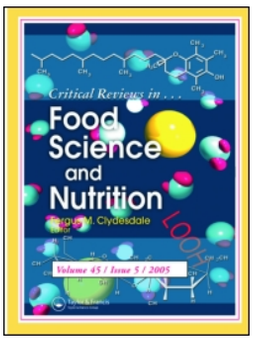

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Management of diabetic complications through fruit flavonoids as a natural remedy

Amna Tanveer[a], Kashif Akram[a], Umar Farooq[a], Zafar Hayat[b], and Afshan Shafi[a]

[a]Institute of Food Science and Nutrition, University of Sargodha, Sargodha, Pakistan; [b]Department of Animal Sciences, University College of Agriculture, University of Sargodha, Sargodha, Pakistan

ABSTRACT

Diabetes mellitus is a global disorder, and a major issue for health care systems. The current review outlooks the use of fruit flavonoids as natural remedy in the prevention of diabetes mellitus. The onset of diabetes mainly depends upon genetics and lifestyle issues. Currently used therapeutic options for the control of diabetes, like dietary amendments, oral hypoglycemic drugs, and insulin, have their own limitations. Fruit flavonoids possess various antidiabetic, anti-inflammatory, and antioxidant potentials and act on various cellular signaling pathways in pancreas, white adipose tissue, skeletal muscle, and liver function, which in result induces antidiabetic effects. Recently, antidiabetic effect of fruit flavonoids has been studied using various animal models and clinical trials. Research studies revealed a statistically significant potential of fruit flavonoids in managing the altered glucose and oxidative metabolisms in diabetes. Unlike synthetic antidiabetic agents, fruit flavonoids manage diabetes without compromising cellular homeostasis thereby posing no side effects. Further studies are required in purification and characterization of different fruit flavonoids with respect to their beneficial effect for diabetic patients.

KEYWORDS

Diabetes mellitus; fruits; flavonoids; antidiabetic effect

Introduction

Diabetes mellitus is one of the most common metabolic disorders with 382 million patients globally estimated till 2013 (Shi and Hu, 2014). The personal and public health problem of diabetes is continuously escalating exponentially (2.6% annually) throughout the world (Danaei et al., 2011) and according to World Health Organization, diabetes will be the seventh leading cause of death in 2030 (Alwan et al., 2011). Symptomatically, diabetes mellitus is characterized by chronic hyperglycemia (elevated concentration of glucose in the blood $\geq$ 7.0 mmol/L or 126 mg/dL) (WHO, 2006). Other symptoms include, but are not limited to, severe thirst (polydipsia), frequent urination (polyurea), increased hunger (polyphagia), unconsciousness, weight loss, and coma leading to death or many medical complications that may occur in the absence of effective treatment. This worldwide rapidly growing health threat occurs due to combination of multiple genetic and environmental factors (Philippe and Raccah, 2009).

Diabetes has complex and various degrees of heterogeneity in its etiology. Evidently, diabetes is manifested when the body becomes resistant to insulin (a hormone secreted by β-cells of pancreas gland) or when enough insulin is not produced to regulate glucose metabolism (DM, 2010; Mohan and Nandhakumar, 2014). Type 1 and type 2 diabetes are two main types of this disease (Roglic and Unwin, 2010) besides other similar conditions like prediabetes (impaired glucose regulation) and gestational diabetes (Zierath and Wallberg-Henriksson, 2002). In type 1 diabetes (insulin-dependent diabetes mellitus or juvenile diabetes), the body cannot produce insulin due to autoimmune or infectious destruction of β-cells of pancreas gland and insulin is required to be externally administered (Rother, 2007). Type 2 diabetes, previously known as noninsulin-dependent diabetes mellitus, is characterized by the body's ineffective use of insulin and is the most common and prevalent form (90–95%) of diabetes mellitus (WHO, 1999).

Exact mechanism of the development and progression of diabetes is still unclear. It is postulated that diabetes occurs when the tightly controlled mechanisms have been disturbed due to any reason. Notable increase has been seen in the identification of the molecular components and all the signaling pathways used in the regulation of glucose absorption (Krentz and Bailey, 2005). Chronic hyperglycemia affects nervous system, heart, kidneys, eyes, and other systems of body. Diabetes is the leading cause of many disease conditions like strokes, cardiovascular disease, renal failure, visual impairment, blindness, lower limb amputations, erectile dysfunction, and insignificant wound healing (Levitan et al., 2004; Resnikoff et al., 2004; Mendis et al., 2007; Boden-Albala et al., 2008; Icks et al., 2009; Akkati et al., 2011; Rizvi and Mishra, 2013; Mendis and Chestnov, 2014). Sometimes diabetes is not diagnosed until the development of other health problems. Stress, lethargic life style, smoking, hypertension, eating habits, processing, and nutritional composition of food are some of the predisposing environmental factors in the development of diabetes mellitus (Adler et al., 2000; Willi et al., 2007; Lee et al., 2012). On the food and nutrition forefront, refined grains, highly processed food, energy-dense junks, saturated fat, excessive alcohol, sugar sweetened beverages are the major culprits (Riserus et al., 2009; Malik et al., 2010).

CONTACT Umar Farooq umarfarooq@uos.edu.pk Institute of Food Science and Nutrition, University of Sargodha, Sargodha, Pakistan.

Management of diabetes

Diabetes is a lifelong disease and no cure for diabetes is yet to be found, however; different pharmacological and nonpharmacological therapeutic measures have positively been employed to enhance the life quality of individuals suffering from diabetes and its micro and macro-vascular complications (ADA, 2011). As diabetes is characterized by chronically increased levels of blood glucose, thus main theme of current diabetes management is to better regulate the glucose metabolism (McCrimmon and Sherwin, 2010). However, this is not so simple as the complex disorder needs continuous medical attention, support, self-management, and education of the patient to avoid serious complications and to diminish the risk of long-term complications; accordingly, its management is multifarious and needs many issues, beyond glycemic control, to be addressed (Henriksen, 2010). Lifestyle interventions addressing diet and physical activity are considered a first-line intervention for the prevention of type 2 diabetes (Paulweber et al., 2010).

