Send Orders for Reprints to reprints@benthamscience.ae

Current Pharmaceutical Design, **2016,** *22,* **549-565**

Polyphenols: Potential Future Arsenals in the Treatment of Diabetes

Md. Solayman[#1], Yousuf Ali[#1], Fahmida Alam[2], Md. Asiful Islam[2], Nadia Alam[2], Md. Ibrahim Khalil[1,2] and Siew Hua Gan[2*]

[1]*Laboratory of Preventive and Integrative Bio-medicine, Department of Biochemistry and Molecular Biology, Jahangirnagar University, Savar, Dhaka 1342, Bangladesh;* [2]*Human Genome Centre, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia*

Md. Solayman

Abstract: Diabetes mellitus (DM) is one of the most common endocrine metabolic disorders. In addition to exercise and diet, oral anti-diabetic drugs have been used as a part of the management strategy worldwide. Unfortunately, none of the conventional anti-diabetic drugs are without side effects, and these drugs pose an economic burden. Therefore, the investigation of novel anti-diabetic regimens is a major challenge for researchers, in which nature has been the primary resource for the discovery of potential therapeutics. Many plants have been shown to act as anti-diabetic agents, in which the main active constituents are believed to be polyphenols. Natural products containing high polyphenol levels can control carbohydrate metabolism by various mechanisms, such as protecting and restoring beta-cell integrity, enhancing insulin releasing activity, and increasing cellular glucose uptake. Blackberries, red grapes, apricots, eggplant and popular drinks such as coffee, cocoa and green tea are all rich in polyphenols, which may dampen insulin resistance and be natural alternatives in the treatment of diabetes. Therefore, the aim of this review is to report on the available anti-diabetic polyphenols (medicinal plants, fruits and vegetables), their mechanisms in the various pathways of DM and their correlations with DM. Additionally, this review emphasizes the types of polyphenols that could be potential future resources in the treatment of DM via either novel regimens or as supplementary agents.

Keywords: Diabetes mellitus, polyphenols, insulin resistance, glucose transport, gluconeogenesis.

INTRODUCTION

Diabetes mellitus (DM) is one of the most common systemic metabolic disorders and is characterized by a high blood glucose level (hyperglycemia). It is associated with impairment in insulin secretion and/or insulin activity in target cells. Additional abnormalities in intermediary metabolism of carbohydrates, lipids and proteins are also commonly seen [1]. DM is the world's leading endocrine disease with an estimated 382 million people worldwide with diabetes in 2013, and this number is expected to reach as high as 592 million by the year 2035 [2]. Most diabetic patients live in low and middle income countries, and increased incidence is expected among those with poor income around the world especially in the next 22 years [2].

Both types [type 1 DM (T1DM) and type 2 DM] can cause serious health complications, including ketoacidosis, heart disease, kidney failure, blurred vision, itchiness, peripheral neuropathy, fatigue and even coma [3]. Usually, patients are diagnosed with diabetes when clinical signs such as excessive thirst, urination and hunger are detected [4].

Conventionally, DM is classified based on whether the patient is insulin dependent or independent [5]. Recently, some studies have classified DM and their etiopathogenetic mechanisms as (i) type 1A (auto-immune mediated), (ii) type 1B (idiopathic or non-auto-immune mediated), (iii) type 2 (insulin resistance), (iv) gestational (identified for the first time in pregnancy but generally characterized by insulin resistance) and (v) other specific etiologies (secondary to other diseases and recognized gene mutations) [6, 7]. Although the direct symptoms of T2DM may be insignificant and cause negligible interruption to activities of daily living, the complications that lead to impairment of vital organs may cause substantial morbidity and mortality. Hence, the treatment of this universal threat is approached first with appropriate diet and exercise in addition to insulin treatment and oral hypoglycemic drugs (i.e., thiazolidines, biguanides, meglitinide analogs, sulfonylureas, D-phenylalanine and α-glucosidase inhibitors) [8].

Generally medications are needed for the patients who fail in preliminary therapy. Generally medications are needed for patients who fail the preliminary therapy.

However, no oral medication can be deemed the ideal treatment due to their side effect profiles, high costs and, sometimes, attenuation in response after prolonged use [9, 10]. For example, the highly utilised anti-diabetic drug metformin causes lactic acidosis, and general sickness with the use of alcohol while sulphonylurea generally causes hypoglycemia, skin rash or itching [11]. In addition, alpha-glucosidase inhibitors can lead to bloating and diarrhea [12] while meglitinides contribute to weight gain as well as hypoglycemia [13] whereas thiazolidinediones have direct effect on weight gain and risk of liver diseases [14].

To overcome these challenges associated with existing synthetic oral hypoglycemic agents, a search for novel targets or newer drugs is needed. Therefore, based on their traditional use, several phytoconstituents and phyto-products have become potential alternative sources for developing new antioxidant and anti-diabetic agents. It has been reported that there are approximately 200 pure compounds, including various types of polyphenols, isolated from plant sources with blood glucose lowering activity, fewer side effects and low costs [15].

Polyphenols are secondary metabolites that are generally involved in the defense against ultraviolet radiation or infection by pathogens [16]. From the beginning of the 21th century, epidemiological studies and associated meta-analyses strongly suggested that long-term consumption of diets rich in plant polyphenols offered some resistance against the development of diabetes, cancers, osteoporosis, cardiovascular diseases and neurodegenerative diseases [17, 18]. The mechanisms of polyphenol and phenolic compounds in controlling blood glucose in diabetic patients include inhibition of glucose absorption, protection of pancreatic β-cell damage, im-

*Address correspondence to this author at the Human Genome Centre, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia; E-mail: shgan@usm.my

[#]Md. Solayman and Yousuf Ali contributed equally to this work.

1873-4286/16 $58.00+.00

provement of insulin release and sensitivity, diminution of inflammation, modulation of the carbohydrate metabolism pathway and regulation of insulin dependent and independent signaling pathways [15, 19, 20]. As a result, these polyphenolic compounds have gained scientific interest to more precisely and accurately investigate the mechanisms of their anti-diabetic effects. Therefore, the aim of this review is to accumulate all the available data on polyphenols as potential anti-diabetic agents from medicinal plants, fruits and vegetables with their respective mechanisms. These compounds may be a potential future resource in discovering novel regimens and/or developing existing synthetic anti-diabetic drugs with fewer or no side effects.

PATHOGENESIS OF DIABETES

Genetically susceptible individuals are the target of T1DM, and it is assumed to be triggered by viruses and one or more environmental agents. The genetic markers, immune markers and metabolic markers of T1DM individuals are detectable after birth, after the initiation of the autoimmune process and after the destruction of enough β-cells to be detected by sensitive tests [21]. Unfortunately, autoimmune destruction is rarely prevented by immunosuppressive drugs due to side effects. A meta-analysis of genome-wide association studies confirmed the association of genetic polymorphisms with the risk of T1DM [22-24]. T2DM is considered to be a more predominant form of diabetes. Recently, it has become well-known that the functional pancreatic β-cell mass decreases over time if glucolipotoxicity is left untreated, which further continues the progression of T2DM [25]. Despite insulin resistance and impaired insulin secretion, the following metabolic defects are crucial to the development of T2DM: (1) increased glucagon secretion and reduced incretin response; (2) expansion of subcutaneous adipose tissue, (3) hypoadiponectinemia; (4) inflammation of adipose tissue and (5) increased endogenous glucose production [26, 27]. Although the main metabolic defects of T2DM are present to some extent in most patients, this disorder is extremely diverse. Overeating, obesity, stress, smoking, high blood pressure, alcohol intake, increase in cortisol, abnormality in sex hormone secretion, physical inactivity, genetic factors, gestational diabetes, intrauterine growth restriction, aging, lifestyle changes and gut microbiota are considered responsible for the onset of the disease. Insulin resistance, which is largely caused by obesity and physical inactivity, both precedes and predicts T2DM, whereas impaired insulin action, at least in part, is genetically determined. Various susceptibility genes associated with T2DM have been identified that interact with environmental factors during gestation, early childhood and later in life [28-30].

POLYPHENOLS

Polyphenols, which are secondary metabolites of plants, are responsible mainly for the flavor and color of fruits and other plant products. They are present in fresh fruits and vegetables and found in various natural beverages such as red wines, teas and cocoa. Structurally, they are mainly divided into two types - flavonoids and non-flavonoids. Flavonoids are sub-divided into six classes: (i) flavonols (i.e., quercetin, myricetin and rutin), (ii) flavones (i.e., chrysin), (iii) isoflavones (i.e., genistein), (iv) flavanones (i.e., naringenin), (v) anthocyanidins (i.e., malvidin) and (vi) flavanols [i.e., catechin, epicatechin (EC) and epigallocatechin gallate (EGCG)]. The major non-flavonoids are phenolic acids, which are subdivided into derivatives of benzoic acid (gallic and protocatechuic acids) and derivatives of cinnamic acid (coumaric, caffeic and ferulic acids). Other non-flavonoids include stilbenes (*cis* and *trans* resveratrol), lignans (secoisolariciresinol) and tannins (i.e., ellagitannin) [31, 32].

Edible natural products (i.e., fruits, vegetables and medicinal plants) have long been considered a source of natural polyphenols. Dietary polyphenols were found to exert various biological protective activities against human diseases including Alzheimer's disease [33-36], various cancers [37-46], thalassemia [47-49], gastrointestinal diseases [50-53], cardiovascular diseases [54-57], infectious diseases [31, 58-60] and diabetes [61-66]. Due to its diverse biological activities, polyphenols are therefore believed to be a potential future resource in the development of therapeutic substances [65, 66]. Here, we discuss and highlight the most potential natural polyphenols that exert their effects in various pathogenic pathways of diabetes (Fig. **1**); they can be expected to be an emerging source of anti-diabetic drug discovery and development.

Inhibition of α-Amylase and α-Glucosidase

α-amylase is a digestive enzyme found in saliva and pancreatic juice and is primarily responsible for the hydrolysis of the α-bonds of large α-linked polysaccharides (starch, glycogen and other glucose polymers), yielding glucose and maltose [67, 68]. α-glucosidase is a brush border enzyme located in the small intestine that acts on 1, 4-α bonds and breaks down starch and disaccharides to monosaccharides [69]. Usually, the products of these enzymes are absorbed by specific transporters in the small intestine [70].

In diabetic patients, the inhibition of carbohydrate catalytic digestive enzymes is considered an effective therapeutic tool that can significantly reduce postprandial blood glucose levels [71]. In addition to the use of currently available anti-diabetic drugs, many polyphenols containing medicinal herbs and plants have been recommended in the treatment of diabetes and can decrease particular adverse effects of conventional regimens (i.e., hypoglycemia at higher doses, hepatic problems, lactic acidosis and diarrhea).

McDougall and Stewart (2005) [72] reviewed the effects of polyphenols from berries on these digestive enzymes. They showed that anthocyanins and ellagitannins have the ability to inhibit α-glucosidase and α-amylase, respectively, which helps to reduce blood glucose levels after starch-rich meals (Fig. **1**). An *in vitro* study showed that molecules with the ability to form quinones or lactones or substances with a 4-oxo-pyrane structure induce an inhibiting effect on α-amylase activity [73]. Herbs containing rosmarinic acid as a main phenolic component have inhibitory effects on pancreatic amylase activity, and they have been used in traditional medicine for a long time to treat DM [74]. Quercetin, a flavonoid, inhibits intestinal α-glucosidase and reduces maltose-induced postprandial hyperglycemia in type 2 diabetes [75]. Another flavonoid, luteolin, which is more precisely known as citrus bioflavonoid, is reported to inhibit α-glucosidase and α-amylase, suggesting that it can suppress postprandial hyperglycemia in patients with non-insulin-dependent DM [76]. *Neriumindicum* extract contains the polyphenol compounds quercetin and catechins, which inhibit α-glucosidase and suppress the postprandial rise of blood glucose [77]. Various polyphenolic components of soft fruits such as *Fragariaananassa, Rubusidaeus, Ribesnigrum,* and *Brassica oleracea* inhibit both α-amylase and α-glucosidase enzymes [78]. Mai *et al*. (2007) found positive correlations between the inhibitory effects of α-glucosidase and polyphenol contents of select Vietnamese edible plants [79].

