citral, and geraniol, were used as ligands, while aldose reductase was used as the receptor in the molecular docking analysis. The docking analysis showed myrcene, with a binding energy of −8.76 kcal/mol as the best amongst citral and geraniol, which had binding energies of −7.24 kcal/mol and −7.93 kcal/mol, respectively, for inhibiting aldose reductase activity.[55]

α-Amaylase is an enzyme that catalyses the hydrolysis of 1,4-glucosidic linkage of complex carbohydrates, such as starch, into simple sugars, namely maltose. Controlling glucose production from complex carbohydrates is effective for controlling diabetes. Thus, inhibition of α-amylase activity is considered to be an important strategy in the management of diabetes. Jumepaeng et al.[56] reported the inhibition of α-amylase by essential oil extracted from *C. citratus*. The study indicated that *C. citratus* essential oil incurred an α-amylase inhibitory activity in the form of IC_{50} of 6.97 ± 0.12 μL/mL[56]

Olive (*Olea europaea*)

The olive tree is a species of evergreen tree belonging to the family Oleaceae and is native to the coastal areas of the Mediterranean, Asia and Africa. Owing to their rich oil contents, the olive fruits are of major agricultural importance to the Mediterranean region. For several millennia, olive oil has been used in food and cooking as well as in lighting, sacrificial offerings, ointment, and anointment for priestly or royal offices.[57] Its significance is well established in Islamic medicine. In the Holy Quran, Allah the almighty says: "And a tree (olive) that springs forth from Mount Sinai, that grows oil, and (it is a) relish for the eaters."[58] Similarly, it has been reported in prophetic tradition by Omar bin Al-Khattab, may Allah be pleased with him, who narrated that the Prophet, peace be upon him, said: "Eat the oil and anoint yourself with it, for it comes from a blessed tree."[59]

A chemical analysis of olive revealed the presence of several triglycerides; phenolic compounds, such as hydroxytyrosol, tyrosol, caffeic acid, phydroxyphenylacetic acid and homovanillic acid; as well as several flavonoid esters.[60,61] In a recent study, high speed counter-current chromatography (HSCCC) coupled with post-column on-line evaluation was developed to screen for the bioactive compounds in olive leaf extracts. The research revealed the presence of oleuropein, ligstroside, hydroxytyrosol, tyrosol and luteolin-7-O-β-D-glucoside.[62] Studies have reported that the healing power of olive oil comes from its high antioxidant activity

coupled with high levels of mono-unsaturated fatty acids in addition to its biocompatibility and digestibility. Several studies have reported the bioactivity of *O. europaea*, including antioxidant,[63] antimicrobial,[64] antiulcerogenic,[65] antinociceptive[66] activities.

Recently, the significance of supplementation with olive leaf extract (OLE) as an antioxidant in reducing metabolic abnormalities in diabetic male albino rats was evaluated.[67] Diabetic rats were administered OLE orally twice daily for 30 days. At the end of the experimental period, levels of serum insulin and glucose in addition to lipid patterns, such as total cholesterol (TC), triglycerides (TG), high density lipoproteins (HDL), low density lipoproteins (LDL), and very low density lipoproteins (VLDL), and renal markers were determined. After OLE administration, diabetic rats showed marked increases in levels of serum insulin accompanied with marked declines in levels of fasting blood glucose compared to controls.[67] It has been reported that oleuropein, a phenylethanoid compound displayed, distinct hypoglycaemic effects at an administrative dose of 16 mg/kg[2].

Powdered mixtures of olive leaf with *Juglans regia*, *Urtica dioica*, and *Atriplex halimus* were reported to decrease glucose absorption from the intestine and lower blood glucose levels in rats and diabetic subjects.[68] Kadan et al.[2] has shown that exposing L6-GLUTmyc cells to 250 mg/mL of olive extract significantly decreased glucose transporter 4 (GLUT4) translocation from 100% to 80% in the basal state without insulin stimulation and from 150% to 105% in insulin-stimulated cells. The research attributed the observed anti-diabetic effects of olive extract to several mechanisms, including GLUT4 translocation. In an advanced study, supplementation of rat diet with 10% olive oil induced improvement of glucose tolerance and insulin secretion.[69] Additionally, histopathological study of the isolated pancreas of rats supplemented with olive oil showed an increased response of Langerhans islets to glucose stimulus by strong oxidation of glucose, which resulted in increased insulin secretion.[69,70]