Insulin is routinely administered in type 1 diabetes mellitus patients, due to auto-destruction of β-cells of pancreas and ultimately incapability of cells to secrete insulin, and for type 2 diabetic patients, in which cells are unable to respond to the normal action of circulating insulin and incapable to meet safe glycemic targets (Bodmer et al., 2008). Some compounds possessing antidiabetic properties have been extensively employed to manage disbetes (Saxena and Vikram, 2004; Rother, 2007). Several surgical procedures (bariatric surgery) are adopted mainly to achieve weight loss in obese persons to manage diabetes especially when the lifestyle and pharmacologic interventions become unable to control type 2 diabetes or its related problems (Catalan et al., 2001). Different degrees and proportions of survival benefits are reported with bariatric surgery (Robinson, 2009); however, no considerable improvement had been witnessed in highly vulnerable population (Maciejewski et al., 2011) and there are also reports of reoccurrence of obesity and associated problems like obesity after surgical interventions depending upon prebariatric history of diabetes (Ramos, 2012).

The clinical evaluation of a patient helps to select the suitable therapy for the treatment. All the above-mentioned preventive measures fulfill their objective to some extent except bariatric surgery (Zia et al., 2001) and diabetes and its related complications are not cured till now. Efficient and sustainable management of diabetes is becoming more important with rapidly increasing morbidity due to this disease globally (Alwan et al., 2011). It is predicted that by year 2035, patients suffering from diabetes would reach to 600 million worldwide (Shi and Hu, 2014).

Commonly used antidiabetes agents and their related problems

Recently used therapeutic antidiabetes agents are sulfonylureas, glinides, biguanides, and α-glucosidase inhibitors (Kim and Egan, 2008) employed singly or in combination. In fact, all antidiabetic agents in practice work directly and indirectly by regulating the blood glucose level (Fig. 1) (Molavi et al., 2007; Kim and Egan, 2008).

- Sulfonylureas are the antidiabetic drugs (glibenclamide and glyburide) that increase the amount of insulin by acting upon the β-cells of pancreas. On β-cells membrane they attach to an ATP-dependent $K^+(K_{ATP})$ and cause positive electric potential over the membrane and open the Ca^{2+} channels. This elevation of intracellular calcium ions results into increased fusion of insulin granule with cell membrane, hence amplifying the secretion of insulin (Kim and Egan, 2008). Incretins like exenatide and liraglutide also increase insulin production by acting on pancreas (Molavi et al., 2007).
- Biguanides and thiazolidinediones increase insulin sensitivity of adipose tissue, liver, and muscle by increasing the

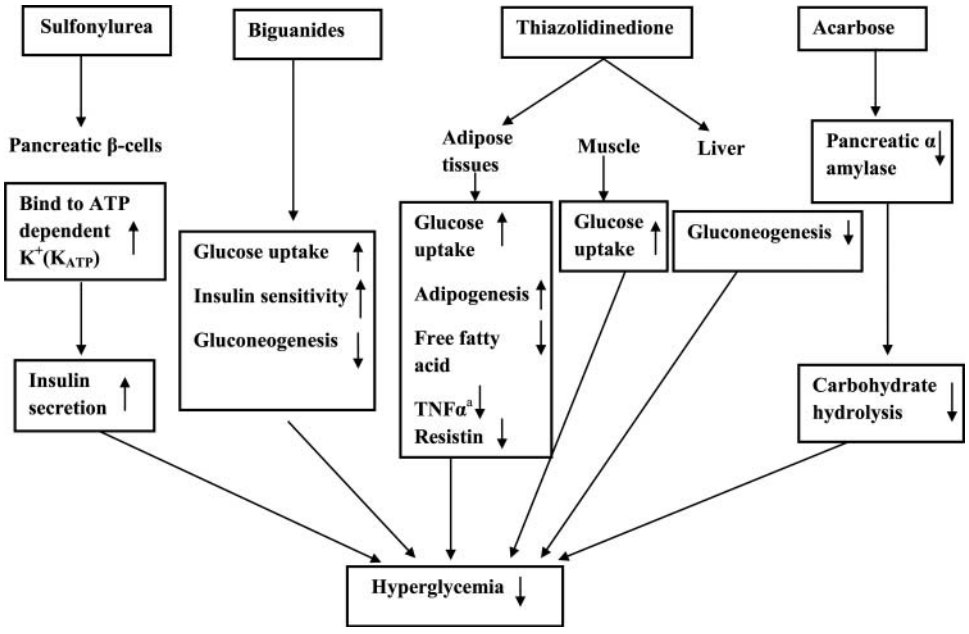

Figure 1. Commonly used antidiabetic agents and their mode of action.[a]TNFα (Tumor necrosis factor α).

uptake of glucose in muscle and decreasing the production of glucose in liver. They include metformin and pioglitazone (Catalan et al., 2001; Bourron et al., 2010).

- Acarbose and miglitol are the antidiabetic agents that slow down the absorption of glucose from gastrointestinal tract. Nutritional supplements also inhibit α-glucosidase and α-amylase activity in gut and ultimately reduce the glucose uptake (Spengler et al., 2005; Dixon et al., 2008).

Unfortunately, the treatment of diabetes through antidiabetic agents has their own flaws including the increased resistance and lack of responsiveness in a large segment of the patient population. In addition, no antihyperglycemic agent properly tackles the elevated lipid level that is common in this disease (Chitra et al., 2010). Most of these oral antidiabetic agents impose serious side effects, so diabetes management without any adverse effect is still a challenge (Liu et al., 2010). Therefore, holistic exploration of more active and safer therapeutic agents in eliminating diabetic syndromes is an important area of investigation (Kao et al., 2000).

