Dietary Phytochemicals and Their Potential Effects on Diabetes Mellitus 2

Rajbala Singh, Imran Kazmi, Muhammad Afzal, and Faisal Imam, Khalid Saad Alharbi

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most important contemporary medical problems; currently the number of people with diabetes exceeds 200 million worldwide, most of them being patients with T2DM. T2DM causes increased risks of cardiovascular disease, kidney failure, blindness, neuropathy, and peripheral circulatory disease. Type 2 diabetes mellitus was formerly called as non-insulin-dependent diabetes mellitus, obesity-related diabetes, or adult-onset diabetes. T2DM is a metabolic disorder that is primarily characterized by insulin resistance, relative insulin deficiency, and hyperglycemia (Dilmec et al. 2010). The loss of traditional dietary habits, increasing consumption of energy-dense foods, and increasing portion sizes, together with less physical activity at work and/or during leisure time, are strongly associated with the explosive increase of these diseases (Heidemann et al. 2005; Montonen et al. 2005). The prevalence of diabetes is rapidly rising all over the globe at an alarming rate (Huizinga and Rothman 2006). The global prevalence of diabetes mellitus has

R. Singh
Siddhartha Institute of Pharmacy, Dehra Dun, Uttarakhand, India

I. Kazmi (✉)
Glocal School of Pharmacy, Glocal University, Saharanpur, Uttar Pradesh, India

M. Afzal (✉) · K. S. Alharbi
Department of Pharmacology College of Pharmacy, Jouf University, Sakaka, Kingdom of Saudi Arabia

F. Imam
College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

M. Ozturk, K. R. Hakeem (eds.), *Plant and Human Health, Volume 3*,
https://doi.org/10.1007/978-3-030-04408-4_4

Table 1 List of top ten countries with diabetes (Wild et al. 2004)

Rank	Country	People with T2DM (million) (year 2000)	Rank	Country	People with T2DM (million) (year 2030)
1	India	31.7	1	India	79.4
2	China	20.8	2	China	42.3
3	USA	17.7	3	USA	30.3
4	Indonesia	8.4	4	Indonesia	21.3
5	Japan	6.8	5	Japan	13.9
6	Pakistan	5.2	6	Pakistan	11.3
7	Russia Fed	4.6	7	Russia Fed	11.1
8	Brazil	4.6	8	Brazil	8.9
9	Italy	4.3	9	Italy	7.8
10	Ukraine	3.2	10	Ukraine	6.7

been estimated at 171 million people and is projected to more than double, to 366 million people, by 2030 (Wild et al. 2004). See Table 1.

The third National Health and Nutrition Examination Study carried out in the USA gives peak prevalence rates of diabetes for men as 21.1% in the 75-plus age group. The peak prevalence for women is 17.8%, which occurs in the 60–74 age range. These data suggest that diabetes is more common in females than males (Harris et al. 1998). In Europe rates are 3–10%, while some Arab, Asian-Indian, and Hispanic-American populations have rates of 14–20%. However in South Africa it is 7.1%. The neighboring country Oman has reported that the prevalence of diabetes mellitus is 13.1% (King and Rewers 1993). In Saudi Arabia, it has been observed as 11.8% and 12.8% for males and females, respectively (Al-Nuaim et al. 1997). The highest rates were found in natives of Nauru, a Pacific Island, and the Pima Indians in the USA that had prevalence rates as high as 50% (King and Rewers 1993). Urbanization is associated with lifestyle changes, which expose individuals to various risk factors that can lead to noncommunicable diseases (WHO and IDF 2006; Richard et al. 2006). Obesity is a key risk factor for T2DM. The association between increasing body mass index (BMI) and greater weight gain increases the risk of diabetes. Genome-wide association studies have catalogued around 20 gene variants, e.g., the chromosome 12q24 in HNF-1α gene, I27L/exon1 (Reynisdottir et al. 2003), rs7903146 in TCF7L2, E23 K in KCNJ11, P12A in PPAR-c (Grant et al. 2006; Gloyn et al. 2003), CRP locus APCS and CRPP1 genes, SNP 133552, and SLC30A8 (Wolford et al. 2003).

Pathogenesis

Insulin resistance is a major risk factor for the pathogenesis of type 2 diabetes and the insulin resistance syndrome (Reaven et al. 1995). Abnormalities in both insulin action and insulin secretion occur early in the pathogenesis of T2DM (Ferrannini

1998; Iwasaki 2001). Primary defects in pancreatic ß-cells have been recognized in maturity-onset diabetes of the young (MODY), a rare form of diabetes resulting from gene mutation; different types of MODY genes have been identified that encode the glycolytic enzyme glucokinase (GCK) and transcription factors include hepatocyte nuclear factor (HNF)-4a/MODY1, glucokinase/MODY2, HNF-I a/MODY3, insulin promoter factor (IPF)-1/MODY4, HNF-1 IMODY5, neurogenic differentiation (NeuroD1)/MODY6, and Islet (Isl)-1/MODY7 (Bell and Polonsky 2001). The HNF-la mutation causes a progressive defect that alters β-cell insulin secretion rather than the sensing of glucose (Pearson et al. 2001). Currently many literature discusses that diabetes has concomitant increased free radical production and depletion of cellular antioxidant defense systems. It is well established that alloxan- and streptozotocin-induced diabetic animals become hyperglycemic as the result of destruction of ß-cells of the pancreas by free radicals (Oberley 1988). Pancreatic β-cells are especially vulnerable to oxidative stress, probably because of their low free radical scavenging enzyme capacity reflected in low superoxide dismutase (SOD), catalase, and glutathione peroxide activities. The reduction of insulin-dependent 2-deoxyglucose uptake was consequently accompanied by decreased P13 kinase activity and GLUT4 translocation and defective insulin-mediated glucose uptake. The imbalance of free radicals and antioxidants is an important pathogenic factor affecting insulin-signaling pathways (Ceriello et al. 2000).

The development of diabetic nephropathy has been reported to correlate with levels of aldose reductase mRNA (Shah et al. 1998). Recent studies have indicated that ROS plays a key role in the development of diabetic nephropathy. High glucose level directly increases hydrogen peroxide production by mesangial cells and lipid peroxidation of glomerular mesangial cells. Hyperglycemia-induced secondary mediator's activation such as protein kinase C (PKC), mitogen-activated protein (MAP) kinases and cytokine production is also responsible for oxidative stress-induced renal injury in the diabetic condition (Anjaneyulu and Chopra 2004). Diabetic dyslipidemia is associated with insulin resistance, visceral obesity, and liver fat content. Islet amyloidal polypeptide (IAPP)-derived amyloid deposition increases along with the duration of type 2 diabetes mellitus; hence hypersecretion of IAPP may be involved in the progression of this disease (Haruhiko 2004). Approximately 20–40% of adults with type 2 diabetes have some signs of retinopathy, and nearly about 8% have more severe vision-threatening retinopathy. Diabetic retinopathy is classified into an earlier stage called nonproliferative diabetic retinopathy (NPDR) and a later, more advanced stage called proliferative diabetic retinopathy (PDR). In NPDR, microaneurysms, hemorrhages, hard exudates, cotton wool spots, intraretinal microvascular abnormalities, and venous beading are common ophthalmoscopic features. PDR is characterized by the presence of new abnormal blood vessels, vitreous hemorrhage, and fibrous scarring. An additional complication of NPDR is the development of macular edema, characterized by swelling and hard exudate deposition near the central macula (Kempen et al. 2004). Diabetic cataract is a major complication of diabetes mellitus, and is primarily

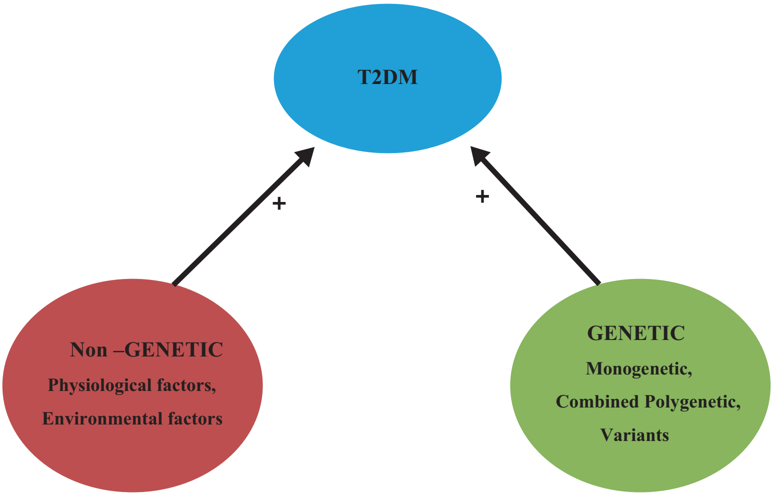

Fig. 1 Factor responsible for type 2 diabetes mellitus (T2DM)

caused by polyol accumulation and glycation within lens fibers and epithelium (Chung et al. 2005), Fig. 1.