Oleanic acid (oleanolic acid), a naturally occurring triterpenoid commonly found in olive oil, has been described to improve insulin response, preserve functionality, increase survival of pancreatic β-cells, and protect against diabetes complications.[71] Oleanic acid is thought to directly modulate enzymes connected to insulin biosynthesis, secretion, and signalling. It interacts with important transduction pathways by activation of the transcription factor Nrf2.[71] Hence, it induces the expression of antioxidant enzymes and phase II response genes, which block NF-kB and repress the polyol pathway and hyperlipidaemia.[71] As mentioned earlier, carbohydrate digestion is facilitated by enteric enzymes, such as α-glucosidase and α-amylase, in small intestinal cells. Their inhibition permits better control of postprandial hyperglycaemia. Studies have shown that oleanic acid inhibits α-glucosidase *in vitro* in a dose-dependent fashion.[72–74] It has also been reported to inhibit α-amylase.[75] The anti-diabetic and antioxidant effects of hydroxytyrosol and oleuropein from olive leaf extracts were evaluated in alloxan-induced diabetic rats.[76] Khlif et al.[77] described the anti-diabetic property of a new methylated oleanic acid isolated from olive stems. The isolated compound was also found to inhibit the activities of α-amylase and lipase.[77] A recent study has indicated that diabetes causes a significant elevation in the level of hepatic arylsulfatase B and a significant reduction of hepatic catalase as an antioxidant enzyme. Supplementation of olive oils returned catalase and arylsulfatase B activities to normal levels, thus exerting hypoglycaemic activity.[78]

Salvadora persica (Miswak)

The mustard tree, commonly called tooth brush tree or 'Miswak' in Arabic, belongs to the taxonomic family of Salvadoraceae.[79] The tree has a pleasant fragrance as well as a warm and pungent taste; the tender branches have been popularly used for centuries as a natural toothbrush, particularly within the Arabian Peninsula as well as in the wider Muslim world.[80,81] Its usage is recorded in the prophetic tradition by Abu Hurairah, may Allah be pleased with him, who narrated that the Prophet, peace be upon him, said: "Had I not thought it difficult for my Ummah, I would have commanded them to use the Miswak (tooth-stick) before every Salah (praying)."[14,82] A phyto-chemical analysis of *S. persica* revealed that the plant contained specific amounts of salvadorine; salvadourea; terpenes; trimethylamine; gypsum; organic compounds, such as pyrrolidine, pyrrole, and piperidine derivatives; chlorides; sulphur; vitamin C; carbohydrates; glycosides; large amounts of fluoride and silica; and trace amounts of tannins, saponins, flavonoids and sterols.[83,84] The anti-hyperglycaemic activity of *S. persica* in streptozotocin-induced diabetic rats has been reported.[85] The research showed that a hydro-alcoholic extract of the *S. persica* significantly and dose-dependently reduced blood glucose level.[85] Previously, the stem decoction of *S. persica* was shown to significantly lower glucose levels in rats, and the reduction of glucose levels was shown to be due to increased plasma insulin levels.[86] Furthermore, the research opined that most phytochemical compounds having sulphur derivatives may incur hypoglycaemic efficacy.[86]

In another approach, different extracts obtained from fungal strains isolated from *Salvadora* were evaluated for anti-diabetic and hypolipidaemic activity in glucose-loaded fasting and alloxan-induced diabetic Wister albino rats.[87] In their research, glucose tolerance tests were used to ascertain the blood glucose levels. They found that only four extracts significantly reduced blood glucose levels, namely unidentified fungus (aqueous), *Aspergillus* sp. JPY2 (methanol), *Aspergillus* sp. JPY1 (methanol) and *Phoma* sp. (acetone).[87] Furthermore, they observed that, in alloxan-induced diabetic rats, the maximum reduction of blood glucose levels was after 5 h in the acute treatment experiment and on the 14th day in the subacute treatment at a dose of 250 mg/kg of body weight. In comparison to the standard drug tolbutamide that reduced the blood glucose level up to 40% in long term treatment, the reduction in blood glucose in the isolate extracts ranged from 11.3% to 28.04%.[87] A study published by Khan et al.[88] induced diabetes in albino Wistar rats by a single intraperitoneal injection of streptozotocin (60 mg/kg). The researchers compared the efficacy of Indian and Arabian *S. persica* root extracts by administering it orally at 250 and 500 mg/kg doses to