Inhibition of Sodium-Dependent Glucose Transporters

Glucose transporters (GLUT) comprise a large group of membrane proteins that assist the intra-transportation of glucose through the plasma membranes of cells. Each GLUT isoform plays a precise role in glucose metabolism determined by its pattern of tissue expression, substrate specificity, transport kinetics and regulated expression in various physiological conditions [80]. Two classes of glucose carriers have been defined in mammalian cells: sodium dependent glucose transporters (SGLTs) and the facilitative GLUTs [81, 82]. SGLT1, SGLT2 and SGLT3 are major members of the SGLT family and are expressed in the intestine, trachea, kidney, heart, brain, testis, liver, thyroid, muscle and prostate [83]. They actively transport glucose from the lumen of the intestine or from

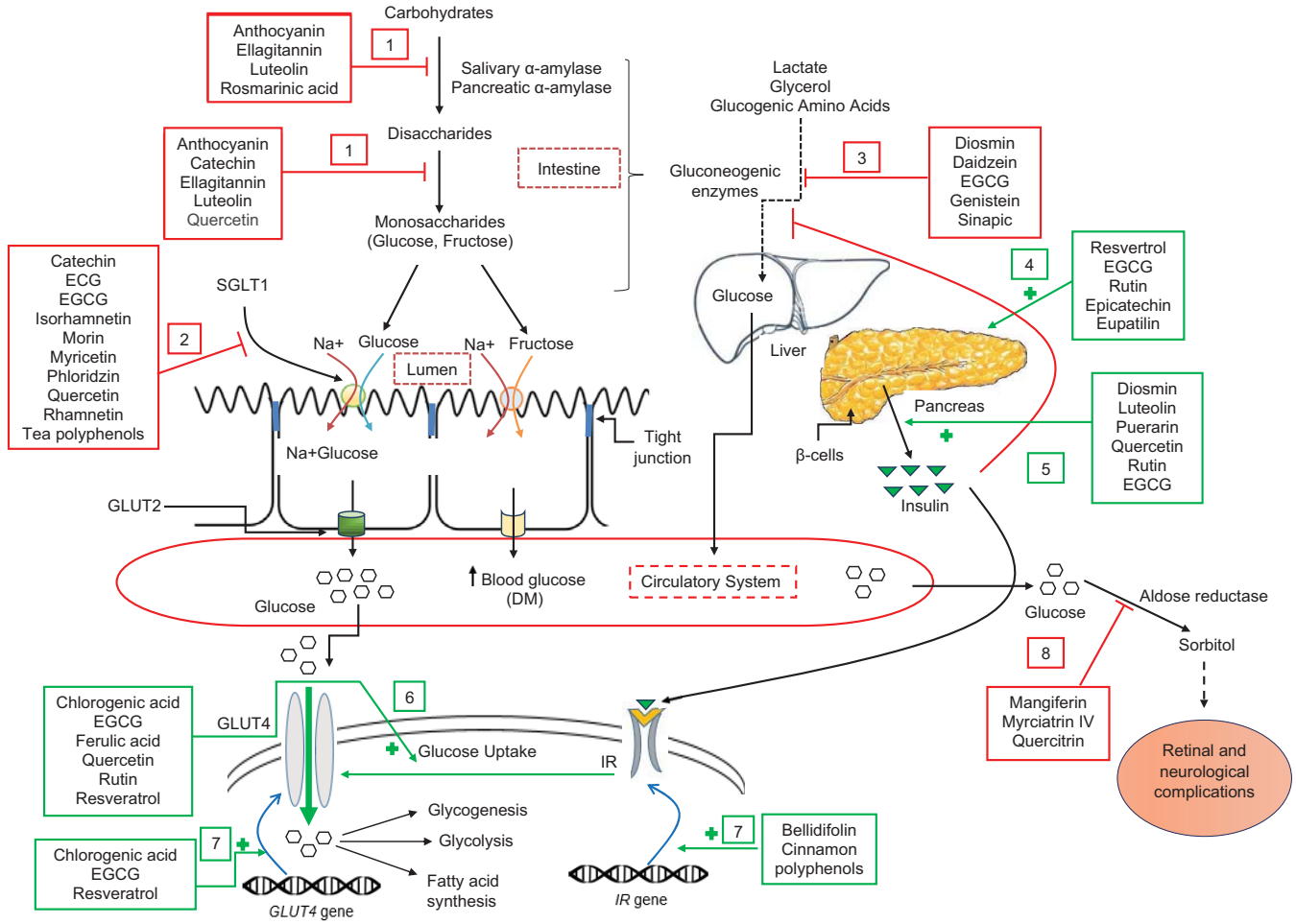

Fig. (1). Possible anti-diabetic treatment strategies with polyphenols. (1) Inhibition of alpha-amylase and alpha-glucosidase by anthocyanine, ellagitannin, luteolin, rosmarinic acid, and quercetin; (2) Inhibition of SGLT1 by catechin, ECG, EGCG, isorhamnetin, morin, myricetin, phloridzin, quercetin, rhamnetin and tea polyphenols; (3) Inhibition of gluconeogenic enzymes by diosmin, daidzein, EGCG, and sinapic; (4) Protection of β-cells by resveratrol, EGCG, rutin, epicatechin, and eupatilin; (5) Increase of insulin secretion by diosmin, luteolin, puerarin, quercetin, EGCG, and rutin; (6) Enhancement of glucose uptake through GLUT4 by chlorogenic acid, EGCG, ferulic acid, quercetin, rutin, and resveratrol; (7) Increase of GLUT4 and IR expression by chlorogenic acid, EGCG, resveratrol and bellidifolin, and cinnamon polyphenols; (8) Blockage of aldose reductase enzyme activity by mangiferin, myrciatrin IV and quercitrin.

the other extra cellular spaces against its concentration gradient by coupling glucose uptake with that of sodium (Na^+), which is being transported down its concentration gradient. The Na^+ gradient is conserved by the active transport of Na^+ across the basolateral (antiluminal) surface of the brush border cells by membrane-bound Na^+-K^+ ATPase [83, 84]. As these transporters play major roles in the regulation of plasma glucose levels, they can be targeted in the treatment of patients with DM.

Many studies of the treatment of diabetic patients have shown inhibition of these GLUTs by plant polyphenols (Fig. **1**). For instance, by using rabbit intestinal brush-border membrane vesicles and by an electrophysiological method, Kobayashi *et al*. (2000) [85] showed that tea polyphenols reduce the blood glucose level by inhibiting intestinal glucose transporters (SGLT1). Welsch *et al*. (1989) [86] have reported that catechin, a major tea polyphenol derivative, has the ability to inhibit SGLT1. This inhibitory activity is most pronounced in polyphenols because of galloyl residues such as epicatechin gallate (ECG) and EGCG [85].

Another polyphenol, quercetin, is also reported to provoke an anti-diabetic effect by inhibiting glucose uptake at the level of the GLUTs [87]. To evaluate the effect of quercetin on Caco-2E intestinal cells, the study by Kwon *et al*. (2007) [88] reported that transportation of fructose and glucose by GLUT2 is strongly inhibited by quercetin. Phloridzin, a phytochemical that belongs to a class of polyphenols found in the bark of pear (*Pyrus communis*), apple, cherry and other fruit trees (*Rosaceae*), has been reported to block intestinal SGLT1 [89]. Phloridzin also helps to excrete glucose into the urine by reducing the SGLT-mediated reabsorption of glucose in renal epithelial cells and to lower the blood glucose level in diabetic animal models [90]. Strobel *et al*. (2005) [91] showed that the flavonoids catechin-gallate, quercetin and myricetin inhibit the uptake of methylglucose (a substrate that enters the cells through the facilitative hexose transporter GLUT4) in insulin-stimulated rat adipocytes. Another important facilitative glucose transporter (GLUT1) is inhibited by genistein, quercetin, myricetin, morin, rhamnetin and isorhamnetin via a direct interaction with this membrane protein [92, 93].

Generally, insulin motivates glucose transport in adipocytes through a mechanism involving the translocation of GLUT4, in which tyrosine phosphorylation plays a crucial role in the signal-transduction cascade [94]. However, genistein, quercetin, apigenin and kaempferol have been described as tyrosine kinase inhibitors in the concentration range of 0.7-100.0μg/ml [95]. Through these mechanisms, the above polyphenols directly or indirectly inhibit various glucose transporters and ultimately suppress the elevation of plasma glucose.

Inhibition of Gluconeogenic Enzymes

Gluconeogenic enzymes such as glucose-6-phosphatase (G6Pase) and fructose-1, 6-bisphosphatase (F1, 6-BPase), are involved in gluconeogenesis, an anabolic pathway in which glucose is synthesized from smaller and simpler non-carbohydrate carbon substrates (i.e., pyruvate, lactate or glycerol) [96]. The gluconeogenesis pathway is a potential therapeutic target in type 2 diabetes, in which glucose formation can be inhibited and glucose uptake can be stimulated by cells [97].

Polyphenols from various medicinal plants and herbs play vital roles in inhibiting several enzymes involved in glucose formation and exhibit potential anti-hyperglycemic effects (Fig. **1**). A study showed that the administration of diosmin (flavone) for 45 days significantly lowered plasma glucose by increasing the activities of hepatic glycolytic enzymes and decreasing gluconeogenic enzymes (i.e., G6Pase and F1, 6-BPase) in streptozotocin-nicotinamide treated rats with anti-hyperglycemic properties [98]. Sinapic acid, a member of the phenylpropanoid family, possesses potential hyperglycemic effects through an increase in insulin production associated with a subsequent increase in the activity of hexokinase and a decrease in the activity of G6Pase and F1, 6-BPase [99]. Ong *et al*. [100] described that polyphenol-rich *Vernonia amygdalina* has antidiabetic effects by suppressing an integral hepatic gluconeogenic enzyme G6Pase (40% inhibition) in streptozotocin-induced diabetic rats. Tea catechins (i.e., epigallocatechin or EGC) and their effects on liver glucose metabolism have also been effectively studied in animal and cell culture models that showed decreased blood glucose levels and concomitant decreases in the effects of DM. For instance, EGCG decreased glucose production by inhibiting the expression of gluconeogenic enzymes [i.e., phosphoenol pyruvate carboxykinase (PEPCK) and G6Pase] [101, 102].

Similar to green tea, soy and soy isoflavones, genistein and daidzein supplementation (0.2 g/kg) have also been found to decrease blood glucose levels and reduce liver TG concentrations in a db/db mice model [103] and in non-obese diabetic mice [104]. Both studies were found to reduce G6Pase and PEPCK liver activities and increase glucokinase activities, suggesting that genistein and daidzein suppress liver glucose output. Studies have also shown that feeding a polyphenol rich fraction of *Emblica officinalis* Gaertn or *Phyllanthus emblica* Linn (colloquially known as Indian gooseberry or amla) (84 days) to alloxan-induced type I diabetic rats was effective in reducing the activity of G6Pase and glucokinase and increasing the levels of glycogen in the liver and skeletal muscles [105]. Many extracts of plants and vegetables also inhibit gluconeogenic enzymes and exhibit hypoglycemic effects; however, their mechanisms of action have not yet been revealed.

Enhancement of Pancreatic β-cell Protection

β-cells are unique cells in the pancreas. They are located in the islets of Langerhans. The main function of a β-cell is to produce, store and release the hormone insulin, which is responsible for controlling blood glucose levels [106]. During digestion, blood glucose starts to rise. At that time, β-cells of the pancreas control the rise of blood glucose by secreting stored insulin and simultaneously producing more. Glucose is transported into β-cells through facilitated diffusion of GLUT2. Intracellular glucose is converted to glucose-6-phosphate by glucokinase. Then, it is metabolized to ATP by phosphorylation, leading to the increase in the ATP/ADP ratio in the cells, causing inactivation of ATP-sensitive potassium channels on the cell membrane. As a result, cell membranes become depolarized. The voltage-gated calcium channels are opened. Calcium ions (Ca^{2+}) then enter into the cell. Increased Ca^{2+} concentration causes the release of insulin by exocytosis from existing storage granules [107-109].

DM occurs when β-cells of the pancreas are unable to meet insulin demands in the body due to the failure or destruction of the β-cell mass or increased insulin needs due to insulin resistance or growth that are higher than the insulin producing capacity [110]. There are many reasons for the failure or destruction of the β-cells, including hyperglycemia, glucotoxicity, lipotoxicity, autoimmunity or inflammation, adipokines, islet amyloid, incretins and insulin resistance [106]. Researchers have confirmed that dietary polyphenols play an important role in preventing DM by protecting β-cells in islets (Fig. **1**). Resveratrol and curcumin polyphenols are found in fruits (Table **1**) and turmeric. In DM, they increase pancreatic β-cell function under both low and high blood glucose concentrations. Administration of either resveratrol or curcumin can lead to an increase in insulin secretion in mouse β-Min6 cells, as well as human islets. They enhanced intracellular levels of cAMPβ-Min6, which is an important secondary messenger in the insulin secretion pathway. They also restore pancreatic β-cell function by inhibiting phosphodiesterase activity in pancreatic β-cells [111].

EGCG and rutin are able to remove glucotoxicity in rat insulin that is secreted from pancreatic β-cells (RIN m5F) [112]. When insulin secretion is suppressed by glucotoxicity in diabetic rats, both EGCG and rutin promote insulin secretion under high blood glucose concentrations. (−) Epicatechin regenerates functional β-cells in the islets of the pancreas in alloxan-induced diabetic rats [113]. Quercetin, a flavonoid antioxidant, prevents and protects β-cell damage in rat pancreas [114]. The eupatilina type of flavonoids isolated from *Artemisia princeps* Pampanini enhances hepatic glucose metabolism and pancreatic β-cell function in T2DM mice by maintaining β-cell integrity. Additionally, eupatilin supplementation for 6 weeks significantly decreased fasting blood glucose concentrations, hemoglobin A1c, plasma glucagon levels, hepatic G-6-ptase and phosphoenolpyruvate carboxykinase activities and increased glucokinase activity in the liver, hepatic glycogen content, and plasma insulin and adiponectin levels [115].

Enhancing Insulin Secretion and Activity

Insulin is a peptide hormone that is produced by the β-cells in the pancreas. It regulates the metabolism of carbohydrates and fats by promoting the absorption of glucose from the blood to skeletal muscles, fat tissues, as well as inhibiting hepatic glucose production [116]. In normal physiological energy metabolism and functions, a sufficient amount of insulin secretion and its proper actions are essential. If there are any disturbances in carbohydrate, fat and protein metabolism associated with absolute or relative deficiency in insulin secretion or action, DM arises as a consequence. However, polyphenols, the most abundant antioxidants in the diet and widespread constituents of fruits, vegetables, cereals, dry legumes, chocolate and beverages (i.e., tea, coffee or wine), display particular anti-diabetic properties by increasing insulin secretion and action (Fig. **1**) [117].