Diabetic foot problems result from complex interactions between peripheral neuropathy (including autonomic dysfunction), peripheral arterial disease, and poor foot hygiene (Malone et al. 1989). The mechanism by which hyperglycemia causes neural degeneration is via the increased oxidative stress that accompanies diabetes. Metabolic and oxidative insults often cause rapid changes in glial cells. Key indicators of this response are increased synthesis of glial fibrillary acidic protein (GFAP) and S100B, both astrocytic markers (Baydas et al. 2003). Diabetic foot ulcers are typically found due to neuropathy, peripheral arterial disease, or poor foot hygiene, and are frequently precipitated by inappropriate footwear. Neuropathic ulcers are usually seen at sites of repetitive pressure. Furthermore also erectile dysfunction as a diabetic complication remains incompletely understood. Diabetes has a known pathologic effect on peripheral tissue innervation and vascularization, both of which are critical for erectile function. Oxidative stress to cavernous tissue may be an important contributory factor to erectile dysfunction in diabetics (Ryu et al. 2005). One of the major complications of diabetes is cardiovascular disease. The established risk factors such as dyslipidemia, hypertension, and smoking cannot explain this increased prevalence of macrovascular disease in diabetes. Oxidative stress plays a crucial role in atherogenesis and causes oxidation of low-density lipoprotein. Increased concentrations of autoantibodies to both oxidized and glycated LDL and glyco-Ox-LDL have been documented in diabetes suggesting that in type 2 diabetes enhanced oxidative stress occurs in vivo (Jialal et al. 2002; Kedziora et al. 2000).

Dietary Phytochemicals

Polyphenols

Polyphenols, including their functional derivatives esters and glycosides, have one to various phenol groups with one hydroxyl-substituted aromatic ring (Dey and Harborne 1998). According to their structure number of phenol rings and the type and number of structural elements binding polyphenols are grouped into different classes:

1. Simple phenolic acids, e.g., ferulic, caffeic, *p*-coumaric, vanillic, gallic, ellagic, *p*-hydroxybenzoic, chlorogenic acids.
2. Stilbenes, e.g., resveratrol.
3. Curcuminoids, e.g., curcumin.
4. Chalcones, e.g., phlorizin, naringenin chalcone.
5. Lignans, e.g., matairesinol, secoisolariciresinol.
6. Flavonoids, composed of seven subclasses: (a) flavonols, e.g., quercetin; (b) flavanols (monomeric, e.g., catechin, epicatechin, oligomeric, and polymeric compounds, e.g., proanthocyanidins, also called condensed tannins); (c) anthocyanins, e.g., cyaniding; (d) flavones, e.g., luteolin, apigenin; (e) flavanones, e.g., naringenin; (f) flavanonols, e.g., taxifolin, (g) isoflavones, e.g., genistein (Bravo 1998; Harborne and Baxter 1999; Williams et al. 2004)

Simple phenolic acids are non-flavonoid phenolic compounds conjugated with other natural chemicals such as flavonoids, alcohols, hydroxy fatty acids, sterols, and glucosides (Nobili et al. 2009; Soobrattee et al. 2005).

Anthocyanins have been shown to act as antioxidants and can regulate adipocytokine gene expression to ameliorate adipocyte function; thus the dietary intake of polyphenol-rich food might be beneficial in preventing the onset of type 2 diabetes mellitus (Clifford 2000).

Cyanidin is the most common anthocyanidin in foods. Its food contents are generally proportional to color intensity and reach values up to 2–4 g/kg fresh wt in blackberries. Wine contains 200–350 mg anthocyanins/L (Clifford 2000). These flavonoids have been shown to have anti-inflammatory activity in obese adipose tissues, which is mediated by PPAR-γ-independent mechanisms (Tsuda 2008). Moreover, cyanidin 3-glucoside (C3G) downregulates the RBP4, which is known to ameliorate insulin sensitivity in the adipose tissue of diabetic mice (Sasaki et al. 2007).

Ferulic acid (FA) is a natural polyphenol which is extracted from the rice bran (Atsuyo et al. 2008), vegetables, fruits such as sweet corn, tomatoes (Chiu-Mei et al. 2010), and most abundant hydroxycinnamic acid in cell wall polysaccharides; it is widely distributed in higher plants, and has antioxidative, hypotensive, and anti-inflammatory, diabetic nephropathy activities. FA is thought to act via the suppression of mesangial cell activation, which is a critical process in diabetic nephropathy, as the suppression of TGF-b1 mRNA expression was observed (Estelle et al. 2002).

Ferulic acid (FA) to the diabetic rats (induced with streptozotocin) resulted in a decrease in the levels of glucose, thiobarbituric acid-reactive substances (TBARS), hydroperoxides, and FFA; increase in reduced glutathione (GSH); increased activities of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx); and expansion of pancreatic islets (Sri Balasubashini et al. 2004).

Resveratrol (3,5,40-trihydroxy-trans-stilbene; RV) is a member of the stilbene family of phenolic compounds (Fernández et al. 2012) and was identified in 1963 as the active constituent of the dried roots of *Polygonum cuspidatum*, also called Ko-jo-kon in Japanese, and used in traditional Asian medicine. It is commonly found in many plants as peanut and its derivatives, pistachio, berries, dark chocolate, and grapes as well as their derivatives; red wine is the most notable dietary source of resveratrol than white wine (Philipp et al. 2008). Electrophysiological measurements allowed demonstrating that resveratrol binds to sulfonylurea receptor (SUR) and is a blocker of pancreatic ATP-sensitive K^+ channels. It was also observed that resveratrol displaced binding of glibenclamide, a sulfonylurea drug that blocks ATP-sensitive K^+ channels in β-cells and is applied in type 2 diabetes mellitus to enhance insulin secretion (Hambrock et al. 2007). ATP-sensitive K^+ channels are normally blocked as a result of the increase in the ATP/ADP ratio resulting from metabolism of glucose or other fuel secretagogues. The rise in the ATP/ADP ratio induces depolarization of the plasma membrane and triggers secretion of insulin (Henquin 2000). The effects of resveratrol on blood insulin concentrations in diabetes were investigated using two experimental animal models: a model of diabetes which is similar to type 1 diabetes in humans (streptozotocin-induced diabetic rats) and a model which is similar to type 2 diabetes in humans (streptozotocin–nicotinamide diabetic rats). In the short-term experiment on streptozotocin–nicotinamide diabetic rats, a considerable hyperinsulinemic effect of resveratrol was shown (Chi et al. 2007). It is also known that resveratrol may influence secretion and blood concentrations of some adipokines (Szkudelska et al. 2009; Rivera et al. 2009). Hydroxytyrosol is a phenyl ethyl alcohol, 2-(3,4-dihydroxyphenyl) ethanol (3,4-DHPEA), and the diet is virgin olive oil, being present, mainly as secoiridoid derivatives or as acetate and free form. Hydroxytyrosol and its derivatives arise from oleuropein (ester of hydroxytyrosol and elenolic acid) present in olives during extraction of olive oil (Fernández et al. 2012). Fiber, phytosterols, polyphenolics, and a high unsaturated to saturated fat ratio may be accountable for the hypocholesterolemic effect of almonds. Almonds may be cardioprotective because they are excellent sources of monounsaturated fats, α-tocopherol, dietary fiber, copper, magnesium, arginine, plant sterols, and polyphenols. Most almond studies in the literature have illustrated the hypolipidemic effect of almonds in healthy subjects or hypercholesterolemic patients (Sing et al. 2011).

Beta-sitosterol, stigmasterol evaluated in *Liriope spicata*: It is a Chinese medicinal plant, which belongs to Liliaceae family. Extract of *Liriope spicata* did not have any appreciable effect on fasting blood glucose level in normal mice, but it caused a marked decrease of fasting blood glucose level and a significant improvement on glucose tolerance and insulin resistance in STZ-induced type 2 diabetic mice. Chalcone compounds naturally found in plants or of synthetic origin are known to exhibit several biological activities and have been involved in glucose metabolism. It is isolated from plants and have improved the glucose uptake in adipocytes and potentiated insulin-stimulated glucose uptake in adipocytes. Furthermore, chalcone derivatives from aryloxypropanolamines have shown potential anti-hyperglycemic effect when administered in hyperglycemic rats (Rosangela et al. 2009). Lignans are a group of phytoestrogen formed of two phenylpropane units. The most important sources of lignans are flaxseed and grain. Flaxseed (linseed) is the richest dietary source of lignans that contains secoisolariciresinol (>3.7 g/kg dry weight) and low quantities of matairesinol (Adlercreutz 2007). Other lignans have been identified in rye, e.g., pinoresinol, lariciresinol, isolariciresinol, and syringaresinol (Hallmans et al. 2003). Other sources of lignans are soya, sesame seed, berries, nuts, broccoli, tea, wine, and a variety of edible plants including algae, leguminous, cereals, vegetables (garlic, asparagus, carrots), and fruits (pears, prunes) (Adlercreutz 2007). Secoisolariciresinol diglucoside was shown to reduce total serum cholesterol and atherosclerosis in rabbits (Prasad 1999); it has antihypertensive effects (Prasad 2004) and reduces the incidence of diabetes in several animal models (Prasad 2000). In several human intervention studies, flaxseed reduces total and LDL cholesterol, without an influence on HDL or total TG (Bloedon and Szapary 2004; Prasad 2001).