Flavonoids: Potential antidiabetic agents

Natural products from fruit and vegetable sources are becoming popular worldwide and broadly accepted as an aid to conventional therapy (Yao et al., 2004). Increasing public awareness and scientific interest headed the research towards the evaluation of fruits' role in health upgradation and disease treatment. In recent years, great attention has been focused on the health-promoting roles of bioactive components known as "flavonoids" (Vessal et al., 2003). Flavonoids are ubiquitously secondary metabolites present in almost all fruits and vegetables (Chen et al., 2014). They comprise of two benzene rings and one heterocyclic ring (Aherne and O'Brien, 2002) and include various subclasses notably flavonols (quercetin and kaempferol), flavones (luteolin and apigenin), flavanols (catechins and proanthocyanidins), anthocyanidins (aurantinidin and cyaniding), flavanones (naringenin and hespertine), and isoflavones (genistein and daidzein) (Scalbert and Williamson, 2000).

Flavonoids have various positive effects on complex metabolic pathologies including diabetes, through multifarious modes of actions (Barone et al., 2009). It is postulated that majority of the bioactivity of flavonoids is due to their α, β ketones and hydroxyl groups (Veerapur et al., 2010).

Metabolism and bioavailability of flavonoids

Flavonoids are used as substrates by conjugating and hydrolyzing enzymes of small intestine, liver, and colon. Then these enzymes convert the flavonoids into *O*-glucuronides, sulfate esters, and *O*-methyl esters (Del-Rio et al., 2010). Flavonoids conjugation first occurs in the small intestine and then in the liver. In the liver, they are further metabolized to produce glucuronides and sulfate derivatives that are facilitated and excreted through urine and bile (Del-Rio et al., 2010). The unabsorbed compounds are further moved to colon and structurally modified by colonic microflora (Scalbert et al., 2002). The flavonoid glucuronides are hydrolyzed into aglycones (by microbiota) after re-entering the enterohepatic circulation (Spencer et al., 2001). Then aglycones further break down to low molecular compounds that can easily be absorbed.

Spencer et al. (2001) reported that during systemic absorption of monomeric flavan-3-ols they are either metabolized into *O*-methylated forms or conjugated to form glucuronides or sulfates. In addition, the monomeric flavan-3-ols (procyanidins) are split into the conjugates of epicatechin. A study by Del-Rio et al. (2010) on the absorption and metabolism of flavan-3-ols in humans illustrated that epigallocatechin-*O*-glucuronide and methyl-epicatechin-sulfate were excreted in urine, hence confirming the above statement. Another recent study by Fernandes et al. (2012) on the bioavailability of an anthocyanin derivative demonstrated the transepithelial transport of flavan-3-ol-anthocyanin dimer [(+)-catechin-4, 8-malvidin-3-glucoside], by using Caco-2 cells. The results were compared with (+)-catechin, procyanidin B3, and malvidin-3-glucoside. All the compounds under study (catechins, procyanidins B3, malvidin-3-glucoside, and flavan-3-ol-anthocyanin dimer) passed the Caco-2 cell model barrier and the absorption of catechin-malvidin dimer was significantly less as compared to individual malvidin or catechins compounds. But the transport efficacy of the catechin-malvidin dimer was more than procyanidin B3 dimer and this increased transport efficacy of catechin-malvidin dimer might be due to presence of the anthocyanin and its glucose moiety in the flavan-3-ol-anthocyanin. Interestingly, after two hours of incubation only the breakdown of parent compounds was observed and no catechin-malvidin dimer metabolites were found. The results of this study illustrated that anthocyanins are absorbed as anthocyanin derivatives and catechin-malvidin dimer is more resistant to metabolism as compared to its parent compounds. A study on the genistein (aglycone) and its glycoside genistein bioavailability showed that the bioavailability of the aglycone was higher in comparison to its glycoside form (Harvey, 2008).

Treatment by kaempferol (10 μM), a fruit flavonol, significantly increased the viability and reduced cellular apoptosis and caspase-3 activity in human beta cells and islets. Furthermore, kaempferol treatment also increased the expression of anti-apoptotic proteins (Bcl-2 and Akt) (Havsteen, 2002). In addition, studies also demonstrated that quercetin flavonoid increased the regeneration of pancreatic islets and ultimately increased the insulin secretion in streptozotocin-induced diabetic rats (Vessal et al., 2003). Recently, more attention is given on research of flavonoids from dietary sources, due to growing evidence of their versatile health benefits. To best understand the mode of action of flavonoids and their potential role in the prevention of diseases, it is important to know their biosynthesis, metabolism, and bioavailability (Hollman, 2004).

Antidiabetic mode of action of flavonoids

Generally, flavonoids exert wide range of their antidiabetic activity on various organs (Fig. 2); that's why holistic corrective actions of fruit flavonoids to combat the complexities of diabetes mellitus are advantageous over the chemical antidiabetic agents that have solitary actions and are notorious to disrupt metabolic equilibrium. Antidiabetic mechanism of flavonoids might be mainly due to their effects on enzymes responsible for glucose metabolism or through other novel mechanisms still to