Quercetin, a widely distributed flavonoid in nature, protects pancreatic β-cells against oxidative damage and conserves their integrity, which leads to insulin secretion [114]. Youl *et al*. (2010) [118] reported that quercetin is a potent flavonoid that can elevate insulin secretion in insulin secreting cell lines (INS-1) induced by glucose and Glibenclamide by ERK1/2 mediated pathway. Another study found that quercetin from sea buckthorn berries stimulates glucose metabolism by enhancing hepatic glucokinase activity and increases insulin release from β-cells by rising intra cytosolic calcium concentration [119]. Puerarin, an isoflavone extracted from the Chinese herb radix of *Pueraria lobata,* had protected against hydrogen peroxide (H_2O_2) induced rat pancreatic islet damage. It also inhibited H_2O_2 induced free radical production and increased catalase and superoxide dismutase (SOD) activities in the isolated pancreatic islets, which caused optimum secretion [120].

Rutin is a citrus flavonoid glycoside that is abundantly found in onions, apples, tea and red wine. It has shown the ability to scavenge free radicals and inhibit lipid peroxidation. Additionally, it has proved to prevent streptozotocin-induced oxidative stress and protects pancreatic β-cells, resulting in the augmentation of insulin

Table 1. Major anti-diabetic polyphenols in edible fruits and vegetables.

Polyphenols	Sources (Name)		Origins	References
	Scientific name	English name		
Fruits				
Anthocyanin	*Vacciniummyrtillus* L.	Bilberry	Lithuania	[185-191]
	Chrysophyllumcainito	Star apple	USA	
	Ficuscarica L.	Fig	Israel	
	Prunuscerasus	Sour cherry	Hungary	
	Reynosiajamaicensis	Blackberry	Jamaica	
	Rubusrosifolius	Red raspberry	Jamaica	
	Rubusracemosus	Black raspberry	Jamaica	
	Kadsuracoccinea	Black tiger	China	
	Prunusarmeniaca L.	Apricot	France	
Ellagitannin	*Punicagranatum* L.	Pomegranate	Brazil	[192-195]
	Rubusrosifolius	Raspberry	Italy	
	Rubusfruticosus	Blackberry	Italy	
	Dovyalishebecarpa	Gooseberry	Brazil	
	Fragariaananassa	Strawberry	Finland	
	Hippophaerhamnoides	Sea buckthorn berry	Finland	
Luteolin	*Actinidiadeliciosa*	Kiwi	Hungary	[196-198]
	Psidiumguajava	Guava	China	
	Oleaeuropaea L.	Olive	Turkey	
Rosmarinic acids	*Citrus paradise*	Grapefruit	Hungary Greece	[199]
	Citrussinensis	Orange	Spain	
	Citrus limon	Lemon		
Catechin	*Ribesuva-crispa* L.	Gooseberry	Netherlands	[200-202]
	Vitisvinifera L.	Black grape	Netherlands	
	Prunusarmeniaca L.	Apricot	Netherlands	
	Prunuspersica	Peach	Netherlands	
	Prunusdomestica	Plum	Bulgaria	
	Prunusavium	Sweet Cherry	Bulgaria	
	Vitisvinifera	White Grape	Bulgeria	
	Diospyros kaki	Persimmon	Japan	
Quercetin	*Prunusarmeniaca* L.	Apricot	Pakistan	[203-205]
	Maluspumila	Apple	Pakistan	
	Morus alba	Mulberry	Pakistan	
	Sorbusaucuparia	Rowan	Poland	
	Amelanchieralnifolia	Saskatoon berry	Canada	
Resveratrol	*Vitisrotundifolia*	Muscadine grapes	Georgia	[206-209]
	Fragariaananassa	Strawberry	USA	
	Vacciniummyrtillus	Bilberry	Estonia	
	Vacciniumvitis-idaea	Cowberry	Estonia	
	Citrus paradise	Grapefruit	Canada	

(Table 1) Contd….

Polyphenols	Sources (Name)		Origins	References
	Scientific name	English name		
Rutin	*Prunusavium*	Sweet Cherry	Bulgaria	[210, 211]
	Aronias sp.	Aronia	Bulgaria	
	Maluspumila	Apple	Poland	
Diosmin	*Citrus limon*	Lemon	Spain	[212, 213]
	citrus aurantifolia	Lime	Japan	
Myricetin	*Maluspumila*	Apple	Pakistan	[203, 206]
	Fragariaananassa	Strawberry	Pakistan	
	Prunusdomestica	Plum	Pakistan	
	Prunusarmeniaca L.	Apricot	Pakistan	
	Vitisrotundifolia	Muscadine grapes	Georgia	
Vegetables				
Anthocyanin	*Ipomoea batatas cv. Ayamurasaki*	Sweet potato	Japan	[214-218]
	Phaseolus vulgaris	French bean	India, USA	
	Lactuca sativa L.	Lettuce	Spain	
	Solanummelongena	Eggplant	USA	
	Raphanussativus	Red radish	USA	
	Brassica oleracea var. capitata f. rubra	Red cabbage	USA	
	Allium cepa	Red onion	Canada	
	Asparagus officinalis var. violetto	Purple asparagus	Canada	
	Solanumtuberosum	Red potato	Canada	
	Brassica oleracea var. botrytis	Purple cauliflower	Canada	
Quercetin	*Allium cepa*	Onion	India, Japan, Pakistan	[203, 218-224]
	Moringaoleifera	Indigenous vegetable	India	
	Phaseolus vulgaris	French bean	India	
	Pisumsativum	Peas	Pakistan	
	Solanumlycopersicum	Tomato	India, Turkey	
	Anethumgraveolens	Dill	Hungary	
	Brassica napobrassica	Swedish Turnip	Hungary	
	Armoracia rusticana	Horse radish	Hungary	
	Brassica oleracea var. italica	Broccoli	Hungary	
Myricetin	*Pisumsativum*	Peas	Pakistan	[203, 222-224]
	Daucuscarota	Carrot	Pakistan	
	Brassica oleracea	Cauliflower	Pakistan	
	Spinaciaoleracea	Spinach	Pakistan	
	Brassica rapa	Turnip	Pakistan	
	Solanumlycopersicum	Tomato	India, Turkey	
	Allium cepa	Onion	India	
	Anethumgraveolens	Dill	Hungary	
	Apiumgraveolens var. dulce	Celery	Hungary	
	Brassica napobrassica	Swedish Turnip	Hungary	

(Table 1) Contd….

Polyphenols	Sources (Name)		Origins	References
	Scientific name	English name		
Kaempferol	*Pisumsativum*	Peas	Pakistan	[203, 223]
	Brassica oleracea	Cabbage	Pakistan	
	Brassica oleracea	Cauliflower	Pakistan	
	Spinaciaoleracea	Spinach	Pakistan	
	Brassica rapa	Turnip	Pakistan	
	Solanumlycopersicum	Tomato	Turkey	
	Brassica napobrassica	Swedish Turnip	Hungary	
	Armoracia rusticana	Horse radish	Hungary	
	Brassica oleracea var. italica	Broccoli	Hungary	
Rutin	*Allium cepa*	Onion	Switzerland	[210, 225, 226]
	Capsicum frutescens	Red pepper	Bulgaria	
	Asparagus officinalis	Asparagus	USA	
Caffeic acid	*Lactuca sativa* L.	Lettuce	Spain	[215, 227-231]
	Brassica oleracea var. botrytis	Cauliflower	China	
	Solanummelongena	Eggplant	Poland	
	Lycopersumesculentum	Tomato	Spain	
	Cichoriumintybus	Chicory	Italy	
	Daucuscarota	Carrot	UK	
	Solanumtuberosum	Potato	Germany	
Luteolin	*Brassica oleracea var. gongylodes*	Kohlrabi	Hungary	[224, 232]
	Brassica oleracea var. capitata	White cabbage	Hungary	
	Spinaciaoleracea	Spinach	Hungary	
	Cucurbita maxima	Pumpkin	Hungary	
	Brassica oleracea	Broccoli	Malaysia	
	Capsicum annuum	Green chilli	Malaysia	
	Phaseolus vulgaris	French bean	Malaysia	
Catechins	*Solanum tuberosum*	Potato	Turkey	[233]
	Allium cepa	Onion	Turkey	
	Allium fustilosum	Spring onion	Turkey	
	Raphanussativus	Red radish	Turkey	
	Brassica oleracea	Red cabbage	Turkey	

secretion and reduction of blood glucose levels [121]. Srinivasan *et al*. (2012) [122] stated that diosmin (a flavonoid), which can be isolated from various plant sources and citrus fruits, lowers plasma glucose, and increases plasma insulin levels in diabetic rats by ameliorating streptozotocin- and nicotinamide-induced oxidative stress.

Another flavonoid, luteolin, which is widely distributed in various plants, such as *Thymus vulgaris*, *Chamomilla recutita*, *Cynara scolymus*, *Limonium sinuatum*, and *Reseda luteola L.*, also showed anti-diabetic properties by increasing blood insulin levels [123]. Zarzuelo *et al*. (1996) [124] studied the hypoglycemic effect of luteolin, and they observed a significant decrease in glycemia levels (> 50%), a 2.5-fold increase in blood insulin levels and elevated pancreatic insulin and DNA content. Recently, luteolin was found to influence insulin action and production of adipokines/cytokines in adipocytes by activating the peroxisome proliferator-activated receptor gamma (PPARγ) pathway, suggesting its role in preventing insulin resistance and T2DM [125]. PPARγ is one of the main regulatory proteins which is the target for the treatment of T2DM as it improves the sensitivity of insulin receptors (IRs). In addition, capsaicin and curcumin have some effects on PPARγ with anti-diabetic activities [126]. Another study has demonstrated that gallic acid, a naturally abundant plant phenol from *Punica granatum* flower extract is responsible for activation of PPARγ thus exerting its anti-diabetic actions [127]. A clinical study revealed that EGCG from *Camellia sinensis* (green tea) protects pancreatic β-cells from free-radical damage and increases insulin secretion [128]. According to the study by Lee *et al*. [129], polyphenols from *Fagopyrum tataricum* (buckwheat) improved glycemia by inducing β-cell regeneration and increasing insulin secretion in diabetic rats compared with controls.

Enhancement of Glucose Uptake

Enhancing peripheral glucose uptake in both insulin-sensitive and non-insulin-sensitive tissues is a major therapeutic approach to treat diabetes. The uptake of peripheral glucose is mediated by GLUT4, which can be found in insulin-responsive tissues, skeletal muscle, adipose tissues and the heart [130].

A study confirmed that the EGCG polyphenol isolated from *Camellia sinensis* (green tea) enhances glucose uptake in muscle [128]. Rutin and quercetin polyphenols isolated from *Fagopyrum tataricum* (buckwheat) enhance glucose uptake in insulin-resistant cells [129]. Chlorogenic acid, a polyphenol of *Coffea arabica* (coffee), increases the uptake of glucose by peripheral tissues (Fig. **1**) [131]. Two plant phenolic compounds, namely chlorogenic and ferulic acids, stimulated glucose uptake with a comparable performance to those of metformin and thiazolodinedione, which are common oral hypoglycemic drugs [132]. Resveratrol increased glucose uptake in C2C12 skeletal muscle cells by activating the AMP-activated protein kinase pathway. If insulin is present, resveratrol stimulates the activity of insulin on glucose uptake via the AMP-activated protein kinase and PI3K-Akt signaling pathways. If insulin is absent, the activity of resveratrol on glucose uptake depends on 5' AMP-activated protein kinase (AMPK) activation only (i.e., without the involvement of the PI3K pathway) [133].

Production of IR and GLUT4

IR is a member of the tyrosine kinase receptor family, which is activated by insulin and plays a key role in the regulation of glucose homeostasis [134]. Insulin binds to IR in the cell membrane and initiates an intracellular signaling cascade, which triggers translocation of GLUT4 vesicles to the membrane. Following integration into the cell membrane, GLUT4 transporters start to transport glucose into the cell [135]. Therefore, the expression of GLUT4, the main glucose transporter in adipose tissues and striated muscle (skeletal and cardiac), is important to delineate targets in the treatment of diabetes. Resveratrol again has demonstrated promising effects on glucose metabolism improvement by enhancing the capacity of muscle to transport glucose by increasing the expression of insulin-sensitive GLUT4 (Fig. **1**) [136] and/or by increasing responsiveness to insulin [137]. A clinical study discovered that EGCG from green tea enhances glucose uptake in muscle and fat cells by influencing glucose GLUT4 expression [128]. A recent study by Ali *et al*. [138] reported that cocoa polyphenols reduced hyperinsulinemia and hyperglycemia by improving obesity and enhancing adiponectin secretion and GLUT4 expression in skeletal muscle.

In another study in db/db mice, chlorogenic acid increased the glucose transport in striated muscle tissue through GLUT4 translocation and decreased fasting blood glucose levels [139]. IR deficiency or dysfunction causes clinical manifestations, including diabetes and cancer [140, 141]. Some studies reported that polyphenols improve glucose and lipid profiles in people with T2DM by affecting the protein and mRNA levels of IR. For instance, Cao *et al*. (2007) [142] reported a novel finding that cinnamon polyphenols with procyanidin type-A polymers may increase the amount of IRβ protein and IR mRNA levels in mouse 3T3-L1 adipocytes.