Curcumin was a yellow spice and pigment in food system, and well known for its antioxidant, anti-inflammatory, antidiabetic, anticancer, and anti-HIV integrase activity (Nurfina et al. 1997). *Curcuma longa* Linn. or turmeric (Zingiberaceae) was a medicinal plant widely cultivated in tropical regions of Asia. The extract from *C. longa*, commonly called curcuminoids, was mainly composed of curcumin (75–90%) and together with a small amount of demethoxycurcumin and bisdemethoxycurcumin (Jayaprakasha et al. 2002) *C. longa* was recommended to use in Chinese traditional medical prescriptions against the diabetic complications. The plant extract of *C. longa* could inhibit the activity of α-glucosidase resulting in lowering the high blood sugar. The interesting discovery of the α-glucosidase inhibitory activity of phenolic compounds like curcuminoids prompted us to study a series of curcumin analogs. Curcuminoids have the ability to scavenge free radicals in vivo, especially peroxyl radicals of the form ROO, where R is an alkyl group. The possible mechanism of curcumin action in cerebellum may be by lowering the blood glucose level which results in rendering the anti-apoptotic property (Zhaoa et al. 2008). The increased blood glucose level and decreased body weight, observed during diabetes, are similar with previous reports as a result of the marked destruction of insulin-secreting pancreatic β-cells by STZ (Junod et al. 1969). Previous reports showed that curcumin has the potential to protect pancreatic islet cells against streptozotocin-induced death dysfunction (Meghana et al. 2007) and increase plasma insulin level in diabetic mice (Seo et al. 2008). Curcumin also inhibited superoxide anion generation in xanthine-xanthine oxidase system to an extent of 40% at the concentration of 75 mM and the generation of hydroxyl radicals (OH) to 76% as measured by deoxyribose degradation. The spice principle also prevented the oxidation of Fe^{2+} in Fenton reaction which generates OH radicals. Curcumin (5–50 mM) inhibited ascorbate/Fe^{2+}-induced lipid peroxidation in a dose-dependent manner in rat liver microsomes. Feeding 0.5% curcumin diet to STZ diabetic rats partially reversed the abnormalities in plasma albumin, urea, creatine, and inorganic phosphorous. It also lowered lipid peroxidation in plasma and urine despite no effect on hyperglycemic status or body weights. The underlying mechanism involved was believed to be on account of its hypocholesterolemic influence, antioxidant nature, and free radical scavenging property (Geetanjali et al. 2010).

Luteolin exhibits anti-lipase activity (17.3%) and enhanced insulin sensitivity via activation of PPAR gamma-transcriptional activity in adipocytes (Zheng et al. 2010) and it inhibits proliferation of human leukemia cells and plays an important role as a promoter of carbohydrate metabolism (Xavier et al. 2009). Green tea polyphenols especially epigallocatechin gallate injected IP into rats significantly reduced food intake, body weight, blood levels of insulin, glucose, cholesterol, and triglyceride.

Epicatechin gallate showed the highest inhibition of glucose uptake by human intestinal epithelial Caco-2-cells suggesting that tea catechins could play a role in controlling the dietary glucose uptake at the intestinal tract and possibly contribute to blood glucose homeostasis.

A polyphenol extract from red wine (200 mg/kg) administered for 6 weeks reduced glycemia and decreased food intake and body growth in STZ diabetic and nondiabetic animals. Ethanol (1 mL/kg) administered alone or in combination with polyphenols corrected the diabetic state.

Dietary gallate esters of tea catechins (epigallocatechin gallate and epicatechin gallate) fed to rats at 1% level for 23 days reduced the activities of enzymes related to hepatic fatty acid synthesis, thereby causing reduction of hepatic triacylglycerol and possibly of visceral fat deposition (Li et al. 2004).

Flavonoid, kakonein, was experimentally identified to be effective to lower the blood glucose level of alloxan- or adrenalin-induced diabetic mice. 7-(6-*O*-malonyl-D-glucopyranosyloxy)-3-(4-hydroxyphenyl)-4*H*-1-benzopyran-4-one is the constituent proved to be useful for treatment of diabetes complications such as cataract, retinopathy, neuropathy, and kidney disorders. Pueraria flavonoid (PF) is a useful preparation for patients with diabetes complicated by hyperlipidemia. Tectorigenin and kaikasaponin III, isolated from the flowers of *Pueraria thunbergiana* (same genus as *Pueraria lobata*), showed potent hypoglycemic and hypolipidemic effects in the streptozotocin-induced diabetic rats. The antioxidant action of tectorigenin and kaikasaponin III may alleviate the streptozotocin-induced toxicity and contribute hypoglycemic and hypolipidemic effects. There is experimental result to show that glycosylation of human serum albumin (HSA) and rat lens protein was effectively inhibited by the ethanol extract of Radix Puerariae, which indicated that the extract can be used in treating diabetic complications (Li et al. 2004). The flavanones, exclusively found in citrus fruit and tomato predominantly as glycosides, undergo similar metabolic routes to flavonols (Andreas et al. 2002). These are benzo-y-pyrone derivatives which resemble coumarin and are ubiquitous in photosynthesizing cells. It occurs as aglycons, glycosides, and methylated derivatives. The flavonoid aglycons all consist of a benzene ring (A) condensed with a six-member ring (C) which in the 2-position carries a phenyl ring (B) as a substituent (Havsteen 1983). Observational and intervention studies have investigated the effect of flavonols on cardiovascular risk factors, including blood pressure, serum lipids, diabetes mellitus, and obesity (Perez and Duarte 2010). In *Artemisia herba-alba* sesquiterpene lactones were found in the aerial parts and a total of eight flavonoids *O*- and *C*-glycoside were isolated and identified. It is a popular folk remedy, used in the treatment of diabetes mellitus. The aqueous extract of the aerial parts of *A. herba-alba* caused a significant fall in plasma glucose levels in both normoglycemic and alloxanized rabbits (Abou et al. 2010). *Combretum micranthum* is a medicinal plant used for treating diabetes in Northwestern Nigeria. The aqueous leaf extract of *Combretum micranthum* has potential antidiabetic property for both type 1 and type 2 diabetes mellitus. Flavonoid of *Parinari excelsa* shows the hypoglycemic effect and the ability to induce insulin secretion in diabetic animal models. The hypoglycemic effect of *Parinari excelsa* was similar to that of glibenclamide and is already observed with some other plant extracts.

The methanolic extract and ethyl acetate-soluble portions of the leaves of *Myrcia multiflora* DC showed an inhibitory activity on aldose reductase and alpha-glucosidase. The plant also inhibited the increase of serum glucose level in sucrose-loaded rats and in alloxan-induced diabetic mice. New flavanone glucosides (myrciacitrins I and II) and new acetophenone glucosides (myrciaphenones A and B) were identified (Mohamed et al. 2006).

Elatoside E was isolated from the root cortex of *Aralia elata* Seem. (Japanese angelica). It was shown to affect the elevation of plasma glucose levels in an oral sugar tolerance test in rats. The hypoglycemic activity of oleanolic acid and nine oleanolic acid glycosides isolated from the root cortex of this plant were tested. Five new saponins named elatosides G, H, I, J, and K were isolated from a garnish foodstuff “Taranome” which is the young root shoot of *A. elata* Seem. Elatosides G, H, and I were found to exhibit potent hypoglycemic activity in the oral glucose tolerance test in rats. Nine oleanolic acid oligoglycosides were isolated from the cortex of *A. elata* (Mohamed et al. 2006).

The stem bark of *Kalopanax pictus Nakai* and seven kinds of chemical constituents including hederagenin glycosides and phenolic glycosides were isolated. The antidiabetic evaluation of these isolates in streptozotocin-induced diabetic rats showed that kalopanax saponin A has a potent antidiabetic activity in contrast to a mild activity of hederagenin. To investigate the relationship between the intestinal bacterial metabolism of kalopanaxsaponin B and H from *K. pictus*, and their antidiabetic effect, kalopanaxsaponin B and H were metabolized by human intestinal microflora and the antidiabetic activity of their metabolites was measured. The main metabolites of kalopanaxsaponin B were kalopanaxsaponin A and hederagenin. The main metabolites of kalopanax H were kalopanaxsaponin I and hederagenin. Among kalopanaxsaponin B, H, and their metabolites, kalopanaxsaponin A showed the most potent antidiabetic activity, followed by hederagenin (Mohamed et al. 2006).