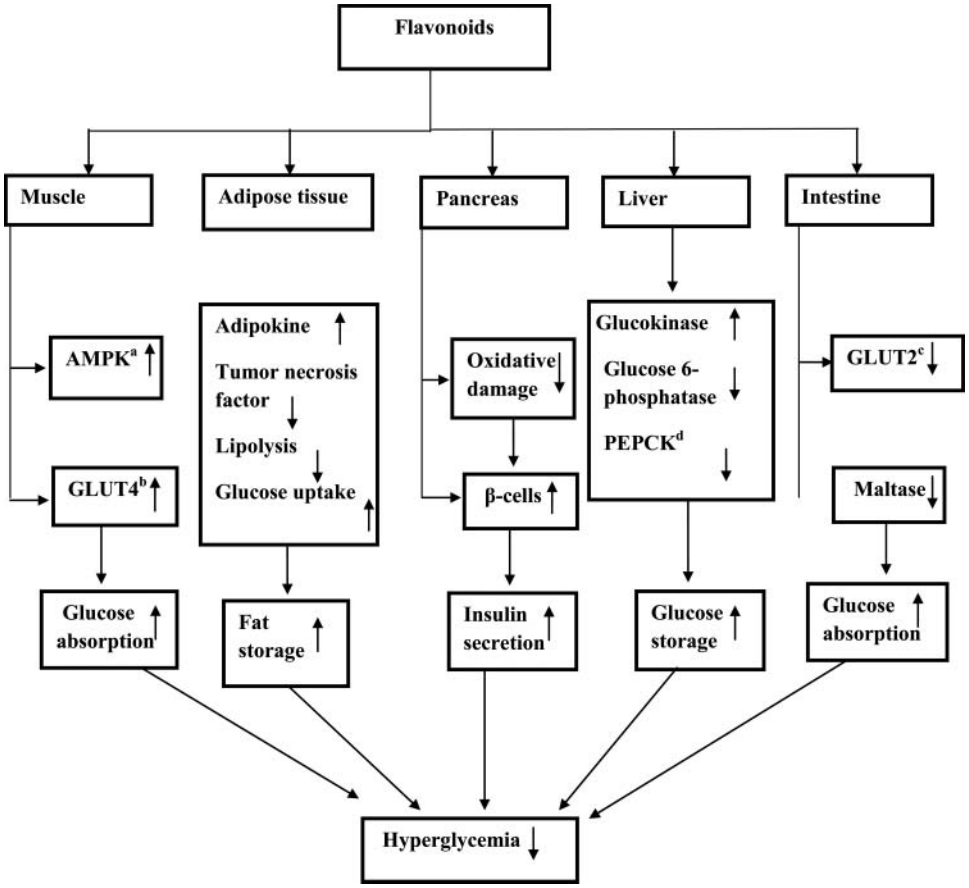

Figure 2. Proposed mechanism of antidiabetic action of fruits flavonoids.

be explored. Importantly, flavonoids exert antidiabetic action by ameliorating the insulin action on skeletal muscle and liver cells to reduce the plasma free fatty acid level, hepatic gluconeogenesis, and increased glucose uptake (Aguirre et al., 2011). In the intestine, flavonoids inhibit the digestion of starch, slow down the gastric emptying, and reduce the absorption of glucose across the membrane (Kannappan and Anuradha, 2010). The regulation of postprandial hyperglycemia is an important strategy of diabetes management. Such approach is to reduce the digestion (intestinal) of complex carbohydrates (disaccharides oligosaccharides, and trisaccharides) by inhibiting the activity of intestinal membrane-bound α-glucosidases (Babu et al., 2013).

Li et al. (2009) demonstrated that flavonols such as quercetin, rutin, and isoquercetin formed complexes with α-glucosidases via hydrophobic binding, thus inhibiting its activity. Fisetin, a tetrahydroxy-flavone mainly present in fruits and vegetables, promoted the hexokinase, glucose-6-phosphate dehydrogenase, pyruvate kinase activities while reduced glucose-6-phosphatase, lactate dehydrogenase, and fructose-1,6-biphosphatase activities that resulted into lowered blood glucose level and elevated plasma insulin concentrations in hepatic and renal tissues of streptozotocin-induced diabetic rats (Prasath et al., 2010). Furthermore, fisetin also improves glucose homeostasis through regulation of enzymes involved in carbohydrate metabolism particularly by increasing the glycogen synthase (enzyme that converts glucose in glycogen) and decreasing glycogen phosphorylase (enzyme that breaks glycogen into glucose subunits) production (Prasath and Subramanian, 2011).

Glucose transporter type-2 is the protein that enables the transfer of glucose between liver and blood and also has a role in transportation of intestinal sugar. Kwon et al. (2007) reported that myricetin, quercetin, and its glucoside bind the glucose transporter type-2 and prevent the transport of glucose in blood stream. Flavonoids also affect glucose transporter type-4, which is insulin-regulated glucose transporter mainly found in adipocytes and skeletal muscles. Postulated mechanism is that when blood sugar concentration increases insulin translocate the glucose transporter type-4, which increases the uptake of glucose from blood to adipose and skeletal muscles (McCarthy and Elmendorf, 2007). Prasad et al. (2010) reported that gallic acid increased glucose transporter type-4 translocation and glucose uptake in Akt-independent manner. The authors also reported that glucose uptake and glucose transporter type-4 translocation is mediated by protein kinase C pathway. Phosphatidylinositol (3,4,5)-trisphosphate (PIP3), the product of insulin-mediated protein kinase C activation, uses phosphoinsositide-dependent kinase-1 to translocate in membrane where it activates protein kinase C through phosphorylation (Balendran et al., 2000).

Fruit flavonoids can exhibit their antidiabetic activity by causing reduction in phosphoenolpyruvate carboxykinase and glucose 6-phosphatase that are the main enzymes involved in gluconeogenesis. In diabetic condition, the levels of these enzymes raise that lead to reduced utilization of glucose and

hence elevated production of glucose (Munoz et al., 2001). Choi and Ahn (2008) reported that genistein and daidzein inhibited the activities of phosphoenolpyruvate carboxykinase and glucose 6-phosphatase and elevated the insulin level in body.

Flavon-3-ol like epigallocatechin gallate conserved the β-cells viability and glucose-stimulated insulin secretion by regulating the expression of B-cell lymphoma 2 (anti-apoptotic protein) and inhibition of Bcl-2-associated X protein (apoptotic protein) translocation (Zhang et al., 2011). Epigallocatechin gallate increases the production of β-cell lymphoma 2 protein, which inhibits the oxidative stress and controls the mitochondrial transitional pore opening by reducing the effect of Bcl-2-associated X protein and ultimately blocking the production of cytochrome c and caspase activity. Cytochrome c and caspase are proteins involved in programmed cell death of islets (Low et al., 2010; Zhang et al., 2011).

Certain flavonols (quercetin) use ERK1/2 (protein kinase involved in proliferation, differentiation, and apoptosis) pathway and improve the glucose-stimulated insulin production and prevent the oxidative damage of insulin-1 cells (Youl et al., 2010). Moreover, quercetin and its glycoside quercitrin also protect clonal β-cells against cytokine-induced cell death by inhibiting the translocation of nuclear-factor kappa-B and suppressing nitric oxide formation, which consequently reduces the expression of inducible nitric oxide synthase (enzyme responsible for inflammation-related insulin resistance) (Dai et al., 2013).