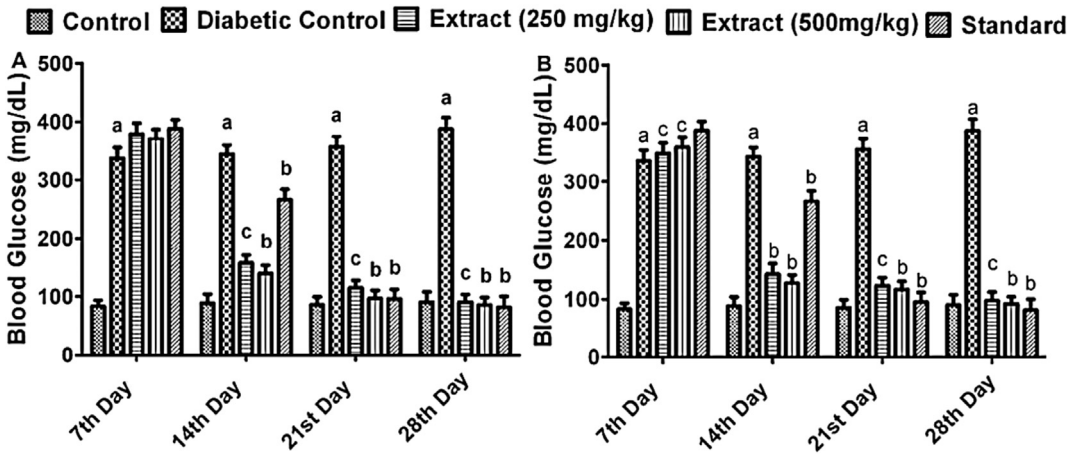

Figure 2: Effect of Arabic origin (**A**) and Indian origin (**B**) aqueous extracts of *Salvadora persica* on hyperglycaemia. a, b, c are statistically significant levels at $P < 0.001$ and $P < 0.05$ compared with the control group. Adopted from Khan et al.[88]

albino Wister rats for 28 days (Figure 2). The research described that arabic *S. persica* aqueous extracts at 500 mg/kg dose level possessed significant hypoglycaemic and hypolipidaemic activities and regenerated pancreatic β-cells in streptozotocin-treated diabetic rats.[88]

Honey

Honey is considered one of nature's valuable functional and medicinal foods.[89] In the Holy Quran, Allah the almighty says: "And your Lord inspired to the bee, take for yourself among the mountains, houses, and among the trees and [in] that which they construct. Then, eat from all the fruits and follow the ways of your Lord laid down [for you]. There emerges from their bellies a drink, varying in colours, in which there is healing for people. Indeed in that is a sign for a people who give thought."[58] Abu Sa'eed al-Khudree, may Allah be pleased with him, narrated, "A man came to the Prophet, peace be upon him, and said, 'My brother has pain in his stomach,' so the Messenger, peace be upon him, said: 'Give him honey to drink.' The man came back and said, 'O Messenger of Allah! It only increased his illness!' So the Messenger, peace be upon him, said, 'Give him honey to drink.' The man came back and said, 'O Messenger of Allah! It only increased his illness!' The Messenger of Allah, peace be upon him, said 'Allah spoke the truth and your brother's belly has lied. Go and give him honey to drink.' He went and gave him honey and was cured."[14,82]

Honey is a natural food and a complex mixture of sugars, in which fructose and glucose are the main constituents. It has been shown to possess novel antioxidant[90] and antimicrobial[91] properties. Due to the reduced secretion of insulin in response to glucose in the blood, diabetes patients are restricted to specific food types. The restriction put on their diet deprives them of many elements in their natural form. Thus, synthetic sweeteners, such as aspartame, saccharin and other artificial and chemical sweeteners that have no food value, are used to replace sugar in their food and drinks. It has been proposed that pure natural honeys in low doses could be recommended as a source of carbohydrates and even as a sweetening agent in place of sucrose to human patients suffering from diabetes mellitus.[92] The effect of natural honey supplementation on the blood glucose levels of alloxan-induced diabetic rats has been reported.[92] The research noted that daily ingestion of honey for three weeks effectively reduced blood glucose levels in rats with alloxan-induced diabetes. However, the honey supplement did not reduce blood glucose in healthy controlled rats.[92] It is thus asserted that honey may be a useful adjunct in the management of diabetes, while serving as a sweetener, especially if taken in moderate quantities.[92]