Amino Acid

4-Hydroxyisoleucine, a novel amino acid, has been extracted and purified from fenugreek seeds. It increased glucose-induced insulin release (ranging from 100 to 1 mmol/L) through a direct effect on the isolated islets of Langerhans in both rats and humans (Li et al. 2004). The insulinotropic effect of *Citrullus colocynthis Schrad.* fruits: Different extracts were obtained from the seeds of this plant: RN II (crude extract), RN VI (aqueous alcoholic extract), RN X (purified extract), and RN XVII (beta-pyrazol-1-ylalanine, the major free amino acid derivative present in the seeds) (Mohamed et al. 2006).

S-allyl cysteine sulfoxide (SACS), a sulfur-containing amino acid of *Allium sativum* L. (garlic) that is the precursor of allicin and garlic oil, has been found to show significant antidiabetic effects in alloxan diabetic rats. Administration of a dose of 200 mg/kg significantly decreased the concentration of serum lipids, blood glucose, and activities of serum enzymes like alkaline phosphatase, acid phosphatase, and lactate dehydrogenase and liver glucose-6-phosphatase. SACS significantly stimulated in vitro insulin secretion from β-cells isolated from healthy rats. Hence it can be surmised that the beneficial effects of SACS could be due to both its antioxidant and its secretagogue actions (Mohamed et al. 2006).

Oral administration of *Allium cepa* L. (onion) *S*-methyl cysteine sulfoxide (SMCS) daily at a dose of 200 mg/kg body weight for a period of 45 days to alloxan diabetic rats controlled the blood glucose and lipids in serum and tissues and altered the activities of liver hexokinase, glucose 6-phosphatase, and HMG CoA reductase towards normal values (Mohamed et al. 2006).

Saponins

Saponins such as ginsenoside Rb1, Rg1Re, Rg3, CEG, Rb2, CY, and DPG-3-2 were isolated roots and rhizomes of *Panax ginseng* C.A. Mey, family *Araliaceae*. Ginseng lowers hyperglycemia and raises hypoglycemia, not to influence normal blood glucose. The mechanism of action of these saponins is to regulate the activity of enzymes related to glucose metabolism directly and/or indirectly, inhibit the renal disorder, and promote insulin secretion (Li et al. 2004). Saponin isolated from the leaves of *Acanthopanax senticosus* injected to mice (100, 200 mg/kg, i.p.) decreased experimental hyperglycemia induced by injection of adrenaline, glucose, and alloxan, without affecting the levels of blood sugar in untreated mice (Mohamed et al. 2006).

Litchi water extract improved the metabolic profile of rats, characterized by decreased body weight, fasting blood glucose, total cholesterol, triglycerides, free fatty acid (FFA), leptin, and fasting insulin levels. The water extract of litchi has been found to have the antidiabetic potential and also enhances basal prostaglandin E2 (PGE2) production in a macrophage cell line (RAW264.7). *Psidium guajava* (guava) in the type 2 diabetic and fatty liver disease phenotype in Lep db/db mice: Extract of *P. guajava* (10 mg/kg body weight) significantly decreased blood glucose levels and accumulation of fat droplets in liver tissues of Lep db/db mice. This effect was mediated through the inhibition of protein tyrosine phosphatase 1B (a negative regulator of insulin signaling). The combination of pomegranate seed oil (PSO) and brown marine algae fucoxanthin (xanthigen) significantly reduced the occurrence of fatty liver disease in human subjects. The findings were characterized by significantly decreased body weight, waist circumference, hepatic fat content, and triglyceride and improved liver function tests. The mechanism of xanthigen for these beneficial effects was through increased whole-body energy expenditure that was characterized by increased resting energy expenditure in xanthigen-fed subjects (Samir et al. 2011).

In Korea, there are several traditional fermented soybean products, the most commonly used being chungkookjang, doenjang, kochujang, and soy sauce. The isoflavonoid aglycons act though PPAR-gamma; it is the central regulator of insulin and glucose metabolism and helps improve insulin sensitivity in type 2 diabetic patients and in diabetic rodent models. PPAR-g agonists are well-characterized insulin sensitizers. The components of isoflavonoids and peptides were changed according to the fermentation periods and these changes altered antidiabetic actions as evidenced by their effects on insulin sensitivity and insulin and GLP-1 secretion. Daidzein enhanced PPAR-gamma activity to increase insulin-stimulated glucose uptake in 3T3-L1 adipocytes, whereas genistein potentiated insulinotropic actions in Min6 cells and GLP-1 secretion in NCI-H716 cells (Dae et al. 2011).

Terpenoids (Isoprenoids)

Terpenoids (isoprenoids) constitute one of the largest families of natural products, accounting for more than 40,000 compounds of both primary and secondary metabolisms (Goto et al. 2010). The simplest unifying feature present in the structure of all terpenoids is the isoprene unit ($CH_2C(CH_3)$–$CHCH_2$). Based on the number of carbon atoms, terpenoids can be classified into further groups: hemiterpenoid (C5), monoterpenoids (C10), sesquiterpenoids (C15), diterpenoid (C20), sesterterpenoid (C25), triterpenoids (C30), tetraterpenoid (C40), and polyterpenoid (C>40). Most of the terpenoids are of plant origin and are present in vegetables and fruits. Geranylgeraniol, farnesol, and geraniol terpenoids are ligands with potential to activate PPAR-gamma, dietary lipid sensors that control energy homeostasis and lipid and carbohydrate disorders (Goto et al. 2010; Takahashi et al. 2002). *Lantana camara* L. is regarded as a notorious weed; extract of this plant is used in folk medicine for the treatment of cancers, chicken pox, measles, asthma, ulcers, swellings, eczema, tumors, high blood pressure, bilious fevers, catarrhal infections, tetanus, rheumatism, malaria, and ataxy of abdominal viscera, and for its anticonvulsant, termicidal, wound healing, anticancer, antiulcer, antioxidant, antidiabetic, analgesic, anti-inflammatory, anti-motility, anti-feedant, larval mortality/repellency, antifungal, and antibacterial activities. The presence of new triterpenoid glycoside ester urs-12-en-3β-ol-28-oic acid 3β-D-glucopyranosyl-4′-octadecanoate in *Lantana camara* was evaluated for its antidiabetic action (Kazmi et al. 2012).

Abscisic Acid (ABA)

This significantly improved glucose tolerance, or the glucose-normalizing ability; decreased fasting blood glucose concentrations; reduced TNF-a mRNA and the number of macrophages; reduced average adipocyte size; increased adipocyte differentiation and adipogenesis; and increased the expression of PPAR-gamma and its responsive genes (i.e., adiponectin, aP2, and CD36), which are involved in lipid metabolism in white adipose tissue. ABA supplementation was also associated with significant improvements in hepatic steatosis and plasma triglyceride levels (Guri et al. 2007, 2008).

Lycopene and b-Carotene

Two kinds of important fat-soluble carotenoids are essential nutrients in human diet mainly found in tomatoes, red peppers, and some fruits including watermelon and pink grapefruits; its fat solubility and heating process make it more easily absorbed (Stahl and Sies 2005). It is a powerful antioxidant with a strong ability to scavenge free radicals and, because of its high number of conjugated dienes, is the most potent singlet oxygen quencher among the natural carotenoids (Arab and Steck 2000). Recent studies have demonstrated that mechanisms other than the antioxidant ones are responsible for the biological activities of lycopene. Examples include intercellular gap junction communication, hormonal and immune system modulation, induction of phase II enzymes, suppression of insulin-like growth factor-1-stimulated cell proliferation, antiangiogenesis and inhibition of cell proliferation; and induction of apoptosis (Kun et al. 2006).

Vitamin D levels are inversely related to body mass index (BMI), waistline, and HbA1c. In addition, there are seasonal variations of HbA1c levels and incidental type 2 DM. The supplementation of calcium and vitamin D at 800 IU daily, instead of the prior recommendation of 400 IU, decreased the risk of type 2 DM by 33%. Human subjects obtain vitamin D from sunlight exposure, diet, or dietary supplements. UVB radiation, wavelength from 290 to 315 nm, penetrates the skin and converts 7-dehydrocholesterol to pre-vitamin D, which is converted to 25-hydroxycholecalciferol vitamin D3 (25(OH)D). The hydroxylation of 25(OH)D to its active form 1a,25$(OH)_2$ vitamin D3 (1,25(OH_2)D) takes place in different parts of the body, such as the endothelium, the pancreas, but mainly in the kidney. Thus, an inverse relationship exists between vitamin D levels and the frequency of type 2 DM (Pelle et al. 2010).

Alcohol consumption light to moderate seems to reduce the risk of type 2 diabetes by 30%, while heavy drinkers have the same or higher risk than total abstainers. Alcohol should, however, be restricted in type 2 diabetic patients who are overweight, suffering from hypertension or hypertriglyceridemia. Alcohol abstention is advised in patients with advanced neuropathy and erectile dysfunction and total abstention is recommended to pregnant women and to people with a history of former alcohol abuse or pancreatitis (Pietraszek and Hermansen 2010).