Similarly, flavones like apigenin and luteolin prevent interleukin-1β- and interferon-γ-induced apoptosis of β-cells, via inhibition of nuclear-factor kappa-B activation and inducible nitric oxide synthase expression (Kim et al., 2007a). It is reported that apigenin improved the phosphorylation of adenosine monophosphate activated protein kinase in hepatocytes (Zang et al., 2006). Furthermore, apigenin also inhibited Acetyl Co-A carboxylase phosphorylation and lipid accumulation in hepatocytes by improving the action of adenosine monophosphate activated protein kinase (Zang et al., 2006). Adenosine monophosphate activated protein kinase is an energy-sensing molecule and involved in body energy homeostasis, adipocyte lipolysis inhibition, and stimulating glucose uptake. It improves the glycemic level and lipid profile in insulin resistant rodents (Zhang et al., 2009). Genistein (flavones) improved the production of human islet β-cells by activating the cAMPK/PKA-dependent ERK1/2 signaling pathway (Fu et al., 2010). Moreover, genistein also suppressed nuclear factor kappa-B and ERK-1/2 pathway in order to prevent alteration in β-cells (Kim et al., 2007b).

Promising antidiabetic role of flavonoids of various fruits

Numerous studies demonstrated that many plants especially fruits are traditionally used for the treatment of diabetes (Sabu et al., 2002; Steensma et al., 2006). Epidemiological studies and meta-analyses described the use of fruits rich in flavonoids decreases diabetes (Arts and Hollman, 2005; Graf et al., 2005). Many in-vitro and animal studies support the positive effects of various fruits flavonoids on glucose homeostasis (Jung et al., 2006; Cai and Lin, 2009; Fu et al., 2010; Hanhineva et al., 2010; Fu et al., 2011; Zhang and Liu, 2011; Zhu et al., 2012). The fruits flavonoids and their antidiabetic roles are presented in Table 1.

Citrus flavonoids

In recent years, citrus flavonoids gained much attention because of their potential therapeutic properties and comparatively low toxicity to animals (Manthey et al., 2001; Benavente-Garcia and Castillo, 2008; Choi and Ahn, 2008). Shen et al. (2012) reported that citrus flavonoids like hesperidin, nobiletin, neohesperidin, and naringin showed antidiabetic properties by binding starch and slowing down its digestion. Moreover, numerous studies reported that hesperidin, naringin, and nobiletin enhanced the insulin sensitivity and induced the hypoglycemic effect in diabetic animals (Kobayashi et al., 2000; Akiyama et al., 2009; Akiyama et al., 2010; Lee et al., 2010). Naringenin, a major flavonoid found in citrus fruits, possessed antidiabetic properties (Lim et al., 2008). Lim et al. (2008) demonstrated that naringenin exhibited insulin-sensitive effect at a concentration of 100 μM, by enhancing the uptake of glucose in primary rat adipocytes (163%) as compared to insulin (130%). The studies of Huong et al. (2006) demonstrated that fruits rich in naringenin (1%) improved the oxidation of hepatic fatty acid by regulating the gene that encodes the enzyme for peroxisomal β-oxidation in mice and this change may account for its capability of inducing low serum lipid levels. Moreover, naringenin reduced the lipid level by increasing the low-density lipoprotein receptor expression through phosphatidylinositol 3-kinase facilitated upregulation of sterol regulatory element-binding protein (Borradaile et al., 2003). Phosphoenolpyruvate carboxykinase and glucose 6-phosphatase are the main enzymes involved in gluconeogenesis. In diabetic condition, the levels of these enzymes raise that lead to reduced utilization of glucose and elevated hence production of glucose (Munoz et al., 2001). Naringin and hesperidin belong to citrus flavonoids and suppress the expression of phosphoenolpyruvate carboxykinase and glucose 6-phosphatase and reduce the hepatic glucose production (Kim et al., 2012).

Berries flavonoids

Procyanidin from the extract of grapes seeds increased the concentration of insulin transporter: glucose transporter-4 in plasma membrane increased the uptake of glucose in adipocytes, and ultimately induced the antihyperglycemic effect in streptozotocin-induced diabetic rats (Pinent et al., 2004). Glucose transporter-4 is the main insulin regulating transporter that is expressed in skeletal muscle and adipose tissue. In diabetic db/db mice adipocyte, the expression of glucose transpoter-4 improves the glycemic control by ameliorating insulin resistance (Gibbs et al., 1995).

Cai and Lin (2009) reported the antidiabetic effect of epigallocatechin gallate on glucose-induced toxicity in the pancreatic β-cells of a rat insulinoma-m5F cells. The results demonstrated that 0.1 and 10 μM concentration of epigallocatechin gallate enhanced insulin secretory function and viability of β-cells in glucotoxic conditions. These properties were partially facilitated via increased expression of insulin receptor substrate-2,

Table 1. Different fruits flavonoids, their sources, antidiabetic properties, and underlying mode of action.