A recent clinical trial reported on a volunteer patient with coronary heart disease (CHD), hypertension and type 2 diabetes mellitus who stopped all conventional medications and used honey as an alternative therapy for almost 11 years. In spite of persistent hyperglycaemia and dyslipidaemia, his blood pressure was unexpectedly controlled, his CHD improved or at least stabilized, and he did not develop cerebral strokes. Moreover, he did not develop diabetic ketoacidosis or a hyper-osmolar coma. However, he developed micro-vascular complications in the form of peripheral neuritis and non-proliferative retinopathy after 6 and 8 years, respectively.[93] The potential benefit of honey in type 2 diabetes mellitus has been extensively reviewed.[94] Previously, a study showed that honey intake considerably decreased the postprandial glycaemic response or had a less adverse effect on plasma glucose than other sugars or sweeteners in diabetic patients. However, a contradictory report based on 8-week consumption of natural honey led to a significant elevation in glycosylated haemoglobin (HbA1C) levels, with no significant change in fasting blood sugar (FBS) concentrations in diabetic patients.[95] Similarly, Omotayo et al.[96] showed an increase in serum antioxidant capacity with honey consumption. Because oxidative stress has been implicated both in the development of diabetes as well as its complications, the novel antioxidant efficacy of honey compounds might also afford an organ-protective effect, which could limit the progression of diabetes and reduce complications. It has been proposed that fructose and oligosaccharides might contribute to the anti-diabetic effect of honey.[97,98] Research has demonstrated that fructose exerts a

synergistic effect on the gastrointestinal tract and pancreas. This synergistic effect might enhance intestinal fructose absorption and stimulate insulin secretion. Thus, it may enhance hepatic glucose uptake and glycogen synthesis and storage via activation of hepatic glucokinase and glycogen synthase, respectively.[98] A study found that fructose-fed rats had increased plasma insulin levels, and supplementation with oligofructose restored plasma insulin levels to those of controls.[99] In streptozotocin-induced diabetic rats, oligofructose increased portal and pancreatic insulin concentrations.[100] Similarly, type 2 diabetic subjects or individuals with impaired glucose tolerance treated with arabinoxylan had reduced insulin levels.[101] A combination of oligofructose and polydextrose was reported to increase insulin and C-peptide levels in type 2 diabetic patients.[102] Natural honey lowered plasma glucose, C-reactive protein, homocysteine, and blood lipids in healthy, diabetic, and hyperlipidaemic subjects. The research reported that, in diabetic patients, honey caused a significantly lower rise of plasma glucose levels compared with dextrose.[103]

Dates (*Phoenix dactylifera*)

Date palm is one of the oldest cultivated plant known to mankind. Dates are mentioned in the Holy Quran: Allah the almighty says: "And from the fruits of date palms and grapes, you derive strong drink and a goodly provision. Verily, therein is indeed a sign for people who have wisdom."[58] It has been reported that the Prophet Muhammed (peace be upon him) has elaborated on the medicinal important of dates in curing several disorders, and he suggested that Muslims eat date palm.[104,105] S'ad bin Abi Waqas, may Allah be pleased with him, narrated that the Messenger of Allah, peace be upon him, said, "He who eats seven dates of Madina (Ajwa dates) every morning will not be affected by poison and magic on the day he eats them."[14]

The exact mode of action of dates in the control of diabetes is poorly understood and still under the scope of research. Due to its reported antioxidant activities,[106,107] one could attribute such efficacy to enhanced insulin secretion and inhibited absorption of glucose. Various active compounds (flavenoids, steroids, phenol and saponines) present in the extract of *P. dactylifera* were shown to play an anti-diabetic role and scavenge free radicals liberated by alloxan in diabetic rats.[104] Recently, a diosmetin isolated from an epicarp of date palm fruits was illustrated to play a significant role in the improvement of different biochemical results in diabetic rats.[108]

In a previous study, Mard et al.[109] evaluated the anti-diabetic and anti-lipidaemic activities of the hydroalcoholic extract of *P. dactylifera* palm leaves and its fractions in alloxan-induced diabetic rats. In their study, the researchers demonstrated that oral administration of the extract and its fractions improved body weight via decreased water intake and caused hypoglycaemia in alloxan-induced diabetic rats.[109] A previous study opined that date palm consumption could ameliorate hyperglycaemia and hyperlipidaemia in diabetic patients.[110] Results of this study demonstrate significant anti-hyperglycaemic and anti-lipaemic effects. Additionally, the mechanism of date palm hypoglycaemic activity was demonstrated to be similar to that of hypoglycaemic sulphonylureas.[111]