Oxyphytosterol

Dietary 5-campestenone (24-methylcholest-5-en-3-one) was recently shown to activate enzymes responsible for b-oxidation and to suppress enzymes responsible for fatty acid synthesis in rats. It activated peroxisome proliferator-activated receptor (PPAR) in a specific ligand assay. PPAR regulates the mRNA expression of enzymes involved in b-oxidation. When 0.3% 5-campestenone was added to the diet of obese type 2 diabetes C57BL/KsJ-db/db mice, blood and urinary glucose, as well as plasma free fatty acid, were reduced (Konno et al. 2005).

5-Campestenone was shown to decrease serum triacylglycerols in rodents (Ikeda et al. 2006; Suzuki et al. 2002; Konno et al. 2005). Similar results were obtained with 24-ethylcholest-4-en-3-one. In line with the observed decrease in serum triglycerides, the concentration of liver triacylglycerols was reduced (Ikeda et al. 2006).

Organosulfur compounds are particularly abundant in Allium vegetables including garlic, onion, scallion, chive, shallot, and leek that contain bioactive substances such as allicin, allixin, and allyl sulfides (Sahu 2002). These molecules account for the distinctive flavor and aroma as well as the many purported medicinal effects of these vegetables. Organosulfurs provide glucosinolates, which are converted in the human body in thiosulfonates, indoles (indole-3-carbinol), and isothiocyanates (Cartea and Velasco 2008).

Phytosterols/Stanols

Phytosterols/stanols reduce serum low-density lipoprotein cholesterol levels, and food products containing these plant compounds are widely used as a therapeutic dietary option to reduce hypercholesterolemia and atherosclerotic risk (NCEP EP 2001). Aloe vera-derived phytosterols ameliorated hyperglycemia in treated db/db type 2 diabetic mice (Tanaka et al. 2006). Also a phytostanol mixture induced improvement in glucose tolerance in fat Zucker rats (Wasan et al. 2003). Two stigmasterol-derived compounds extracted from the cashew plant produced a significant reduction in blood glucose levels when intravenously administered to dogs (Alexander et al. 2004). Furthermore, changes in intestinal cholesterol absorption could correlate with insulin sensitivity, as type 2 diabetic patients present increased cholesterol synthesis but decreased absorption (Simonen et al. 2000).

Legumes are low in fat, and rich in proteins, complex hydrocarbons, and minerals, exhibiting lower glycemic index compared to other starchy foods. It contains a rich variety of phytochemicals, including phytosterols, natural antioxidants, and bioactive carbohydrates (Amarowicz and Pegg 2008; Rochfort and Panozzo 2007). Legumes contain antinutritional factors, such as trypsin inhibitors, phytic acid, a-galactosides, and phenolics, that can diminish protein digestibility and mineral bioavailability; thus they have to be appropriately treated prior to consumption (Chung et al. 1998; Sendberg 2002; Vidal et al. 2002).

Flax seeds (*Linum usitatissimum* L., member of Linaceae family) and pumpkin seeds (*Cucurbita pepo* L., member of Cucurbitaceae family) contain high levels of Omega-3 fatty acid (Burdge and Calder 2005), fiber components, and phytochemicals such as lignans (Vijaimohan et al. 2006). The high linoleic acid contributes to antioxidant properties (Simopoulos 1991) against various diseases, including atherosclerosis, diabetes, and hypertension, and anti-inflammatory and anticarcinogenic effects (Simopoulos 1991; Fukuda et al. 1985).

Omega-6 fatty acids have a number of biological applications. In addition to anti-inflammatory and hypolipidemic effects, they also have significant antioxidant activity (Suresh and Das 2003). DAG and conventional edible oil containing triacylglycerol (TAG) are almost identical in terms of digestibility and caloric value. DAG reduces postprandial levels of serum TAG (Taguchi et al. 2000, 2001; Tada et al. 2001). It also reduces body fat in obese/overweight Japanese and American adults as well as Japanese children (Takase et al. 2005; Nagao et al. 2000; Takahashi et al. 2002). DAG oil has a beneficial effect for type 2 DM patients in relation to body weight, BMI, waist circumference, HOMA-IR, blood levels of insulin, glucose, and leptin (Duo et al. 2008).

The stevioside, diterpene glycoside isolated from *Stevia rebaudiana* (Bertoni), exhibits a direct insulin tropic action in both isolated mouse islets and the clonal β-cell lines (INS-1) and possesses insulin tropic, glucagon static, and anti-hyperglycemic effects in diabetic animals. Stevioside caused only the decrease of adrenalin-induced hyperglycemia. BBCr product prevented the onset of experimental diabetes in mice caused by alloxan. Based on these results it can be concluded that BBCr has its role in the prevention and treatment of hyperglycemia in mice (Jeppesen et al. 1996, 2000).

Berberine is a plant alkaloid found in *Hydrastis canadensis* (goldenseal), *Coptis chinensis* (Coptis or goldenthread), *Berberis aquifolium* (Oregon grape), *Berberis vulgaris* (barberry), and *Berberisaristata* (tree turmeric). Berberine has been found to act on glucose metabolism through several mechanisms: mimicking insulin action; improving insulin action by activating AMPK; reducing insulin resistance through protein kinase C-dependent upregulation of insulin receptor expression; inducing glycolysis; promoting GLP-1 secretion and modulating its release; and inhibiting DPP-4 (Sterti 2010).

Charantin which is composed of sitosteryl glucoside and stigmasteryl glucoside can potentially replace treatment by insulin. Another compound, polypeptide p (plant insulin) found in seeds and fruits of *Momordica charantia* [bitter melon], is similar to insulin in composition; bitter melon alkaloids have also been noted to have a blood sugar-lowering effect. Compounds known as oleanolic acid glycosides have been found to improve glucose tolerance in type 2 diabetes (Ibraheem et al. 2012). *M. charantin* markedly reduced the STZ-induced lipid peroxidation in the pancreas of mice, RIN cells (rat insulinoma cell line), and islets. Ethanolic extract of *M. charantia* (250 mg/kg dose orally) significantly lowered blood sugar in fasted as well as glucose-loaded nondiabetic rats. *M. charantia* may cause hypoglycemia via an increase in glucose oxidation through the activation of glucose metabolism and/or the inhibition of glucose absorption in the gut. There is an increase in the levels of intestinal Na^+/glucose cotransporters (SGLT1) in STZ-induced diabetes resulting in increased glucose uptake in the gut of these animals. The increase of Na^+- and K^+-dependent glucose uptake by small intestine brush border membrane (BBM) vesicles in STZ-induced diabetes has been demonstrated recently (Celia et al. 2003). Gymnemic acid found in *Gymnema sylvestre* (leaf extract) which is said to inhibit the adenohypophyseal stress response, and the hyperglycemic response to adrenaline and growth hormone. It may also help by increasing peripheral utilization of glucose.

Tinospora cordifolia also increases peripheral utilization of glucose, and inhibits hepatic glucose release caused by adrenaline. *Pterocarpus marsupium* has been reported to block glucose absorption from gut. Pterocarpus extract has been reported to promote β-cell regeneration in pancreas. Shilajeet has anabolic and pancreatotrophic effects (Anturlikar et al. 1995).

Fagomine increased plasma insulin levels in diabetic mice and potentiated the 8.3 mM glucose-induced insulin release from the rat isolated perfused pancreas. The fagomine-induced potentiation of insulin release may contribute in part to its antihyperglycemic action. Seven polysaccharides and peptidoglycans obtained from the seeds of *Malva verticillata* were tested for hypoglycemic activity. Neutral polysaccharide especially exhibited promising hypoglycemic effects in non-insulin-dependent diabetes mellitus.

The hypoglycemic activity of the extract of jamun pulp from the fruit of *Eugenia jambolana* Lam. (Gambol) *Syzygium cumini* Skeels (Jamun) was seen after 30 min, while the seeds of the same fruit required 24 h to produce the same effect. These results were confirmed in streptozotocin-induced diabetic animals. The oral administration of the extract resulted in the enhancement of insulinemia in normoglycemic and diabetic rats. The incubation of isolated pancreatic islet cells of normal and diabetic animals with this plant extract resulted in increased insulin secretion. A new tetrahydropyran was isolated from the methanolic extract of roots from *Acrocomia mexicana* Karw. The extract was hypoglycemic in healthy and alloxan-induced diabetic mice (2.5–40 mg/kg i.p.). Masoprocol (nordihydroguaiaretic acid, a lipoxygenase inhibitor) is a pure compound isolated from *Larrea tridentata* (Creosote bush). The oral administration of masoprocol produced a fall in the plasma glucose concentrations in two mouse models of type 2 diabetes, without any change in plasma insulin concentrations. In addition, oral glucose tolerance improved and the ability of insulin to lower plasma glucose concentrations was accentuated in masoprocol-treated db/db mice (Mohamed et al. 2006), Fig. 2.