Flavonoids	Sources	Functionality	Mode of action	References
Quercetin	Grape fruit, apple, cranberries	Improves glucose absorption	Acts upon adenosine monophosphate-activated protein kinase, which mediates glucose transporter-4 translocation	Eid et al. (2010)
Kaempferol	Strawberries, gooseberries, cranberries, grapefruit, apple	Improves the insulin secretion	Improves the expression of Akt and Bcl-2[a] and inhibits the capase-3 activity in β-cells; so ultimately protects the β-cells' survival	Zhang and Liu (2011)
Myricetin	Grapes, berries, walnuts	Improves insulin sensitivity	Improves the impaired signaling downstream of insulin receptors; then affects the phosphorylation of insulin receptors:insulin receptor substrate-1, phosphatidylinositol 3-kinase, which effects glucose transporter-4 translocation in muscles	Tzeng et al. (2011)
Rutin	Citrus fruits, oranges, lemon, berries, limes, grapefruit, peaches, apples	Improves the insulin secretion	Scavenges the free radicals, inhibits the lipid peroxidation, prevents the oxidative stress, and ultimately protects β-cell damage through oxidative stress	Coskun et al. (2005)
Hesperidin	Citrus fruits	Ameliorates hyperglycemia	Increases hepatic glycolysis and glycogen concentration or lowers hepatic gluconeogenesis	Jung et al. (2004)
Naringenin	Citrus fruits	Induces the hypolipidemic action	Increases low-density lipoprotein receptor expression through phosphatidylinositol 3-kinase mediated upregulation of sterol regulatory element binding protein	Kannappan and Anuradha (2010)
		Reduces the glucose uptake from intestine	Inhibits the α-glycosidase activity	Priscilla et al. (2014)
Tangeritin	Tangerine and citrus peels	Improves the glucose uptake	Increases the adenosine monophosphate-activated protein kinase phosphorylation and alters the secretions of adipocytokines such as leptin, adiponectin, resistin, interleukin 6, and monocyte chemotactic protein-1	Kim et al. (2012)
Catechin	Grapes, apple juice	Reduces the blood glucose level	Inhibits the transport of glucose across the intestinal membrane	Kobayashi et al. (2000)
Epigallocatechin gallate	Pomegranate juice	Improves the β-cells viability	Increases the expression of insulin receptor substrate-2, Akt, the fork head box protein 01, and pancreatic duodenal home box-1 and ultimately protects the β-cells from damage	Cai and Lin (2009)
Anthocyanins and anthocyanidins	Bilberry, raspberry, strawberry, black currants, peach, plum	Improve the insulin sensitivity	Upregulate glucose transporter-4 expression, which in turn leads to downregulated theretinol binding protein-4 expression	Takikawa et al. (2010)
		Reduce postprandial hyperglycemia	Inhibit the α-glucosidase activity; so inhibit the glucose liberation from dietary carbohydrates and ultimately delay the glucose absorption in plasma	Kumar et al. (2011)

[a]Bcl-2 (B-cell lymphoma 2) are cell death regulatory proteins.

the forkhead box protein O1, Akt (glucose metabolizing protein kinase), and pancreatic duodenal homeobox1. Insulin receptor substrate protein mediates the insulin action and regulates the β-cells viability and proliferation. The forkhead box protein O1 regulates the cellular proliferation and protects the β-cells from apoptosis (Buteau and Accili, 2007). Pancreatic duodenal homeobox1 is a transcription factor that is expressed in islets of Langerhans and increases the viable count of islets (McKinnon and Docherty, 2001).

Strawberry is a fruit of nutritional importance and now gaining attention because of antidiabetic property of its flavonoids (Hannum, 2004; Aaby et al., 2005). In general, α-amylase and α-glucosidase are the key enzymes involved in catalytic breakdown of carbohydrates into glucose. In antidiabetic analyses, IC_{50} value for α-amylase and α-glucosidase activity of fruit extract of strawberry was found to be 86.47 $\pm$ 1.12 μg/mL and 76.83 $\pm$ 0.93 μg/mL, respectively. Maximum inhibition of 52.35% at a concentration of 97 $\mu g/\mu L$ was done by strawberry extract (rich in phytochemicals) and in comparison with standard acarbose, which exhibited maximum inhibition of 72.10% at a concentration of 92 $\mu g/\mu L$. In addition, at the concentration of 91 $\mu g/\mu L$, strawberry extract induced 58.83% of inhibition. Standard acarbose exhibited maximum inhibition of 69.43% at a concentration of 96 $\mu g/\mu L$ (Mandave et al., 2013). The studies also demonstrated the antidiabetic effects of bayberry fruit extract. Sun et al. (2012) reported that bayberry extract (rich in cyanidin-3-glucoside) decreased the risk of oxidative stress and ultimately reduced the β-cell damage. Initial treatments of β-cells with bayberry fruit extract (comprising 0.5 μM cyanidin-3-glucoside) stopped cell death by hydrogen peroxide, mitochondrial reactive oxygen species production, and cell necrosis.

The bioactive components present in most of the berries and cherries appear as glycosides of anthocyanidins. Dried cherries of *Cornus* spp. have been traditionally used for diabetes treatment in China (Yamahara et al., 1981). The cyanidin-, delphinidin-, and pelargonidin glycosides are the important bioactive component of *Cornus* fruits (Seeram et al., 2002; Jayaprakasam et al., 2005). These anthocyanidins and anthocyanins components improved the insulin secretion by acting on β-cells of pancreas. The pancreatic β-cells were treated with cyanidin-3-glucoside and delphinidin-3-glucoside for 60 minutes and they increased the glucose-stimulated insulin secretion. However, pelargonidin-3-galactoside, cyanadin-3-galactoside, and

aglycones, such as cyanidin, pelargonidin, delphinidin, and malvidin, had negligible to marginal effects on glucose-stimulated insulin secretion (Scazzocchio et al., 2011). Cyanidin 3-glucoside (50 μM) and protocatechuic acid improved the glucose uptake and translocation of glucose transporter in human and rat adipocytes (Guo et al., 2012).

Rostamian et al. (2011) demonstrated the antidiabetic action of hydroalcoholic extract of strawberry leaves rich in flavonoids. For this purpose, 24 male adult rats were selected randomly and were divided into nonantidiabetic control group, diabetic control, and diabetic group. Diabetic group was administered with alloxan then intraperitoneally injected with extract (100 mg/kg). The analysis of glucose, triglyceride, high-density lipoprotein, cholesterol, and low-density lipoprotein content showed that the extract rich in flavonoids meaningfully reduced the glucose, triglyceride, and cholesterol, and elevated the level of high-density lipoproteins but did not affect the low-density lipoprotein content.