A recent study used a multi-model analysis to evaluate the efficacy of date palm fruit aqueous extract on streptozotocin-induced diabetic rats.[112] The study demonstrated that *P. dactylifera* has the potential to prevent diabetes hazards and can potentially improve diabetic neuropathy.[112]

Barley (*Hordeum Vulgare*)

Barley has been an important foodstuff in the Arabian Peninsula since ancient times. It is reported that Aisha, may Allah be pleased with her, used to recommend Talbina (a meal made from powdered barley) for the sick or for those grieving a deceased person. She (Aisha), may Allah be pleased with her, said, "I heard the Messenger saying, 'The Talbina gives rest to the heart of the patient and makes it active and relieves some of his sorrow and grief'."[82]

Non-starch polysaccharides, resistant oligosaccharides, lignin, and lignin complexes in plants, including other analogous-carbohydrates, such as resistant starch, dextrins, and synthesized carbohydrate compounds, such as polydextrose, are categorized as dietary fibre.[113] These kinds of dietary fibres are mostly concentrated in cereals, fruits, and vegetables. Research has demonstrated that daily dietary fibre intake helps prevent many nutritional disorders, including cardiovascular diseases, type 2 diabetes and obesity.[114,115]

Barley is rich in fibre, particularly the soluble fibres β-glucans (a viscous polysaccharide consisting of several D-glucose units) and pectin.[113] Clinical studies with diets containing foods enriched in barley β-glucans revealed a reduction of the glycaemic index (GI) and insulinaemic response (GII).[116] The high viscosity of barley's β-glucans in the gastrointestinal track incur a reduction of starch digestion by α-amylase, and this is suspected to be the likely mechanism by which β-glucans decrease the postprandial glucose response.[113,117] Furthermore, the health benefits of β-glucans, such as reducing blood serum cholesterol and regulating blood glucose levels, were shown to be correlated with the amount and molecular weight of the solubilized β-glucans in the gastrointestinal tract.[117] The effect of barley consumption on the livers of diabetic rat was investigated,[118] and the study demonstrated the amelioration of liver cells by barley consumption.

Dou et al.[119] evaluated for the first time the relationship between anti-diabetic activity and molecular conformation of barley starch during the germination process. The research employed the ability of asymmetrical flow field-flow fractionation (AF4) coupled online with multi-angle light scattering (MALS) and refractive index detectors (RI) for monitoring changes in molecular conformation. The study revealed that the ratio of the starch molecular radius of gyration to the hydrodynamic radius and the apparent density are among the primary parameters for the anti-diabetic effect of barley's starch.[119] The results showed that, when germinated, the apparent density and the anti-diabetic activity of barley were significantly increased, suggesting that germination makes the molecules more compact; this could contribute to the enhancement of their anti-diabetic activity (Figure 3).[119]

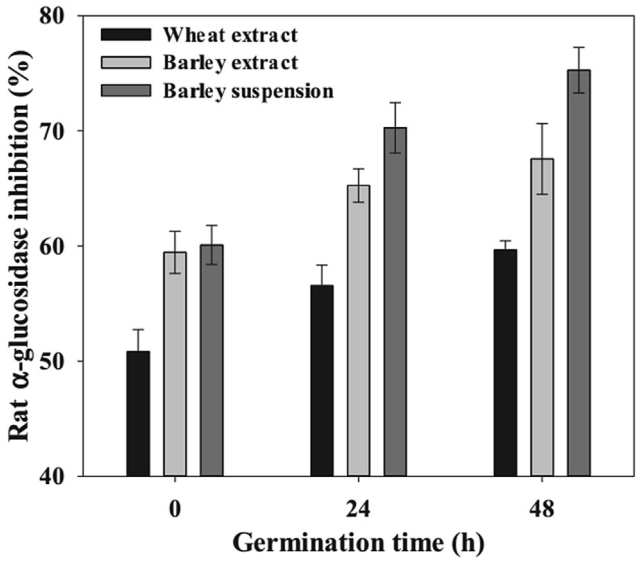

Figure 3: Variations of rat α-glucosidase inhibition with germination time for three different samples. Adopted from Dou et al.[119]