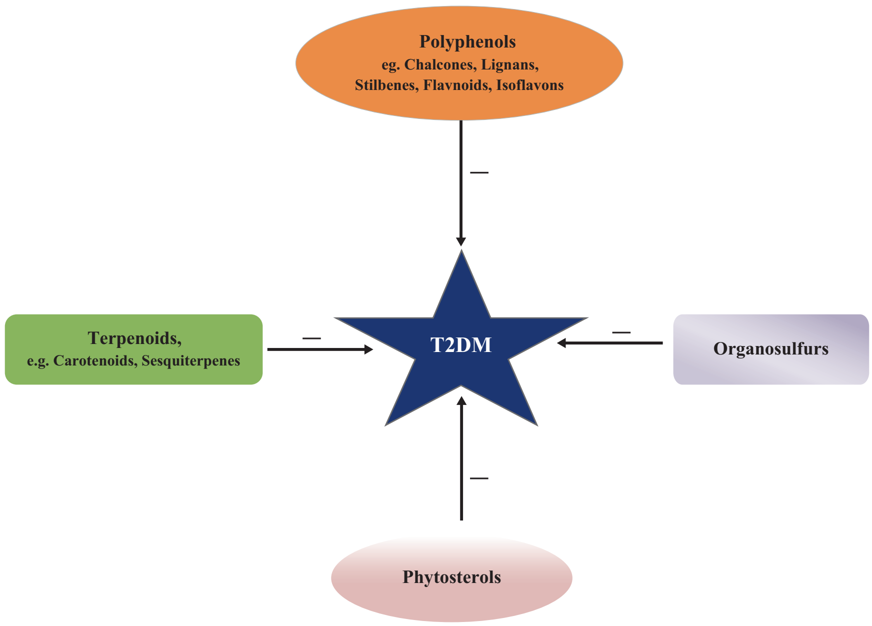

Fig. 2 Dietary fibers which are helpful in the treatment of type 2 diabetes mellitus (T2DM)

Conclusion

It was concluded that phytochemicals present in various dietary fibers can be helpful in the treatment of type 2 diabetes mellitus.

Future Consideration

More diabetes research and studies should be considered on the dietary phytochemicals, so that it can be beneficial for the patients having type 2 diabetes mellitus.

References

Abou EM, Magdi HA, El-Sayed M, Hegazy E, Soleiman EH, Abeer ME, Naglaa SM (2010) Chemical constituents and biological activities of Artemisia herba-alba. Rec Nat Prod 4(1):1–25
Adlercreutz H (2007) Lignans and human health. Crit Rev Clin Lab Sci 44(5–6):483–525
Alexander LRL, Morrison EY, Nair MG (2004) Hypoglycaemic effect of stigmast-4-en-3-one and its corresponding alcohol from the bark of Anacardium occidentale (cashew). Phytother Res 18:403–407

Al-Nuaim A, Al-Rubeaan K, Al-Mazrou Y (1997) National chronic metabolic diseases survey 1995. Ministry of Health and King Saud University, Riyadh, pp 23–54
Amarowicz R, Pegg RB (2008) Legumes as a source of natural antioxidants. Eur J Lipid Sci Technol 110:865–878
Andreas RR, Kuhnle G, Paul B, Gary P, Hubbard KP, Moore C, Rice E (2002) The metabolic fate of dietary polyphenols in humans. Free Radic Biol Med 33(2):220–235
Anjaneyulu M, Chopra K (2004) Nordihydroguaiaretic acid, a lignin, prevents oxidative stress and the development of diabetic nephropathy in rats. Pharmacology 72:42–50
Anturlikar SD, Gopumadhavan S, Chauhan BL, Mitra SK (1995) Effect of D-400, a herbal formulation, on blood sugar of normal and alloxan-induced diabetic rats. Indian J Physiol Pharmacol 39(2):95–100
Arab L, Steck S (2000) Lycopene and cardiovascular disease. Am J Clin Nutr 71:1691–1695
Atsuyo F, Hideyuki S, Asako D, Kunihisa O, Shohei M, Hiroto F, Masahiro N, Taisei N, Takuo T, Hisaji T, Kishio N (2008) Ferulic acid prevents pathological and functional abnormalities of the kidney in Otsuka Long-Evans Tokushima Fatty diabetic rats. Diabetes Res Clin Pract 79:11–17
Baydas G, Reiter RJ, Yaser A, Tuzcu M, Akdemir I, Nedzvetskii V (2003) Melatonin produces glial reactivity in the hippocampus, cortex, and cerebellum of streptozocin-induced diabetic rats. Free Radic Biol Med 35(7):797–804
Bell GI, Polonsky SK (2001) Diabetes mellitus and genetically programmed defects in ß-cell function. Nature 414:788–791
Bloedon LT, Szapary PO (2004) Flaxseed and cardiovascular risk. Nutr Rev 62(1):18–27
Bravo L (1998) Polyphenols: chemistry, dietary sources, metabolism and nutritional significance. Nutr Rev 56:317–333
Burdge GC, Calder PC (2005) α-Linoleic acid metabolism in adult humans: the effect of gender and age on conversion to longer chain polyunsaturated fatty acids. Eur J Lipid Sci Technol 107:426–439
Cartea ME, Velasco P (2008) Glucosinolates is Brassica foods: bioavailability in food and significance for human health. Phytochem Rev 7(2):213–229
Celia G, Cummings E, Phoenix DA, Singh J (2003) Beneficial effect and mechanism of action of Momordica charantia in the treatment of diabetes mellitus: a mini review. Int J Diabetes Metab 11:46–55
Ceriello A, Morocutti A, Mercuri F, Quagliaro L, Moro M, Damante G, Viberti GC (2000) Defective intracellular antioxidant enzyme production in type I diabetic patients with nephropathy. Diabetes 49:2170–2177
Chi TC, Chen WP, Chi TL, Kuo TF, Lee SS, Cheng JT, Su MJ (2007) Phosphatidylinositol-3-kinase is involved in the antihyperglycemic effect induced by resveratrol in streptozotocin-induced diabetic rats. Life Sci 80:1713–1720
Chiu-Mei L, Jen-Hwey C, Wu IH, Wang BW, Chun-Ming P, Yen-Hsu C (2010) Ferulic acid augments angiogenesis via VEGF, PDGF and HIF-1α. J Nutr Biochem 21:627–633
Chung K, Wong TY, Wei C, Huang YW, Lin Y (1998) Tannins and human health: a review. Crit Rev Food Sci Nutr 38:421–464
Chung YS, Choi YH, Lee SJ, Choi S, Lee JH, Kimb H, Honga EK (2005) Water extract of Aralia elata prevents cataractogenesis in vitro and in vivo. J Ethnopharmacol 101:49–54
Clifford MN (2000) Anthocyanins-nature, occurrence and dietary burden. J Sci Food Agr 80:1063–1072
Dae YK, Sang M, Hong MS, Sung Ahn MS, Min Jung Kim MS (2011) Isoflavonoids and peptides from meju, long-term fermented soybeans, increase insulin sensitivity and exert insulinotropic effects in vitro. Nutrition 27:244–252
Dey PM, Harborne JB (1998) Diabetes mellitus: problems and prospectus. Endocr Rev 19:477–490
Dilmec F, Uzer E, Akkafa F, Kose E, van Kuilenburg AB (2010) Detection of VDR gene ApaI and TaqI polymorphisms in patients with type 2 diabetes mellitus using PCR-RFLP method in a Turkish population. J Diabetes Complications 24:186–191

Duo L, Tongcheng X, Hideto T, Ichiro T, Pianhong Z, Qingqing W, Xiaomei Y, Aizhen Z (2008) Diacylglycerol-induced improvement of whole-body insulin sensitivity in type 2 diabetes mellitus: a long-term randomized, double-blind controlled study. Clin Nutr 27:203–211

Estelle B, Luc S, Magali B, Cécile M, Laurence LM, Marcel A, Jean-François T (2002) Release of ferulic acid from agroindustrial by-products by the cell wall-degrading enzymes produced by Aspergillus niger I-1472. Enzym Microb Technol 31:1000–1005

Fernández MIM, Mateos R, García-Parrilla MC, Puertas B, Cantos VE (2012) Bioactive compounds in wine: resveratrol, hydroxytyrosol and melatonin: a review. Food Chem 130:797–813

Ferrannini E (1998) Insulin resistance versus insulin deficiency in non-insulin-dependent diabetes mellitus: problems and prospects. Endocr Rev 19:477–490

Fukuda Y, Osawa T, Namiki M, Ozaki T (1985) Studies on antioxidative substances in sesame seed. Agric Biol Chem 49:301–306

Geetanjali K, Santosh S, Rakesh KK, Naik SN (2010) Commonly consumed Indian plant food materials in the management of diabetes mellitus. Diabetes Metab Syndr Clin Res Rev 4:21–40