Eid et al. (2010) elucidated the mode of action of quercetin rich extract of *Vaccinumvitis-idaea* (cowberry) in the treatment of diabetes. For this purpose, 10 compounds (found in berries) involved in glucose absorption were analyzed in C2C12 murine skeletal myoblasts and H4IIE murine hepatocytes (main cells of liver tissue). The results revealed that quercetin-3-*O*-glycoside and quercetin aglycone were the active components involved in glucose absorption. This effect is facilitated by adenosine monophosphate activated protein kinase, which mediates the translocation of glucose transporter type-4. Adenosine monophosphate activated protein kinase is an energy-sensing molecule and involved in body energy homeostasis. It improved the glycemic level and lipid profile in insulin-resistant rodents (Zhang et al., 2009). Therefore, adenosine monophosphate activated protein kinase is considered as an attractive target for developing new strategies to treat diabetes.

Bilberries are the rich source of anthocyanins (Katsube et al., 2003). Takikawa et al. (2010) elucidated the metabolic properties of bilberry extract (27 g bilberry extract containing 10 g anthocyanin/kg diet) in mice with type 2 diabetes. Bilberries extract enhanced hypoglycemia and insulin sensitivity in diabetic mice by targeting adenosine monophosphate activated protein kinase, glucose transporter type-4, and other metabolic enzymes.

Persimmon flavonoids

The persimmon belongs to the family of *Ebenaceae* and is inhabitant of Japan and China. Several studies demonstrated the antidiabetic and antiobesity effects of persimmon flavonoids (Matsumoto et al., 2006; Dewanjee et al., 2009). Proanthocyanidin, a major flavonoid obtained from persimmon peel, was reported to possess antidiabetic and antiobesity properties. Administration of proanthocyanidin (from persimmon peel) to streptozotocin-induced diabetic rats reduced the elevated level of lipid peroxidation, inhibited the reactive oxygen species generation, and reduced the serum glucose, glycosylation of hemoglobin, urinary protein, glycation products, and serum urea nitrogen. Hence, this protective effect of proanthocyanidin showed its antidiabetic potentials (Lee et al., 2007). In addition, Dewanjee et al. (2009) reported that proanthocyanidins elevated the level of super oxide dismutase, glutathione, and catalase activity in the liver and kidney, and finally prevented the oxidative stress mediated diabetic complications in this severe diabetic model.

Matsumoto et al. (2006) demonstrated that persimmon significantly reduced the elevation in plasma lipids (total cholesterol, LDL cholesterol, and triglyceride) in the diet-induced obesity mouse model. Moreover, Lee at al. (2008) reported that proanthocyanidin reduced the plasma glucose, glycosylation of protein, and hyperlipidemia and ultimately reduced the hyperglycemia in male db/db mice (leptin receptor deficient). Proanthocyanidins polymers showed a strong inhibitory effect on α-amylase, while oligomers induced a stronger protective effect against α-glucosidase activity and angiotensin converting enzyme formation, suggesting that oligomers may have more potential as antidiabetic agents. Moreover, persimmon proanthocyanidin also reduced the elevated oxidative stress in db/db mice by reducing the lipid peroxidation, reactive oxygen species, protein expression of inducible nitric oxide synthase, and cyclooxygenase-2 and improved the glutathione/oxidized ratio (Lee et al., 2007). Inducible nitric oxide synthase mediate inflammation-related insulin resistance. Cyclooxygenase-2 is the enzyme involved in β-cell dysfunction. Gu et al. (2008) reported the antidiabetic effect of tannins extracted from persimmon pulp. The results demonstrated that tannins exhibited their activity by scavenging the hydroxyl radical and induced the antioxidant effect. Overall, the studies proposed that proanthocyanidin polymerization has ability to combat the obese and diabetic phenotype, and that its oligomers are the more potent and promising compounds.

Guava flavonoids

Guava is a tropical fruit and rich source of natural antioxidants like vitamin C and polyphenolic compounds (Thaipong et al., 2005; Akinmoladun et al., 2010). Numerous studies have demonstrated that the leaves and fruit of guava induced antidiabetic effects in alloxan- or streptozotocin-induced diabetic models (Gutierrez et al., 2008); Cheng et al., 2009).

Wu et al. (2009) demonstrated the antiglycation activity of guava leaves extract and its active compounds. The results revealed that guava leaves extract and its compounds inhibited the process of glycation in albumin and their potency was compared with polyphenol 60 (polyphenolic compound extracted from plants) and antiglycation agent (aminoguanidine). The results revealed that inhibitory effect of guava leaf extracts against α-dicarbonyl compounds formation were over 95% at 50 μg/mL. Guava leaf extracts also induced strong inhibition on the generation of amadori product (intermediate product in advance glycation end product formation) and advance glycation end products in albumin in the presence of glucose. The catechins and quercetin induced 80% of the antiglycated effect. Among all the phenolic compounds that were under study, quercetin showed highest activity (95%) at 100 μg/mL and no activity was shown by ferulic acid.

Cheng et al. (2009) isolated quercetin flavonoid from aqueous extract of guava leaves by column chromatography and analyzed its efficacy. The results revealed that quercetin separated from the guava leaves extract increased the glucose uptake

in rat clone 9-hepatocytes (liver cells). So quercetin contributes to mitigate hyperglycemia in diabetes as a consequence.

Shen et al. (2008) reported the antidiabetic effect of aqueous and ethanolic extracts of guava leaves in low-dose streptozotocin and nicotinamide-induced rats. The results indicated that aqueous extract increased the activities of hepatic hexokinase, phosphofructokinase, and glucose-6-phosphate dehydrogenase in diabetic rats as compared to the normal diabetic group. Furthermore, ethanolic extract only elevated the hepatic hexokinase and glucose-6-phosphate dehydrogenase activity in diabetic rats. Due to these effects of the extracts, the assimilation of glucose in glycolytic pathway and pentose monophosphate shunt was increased and resulted into depression of the blood glucose level. Huang et al. (2011) demonstrated the blood glucose lowering effect of guava in streptozotocin-induced diabetic rats. They reported that guava induced its hypoglycemic effect by protecting the viability of β-cells from lipid peroxidation and breakdown of DNA strands and ultimately improved the insulin secretion. In addition, guava also inhibited the expression of pancreatic nuclear factor-kappa B protein and improved the activities of superoxide dismutase, catalase, and glutathione peroxidase, which are involved in antioxidant activity. Begum et al. (2004) identified more than 20 compounds in guava fruit extract. In addition, studies reported the positive correlation between antihyperglycemic activity and phenolic content especially flavonoids in fruits (Ramkumar et al., 2007).