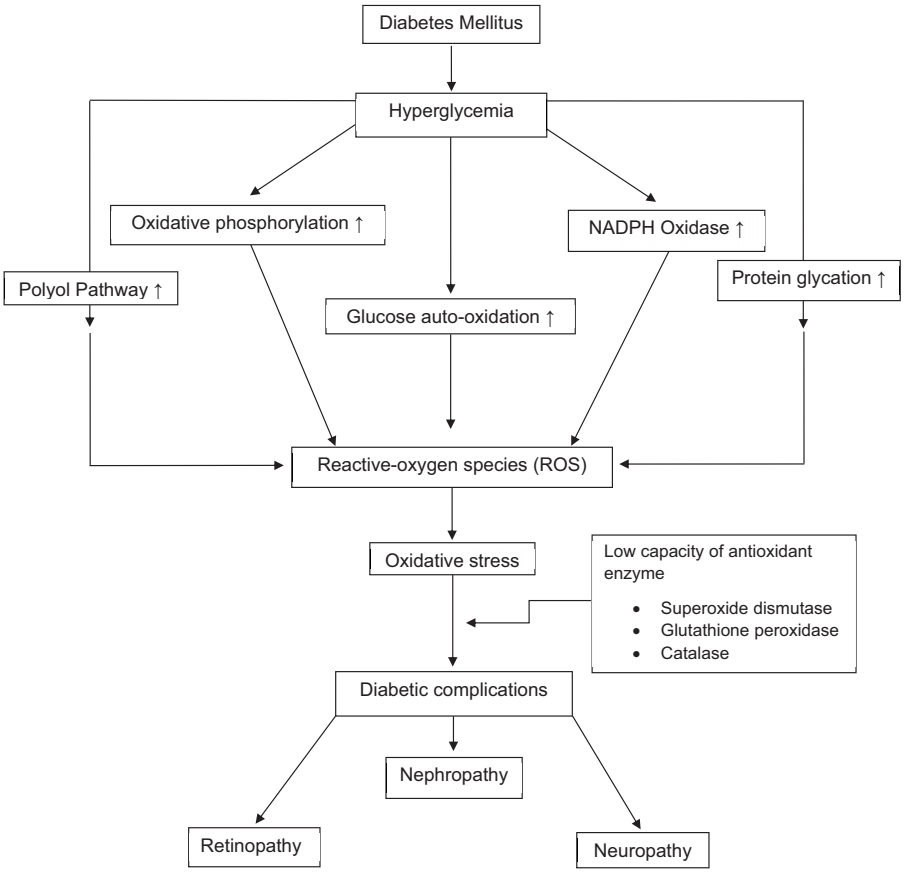

Fig. (2). Effect of oxidative stress on diabetic complications.

A type of legume, *Trigonella foenumgraecum* (fenugreek), which is broadly cultivated in India, North Africa and the Mediterranean was found to have hypoglycemic effects by slowing carbohydrate absorption, inhibiting glucose transport from the fiber content, and increasing erythrocyte IRs, and these effects were associated with the fiber, saponins, proteins and polyphenols of the plant [143, 144]. Further research should be conducted to isolate active components and more precisely explain the anti-diabetic mechanism. Another polyphenolic compound, bellidifolin (isolated from *Swertia chirata* and *Gentianella campestris*), demonstrated hypoglycemic activity through stimulating glucose uptake in streptozotocin (STZ)-induced diabetic rats expressing IRs [145, 146].

Inhibition of Aldose Reductase

Aldose reductase is the first enzyme in the polyol pathway. It catalyzes the reduction of glucose to sorbitol, which is the first step in the polyol pathway of glucose metabolism. It reduces toxic aldehydes and carbonyls and is an important factor in the pathogenesis of many diseases associated with DM, such as retinopathy [147], neuropathy [148], nephropathy [149] and cataract [150]. Therapeutic strategies involving inhibitors of aldose reductase have been proposed to prevent or ameliorate long-term diabetic complications.

Acylated flavanone glucoside myrciatrin IV isolated from the leaves of *M. multiflora* inhibits rat lens aldose reductase (Fig. **1**) [151]. Flavone derivatives such as quercitrin and quercitrin 2″-acetate are highly potent inhibitors of aldose reductase and can prevent diabetic cataracts [152]. Mangiferin was found to inhibit aldose reductase [153].

Reduction of Oxidative Stress

Oxidative stress is an imbalance between the production of reactive oxygen species (free radicals) and the ability of the body to detoxify their harmful effects through neutralization by antioxidants [154]. It is considered to be a potential contributor to the development of diabetes complications. Oxidative stress causes tissue damage in DM [154] and leads to many pathophysiological conditions in the body. Some of these include neurodegenerative diseases such as Parkinson's disease [155] and Alzheimer's disease [156], gene mutations and cancers [157], nephropathy [158], atherosclerosis [159], retinopathy [160], myocardial injury [161] and inflammatory diseases [162]. A relationship has been established between hyperglycemia and oxidative stress in DM. Hyperglycemia promotes auto-oxidation of glucose and stimulates activity of NADPH oxidase, oxidative phosphorylation, protein, glycation and polyol pathway. All these mechanisms generate reactive-oxygen species. As a result, oxidative stress occurs, and oxidative stress is a major factor in the occurrence of DM (Fig. **2**).

Antioxidants are effective in reducing oxidative stress, indicating that it may be beneficial to either ingest natural antioxidants or through dietary supplementation [163, 164]. Therefore, the supplementation of antioxidants in diabetic animals may reduce oxidative stress. Dietary polyphenols also act as antioxidants, and supplementation of these polyphenols might play a role in the treatment of diabetes. Green tea polyphenols (GTP) contain gallocatechin (GC), EGC, EC, EGCG and ECG, which reduced oxidative stress in experimental diabetes by inhibiting lipid peroxidation (LP), scavenge hydroxyl and superoxide radicals [165]. Cocoa polyphenols contain catechin, EC and procyanidins. Those bioactive polyphenols in cocoa reduced oxidative stress in diabetes [166]. Red wine polyphenols such as resveratrol, quercetin, catechins, and anthocyanins reduced oxidative stress in streptozotocin-diabetic rats [167]. Resveratrol, a plant polyphenol, acts as an antioxidant in the central nervous system without cellular proliferative effects during experimental diabetes [168]. Quercetin prevents oxidative stress by various mechanisms, including scavenging free radicals, inhibiting xanthine oxidase and lipid peroxidation and chelating metal ions [169]. The anti-diabetic action of 7-*O*galloyl-D-sedoheptulose, a polyphenol from *Cornifructus*, reduced inflammation-related oxidative stress in the pancreas of type 2 diabetics. Fruit peel polyphenols of *psidium guajava* reduced oxidative stress of the pancreas in a streptozotocin-induced diabetic rat model [170].

Insulin Mimetic Action

Insulin is a peptide hormone secreted by the β-cells in the pancreas. It regulates the blood glucose level in the body. Increased blood glucose levels in the body ultimately elevate concentrations of glucose in systemic circulation, which subsequently stimulates the release of insulin. This insulin acts on cells throughout the body to stimulate uptake, utilization and storage of glucose. The body begins to use stored glucose through metabolic pathways (glycogenolysis and gluconeogenesis) when blood glucose levels decrease under a particular level. DM is a metabolic disorder that occurs if insulin levels become lower than the normal level in the body. T1DM occurs when insulin is not produced in a sufficient amount due to the destruction of pancreatic β-cells. T2DM occurs when target tissues fail to respond to insulin.

Few studies have shown that regular dietary intake of polyphenol containing foods has been associated with insulin mimetic action. Quercetin, a flavonoid, increases insulin release in streptozocin-induced diabetic rats through the regeneration of the pancreatic islets [171]. Kaempferitrin (kaempferol-3, 7-O-(α)-l-dirhamnoside) is the major flavonol glycoside isolated from *Bauhinia forficata* leaves and plays an important role in lowering blood glucose level in diabetic rats and stimulates glucose uptake by secreting insulin [172]. EGCG, a green tea flavonoid, has a glucose lowering effect in experimental animals. It decreases hepatic glucose production and increases tyrosine phosphorylation of the insulin receptor substrate-1 (IRS-1) and has an insulin mimetic action by increasing the activities of PI3 and MAP Kinase [102].

Catechin isolated from *Cassia fistula* reduced the blood glucose levels in streptozotocin-induced diabetic rats by increasing tissue glycogen and 14C-glucose oxidation without causing any change in plasma insulin and C-peptide. It also restored the levels of altered glucokinase, G6Pase, glycogen synthase and glycogen phosphorylase in a diabetic rat model. Overall, this information showed that catechin has hypoglycemic, glucose-oxidizing and insulin-mimetic activities [173]. Additionally, (-) epicatechin isolated from the bark of *Pterocarpus marsupium* has been reported to have insulin-mimetic action on the osmotic fragility of human erythrocytes [174].

Inhibition of Advanced Glycation End Products (AGEs)

Advanced glycation end products (AGEs) are non-enzymatic yields formed as a result of a Maillard or 'browning' reaction in which glucose forms adducts with proteins, lipids and nucleic acids. They are a group of chemically heterogeneous compounds which are produced as a result of successive chemical reactions like dehydration, oxidation, rearrangement and fragmentation. Usually, they accumulated due to progressive aging, a process that is further enhanced under hyperglycemic and oxidative stress conditions [175]. The formation of AGEs contribute to structural and functional changes in proteins such as collagen, elastin and albumin, thus leading to the development of numerous complications associated with diabetes including angiopathy, neuropathy, nephropathy, retinopathy and cataract [176]. Therefore, developing pharmacological inhibitors that hinder AGEs formation may be a basis for a unique therapeutic approach for delaying and averting diabetic complications.

Some recent studies have shown interesting outcomes indicating that naturally occurring phenolic compounds exert inhibitory effects on the formation of AGEs. Wu *et al*. [177] have reported that oligomeric procyanidins of lotus seedpod can reduce hyperglycemic and diabetes-related complications via its antioxidant and

Table 2. Clinical studies on diabetes mellitus using intervention with polyphenol-containing natural products.

No	Type of study	Participants	Age (Years)	Intervention	Comparison / Control	Polyphenols	Period of intervention	Outcomes	Year, References
1	RCT	First-degree relatives of T2D patients (n = 38; 18 M and 20 F)	30 - 65	Grape polyphenols (2 g / day)	Placebo	ND	9 weeks (but in the final 6 days both groups received 3 g /kg of fat-free mass/day of fructose)	Grape polyphenols at nutritional doses effectively prevent fructose-induced oxidative stress and insulin resistance.	2013, [234]
2	RCT	Both males and females (n = 114) with new onset of T2D	40 - 65	Polyphenol-rich supplement of pomegranate extract (500 mg), green tea extract (300 mg) and ascorbic acid (60 mg) (n = 56; 22 M and 34 F)	Placebo (n = 58, 21 M and 37 F)	ND	3 months	Polyphenol-rich antioxidant supplementations produced antagonizing effects on oxidative stress and lipid peroxidation	2010, [235]
3	RCT	T2D subjects (n = 13; 6 F and 7 M)	59 - 64	Sweetened dried cranberries (SDC), raw cranberries (RC), SDC containing less sugar (SDC-LS) in T2D subjects	White bread (WB) as control in T2D subjects	5-caffeoylquinic acid Quercetin-3-galactoside Quercetin-3-rhamnoside 3-caffeoylquinic acid 4-caffeoylquinic acid Myricetin-3-galactoside Quercetin-3-arabinopyranoside Quercetin-3-arabinofuranoside Quercetin Quercetin-3-benzoylgalactoside Epicatechin (found in SDC and SDC-LS)	Not stated	SDC-LS favored glycemic and insulinemic responses in T2D subjects	2010, [236]
4	RCT	Subjects with borderline T2D (n = 60; 49 M and 11 F)	32 - 73	Early intervention group (n = 7): Green tea-extract powder (GTEP) for the first 2 months and then entered the 2-month non-intervention period	Later intervention (comparison) group (n = 9): Under observation for first 2 months and then consumed GTEP for the subsequent 2 months	GTEP containing 544 mg polyphenols (456 mg catechins)	2 months, daily administration	Lowered the glycated haemoglobin (HbA1c) levels in both groups	2008, [237]

(Table 2) Contd….