Gloyn AL, Weedon MN, Owen KR, Turner MJ, Knight BA, Hitman G (2003) Large-scale association studies of variants in genes encoding the pancreatic beta-cell K-ATP channel subunits Kir6.2 (KCNJ11) and SUR1 (ABCC8) confirm that the KCNJ11 E23K variant is associated with type 2 diabetes. Diabetes 52:568–572

Goto T, Takahashi N, Hirai S, Kawada T (2010) Various terpenoids derived from herbal and dietary plants function as PPAR modulators and regulate carbohydrate and lipid metabolism. PPAR Res 2010:9

Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J (2006) Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat Genet 38:320–323

Guri AJ, Hontecillas R, Si H, Liu D, Bassaganya RJ (2007) Dietary abscisic acid ameliorates glucose tolerance and obesity-related inflammation in db/db mice fed high-fat diets. Clin Nutr 26(1):107–116

Guri AJ, Hontecillas R, Ferrer G, Casagran O, Wankhade I, Noble AM (2008) Loss of PPARg in immune cells impairs the ability of abscisic acid to improve insulin sensitivity by suppressing monocyte chemoattractant protein-1 expression and macrophage infiltration into white adipose tissue. J Nutr Biochem 19:216–228

Hallmans G, Zhang J, Lundin E, Stattin P, Johansson A (2003) Rye, lignans and human health. Proc Nutr Soc 62:193–199

Hambrock A, de Oliveira Franz CB, Hiller S, Grenz A, Ackermann S, Schulze DU, Drews G, Osswald H (2007) Resveratrol binds to the sulfonylurea receptor (SUR) and induces apoptosis in a SUR subtype-specific manner. J Biol Chem 282:3347–3356

Harborne JB, Baxter H (1999) The handbook of natural flavonoids, US Department of Agriculture. USDA Database for the Flavonoid Content of Selected Foods—2003, vol 2. Wiley, West Sussex

Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR (1998) Prevalence of diabetes, impaired fasting glucose and impaired glucose tolerance in US adults, the third National health and Nutrition examination survey, 1988–1994. Diabetes Care 21:518–524

Haruhiko OAK (2004) Islet amyloid polypeptide-derived amyloid deposition increases along with the duration of type 2 diabetes mellitus. Available online 22 Apr

Havsteen B (1983) flavonoids, a class of natural products of high pharmacological potency. Biochem Pharmacol 32(7):1141–1148

Heidemann C, Hoffmann K, Spranger J, Klipstein GK, Mohlig M, Pfeiffer AF (2005) A dietary pattern protective against type 2 diabetes in the European prospective investigation into cancer and nutrition (EPIC)—potsdam study cohort. Diabetologia 48(6):1126–1134

Henquin JC (2000) Triggering and amplifying pathways of regulation of insulin secretion by glucose. Diabetes 49:1751–1760

Huizinga MM, Rothman RL (2006) Addressing the diabetes pandemic: a comprehensive approach. Indian J Med Res 124:481–484

Ibraheem M, Samah E, Sanaa M, Madeha E (2012) An evaluation of anti-diabetic and anti-lipidemic properties of Momordica charantia (Bitter Melon) fruit extract in experimentally induced diabetes. Life Sci J 9(2):363–374

Ikeda I, Konno R, Shimizu T, Ide T, Takahashi N, Kawada T (2006) Campest-5-en-3-one, an oxidized derivative of campesterol, activates PPAR-alpha, promotes energy consumption and reduces visceral fat deposition in rats. Biochim Biophys Acta 1760:800–807

Iwasaki N (2001) Diabetes mellitus. Rinsho Byori 49(2):161–164

Jayaprakasha GK, Rao LJM, Sakariah KK (2002) Improved HPLC method for the determination of curcumin, demethoxycurcumin, and bisdemethoxycurcumin. J Agric Food Chem 50:3668–3672

Jeppesen PB, Gregersen S, Hermansen K (1996) Stevioside and steviol stimulate insulin secretion from isolated mouse islets. Diabetologia 125:472

Jeppesen PB, Gregersen S, Poulsen CR, Hermansen K (2000) Stevioside acts directly on pancreatic beta cells to secrete insulin: actions independent of cyclic adenosine monophosphate and adenosine triphosphate-sensitive K+-channel activity. Metabolism 49:208–214

Jialal I, Devaraj S, Venugopal SK (2002) Oxidative stress, inflammation, and diabetic vasculopathies: the role of alpha tocopherol therapy. Free Radic Res 36(12):1331–1336

Junod A, Lambert AE, Staufferacher W, Renold AE (1969) Diabetogenic action of streptozotocin relationship of dose to metabolic response. J Clin Investig 48(11):2129–2139

Kazmi I, Mahfoozur R, Muhammad A, Gaurav G, Shakir S, Obaid A, Md. Adil S, Ujjwal N, Sayeed A, Firoz A (2012) Anti-diabetic potential of ursolic acid stearoyl glucoside: a new triterpenic glycosidic ester from Lantana camara. Fitoterapia 83:142–146

Kedziora KKZ, Luciak M, Paszkowski J (2000) Lipid peroxidation and activities of antioxidant enzymes in the diabetic kidney: effect of treatment with angiotensin convertase inhibitors. IUBMB Life 49:303–307

Kempen JH, Colmain BJO, Leske MC (2004) Eye Diseases Prevalence Research Group. The prevalence of diabetic retinopathy among adults in the United States. Arch Ophthalmol 122:552–563

King H, Rewers M (1993) Global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults. Diabetes Care 16:157–177

Konno R, Kaneko Y, Suzuki K, Matsui Y (2005) Effect of 5-campestenone (24-methylcholest-5-en-3-one) on Zucker diabetic fatty rats as a type 2 diabetes mellitus model. Horm Metab Res 37:79–83

Kun Y, Lule US, Xiao LD (2006) Lycopene: its properties and relationship to human health. Food Rev Int 22(4):309–333

Laakso M, Kesaniemi YA, Kervinen K, Jauhiainen M, Pyorala K (1991) Relationship of coronary heart disease and apolipoprotein E phenotype in patients with non-insulin-dependent diabetes. BMJ 303:1159–1162

Li WL, Zheng HC, Bukuru J, Kimpe ND (2004) Natural medicines used in the traditional Chinese medical system for therapy of diabetes mellitus. J Ethnopharmacol 92:1–21

Malone JM, Snyder M, Anderson G (1989) Prevention of amputation by diabetic education. Am J Surg 158:520–524

Meghana K, Sanjeev G, Ramesh B (2007) Curcumin prevents streptozotocin-induced islet damage by scavenging free radicals: a prophylactic and protective role. Eur J Pharmacol 577(1–3):183–191

Mohamed B, Abderrahim Z, Hassane M, Abdelhafid T, Abdelkhaleq L (2006) Medicinal plants with potential antidiabetic activity—a review of ten years of herbal medicine research (1990–2000). Int J Diabetes Metab 14:1–25

Montonen J, Knekt P, Harkanen T, Jarvinen R, Heliovaara M, Aromaa A (2005) Dietary patterns and the incidence of type 2 diabetes. Am J Epidemiol 161(3):219–227

Nagao T, Watanabe H, Goto N (2000) Dietary diacylglycerol suppresses accumulation of body fat compared to triacylglycerol in men in a double-blind controlled trial. J Nutr 130:792–798

NCEP EP (2001) Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 285:2486–2497

Nobili S, Lippi D, Witort E, Donnini M, Bausi L (2009) Natural compounds for cancer treatment and prevention. Pharmacol Res 59(6):365–378

Nurfina AN, Reksohadiprodjo MS, Timmerman H, Jenie UA, Sugiyanto D, van der Goot H (1997) Synthesis of some symmetrical curcumin derivatives and their anti-inflammatory activity. Eur J Med Chem 32:321–328

Oberley L (1988) Free radicals and diabetes. Free Radic Biol Med 5:113–124

Pearson ER, Velho G, Clark P, Stride A, Shepherd M, Frayling TM, Bulman PM, Ellard S, Fronguel P, Hattersley T (2001) ß-Cell genes and diabetes: quantitative and qualitative differences in the pathophysiology of hepatic nuclear factor-1 and glucokinase mutations. Diabetes 50:5101–5107

Pelle GL, Olsson HK, Mona LO (2010) Are active sun exposure habits related to lowering risk of type 2 diabetes mellitus in women, a prospective cohort study? Diabetes Res Clin Pract 90:109–114

Perez VF, Duarte J (2010) Phytochemicals and cardiovascular protection: flavonols and cardiovascular disease. Mol Asp Med 31(6):478–494

Philipp S, Akos S, Walter J, Thomas S (2008) Resveratrol and its analogs: defense against cancer, coronary disease and neurodegenerative maladies or just a fad? Mutat Res 658:68–94

Pietraszek AG, Hermansen SK (2010) Alcohol and type 2 diabetes, a review. Nutr Metab Cardiovasc Dis 20:366–375

Prasad K (1999) Reduction of serum cholesterol and hypercholesterolemic atherosclerosis in rabbits by secoisolariciresinol diglucoside isolated from flaxseed. Circulation 99(10):1355–1362