Zamzam water

Alkaline water is known to display strong antioxidant activity that enhances its biological activity. Zamzam water is a natural alkaline water that has also displayed the same antioxidant activity as other alkaline waters.[120] It is therefore not surprising that its medicinal significance was highlighted in the prophetic tradition. The Prophet, peace be upon him, said: "The best water on the face of the earth is the water of Zamzam; it is a kind of food and a healing from sickness."[121] Ibn Abbas, may Allah be pleased with him, narrated that The Prophet, peace be upon him, said: "The water of Zamzam is for whatever it is drunk for."[122]

Zamzam water has been reported to increase total antioxidants in rats with gentamycin-induced stress[123] and to possess oncolytic activity.[124] It was also shown to cause downregulation of genes that affect growth, integrin, insulin-like growth factor and nuclear factor kappa beta, and interleukins.[125] It has been found that HbA1c is negatively and significantly correlated with reduced glutathione in diabetic patients.[126] Recently, zamzam water was shown to ameliorate oxidative stress and reduce HbA1c in type 2 diabetic patients. The study reports that zamzam group patients showed a significant increase in serum levels of total antioxidants, catalase, superoxide dismutase, and glutathione. Furthermore, patients who received zamzam water had a significant decrease in HbA1c.[126]

Vinegar

Vinegar is a liquid produced via carbohydrate fermentation. Typically, it contains acetic acid at a concentration of 4–8%.[127] The significance of vinegar in Islamic medicine was established according to Aisha, may Allah be pleased with her, who narrated that The Prophet, peace be upon him, said: "The best of condiments is vinegar."[82] Naturally, it also contains small amounts of vitamins, mineral salts, amino acids, polyphenolic compounds and non-volatile organic acids.[127] Although vinegar is mainly used as a cooking ingredient, it has long been used in many ailments, with claims of antiseptic, cardiovascular-protective, antitumour and blood glucose-lowering effects.[127] The earliest known use of vinegar dates to more than a millennium ago, and flavoured vinegar has been produced and sold as a commercial product for five millennia.[128] Recent studies in both animal and human subjects have shown that vinegar possesses hypoglycaemic activity.[129,130]

In rats, the effect of apple vinegar on serum glucose has been investigated, and it has been reported that administration of apple vinegar results in a significant reduction in serum glucose of diabetic animals (8.3 ± 0.75 mmol/L) in comparison with the control group (24.6 ± 8.45 mmol/L).[131] The study further iterated that the mode of action could be mediated through enhanced secretion of insulin from the β-cells of Langerhans or through an extrapancreatic mechanism.[131] Similar studies have attributed the hypoglycaemic activity of vinegar to the presence of acetic acid, which could prevent the complete digestion of complex carbohydrates[132] by either accelerating gastric emptying or increasing the uptake of glucose by tissues, thus lowering serum glucose.[133] In humans, vinegar was found to improve insulin sensitivity to a high carbohydrate meal in subjects with insulin resistance or type 2 diabetes.[134] The beneficial effect of vinegar in streptozotocin-induced diabetic rats was evaluated.[127] After a month of administration, the researchers assayed the fasting serum insulin concentrations by ELISA and the pancreatic β and α-cell proportions using immunofluorescence microscopy. Periodic acid Schiff staining was performed to access glycogen contents and histological changes in liver tissues. Compared with control animals, the vinegar-treated rats were found to exhibit weight loss, lower fasting and random blood glucose, higher fasting serum insulin and higher β-cell proportions.[127]

Costus

Umm Qais, may Allah be pleased with her, narrated: I went to The Prophet, peace be upon him, along with a son of mine whose palate and tonsils I had pressed with my finger as a treatment for a (throat and tonsil) disease. The Prophet, peace be upon him, said, "Why do you pain your children by pressing their throats! Use Oud Al-Hindi (Indian aloe wood, costus) for it cures seven diseases, one of which is pleurisy."[14]