No	Type of study	Participants	Age (Years)	Intervention	Comparison / Control	Polyphenols	Period of intervention	Outcomes	Year, References
5	Randomized crossover trial	T2D volunteers (n = 9) Healthy volunteers (n = 10)	-	Brown rice (BR) intake in both T2D and healthy volunteers	Milled rice (MR) intake in both T2D and healthy volunteers	BR with 70% total polyphenols (undefined) MR with 40% total polyphenols (undefined)	-	In healthy volunteers with BR, the glycemic area (19.8%) and glycemic index (12.1%) was lower ($p < 0.05$) than MR. In diabetics with BR, the glycemic area were 35.2% while glycemic index were 35.6% lower than MR.	2006, [238]
6	Controlled Clinical Trial	Healthy controls (n = 10) T2D subjects (n = 10)	35 - 71	Pomegranate juice (PJ) consumption in T2D group	PJ consumption in healthy control group	ND	3 months, 50 ml daily	PJ consumption by diabetic patients did not worsen the diabetic parameters and exhibited antioxidative effects on serum and macrophages	2006, [239]
7	RCT	T2D subjects [n = 29; Muscadine grape juice (MJ) = 10, Muscadine grape wine (MW) = 10, or dealcoholised muscadine grape wine (Dz-W) = 9] Control subjects (n = 15) Non-diabetics with MJ (n = 8)	50 - 60	(MJ, MW and Dz-W supplement in T2D group	Control group without supplement Non-diabetics group consumed MJ	ND	28 days, 150 mL daily after dinner	MW or Dz-W with meals lowered blood glucose, insulin, and HbA1c level among diabetics compared with diabetics given MJ	2006, [240]
8	RCT	Subjects with borderline diabetes or diabetes (n = 66; 53 M and 13 F)	32 - 73	A packet of GTEP	Control group were simply followed	544 mg of polyphenols (456 mg catechins)	2 months, daily after every meal or snack	The effects of polyphenol intake on blood glucose level, HbA1c level, insulin resistance or inflammation markers were unclear.	2005, [241]

Randomized Controlled Trial = RCT; Male = M, Female = F; Not defined = ND; Sweetened dried cranberries = SDC; SDC containing less sugar = SDC-LS; White bread = WB; Green tea-extract powder = GTEP; Milled rice = MR, Brown rice = BR; Pomegranate juice = PJ; Type 2 diabetes = T2D; n = Total number of subjects; Muscadine grape juice = MJ; Muscadine grape wine = MW; de-alcoholized muscadine grape wine = Dz-W; HbA1c = Glycated hemoglobin.

insulin potentiating activities. Another study showed that luteolin has the most potent inhibitory effects on each stage of protein glycation which provides a protective effect against hyperglycemia-mediated protein damage [178]. A new flavonoid 2", 4"-*O*-diacetylquercitrin (which can be extracted from the aerial parts of *Melastoma sanguineum*) have shown strong inhibitory activities against AGEs formation thus revealing a promising agent that can be used in prevention or treatment of diabetic complications and other related diseases [179]. The anti-glycation activities of polyphenols are dependent on their properties and molecular structures such as hydroxylation on A, B or C rings, methylation, glycosyla-

tion of hydroxyl group and galloyl groups in phenolic compounds [180].

CLINICAL TRIALS

To determine appropriate clinical trials based on polyphenols among diabetic patients, PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to yield 28 clinical trials. However, only eight studies were shortlisted (Table **2**) based on the precise population (DM), intervention (natural compounds containing polyphenols) and available outcomes [metabolic markers of diabetes (levels of blood glucose and HbA1c, glycemic area and index, effects on insulin resistance and oxidative stress)]. Most of the RCTs did not mention the precise type of polyphenols used although some intervention strategies involved mainly green tea, brown rice, pomegranate juice, grape and cranberries (fresh and dry).

FUTURE DIRECTIONS

Natural products have long been an important resource in the discovery of innovative drugs due to their diverse chemical compounds and ability to act on numerous biological targets. Polyphenols from natural products are currently the focus of attention for drug discovery and drug development, as many of these compounds are potential therapeutics that interferes in various stages of diabetes development. Because *in vitro* and animal studies provide evidence of positive effects of many polyphenols on glucose homeostasis, extensive studies of each polyphenol are needed to provide information about their potential to be used as pharmaceutical agents in the treatment of diabetes. Polyphenols in fruits, vegetables, green tea and edible plants represented in table 1 can be used as prophylactics or as synergistic compounds in addition to conventional regimens against DM. In addition to nutraceutical use, promising new drugs with a specific target pathway in diabetes pathogenesis and dosage can be designed and produced to reduce the burden of diabetes.

For clinical applications, the inadequate supply of polyphenols due to costly chemical synthesis or minimal isolation from natural sources needs to be remedied. To meet the demand of polyphenols, model microorganisms (such as *Escherichia coli* and *Saccharomyces cerevisiae*) can be used to provide sufficient quantities of polyphenols from inexpensive substrates by metabolic engineering or recombinant technology. For example, in the past few years, some studies have reported the production of plant-specific polyphenols such as pinosylvin, naringenin and resveratrol in microorganisms [181-183].

Currently, the aldose reductase inhibition property of polyphenols has gained importance in diabetes treatment. Polyphenols such as gallic, vanillic, syringic, ferulic, protocatechuic and cinnamic acids found in the genus *Scrophularia* have been reported to inhibit aldose reductase enzyme activity. A more recently published study has given molecular insights into receptor-ligand interactions in the development of novel aldose reductase inhibitors from the genus *Scrophularia* [184]. Therefore, polyphenols can also be used to identify new ligand binding sites on target proteins using computational approaches such as molecular docking and molecular dynamics. In addition with the numbers of both *in vitro* and *in vivo* experiments, to date, there are a number of controlled trials for clinical evaluation of polyphenols in the treatment of DM. However more appropriately designed RCTs are warranted to assess the clinical implications of precise polyphenols as complementary natural regimens besides the use of conventional anti-diabetic drugs.

CONCLUSION

Based on all compiled evidences presented in this review, it is concluded that polyphenols exert anti-diabetic activities via different mechanistic pathways. However, more detailed *in vivo*, *in vitro* or *ex vivo* investigations are warranted to confirm the anti-diabetic mechanisms of polyphenols before they can be used as good alternative and supplementary resources in the management of diabetic patients as well as potential future sources for drug development and discovery.

LIST OF ABBREVIATIONS

DM	=	Diabetes mellitus
EGCG	=	Eepigallocatechin gallate
F1, 6-BPase	=	Fructose-1, 6-bisphosphatase
GLUT	=	Glucose transporters
G6Pase	=	Glucose-6-phosphatase
IR	=	Insulin receptor:
SGLT	=	Sodium dependent glucose transporters
T1DM	=	Type 1 diabetes mellitus
T2DM	=	Type 2 diabetes mellitus

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

We would like to acknowledge Universiti Sains Malaysia (USM) Global Fellowship (2014/2015) for financially supporting Fahmida Alam to pursue her PhD. We would also like to acknowledge Vice-Chancellor Award (2015/2016), USM for supporting Md. Asiful Islam during pursuit of the PhD.

REFERENCES

[1] Alberti KGMM, Zimmet Pf. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabetic Med 1998; 15: 539-53.

[2] Guariguata L, Whiting D, Hambleton I, Beagley J, Linnenkamp U, Shaw J. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract 2014; 103: 137-49.

[3] Stolar M. Glycemic control and complications in type 2 diabetes mellitus. Am J Med 2010; 123: S3-11.

[4] Van Belle TL, Coppieters KT, Von Herrath MG. Type 1 diabetes: etiology, immunology, and therapeutic strategies. Physiol Rev 2011; 91: 79-118.

[5] WHO Study Group on Diabetes Mellitus, World Health Organization. Diabetes Mellitus: Report of a WHO Study Group [meeting held in Geneva from 11 to 16 February 1985]. Geneva: World Health Organization 1985; pp. 113.

[6] Vlad A, Timar R. Pathogenesis of Type 1 diabetes mellitus: a brief overview. Romanian J Diabetes Nut Metabol Dis 2012; 19: 67-72.

[7] Association AD. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014; 37: S81-90.

[8] Bastaki A. Diabetes mellitus and its treatment. Int J Diabetes Metabol 2005; 13: 111.

[9] Sahra IB, Laurent K, Loubat A, *et al*. The antidiabetic drug metformin exerts an antitumoral effect *in vitro* and *in vivo* through a decrease of cyclin D1 level. Oncogene 2008; 27: 3576-86.

[10] Inzucchi SE, Maggs DG, Spollett GR, *et al*. Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. N Engl J Med 1998; 338: 867-73.

[11] Bodmer M, Meier C, Krähenbühl S, Jick SS, Meier CR. Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia A nested case-control analysis. Diabetes Care 2008; 31: 2086-91.

[12] Abraham B, Sellin JH. Drug-induced diarrhea. Curr Gastroenterol Reports 2007; 9: 365-72.

[13] Levetan C. Oral antidiabetic agents in type 2 diabetes. Curr Med Res Opinion® 2007; 23: 945-52.

[14] Fonseca V. Effect of thiazolidinediones on body weight in patients with diabetes mellitus. Am J Med 2003; 115: 42-48.

[15] Patel D, Kumar R, Laloo D, Hemalatha S. Diabetes mellitus: an overview on its pharmacological aspects and reported medicinal

plants having antidiabetic activity. Asian Pacific J Trop Biomed 2012; 2: 411-20.
[16] Beckman CH. Phenolic-storing cells: keys to programmed cell death and periderm formation in wilt disease resistance and in general defence responses in plants? Physiol Mol Plant Pathol 2000; 57: 101-10.
[17] Graf BA, Milbury PE, Blumberg JB. Flavonols, flavones, flavanones, and human health: epidemiological evidence. J Med Food 2005; 8: 281-90.
[18] Arts IC, Hollman PC. Polyphenols and disease risk in epidemiologic studies. Am J Clin Nutr 2005; 81: 317S-25.
[19] Bahadoran Z, Mirmiran P, Azizi F. Dietary polyphenols as potential nutraceuticals in management of diabetes: a review. J Diabetes Metabol Disord 2013; 12: 43.
[20] Williamson G. Possible effects of dietary polyphenols on sugar absorption and digestion. Mol Nut Food Res 2013; 57: 48-57.
[21] McCulloch D, Palmer J. The appropriate use of B-cell function testing in the preclinical period of type 1 diabetes. Diabetic Med 1991; 8: 800-4.
[22] Smyth DJ, Cooper JD, Bailey R, *et al*. A genome-wide association study of nonsynonymous SNPs identifies a type 1 diabetes locus in the interferon-induced helicase (IFIH1) region. Nat Genet 2006; 38: 617-9.
[23] Hakonarson H, Grant SF, Bradfield JP, *et al*. A genome-wide association study identifies KIAA0350 as a type 1 diabetes gene. Nature 2007; 448: 591-4.
[24] Lowe CE, Cooper JD, Brusko T, *et al*. Large-scale genetic fine mapping and genotype-phenotype associations implicate polymorphism in the IL2RA region in type 1 diabetes. Nat Genet 2007; 39: 1074-82.
[25] Wass JA, Stewart PM. Oxford textbook of endocrinology and diabetes. UK: Oxford University Press 2011.
[26] Meier JJ, Nauck MA. Is the diminished incretin effect in type 2 diabetes just an epi-phenomenon of impaired β-cell function? Diabetes 2010; 59: 1117-25.
[27] Unger RH, Scherer PE. Gluttony, sloth and the metabolic syndrome: a roadmap to lipotoxicity. Trends Endocrinol Metabol 2010; 21: 345-52.
[28] Voight BF, Scott LJ, Steinthorsdottir V, *et al*. Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. Nat Genet 2010; 42: 579-89.
[29] Herder C, Roden M. Genetics of type 2 diabetes: pathophysiologic and clinical relevance. Eur J ClinInvest 2011; 41: 679-92.
[30] Dabelea D, Hanson RL, Lindsay RS, *et al*. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. Diabetes 2000; 49: 2208-11.
[31] Daglia M. Polyphenols as antimicrobial agents. Curr Opin Biotechnol 2012; 23: 174-81.
[32] Quideau S, Deffieux D, Douat-Casassus C, Pouységu L. Plant polyphenols: chemical properties, biological activities, and synthesis. Angew Chem Int Ed 2011; 50: 586-621.
[33] Pasinetti GM, Wang J, Ho L, Zhao W, Dubner L. Roles of resveratrol and other grape-derived polyphenols in Alzheimer's disease prevention and treatment. Biochim Biophys Acta (BBA)-Mol Basis Dis 2015; 1852: 1202-8.
[34] Pate KM, Rogers M, Moss M. The ability of polyphenols to reduce Aβ-induced apoptosis associated with Alzheimer's disease. Biophys J 2015; 108: 66a.
[35] Wang J, Bi W, Cheng A, Freire D, *et al*. Targeting multiple pathogenic mechanisms with polyphenols for the treatment of Alzheimer's disease-experimental approach and therapeutic implications. Front Aging Neurosci 2014; 6: 42.
[36] Chastain SE, Moss M. Green and black tea polyphenols mechanistically inhibit the aggregation of amyloid-β in Alzheimer's disease. Biophys J 2015; 108: 357a.
[37] Yang CS, Chung JY, Yang G-y, Chhabra SK, Lee M-J. Tea and tea polyphenols in cancer prevention. J Nut 2000; 130: 472S-8.
[38] Singh M, Bhui K, Singh R, Shukla Y. Tea polyphenols enhance cisplatin chemosensitivity in cervical cancer cells via induction of apoptosis. Life Sci 2013; 93: 7-16.
[39] Ramos S. Cancer chemoprevention and chemotherapy: dietary polyphenols and signalling pathways. Mol Nutr Food Res 2008; 52: 507-26.
[40] Damianaki A, Bakogeorgou E, Kampa M, *et al*. Potent inhibitory action of red wine polyphenols on human breast cancer cells. J Cell Biochem 2000; 78: 429-41.
[41] Khan N, Mukhtar H. Multitargeted therapy of cancer by green tea polyphenols. Cancer Lett 2008; 269: 269-80.
[42] Lambert JD, Elias RJ. The antioxidant and pro-oxidant activities of green tea polyphenols: a role in cancer prevention. Arc Biochem Biophys 2010; 501: 65-72.
[43] Zamora-Ros R, Knaze V, Rothwell JA, *et al*. Dietary polyphenol intake in Europe: the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Eur J Nut 2015: 1-17.
[44] Lall RK, Syed DN, Adhami VM, Khan MI, Mukhtar H. Dietary polyphenols in prevention and treatment of prostate cancer. Int J Mol Sci 2015; 16: 3350-76.
[45] Kona FR, Shen M, Chen D, Chan TH, Ping Dou Q. Discovery of polyphenol-based drugs for cancer prevention and treatment: the tumor proteasome as a novel target. Rec Adv Polyphenol Res 2014; 4: 209-37.
[46] Turrini E, Ferruzzi L, Fimognari C. Potential effects of pomegranate polyphenols in cancer prevention and therapy. Oxidat Med Cell Longev 2015; 2015: 938475.
[47] Srichairatanakool S, Fucharoen S. Antioxidants as complementary medication in thalassemia. In: Atroshi F, Ed. Pharmacology and nutritional intervention in the treatment of disease. USA: InTech 2014.
[48] Fibach E, Rachmilewitz EA. The role of antioxidants and iron chelators in the treatment of oxidative stress in thalassemia. Annl NY Acad Sci 2010; 1202: 10-6.
[49] Kukreja A, Wadhwa N, Tiwari A. Therapeutic role of natural agents in beta-thalassemia: a review. J Pharm Res 2013; 6: 954-9.
[50] Parkar SG, Stevenson DE, Skinner MA. The potential influence of fruit polyphenols on colonic microflora and human gut health. Int J Food Microbiol 2008; 124: 295-8.
[51] Dryden GW, Song M, McClain C. Polyphenols and gastrointestinal diseases. Curr Opin Gastroenterol 2006; 22: 165.
[52] Shapiro H, Singer P, Halpern Z, Bruck R. Polyphenols in the treatment of inflammatory bowel disease and acute pancreatitis. Gut 2007; 56: 426-36.
[53] Cardona F, Andrés-Lacueva C, Tulipani S, Tinahones FJ, Queipo-Ortuño MI. Benefits of polyphenols on gut microbiota and implications in human health. J Nutr Biochem 2013; 24: 1415-22.
[54] Manach C, Mazur A, Scalbert A. Polyphenols and prevention of cardiovascular diseases. Curr Opin Lipidol 2005; 16: 77-84.
[55] Quiñones M, Miguel M, Aleixandre A. Beneficial effects of polyphenols on cardiovascular disease. Pharmacol Res 2013; 68: 125-31.
[56] Perez-Vizcaino F, Duarte J, Andriantsitohaina R. Endothelial function and cardiovascular disease: effects of quercetin and wine polyphenols. Free Radic Res 2006; 40: 1054-65.
[57] Michalska M, Gluba A, Mikhailidis DP, *et al*. The role of polyphenols in cardiovascular disease. Med Sci Monit Basic Res 2010; 16.
[58] Okoro IO, Osagie A, Asibor EO. Antioxidant and antimicrobial activities of polyphenols from ethnomedicinal plants of Nigeria. African J Biotechnol 2010; 9: 2989-93.
[59] Moreno S, Scheyer T, Romano CS, Vojnov AA. Antioxidant and antimicrobial activities of rosemary extracts linked to their polyphenol composition. Free Radical Res 2006; 40: 223-31.
[60] Fattouch S, Caboni P, Coroneo V, *et al*. Antimicrobial activity of Tunisian quince (Cydonia oblonga Miller) pulp and peel polyphenolic extracts. J Agric Food Chem 2007; 55: 963-9.
[61] Striegel L, Kang B, Pilkenton SJ, Rychlik M, Apostolidis E. Effect of black tea and black tea pomace polyphenols on α-glucosidase and α-amylase inhibition, relevant to type 2 diabetes prevention. Front Nutr 2015; 2: 3.
[62] Xiao J, Hogger P. Dietary polyphenols and type 2 diabetes: current insights and future perspectives. Curr Med Chem 2015; 22: 23-38.
[63] Carpéné C, Gomez-Zorita S, Deleruyelle S, Carpéné M. Novel strategies for preventing diabetes and obesity complications with natural polyphenols. Curr Med Chem 2015; 22: 150-64.
[64] Kusirisin W, Srichairatanakool S, Lerttrakarnnon P, *et al*. Antioxidative activity, polyphenolic content and anti-glycation effect of some Thai medicinal plants traditionally used in diabetic patients. Med Chem 2009; 5: 139-47.
[65] Quideau S. Plant "polyphenolic" small molecules can induce a calorie restriction-mimetic life-span extension by activating sirtuins: will "polyphenols" someday be used as chemotherapeutic drugs in western medicine? ChemBioChem 2004; 5: 427-30.