Prasad K (2000) Antioxidant activity of secoisolariciresinol diglucoside-derived metabolites, secoisolariciresinol, enterodiol, and enterolactone. Int J Angiol 9:220–225

Prasad K (2001) Secoisolariciresinol diglucoside from flaxseed delays the development of type 2 diabetes in Zucker rat. J Lab Clin Med 138:32–39

Prasad K (2004) Antihypertensive activity of secoisolariciresinol diglucoside (SDG) isolated from flaxseed: role of guanylate cyclase. Int J Angiol 13:7–14

Reaven PD, Herlod DA, Barnet J, Edelman S (1995) Effects on vitamin E on susceptibility of low density lipoprotein subfraction to oxidation and protein glycation in NIDDM. Diabetes Care 18:807–816

Reynisdottir G, Thorleifsson R, Benediktsson G, Sigurdsson VE, Einarsdottir AS (2003) Localization of a susceptibility gene for type 2 diabetes to chromosome 5q34–q35. 2. Am J Hum Genet 73:323–335

Richard S, Shaw J, Zimmet P (2006) Prevalence and projections. In: Gan D (ed) International Diabetes Atlas, 3rd edn. Brussels, International Diabetes Federation, pp 15–104

Rivera L, Morón R, Zarzuelo A, Galisteo M (2009) Long-term resveratrol administration reduces metabolic disturbances and lowers blood pressure in obese Zucker rats. Biochem Pharmacol 77:1053–1063

Rochfort S, Panozzo J (2007) Phytochemicals for health, the role of pulses. J Agric Food Chem 55:7981–7994

Rosangela GD, Zanatta AP, Cazarolli LH, Alessandra M, Louise DC, Ricardo JN, Rosendo AY, Fatima RM, Barreto S (2009) Nitrochalcones: potential in vivo insulin secretagogues. Biochimie 91:1493–1498

Ryu JK, Lee T, Kim DJ (2005) Free radical scavenging activity of Korean red ginseng for erectile dysfunction in non insulin dependent diabetes mellitus rats. Urology 65:611–615

Sahu SC (2002) Dual role of organosulfur compounds in foods: a review. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev 20:61–76

Samir D, Shalini J, Hariom Y (2011) Exotic fruits as therapeutic complements for diabetes, obesity and metabolic syndrome. Food Res Int 44:1856–1865

Sasaki R, Nishimura N, Hoshino H, Isa Y, Kadowaki M (2007) Cyanidin 3-glucoside ameliorates hyperglycemia and insulin sensitivity due to down regulation of retinol binding protein 4 expression in diabetic mice. Biochem Pharmacol 74(11):1619–1627

Sendberg AS (2002) Bioavailability of minerals in legumes. Br J Nutr 88:281–285

Seo K, Choi MS, Jung UJ, Kim HJ, Yeo J, Jeon SM, Lee MK (2008) Effect of curcumin supplementation on blood glucose, plasma insulin, and glucose homeostasis related enzyme activities in diabetic db/db mice. Mol Nutr Food Res 52(9):995–1004

Shah VO, Scavini M, Nikolic J, Sun Y, Vai S, Griffith KJ (1998) Z-2 microsatellite allele is linked to increased expression of the aldose reductase gene in diabetic nephropathy. J Clin Endocrinol Metab 83:2886–2891

Simonen P, Gylling H, Howard AN, Miettinen TA (2000) Introducing a new component of the metabolic syndrome: low cholesterol absorption. Am J Clin Nutr 72:82–88

Simopoulos AP (1991) Omega-3 fatty acids in health and disease and in growth and development. Am J Clin Nutr 54:438–463

Sing CL, Yen HL, Jen FL, Wen HC, Chiao MC, Chen CYO (2011) Almond consumption improved glycemic control and lipid profiles in patients with type 2 diabetes mellitus. Metab Clin Exp 60:474–479

Soobrattee MA, Neergheen VS, Luximon RA, Aruoma OIB (2005) Phenolics as potential antioxidant therapeutic agents: mechanism and actions. Mutat Res 579:200–213

Sri Balasubashini M, Rukkumani R, Viswanathan P, Venugopal PM (2004) Ferulic acid alleviates lipid peroxidation in diabetic rats. Phytother Res 18(4):310–314

Stahl W, Sies H (2005) Bioactivity and protective effects of natural carotenoids. BBA—Mol Basis Dis 1740(2):101–117

Sterti R (2010) Berberine for diabetes mellitus type 2. Nat Med J 2(10):5–6

Suresh Y, Das UN (2003) Long-chain polyunsaturated fatty acids and chemically induced diabetes mellitus: effect of ω-6 fatty acids. Nutrition 19:93–114

Suzuki K, Tanaka M, Konno R, Kaneko Y (2002) Effects of 5-campestenone (24-methylcholest-5-en-3-one) on the type 2 diabetes mellitus model animal C57BL/KsJ-db/db mice. Horm Metab Res 34:121–126

Szkudelska K, Nogowski L, Szkudelski T (2009) The inhibitory effect of resveratrol on leptin secretion from rat adipocytes. Eur J Clin Investig 39:899–905

Tada N, Watanabe H, Matsuo N, Tokimitsu I, Okazaki M (2001) Dynamics of postprandial remnant-like lipoprotein particles in serum after loading of diacylglycerols. Clin Chim Acta 311:109–117

Taguchi H, Watanabe H, Onizawa K (2000) Double-blind controlled study on the effects of dietary diacylglycerol on postprandial serum and chylomicron triacylglycerol responses in healthy humans. J Am Coll Nutr 19:789–796

Taguchi H, Nagao T, Watanabe H (2001) Energy value and digestibility of dietary oil containing mainly 1,3-diacylglycerol are similar to those of triacylglycerol. Lipids 36:379–382

Takahashi N, Kawada T, Goto T, Yamamoto T, Taimatsu A (2002) Dual action of isoprenols from herbal medicines on both PPAR and PPAR-gamma in 3T3-L1 adipocytes and HepG2 hepatocytes. FEBS Lett 514(2–3):315–322

Takase H, Shoji K, Hase T, Tokimitsu I (2005) Effect of diacylglycerol on postprandial lipid metabolism in non-diabetic subjects with and without insulin resistance. Atherosclerosis 180:197–204

Tanaka M, Misawa E, Ito Y, Habara N, Nomaguchi K, Yamada M (2006) Identification of five phytosterols from Aloe vera gel as antidiabetic compounds. Biol Pharm Bull 29:1418–1422

Tsuda T (2008) Regulation of adipocyte function by anthocyanins; possibility of preventing the metabolic syndrome. J Agric Food Chem 56(3):642–646

Ubels FL, Links TP, Sluiter WJ, Reitsma WD, Smit AJ (1999) Walking training for intermittent claudification in diabetes. Diabetes Care 22:198–201

Vidal VC, Frías J, Sierra I, Blazquez I, Lambien F, Kuo YH (2002) New functional legume food by germination. Effect on the nutritive value of beans, lentils and peas. Eur Food Res Technol 215:472–476

Vijaimohan K, Jainu M, Sabitha KE, Subramaniyam S, Anandhan C, Shyamala DCS (2006) Beneficial effects of alpha linolenic acid rich flaxseed oil on growth performance and hepatic cholesterol metabolism in high fat diet fed rats. Life Sci 79:448–454

Wasan KM, Zamfir C, Pritchard PH, Pederson RA (2003) Influence of phytostanol phosphoryl ascorbate (FM-VP4) on insulin resistance, hyperglycemia, plasma lipid levels, and gastrointestinal absorption of exogenous cholesterol in Zucker (fa/fa) fatty and lean rats. J Pharm Sci 92:281–288

WHO, IDF (2006) Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: 2006. World Health Organization, Geneva

Wild S, Roglic G, Green A, Sicree R, King H (2004) Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 27:1047–1053

Williams RJ, Spencer JP, Rice EC (2004) Flavonoids: antioxidants or signaling molecules. Free Radic Biol Med 36:838–849

Wolford JK, Gruber JD, Ossowski VM, Vozarova B, Antonio Tataranni P, Bogardus C, Hanson RL (2003) A C-reactive protein promoter polymorphism is associated with type 2 diabetes mellitus in Pima Indians. Mol Genet Metab 78:136–144

Xavier CPR, Lima CF, Preto A, Seruca R, Fernandes FM, Pereira WC (2009) Luteolin, quercetin and ursolic acid are potent inhibitors of proliferation and inducers of apoptosis in both KRAS and BRAF mutated human colorectal cancer cells. Cancer Lett 281(2):162–170

Zhaoa J, Zhaob Y, Zhenga W, Lub Y, Fengb G, Yub S (2008) Neuroprotective effect of curcumin on transient focal cerebral ischemia in rats. Brain Res 1229:224–232

Zheng CD, Duan YQ, Gao JM, Ruan ZG (2010) Screening for anti-lipase properties of 37 traditional Chinese medicinal herbs. J Chin Med Assoc 73(6):319–324