According to contemporary medicine, costus, commonly known as 'insulin plant,' is a member of the Zingiberacea family and is used as a munching dietary supplement for the treatment of diabetes in many parts of the world.[135] Eliza et al.[136] evaluated the anti-diabetic and anti-lipidaemic activity of eremanthin from *Costus speciosus* in streptozotocin-induced diabetic rats. In this study, the isolated eremanthin was administered to streptozotocin-induced diabetic male Wistar rats at different doses (5, 10, 20 mg/kg bw) for 60 days. They reported that the treatment significantly reduced plasma glucose levels in a dose-dependent manner when compared to the controls. In addition, oral administration of eremanthin (20 mg/kg bw) significantly decreased

glycosylated haemoglobin (HbA1c), serum total cholesterol, triglyceride, LDL-cholesterol and markedly increased plasma insulin, tissue glycogen, HDL-cholesterol and serum protein. Eremanthin also restored the altered plasma enzyme (aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase and acid phosphatase) levels to near normal.[136] In a similar study, the hypoglycaemic efficacy of *Chrysolophus pictus* leaf extract was evaluated in normal as well as in streptozotocin-induced diabetic rats.[135] Orogastric intubation of the aqueous leaf solution of this plant in diabetic rats for 28 days at a dosage of 2 mg/kg body weight exhibited a significant reduction in fasting blood glucose levels and a remarkable increase in serum insulin levels. It further incurred significant reductions in serum parameters, such as SGOT, SGPT, lipids, triglycerides, total cholesterol, urea, TBARS, and albumin, in diabetic rats treated with leaf solution. Additionally, the body weight of diabetic rats was restored to normal when treated with the extract. Morphometric analysis of extract-treated pancreatic islets showed a significant increase in the number and area of islets when compared with normal and diabetic control rats.[135] Previously, Jayasri et al.[137] evaluated *C. pictus* extract for its ability to inhibit α-amylase and α-glucosidase as an alternative management of diabetes. *In vitro* assays revealed that methanol, aqueous, ethyl acetate and ethanolic extracts of *C. pictus* had good inhibitory effects on carbohydrate hydrolysing enzymes, such as like α-glucosidase and α-amylase. The study illustrated that all the tested extracts of *C. pictus* showed good inhibitory activity, and higher α-amylase inhibitory effects were shown by aqueous extracts of approximately 84.16% at a concentration of 100 mg/ml. Similarly, the aqueous extract also showed a higher inhibitory effect (79%) in an α-glucosidase inhibitory assay.[137] Similarly, anti-diabetic activity of *C. pictus* on alloxan-induced diabetic rats has been shown.[138] As expected, the study also reported a significant reduction in serum glucose levels and lipid profiles.[138] The anti-hyperglycaemic activity of various extracts of *C. speciosus* rhizomes in streptozotocin-induced diabetes[139] and alloxan-induced type 2 diabetes mellitus in albino rats[140] has also been reported.

Truffle (Terfeziaceae)

Truffle is a fruiting body of a subterranean fungus, the majority of which belongs to the genus Tuber. Mushrooms are an important source of nutrients and physiologically beneficial, non-toxic medicines.[141] In fact, mushrooms have been used in folk medicine throughout the world since ancient times. The Prophet, peace be upon him, said: "The kam'ah (truffle) is from al-Mann (which is a food mentioned in the Quran, Surah al-Baqarah), and its water is a cure for the eye."[14,82] Biochemical analyses have shown mushrooms to contain large amounts of vitamin A, C and β-carotene, all of which are known for their antioxidant properties.[141] Aldose reductase is a cytosolic NADPH-dependent oxidoreductase enzyme that catalyses the reduction of glucose to sorbitol as the first step of the noxious polyol pathway of glucose metabolism. Lee et al.[142] isolated eight biochemical compounds from the truffles of *Ganoderma applanatum*, and the isolated compounds were found to exhibit inhibitory properties against aldose reductase.[142]

Fig (*Ficus carica*)

F. carica L. belongs to the family Moraceae. It is such a revered plant that Allah has sworn with it in the holy Quran: "By the fig and the olive! And the mount of Sinai, and this safe country (Makkah)! Indeed, we created the human with the fairest stature."[58] Fig is grown in nearly all tropical and sub-tropical countries.[143] Aqueous extracts of *F. carica* have hypoglycaemic activity in streptozotocin-induced diabetic rats.[144] The study reported administering a decoction to rats for three weeks. The extract was found to significantly decrease plasma glucose levels in diabetic rats. Plasma insulin levels were also significantly increased by treatment of non-diabetic rats.[144] The hypoglycaemic effect of fig fruit and leaf extracts on alloxan-induced diabetic rats has been reported.[145] Vitexin and isovitexin (Figure 4) isolated from *Ficus deltoidea* were shown to possess inhibitory effects on α-glucosidase.[146] Oral administration of 1 mg/kg of either vitexin or isovitexin significantly reduced postprandial blood glucose levels in sucrose loaded normoglycaemic mice after 30 min. Khan et al.[147] have written a detailed review on the hypoglycaemic effect of the genus *Ficus spp*.