[66] Correia-da-Silva M, Sousa E, Pinto MM. Emerging sulfated flavonoids and other polyphenols as drugs: Nature as an inspiration. Med Res Rev 2014; 34: 223-79.
[67] Terra W, Ferreira C, Jordao B, Dillon R. Digestive enzymes. In: Lehane M, Billingsley P, Eds. Biology of the insect midgut. Springer 1996; pp. 153-94.
[68] Zakowski JJ, Bruns DE. Biochemistry of human alpha amylase isoenzymes. Crit Rev Clin Lab Sci 1985; 21: 283-322.
[69] Chiba S. Molecular mechanism in α-glucosidase and glucoamylase. Biosci Biotechnol Biochem 1997; 61: 1233-9.
[70] Levin RJ. Digestion and absorption of carbohydrates-from molecules and membranes to humans. Am J Clin Nutr 1994; 59: 690S-8.
[71] Tundis R, Loizzo M, Menichini F. Natural products as α-amylase and α-glucosidase inhibitors and their hypoglycaemic potential in the treatment of diabetes: an update. Mini Rev Med Chem 2010; 10: 315-31.
[72] McDougall GJ, Stewart D. The inhibitory effects of berry polyphenols on digestive enzymes. Biofactors 2005; 23: 189-95.
[73] Funke I, Melzig M. Effect of different phenolic compounds on α-amylase activity: Screening by microplate-reader based kinetic assay. Die Pharm-An Int J Pharm Sci 2005; 60: 796-7.
[74] Eddouks M, Maghrani M, Lemhadri A, Ouahidi M-L, Jouad H. Ethnopharmacological survey of medicinal plants used for the treatment of diabetes mellitus, hypertension and cardiac diseases in the south-east region of Morocco (Tafilalet). J Ethnopharmacol 2002; 82: 97-103.
[75] Hussain S, Mahwi T, Aziz T. Quercetin dampens postprandial hyperglycemia in type 2 diabetic patients challenged with carbohydrates load. Int J Diabetes Res 2012; 1: 32-5.
[76] Kim J-S, Kwon C-S, Son KH. Inhibition of alpha-glucosidase and amylase by luteolin, a flavonoid. Biosci Biotechnol Biochem 2000; 64: 2458-61.
[77] Ishikawa A, Yamashita H, Hiemori M, *et al*. Characterization of inhibitors of postprandial hyperglycemia from the leaves of Nerium indicum. J Nutr Sci Vitaminol 2007; 53: 166-73.
[78] McDougall GJ, Shpiro F, Dobson P, Smith P, Blake A, Stewart D. Different polyphenolic components of soft fruits inhibit α-amylase and α-glucosidase. J Agric Food Chem 2005; 53: 2760-6.
[79] Mai TT, Thu NN, Tien PG, Van Chuyen N. Alpha-glucosidase inhibitory and antioxidant activities of Vietnamese edible plants and their relationships with polyphenol contents. J Nutr Sci Vitaminol 2007; 53: 267-76.
[80] Thorens B. Glucose transporters in the regulation of intestinal, renal, and liver glucose fluxes. Am J Physiol-Gastrointestinal Liver Physiol 1996; 270: G541-53.
[81] Wright EM, Loo DD, Hirayama BA. Biology of human sodium glucose transporters. Physiol Rev 2011; 91: 733-94.
[82] Scheepers A, Joost H-G, Schurmann A. The glucose transporter families SGLT and GLUT: molecular basis of normal and aberrant function. J Parenteral Enteral Nutr 2004; 28: 364-71.
[83] Wright EM. Renal Na+-glucose cotransporters. Am J Physiol-Renal Physiol 2001; 280: F10-8.
[84] Bell GI, Kayano T, Buse JB, *et al*. Molecular biology of mammalian glucose transporters. Diabetes Care 1990; 13: 198-208.
[85] Kobayashi Y, Suzuki M, Satsu H, *et al*. Green tea polyphenols inhibit the sodium-dependent glucose transporter of intestinal epithelial cells by a competitive mechanism. J Agric Food Chem 2000; 48: 5618-23.
[86] Welsch CA, Lachance PA, Wasserman BP. Dietary phenolic compounds: inhibition of Na+-dependent D-glucose uptake in rat intestinal brush border membrane vesicles. J Nutr 1989; 119: 1698-704.
[87] Aguirre L, Arias N, Macarulla MT, Gracia A, Portillo MP. Beneficial effects of quercetin on obesity and diabetes. Open Nutraceuticals J 2011; 4: 189-98.
[88] Kwon O, Eck P, Chen S, *et al*. Inhibition of the intestinal glucose transporter GLUT2 by flavonoids. FASEB J 2007; 21: 366-77.
[89] Alvarado F. Hypothesis for the interaction of phlorizin and phloretin with membrane carriers for sugars. Biochim Biophys Acta (BBA)-Biomembr 1967; 135: 483-95.
[90] Krook A, Kawano Y, Song XM, *et al*. Improved glucose tolerance restores insulin-stimulated Akt kinase activity and glucose transport in skeletal muscle from diabetic Goto-Kakizaki rats. Diabetes 1997; 46: 2110-4.
[91] Strobel P, Allard C, Perez-Acle T, Calderon R, Aldunate R, Leighton F. Myricetin, quercetin and catechin-gallate inhibit glucose uptake in isolated rat adipocytes. Biochem J 2005; 386: 471-8.
[92] Vera JC, Reyes AM, Velásquez FV, *et al*. Direct inhibition of the hexose transporter GLUT1 by tyrosine kinase inhibitors. Biochemistry 2001; 40: 777-90.
[93] Vera JC, Reyes AM, Cárcamo JG, *et al*. Genistein is a natural inhibitor of hexose and dehydroascorbic acid transport through the glucose transporter, GLUT1. J Biol Chem 1996; 271: 8719-24.
[94] Watanabe T, Kondo K, Oishi M. Induction of *in vitro* differentiation of mouse erythroleukemia cells by genistein, an inhibitor of tyrosine protein kinases. Cancer Res 1991; 51: 764-8.
[95] Akiyama T, Ishida J, Nakagawa S, *et al*. Genistein, a specific inhibitor of tyrosine-specific protein kinases. J Biol Chem 1987; 262: 5592-5.
[96] Scrutton MC, Utter MF. The regulation of glycolysis and gluconeogenesis in animal tissues. Ann Rev Biochem 1968; 37: 249-302.
[97] Hundal RS, Krssak M, Dufour S, *et al*. Mechanism by which metformin reduces glucose production in type 2 diabetes. Diabetes 2000; 49: 2063-9.
[98] Pari L, Srinivasan S. Antihyperglycemic effect of diosmin on hepatic key enzymes of carbohydrate metabolism in streptozotocin-nicotinamide-induced diabetic rats. Biomed Pharmacotherapy 2010; 64: 477-81.
[99] Kanchana G, Shyni WJ, Rajadurai M, Periasamy R. Evaluation of antihyperglycemic effect of sinapic acid in normal and streptozotocin-induced diabetes in albino rats. Global J Pharmacol 2011; 5: 33-9.
[100] Ong KW, Hsu A, Song L, Huang D, Tan BKH. Polyphenols-rich Vernonia amygdalina shows anti-diabetic effects in streptozotocin-induced diabetic rats. J Ethnopharmacol 2011; 133: 598-607.
[101] Collins QF, Liu H-Y, Pi J, Liu Z, Quon MJ, Cao W. Epigallocatechin-3-gallate (EGCG), a green tea polyphenol, suppresses hepatic gluconeogenesis through 5′-AMP-activated protein kinase. J Biol Chem 2007; 282: 30143-9.
[102] Waltner-Law ME, Wang XL, Law BK, Hall RK, Nawano M, Granner DK. Epigallocatechin gallate, a constituent of green tea, represses hepatic glucose production. J Biol Chem 2002; 277: 34933-40.
[103] Park SA, Choi MS, Cho SY, *et al*. Genistein and daidzein modulate hepatic glucose and lipid regulating enzyme activities in C57BL/KsJ-db/db mice. Life Sci 2006; 79: 1207-13.
[104] Choi M, Jung U, Yeo J, Kim M, Lee M. Genistein and daidzein prevent diabetes onset by elevating insulin level and altering hepatic gluconeogenic and lipogenic enzyme activities in non-obese diabetic (NOD) mice. Diabetes/Metabol Res Rev 2008; 24: 74-81.
[105] Pitchai D, Saravana B, Modilal R. Antihyperglycemic effects of Phyllanthus extracts in alloxan-induced diabetic rats. Int J Pharm Sci 2009; 1: 261-4.
[106] Cernea S, Dobreanu M. Diabetes and beta cell function: from mechanisms to evaluation and clinical implications. Biochem Med 2013; 23: 266-80.
[107] Kahn CR, White M. The insulin receptor and the molecular mechanism of insulin action. J Clin Invest 1988; 82: 1151.
[108] Rutter GA. Nutrient–secretion coupling in the pancreatic islet β-cell: recent advances. Mol Aspects Med 2001; 22: 247-84.
[109] Rutter G. Visualising insulin secretion. The Minkowski lecture 2004. Diabetologia 2004; 47: 1861-72.
[110] Buchanan TA, Xiang AH, Peters RK, *et al*. Preservation of pancreatic β-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. Diabetes 2002; 51: 2796-803.
[111] Rouse M, Younès A, Egan JM. Resveratrol and curcumin enhance pancreatic β-cell function by inhibiting phosphodiesterase activity. J Endocrinol 2014; 223: 107-17.
[112] Cai EP, Lin J-K. Epigallocatechin gallate (EGCG) and rutin suppress the glucotoxicity through activating IRS2 and AMPK signaling in rat pancreatic β cells. J Agric Food Chem 2009; 57: 9817-27.
[113] Chakravarthy B, Gupta S, Gode K. Functional cell regeneration in the islets of pancreas in alloxan induced diabetic rats by (-) epicetechin. J Life Sci 1982; 31: 2693-7.
[114] Coskun O, Kanter M, Korkmaz A, Oter S. Quercetin, a flavonoid antioxidant, prevents and protects streptozotocin-induced oxidative stress and β-cell damage in rat pancreas. Pharmacol Res 2005; 51: 117-23.
[115] Kang Y-J, Jung UJ, Lee M-K, *et al*. Eupatilin, isolated from Artemisia princeps Pampanini, enhances hepatic glucose metabolism and