Wang et al. (2010) reported the inhibitory activity of guava leaves extract against α-amylase and α-glucosidase. Seven flavonoids (quercetin, guaijaverin, avicularin, kaempferol, hyperin, apigenin, and myricetin) were isolated from the ethanolic and butanolic extracts of guava leaves extract. The study revealed that querticin, kaempferol, and myricetin flavonoids showed highest inhibitory activity against sucrase with IC_{50} values of 3.5 mM, 5.2 mM, and 3.0 mM, against maltase with IC_{50} values of 4.8 mM, 5.6 mM, and 4.1 mM and against α-amylase with IC_{50} values of 4.8 mM, 5.3 mM, and 4.3 mM, respectively. Among these flavonoids, myricetin (1.5 mg/mL) exhibited the highest inhibition of 70% against sucrase. The results suggested that hydroxyl groups play an important role in the inhibition activity.

Papaya flavonoids

Quercetin 3-*O*-rutinoside and mangiferingallate were the major flavonoids present in papaya (Rivera-Pastrana et al., 2010; Andarwulan et al., 2012). Sellamuthu et al. (2009) also reported that papaya is a rich source of mangiferin and the galloylated forms of mangiferin and isomangiferin, xanthone glycosides. These phytochemicals were described as potent antidiabetic agents.

Sasidharan et al. (2011) demonstrated the antidiabetic effect of ethanolic extract of *Carica papaya* in streptozotocin-induced diabetic rats. Phytochemical screening revealed that this effect was probably due to the presence of certain phytochemicals, especially flavonoids. The phytochemicals-rich extract increased the regeneration of β-cells of pancreas, improved the function of liver tissue, and the recovery of cuboidal tissue of kidney. Juarez-Rojop et al. (2012) reported that aqueous extract of *C. papaya* increased the secretion of insulin by acting on β-cells. A treatment with *C. papaya* significantly reduced the serum triglycerides, cholesterol, and aminotransferases in diabetic rats. Aqueous extract improved the morphology of hepatocytes by preventing the cells disruption and inhibition of glycogen and lipid accumulation.

Miscellaneous

Eugenia jambolana (jamun) is long known for its antidiabetic activities in traditional medicines. Sharma et al. (2008) studied the effect of flavonoid rich extract of seeds of *E. jambolana* on streptozotocin-induced diabetic mice. The results demonstrated that flavonoid rich extract improved the glucose tolerance, glycogen synthesis, glucose absorption, lipid profile, and insulin release in extract-treated subject. In addition, expression and regulation of glucose-6-phosphatase and hexokinase also changed in response to the flavonoid-rich extract. This showed the hypoglycemic and hypolipidemic effect of flavonoid-rich extract of *E. jambolana*.

Rojo et al. (2012) studied the antidiabetic effect of standardized anthocyanin-rich formulation from Maqui berry (*Aristotelia chilensis*) in type 2 diabetic mice model. They also demonstrated the antidiabetic effect of delphinidin 3-sambubioside-5-glucoside (obtained from Maqui berry). Oral administration of anthocyanin-rich formulation decreased the fasting blood glucose levels and glucose tolerance in hyperglycemic obese mice (fed with high fat diet). In addition, ANC decreased the glucose production by reducing the expression of glucose-6-phosphatase. The oral administration of delphinidin 3-sambubioside-5-glucoside in combination with ANC reduced the fasting blood glucose level, increased the glucose absorption in L6 myotubes, and lessened the glucose production in H4IIE rat liver.

Punica granatum is a traditional hypoglycemic plant, commonly known as pomegranate (Vidal et al., 2003). The connection between pomegranate and its diabetic effects are well discussed by Katz et al. (2007). They revealed that pomegranate extracts and their active components possessed strong antidiabetic properties. Therapeutic (Jurenka, 2008) and cardioprotective effects (Basu and Penugonda, 2009) of pomegranate and its juice were also reported. Furthermore, Koren-Gluzer et al. (2011) reported that pomegranate juice, in combination with 50 μmol/L punicalagin, amplified the insulin production from a β-tumor cell line. This property is similar to the activity of the paraoxonase 1 enzyme. Moreover, administration of pomegranate fruit extract with ellagic acid (50–10 μg/mL) has significantly decreased the production and intracellular levels of resistin in differentiated murine 3T3-L1 adipocytes by encouraging its degradation at the protein level (Makino-Wakagi et al., 2012).

Conclusion

Research on diabetes and its management has been of continued interest among the scientists from last many decades. From public health perspective, diabetes is still a challenge and associated with reduced life expectancy due to obscurity of its cure despite of intervening research within the last two centuries. Management of diabetes through diet is a potential area of

research. Compelling evidence from epidemiological studies and in vitro and in vivo trials has converged that several fruits possessed antidiabetic effects due to the presence of certain bioactive components like flavonoids. It is encouraging that some of the flavonoids are comparable in function to the clinically used antidiabetic drugs. Investigation to better understand biochemical nature of antidiabetic effects of flavonoids may lead to the discovery of novel natural source for the management of diabetes with minimal side effects. Further studies are needed to understand the structure–activity relationships of flavonoids to find whether and how flavonoid molecules interact with the cellular components.

Advances in isolation, purification, and characterization of bioactive compounds from fruits should be employed and flavonoids should be isolated from fruits and tested for their dose-dependent efficacy studies in animal and human models to develop a natural and sustainable approach to mange diabetes mellitus.

Coherent series of experiments are needed to formulate dietary guidelines that can be really helpful for people with diabetes to manage this devastating disease. Disparities among the different organizational groups should be addressed on the basis of evidence-based dietary recommendations to present holistic and simplified picture to diabetic patients.

Declaration of interest

The authors have no relevant interests to declare.

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