Cucurbitaceae

The formal account of Cucurbitaceae in the Quran is mentioned in Surah As-Saffat, 146. Allah the almighty says: "And We caused a plant of gourd to grow over him." Unripe fruits, seeds and aerial parts of *Momordica*

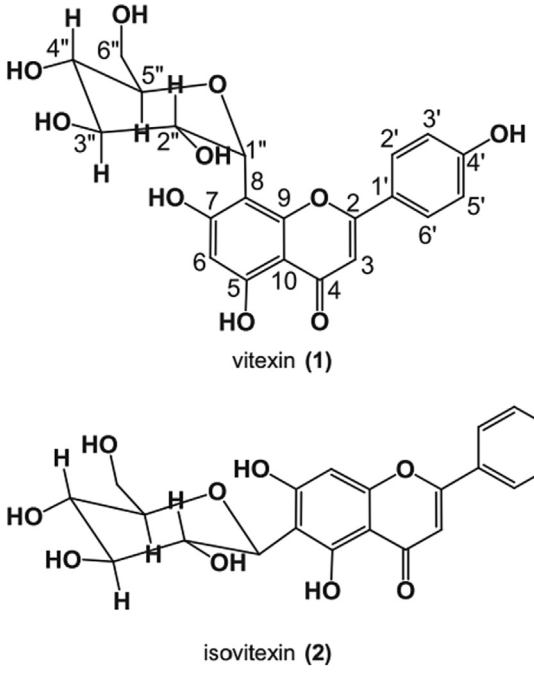

Figure 4: Structures of vitexin (1) and isovitexin (2). Adopted from Choo et al.[146]

charantia Linn. (Cucurbitaceae) have been globally used in the treatment of several ailments. Oral administration of fruit juice or seed powder causes a reduction in fasting blood glucose and improves glucose tolerance in normal and diabetic animals and in humans.[148] Previously, Higashino et al.[149] found that a polar solvent extract of *M. charantia* improved tolerance to both orally and intraperitoneally administered glucose, suggesting the involvement of impaired glucose absorption from the gastrointestinal tract. Bio-guided fractionation of the methanol extract of *M. charantia* dried gourds led to the isolation of three new cucurbitane triterpenoids with hypoglycaemic activity.[150] Previous research has reported the hypoglycaemic activity Cucurbita ficifolia fruit extract on streptozotocin-induced diabetic rats.[151] It has been described that feeding diabetic rats with *C. ficifolia* fruit extract causes a reduction in STZ-induced hyperglycaemia, increased plasma insulin levels, and markedly reduced STZ-induced lipid peroxidation in the pancreas. Further, there was a significant increase in the number of β-cells in *C. ficifolia*-treated animals when compared with untreated diabetic rats.[151] The anti-diabetic activity of protein globulins obtained from several of the selected five species of Cucurbitaceae seeds has been reported.[152] An oral glucose tolerance test showed that the globulins of the seeds of all species except *Cucumeropsis mannii* caused a significant drop in blood sugar compared to the controls.[152] Similar reductions in blood glucose levels were observed with *Coccinia indica* extract.[153]

Conclusions

Considerable evidence from experimental studies has demonstrated that the above mentioned therapeutic items of prophetic medicine may provide benefits in the management of diabetes mellitus. These potential benefits could be both in terms of better control of the hyperglycaemic state as well as interactions with metabolic pathways and a reduction of noxious effects on organs that produce diabetic complications. However, most of the studies on experimental animal models of diabetes have employed synthetic drug (streptozotocin or alloxan)-induced diabetes, which may not truly reflect the development of diabetes in humans, especially type 2. It is therefore necessary that studies are carried out in other animal models, such as high-fat diet fed obese animals or genetically prone animals, which might correlate more closely with human type 2 diabetes. Moreover, the promising bioactivity seen in experimental studies needs to be further investigated in well-designed, controlled clinical trials to determine whether these can be duplicated in clinical scenarios.

Conflict of interest

The author has no conflict of interest to declare.

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