pancreatic β-cell function in type 2 diabetic mice. Diabetes Res Clin Pract 2008; 82: 25-32.
[116] Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. Nature 2001; 414: 799-806.
[117] Scalbert A, Manach C, Morand C, Rémésy C, Jiménez L. Dietary polyphenols and the prevention of diseases. Crit Rev Food Sci Nutr 2005; 45: 287-306.
[118] Youl E, Bardy G, Magous R, *et al*. Quercetin potentiates insulin secretion and protects INS-1 pancreatic β-cells against oxidative damage via the ERK1/2 pathway. Br J Pharmacol 2010; 161: 799-814.
[119] Bardy G, Virsolvy A, Quignard J, *et al*. Quercetin induces insulin secretion by direct activation of L-type calcium channels in pancreatic beta cells. Br J Pharmacol 2013; 169: 1102-13.
[120] Fu-Liang X, Xiao-Hui S, Lu G, Xiang-Liang Y, Hui-Bi X. Puerarin protects rat pancreatic islets from damage by hydrogen peroxide. Eur J Pharmacol 2006; 529: 1-7.
[121] Kamalakkannan N, Prince PSM. Antihyperglycaemic and antioxidant effect of rutin, a polyphenolic flavonoid, in streptozotocin-induced diabetic wistar rats. Basic Clin Pharmacol Toxicol 2006; 98: 97-103.
[122] Srinivasan S, Pari L. Ameliorative effect of diosmin, a citrus flavonoid against streptozotocin-nicotinamide generated oxidative stress induced diabetic rats. Chem-Biol Interact 2012; 195: 43-51.
[123] Lopez-Lazaro M. Distribution and biological activities of the flavonoid luteolin. Mini Rev Med Chem 2009; 9: 31-59.
[124] Zarzuelo A, Jimenez I, Gamez M, *et al*. Effects of luteolin 5-O-β-rutinoside in streptozotocin-induced diabetic rats. Life Sci 1996; 58: 2311-6.
[125] Ding L, Jin D, Chen X. Luteolin enhances insulin sensitivity via activation of PPARγ transcriptional activity in adipocytes. J Nutr Biochem 2010; 21: 941-7.
[126] Hsu CL, Yen GC. Effects of capsaicin on induction of apoptosis and inhibition of adipogenesis in 3T3-L1 cells. J Agric Food Chem 2007; 55: 1730-6.
[127] Huang TH, Peng G, Kota BP, *et al*. Anti-diabetic action of Punica granatum flower extract: activation of PPAR-γ and identification of an active component. Toxicol Appl Pharmacol 2005; 207: 160-9.
[128] Consortium I. Tea consumption and incidence of type 2 diabetes in Europe: the EPIC-InterAct case-cohort study. PLoS One 2012; 7: e36910.
[129] Lee C-C, Hsu W-H, Shen S-R, Cheng Y-H, Wu S-C. Fagopyrum tataricum (buckwheat) improved high-glucose-induced insulin resistance in mouse hepatocytes and diabetes in fructose-rich diet-induced mice. Exp Diabetes Res 2012; 2012.
[130] Epstein FH, Shepherd PR, Kahn BB. Glucose transporters and insulin action—implications for insulin resistance and diabetes mellitus. N Engl J Med 1999; 341: 248-57.
[131] Natella F, Scaccini C. Role of coffee in modulation of diabetes risk. Nutr Rev 2012; 70: 207-17.
[132] Prabhakar PK, Doble M. Synergistic effect of phytochemicals in combination with hypoglycemic drugs on glucose uptake in myotubes. Phytomedicine 2009; 16: 1119-26.
[133] Park CE, Kim M, Lee JH, *et al*. Resveratrol stimulates glucose transport in C2C12 myotubes by activating AMP-activated protein kinase. Exp Mol Med 2007; 39: 222.
[134] Ward CW, Lawrence MC. Ligand-induced activation of the insulin receptor: a multi-step process involving structural changes in both the ligand and the receptor. Bioessays 2009; 31: 422-34.
[135] Minokoshi Y, Kahn CR, Kahn BB. Tissue-specific ablation of the GLUT4 glucose transporter or the insulin receptor challenges assumptions about insulin action and glucose homeostasis. J Biol Chem 2003; 278: 33609-12.
[136] Do GM, Jung UJ, Park HJ, *et al*. Resveratrol ameliorates diabetes-related metabolic changes via activation of AMP-activated protein kinase and its downstream targets in db/db mice. Mol Nut Food Res 2012; 56: 1282-91.
[137] Barger JL, Kayo T, Vann JM, *et al*. A low dose of dietary resveratrol partially mimics caloric restriction and retards aging parameters in mice. PloS One 2008; 3: e2264.
[138] Ali F, Ismail A, Kersten S. Molecular mechanisms underlying the potential antiobesity-related diseases effect of cocoa polyphenols. Mol Nut Food Res 2014; 58: 33-48.
[139] Ong KW, Hsu A, Tan B. Chlorogenic acid stimulates glucose transport in skeletal muscle via AMPK activation: a contributor to the beneficial effects of coffee on diabetes. PloS One 2012; 7: e32718.
[140] Association AD. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010; 33: S62-9.
[141] Malaguarnera R, Sacco A, Voci C, Pandini G, Vigneri R, Belfiore A. Proinsulin binds with high affinity the insulin receptor isoform A and predominantly activates the mitogenic pathway. Endocrinology 2012; 153: 2152-63.
[142] Cao H, Polansky MM, Anderson RA. Cinnamon extract and polyphenols affect the expression of tristetraprolin, insulin receptor, and glucose transporter 4 in mouse 3T3-L1 adipocytes. Arch Biochem Biophys 2007; 459: 214-22.
[143] Sharma R. Effect of fenugreek seeds and leaves on blood glucose and serum insulin responses in human subjects. Nutr Res 1986; 6: 1353-64.
[144] Kannappan S, Anuradha C. Insulin sensitizing actions of fenugreek seed polyphenols, quercetin & metformin in a rat model. Indian J Med Res 2009; 129: 401-8.
[145] Basnet P, Kadota S, Shimizu M, Takata Y, Kobayashi M, Namba T. Bellidifolin stimulates glucose uptake in rat l fibroblasts and ameliorates hyperglycemia in streptozotocin (STZ)-induced diabetic rats. Planta Med 1995; 61: 402-5.
[146] Tian LY, Bai X, Chen XH, Fang JB, Liu SH, Chen JC. Antidiabetic effect of methylswertianin and bellidifolin from Swertia punicea Hemsl. and its potential mechanism. Phytomedicine 2010; 17: 533-9.
[147] Group SRTR. A randomized trial of sorbinil, an aldose reductase inhibitor, in diabetic retinopathy. Arch Ophthalmol 1990; 108: 1234.
[148] Greene D, Arezzo J, Brown M. Effect of aldose reductase inhibition on nerve conduction and morphometry in diabetic neuropathy. Neurology 1999; 53: 580-0.
[149] Dunlop M. Aldose reductase and the role of the polyol pathway in diabetic nephropathy. Kidney Int 2000; 58: S3-12.
[150] Kinoshita JH, Kador P, Catiles M. Aldose reductase in diabetic cataracts. JAMA 1981; 246: 257-61.
[151] Matsuda H, Nishida N, Yoshikawa M. Antidiabetic principles of natural medicines. V. Aldose reductase inhibitors from Myrcia multiflora DC.(2): Structures of myrciacitrins III, IV, and V. Chem Pharm Bull 2002; 50: 429-31.
[152] Varma SD, Kinoshita JH. Inhibition of lens aldose reductase by flavonoids—their possible role in the prevention of diabetic cataracts. Biochem Pharmacol 1976; 25: 2505-13.
[153] Yoshikawa M, Nishida N, Shimoda H, Takada M, Kawahara Y, Matsuda H. Polyphenol constituents from Salacia species: quantitative analysis of mangiferin with alpha-glucosidase and aldose reductase inhibitory activities. J Pharm Soc Japan 2001; 121: 371-8.
[154] Betteridge DJ. What is oxidative stress? Metabolism 2000; 49: 3-8.
[155] Jenner P. Oxidative stress in Parkinson's disease. Annl Neurol 2003; 53: S26-38.
[156] Christen Y. Oxidative stress and Alzheimer disease. Am J Clin Nutr 2000; 71: 621s-9.
[157] Ishii T, Yasuda K, Akatsuka A, Hino O, Hartman PS, Ishii N. A mutation in the SDHC gene of complex II increases oxidative stress, resulting in apoptosis and tumorigenesis. Cancer Res 2005; 65: 203-9.
[158] Ha H, Kim KH. Pathogenesis of diabetic nephropathy: the role of oxidative stress and protein kinase C. Diabetes Res Clin Pract 1999; 45: 147-51.
[159] Singh U, Jialal I. Oxidative stress and atherosclerosis. Pathophysiology 2006; 13: 129-42.
[160] Kowluru RA. Effect of reinstitution of good glycemic control on retinal oxidative stress and nitrative stress in diabetic rats. Diabetes 2003; 52: 818-23.
[161] Cai L, Kang YJ. Oxidative stress and diabetic cardiomyopathy. Cardiovasc Toxicol 2001; 1: 181-93.
[162] Tak PP, Zvaifler NJ, Green DR, Firestein GS. Rheumatoid arthritis and p53: how oxidative stress might alter the course of inflammatory diseases. Immunol Today 2000; 21: 78-82.
[163] Blomhoff R. Antioxidants and oxidative stress. Tidsskrift for Den Norske Laegeforening: Tidsskrift for Praktisk Medicin, ny Raekke 2004; 124: 1643-5.
[164] Urquiaga I, Leighton F. Plant polyphenol antioxidants and oxidative stress. Biol Res 2000; 33: 55-64.

[165] Sabu M, Smitha K, Kuttan R. Anti-diabetic activity of green tea polyphenols and their role in reducing oxidative stress in experimental diabetes. J Ethnopharmacol 2002; 83: 109-16.
[166] Latif R. Chocolate/cocoa and human health: a review. Netherlands J Med 2013; 71: 63-8.
[167] Drel VR, Sybirna N. Protective effects of polyphenolics in red wine on diabetes associated oxidative/nitrative stress in streptozotocin-diabetic rats. Cell Biol Int 2010; 34: 1147-53.
[168] Guilford JM, Pezzuto JM. Wine and health: a review. Am J Enol Viticult 2011; 62: 471-86.
[169] Larocca LM, Teofili L, Sica S, *et al*. Quercetin inhibits the growth of leukemic progenitors and induces the expression of transforming growth factor-beta 1 in these cells. Blood 1995; 85: 3654-61.
[170] Budin SB, Ismail H, Pek LC. *Psidium guajava* fruit peel extract reduces oxidative stress of pancreas in streptozotocin-induced diabetic rats. Sains Malaysiana 2013; 42: 707-13.
[171] Vessal M, Hemmati M, Vasei M. Antidiabetic effects of quercetin in streptozocin-induced diabetic rats. Comp Biochem Physiol C Toxicol Pharmacol 2003; 135: 357-64.
[172] Jorge AP, Horst H, de Sousa E, Pizzolatti MG, Silva FRMB. Insulinomimetic effects of kaempferitrin on glycaemia and on 14 C-glucose uptake in rat soleus muscle. Chem-Biol Interact 2004; 149: 89-96.
[173] Daisy P, Balasubramanian K, Rajalakshmi M, Eliza J, Selvaraj J. Insulin mimetic impact of Catechin isolated from Cassia fistula on the glucose oxidation and molecular mechanisms of glucose uptake on Streptozotocin-induced diabetic Wistar rats. Phytomedicine 2010; 17: 28-36.
[174] Jayaprakasam B, Vareed SK, Olson LK, Nair MG. Insulin secretion by bioactive anthocyanins and anthocyanidins present in fruits. J Agric Food Chem 2005; 53: 28-31.
[175] Singh R, Barden A, Mori T, Beilin L. Advanced glycation end-products: a review. Diabetologia 2001; 44: 129-46.
[176] Ahmed N. Advanced glycation endproducts—role in pathology of diabetic complications. Diabetes Res Clin Pract 2005; 67: 3-21.
[177] Wu Q, Chen H, Lv Z, *et al*. Oligomeric procyanidins of lotus seedpod inhibits the formation of advanced glycation end-products by scavenging reactive carbonyls. Food Chem 2013; 138: 1493-502.
[178] Wu CH, Yen GC. Inhibitory effect of naturally occurring flavonoids on the formation of advanced glycation endproducts. J Agric Food Chem 2005; 53: 3167-73.
[179] Lee I-S, Kim IS, Lee YM, Lee Y, Kim J-H, Kim JS. 2 ″, 4 ″-O-diacetylquercitrin, a novel advanced glycation end-product formation and aldose reductase inhibitor from Melastoma sanguineum. Chem Pharm Bull 2013; 61: 662-5.
[180] Xie Y, Chen X. Structures required of polyphenols for inhibiting advanced glycation end products formation. Curr Drug Metabol 2013; 14: 414-31.
[181] van Summeren-Wesenhagen PV, Marienhagen J. Metabolic engineering of Escherichia coli for the synthesis of the plant polyphenol pinosylvin. Appl Environ Microbiol 2015; 81: 840-9.
[182] Beekwilder J, Wolswinkel R, Jonker H, Hall R, de Vos CR, Bovy A. Production of resveratrol in recombinant microorganisms. Appl Environ Microbiol 2006; 72: 5670-2.
[183] Hwang EI, Kaneko M, Ohnishi Y, Horinouchi S. Production of plant-specific flavanones by *Escherichia coli* containing an artificial gene cluster. Appl Environ Microbiol 2003; 69: 2699-706.
[184] Manivannan A, Soundararajan P, Park YG, Sakkiah S, Jeong BR. Binding mode investigation of polyphenols from scrophularia targeting human aldose reductase using molecular docking and molecular dynamics simulations. J Chem 2015; 2015; Article ID434256.
[185] Burdulis D, Ivanauskas L, Dirse V, Kazlauskas S, Razukas A. Study of diversity of anthocyanin composition in bilberry (*Vaccinium myrtillus* L.) fruits. Medicina (Kaunas, Lithuania) 2007; 43: 971-7.
[186] Einbond LS, Reynertson KA, Luo X-D, Basile MJ, Kennelly EJ. Anthocyanin antioxidants from edible fruits. Food Chem 2004; 84: 23-28.
[187] Solomon A, Golubowicz S, Yablowicz Z, *et al*. Antioxidant activities and anthocyanin content of fresh fruits of common fig (Ficus carica L.). J Agric Food Chem 2006; 54: 7717-23.
[188] Sass-Kiss A, Kiss J, Milotay P, Kerek M, Toth-Markus M. Differences in anthocyanin and carotenoid content of fruits and vegetables. Food Res Int 2005; 38: 1023-9.
[189] Bowen-Forbes CS, Zhang Y, Nair MG. Anthocyanin content, antioxidant, anti-inflammatory and anticancer properties of blackberry and raspberry fruits. J Food Composit Analysis 2010; 23: 554-60.
[190] Sun J, Yao J, Huang S, Long X, Wang J, García-García E. Antioxidant activity of polyphenol and anthocyanin extracts from fruits of Kadsura coccinea (Lem.) AC Smith. Food Chem 2009; 117: 276-81.
[191] Bureau S, Renard CM, Reich M, Ginies C, Audergon JM. Change in anthocyanin concentrations in red apricot fruits during ripening. LWT-Food Sci Technol 2009; 42: 372-7.
[192] Machado TdB, Leal IC, Amaral ACF, Santos K, Silva MGD, Kuster RM. Antimicrobial ellagitannin of Punica granatum fruits. J Brazil Chem Soc 2002; 13: 606-610.
[193] Vrhovsek U, Giongo L, Mattivi F, Viola R. A survey of ellagitannin content in raspberry and blackberry cultivars grown in Trentino (Italy). Eur Food Res Technol 2008; 226: 817-24.
[194] Bochi VC, Godoy HT, Giusti MM. Anthocyanin and other phenolic compounds in Ceylon gooseberry (Dovyalis hebecarpa) fruits. Food Chem 2015; 176: 234-43.
[195] Koponen JM, Happonen AM, Mattila PH, Törrönen AR. Contents of anthocyanins and ellagitannins in selected foods consumed in Finland. J Agric Food Chem 2007; 55: 1612-9.
[196] Lugasi A, Takács M. Flavonoid aglycons in foods of plant origin II. Fresh and dried fruits. Acta Aliment 2002; 31: 63-71.
[197] Fu L, Xu BT, Xu XR, *et al*. Antioxidant capacities and total phenolic contents of 62 fruits. Food Chem 2011; 129: 345-50.
[198] Dağdelen A, Tümen G, Özcan MM, Dündar E. Phenolics profiles of olive fruits (Olea europaea L.) and oils from Ayvalık, Domat and Gemlik varieties at different ripening stages. Food Chem 2013; 136: 41-5.
[199] Füzfai Z, Molnár-Perl I. Gas chromatographic–mass spectrometric fragmentation study of flavonoids as their trimethylsilyl derivatives: Analysis of flavonoids, sugars, carboxylic and amino acids in model systems and in citrus fruits. J Chromatogr A 2007; 1149: 88-101.
[200] Arts IC, van de Putte B, Hollman PC. Catechin contents of foods commonly consumed in The Netherlands. 1. Fruits, vegetables, staple foods, and processed foods. J Agric Food Chem 2000; 48: 1746-51.
[201] Tsanova-Savova S, Ribarova F, Gerova M. (+)-Catechin and (−)-epicatechin in Bulgarian fruits. J Food Composit Anal 2005; 18: 691-8.
[202] Suzuki T, Someya S, Hu F, Tanokura M. Comparative study of catechin compositions in five Japanese persimmons (Diospyros kaki). Food Chem 2005; 93: 149-52.
[203] Sultana B, Anwar F. Flavonols (kaempeferol, quercetin, myricetin) contents of selected fruits, vegetables and medicinal plants. Food Chem 2008; 108: 879-84.
[204] Olszewska M. Separation of quercetin, sexangularetin, kaempferol and isorhamnetin for simultaneous HPLC determination of flavonoid aglycones in inflorescences, leaves and fruits of three Sorbus species. J Pharm Biomed Anal 2008; 48: 629-35.
[205] Ozga JA, Saeed A, Wismer W, Reinecke DM. Characterization of cyanidin-and quercetin-derived flavonoids and other phenolics in mature saskatoon fruits (Amelanchier alnifolia Nutt.). J Agric Food Chem 2007; 55: 10414-24.
[206] Pastrana-Bonilla E, Akoh CC, Sellappan S, Krewer G. Phenolic content and antioxidant capacity of muscadine grapes. J Agric Food Chem 2003; 51: 5497-503.
[207] Wang SY, Chen CT, Wang CY, Chen P. Resveratrol content in strawberry fruit is affected by preharvest conditions. J Agric Food Chem 2007; 55: 8269-74.
[208] Ehala S, Vaher M, Kaljurand M. Characterization of phenolic profiles of Northern European berries by capillary electrophoresis and determination of their antioxidant activity. J Agric Food Chem 2005; 53: 6484-90.
[209] Huang X, Mazza G. Simultaneous analysis of serotonin, melatonin, piceid and resveratrol in fruits using liquid chromatography tandem mass spectrometry. J Chromatogr 2011; 1218: 3890-9.
[210] Atanassova M, Bagdassarian V. Rutin content in plant products. J Univ Chem Technol Metallurgy 2009; 44: 201-3.
[211] Łata B, Trampczynska A, Paczesna J. Cultivar variation in apple peel and whole fruit phenolic composition. Sci Horticulture 2009; 121: 176-81.
[212] Marín FR, Del Río JA. Selection of hybrids and edible Citrus species with a high content in the diosmin functional compound.

Modulating effect of plant growth regulators on contents. J Agric Food Chem 2001; 49: 3356-62.
[213] Kumazawa S, Ikenaga M, USUI Y, *et al*. Comprehensive analysis of polyphenols in fruits consumed in Japan. Food Sci Technol Res 2007; 13: 404-13.
[214] Matsui T, Ebuchi S, Kobayashi M, *et al*. Anti-hyperglycemic effect of diacylated anthocyanin derived from Ipomoea batatas cultivar Ayamurasaki can be achieved through the α-glucosidase inhibitory action. J Agric Food Chem 2002; 50: 7244-8.
[215] Llorach R, Martínez-Sánchez A, Tomás-Barberán FA, Gil MI, Ferreres F. Characterisation of polyphenols and antioxidant properties of five lettuce varieties and escarole. Food Chem 2008; 108: 1028-38.
[216] Wu X, Beecher GR, Holden JM, Haytowitz DB, Gebhardt SE, Prior RL. Concentrations of anthocyanins in common foods in the United States and estimation of normal consumption. J Agric Food Chem 2006; 54: 4069-4075.
[217] Li H, Deng Z, Zhu H, *et al*. Highly pigmented vegetables: Anthocyanin compositions and their role in antioxidant activities. Food Res Int 2012; 46: 250-9.
[218] Handa SS. Indian herbal pharmacopoeia. Reg Res Lab 1998.
[219] Rizvi SI, Mishra N. Anti-oxidant effect of quercetin on type 2 diabetic erythrocytes. J Food Biochem 2009; 33: 404-15.
[220] Murota K, Hotta A, Ido H, *et al*. Antioxidant capacity of albumin-bound quercetin metabolites after onion consumption in humans. J Med Invest 2007; 54: 370-374.
[221] Gupta R, Mathur M, Bajaj VK, *et al*. Evaluation of antidiabetic and antioxidant activity of Moringa oleifera in experimental diabetes. J Diabetes 2012; 4: 164-71.
[222] Kumar A, Malik AK, Tewary DK. A new method for determination of myricetin and quercetin using solid phase microextraction–high performance liquid chromatography–ultra violet/visible system in grapes, vegetables and red wine samples. Anal Chim Acta 2009; 631: 177-81.
[223] Tokuşoğlu Ö, Ünal M, Yıldırım Z. HPLC-UV and GC-MS characterization of the flavonol aglycons quercetin, kaempferol, and myricetin in tomato pastes and other tomato-based products. Acta Chromatogr 2003; 13: 196-207.
[224] Lugasi A, Hóvári J, Sági KV, Bíró L. The role of antioxidant phytonutrients in the prevention of diseases. Acta Biol Szegediensis 2003; 47: 119-25.
[225] Horcajada-Molteni MN, Crespy V, Coxam V, Davicco MJ, Rémésy C, Barlet JP. Rutin inhibits ovariectomy-induced osteopenia in rats. J Bone Mineral Res 2000; 15: 2251-8.
[226] Stevenson A. Rutin content of asparagus. J Food Science 1950; 15: 150-4.
[227] Li P, Wang X, Wang H, Wu Y-N. High performance liquid chromatographic determination of phenolic acids in fruits and vegetables. Biomed Environ Sci 1993; 6: 389-98.
[228] Kowalski R, Kowalska G. Phenolic acid contents in fruits of aubergine (Solanum melongena L.). Polish J Food Nutr Sci 2005; 14: 37-41.
[229] Martínez-Valverde I, Periago MJ, Provan G, Chesson A. Phenolic compounds, lycopene and antioxidant activity in commercial varieties of tomato (Lycopersicum esculentum). J Sci Food Agric 2002; 82: 323-30.
[230] Alasalvar C, Grigor JM, Zhang D, Quantick PC, Shahidi F. Comparison of volatiles, phenolics, sugars, antioxidant vitamins, and sensory quality of different colored carrot varieties. J Agric Food Chem 2001; 49: 1410-6.
[231] Rossetto M, Lante A, Vanzani P, Spettoli P, Scarpa M, Rigo A. Red chicories as potent scavengers of highly reactive radicals: a study on their phenolic composition and peroxyl radical trapping capacity and efficiency. J Agric Food Chem 2005; 53: 8169-75.
[232] Miean KH, Mohamed S. Flavonoid (myricetin, quercetin, kaempferol, luteolin, and apigenin) content of edible tropical plants. J Agric Food Chem 2001; 49: 3106-12.
[233] Karadeniz F, Burdurlu HS, Nuray k, Soyer y. Antioxidant activity of selected fruits and vegetables grown in Turkey. Turkish J Agric Forestry 2005; 29: 297-303.
[234] Hokayem M, Blond E, Vidal H, *et al*. Grape polyphenols prevent fructose-induced oxidative stress and insulin resistance in first-degree relatives of type 2 diabetic patients. Diabetes care 2013; 36: 1454-61.
[235] Fenercioglu AK, Saler T, Genc E, Sabuncu H, Altuntas Y. The effects of polyphenol-containing antioxidants on oxidative stress and lipid peroxidation in Type 2 diabetes mellitus without complications. J Endocrinol Invest 2010; 33: 118-24.
[236] Wilson T, Luebke JL, Morcomb EF, *et al*. Glycemic responses to sweetened dried and raw cranberries in humans with type 2 diabetes. J Food Sci 2010; 75: H218-23.
[237] Fukino Y, Ikeda A, Maruyama K, Aoki N, Okubo T, Iso H. Randomized controlled trial for an effect of green tea-extract powder supplementation on glucose abnormalities. Eur J Clin Nutr 2008; 62: 953-60.
[238] Panlasigui LN, Thompson LU. Blood glucose lowering effects of brown rice in normal and diabetic subjects. Int J Food Sci Nutr 2006; 57: 151-8.
[239] Rosenblat M, Hayek T, Aviram M. Anti-oxidative effects of pomegranate juice (PJ) consumption by diabetic patients on serum and on macrophages. Atherosclerosis 2006; 187: 363-71.
[240] Banini AE, Boyd LC, Allen JC, Allen HG, Sauls DL. Muscadine grape products intake, diet and blood constituents of non-diabetic and type 2 diabetic subjects. Nutrition 2006; 22: 1137-45.
[241] Fukino Y, Shimbo M, Aoki N, Okubo T, Iso H. Randomized controlled trial for an effect of green tea consumption on insulin resistance and inflammation markers. J Nutr Sci Vitaminol 2005; 51: 335-42.

Received: October 10, 2015 **Accepted: November 24, 2015**