

Review

Dietary Flavonoids in the Prevention of T2D: An Overview

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Abstract: Type 2 diabetes (T2D) is a progressive metabolic disease that is increasing in prevalence globally. It is well established that insulin resistance (IR) and a progressive decline in functional β -cell mass are hallmarks of developing T2D. Obesity is a leading pathogenic factor for developing IR. Constant IR will progress to T2D when β -cells are unable to secrete adequate amounts of insulin to compensate for decreased insulin sensitivity. Recently, a considerable amount of research has been devoted to identifying naturally occurring anti-diabetic compounds that are abundant in certain types of foods. Flavonoids are a group of polyphenols that have drawn great interest for their various health benefits. Results from many clinical and animal studies demonstrate that dietary intake of flavonoids might be helpful in preventing T2D, although cellular and molecular mechanisms underlying these effects are still not completely understood. This review discusses our current understanding of the pathophysiology of T2D and highlights the potential anti-diabetic effects of flavonoids and mechanisms of their actions.

Keywords: flavonoids; type 2 diabetes; insulin resistance

1. Introduction

The prevalence of diabetes is rapidly rising. In 2012, 9.3% of the US population was diabetic [1], and this number is expected to double by 2050 [2]. In addition, the cost of treating diabetes and its complications is an increasing economic burden [3]. In the U.S, the estimated annual cost of diagnosed diabetes increased from \$174 billion to \$245 billion between the years of 2007 and 2012 [4]. Type 2 diabetes (T2D) is a progressive metabolic disorder with a characteristic hyperglycemia accompanied by abnormalities in carbohydrate [5], lipid [6], and protein metabolism [7]. The cascade of events that lead to the development of T2D has long been the subject of debate [8,9]. However, it is well recognized that insulin resistance (IR), defects in insulin action, and impaired β -cell function are key features in T2D [10]. Subjects with IR will progress to overt diabetes if β -cells fail to secrete adequate amounts of insulin to compensate for the defects in its action [11]. Thus, β -cell failure plays a central role in the development T2D.

There is a strong evidence suggesting that hyperglycemia plays a major role in the pathogenesis of diabetic complications that affects various organs in the body [12,13]. Hyperglycemia increases glucose metabolism, which can lead to excessive reactive oxygen species (ROS) production that will impair cell function and survival [14]. Moreover, hyperglycemia, in turn, aggravates IR, thereby forming a vicious circle [15]. Improved glucose control was shown to reduce the risk of diabetic complications such as microvascular complications [16–18]. The type and starting time of treatment upon diagnosis was associated with the risk of developing the complications [17,19]. In addition to insulin therapy,

diabetes treatments include inhibiting oligo- and disaccharide degradation, reducing insulin demand, stimulating endogenous insulin secretion, and enhancing insulin action at target tissues [20,21].

There is a considerable amount of knowledge about the means to prevent and treat T2D, however, this knowledge is not fully applied or practiced in public health [22]. Also, some diabetes therapies have side effects [21] which necessitates the search for naturally occurring, cheaper, and safer compounds for preventing T2D. Flavonoids, polyphenolic compounds abundant in some fruits, vegetables, and medicinal herbs, exert many beneficial effects in various chronic diseases including diabetes [23]. This review will first summarize the current knowledge of IR and pathogenesis of pancreatic β -cell dysfunction in the context of the development of T2D. We will then briefly discuss the bioactivity of the various classes of flavonoids, including the pathways of absorption and metabolism. Primarily, this review will compile recent information from experimental studies, epidemiological observations, and clinical trials on the effects of flavonoids on T2D and the mechanisms of their actions.

2. Type 2 Diabetes

Glucose homeostasis is tightly controlled by the harmonization of multiple pathways in the postprandial (fed) and post-absorptive (fasted) states [24]. After the ingestion of a meal, the majority of glucose is transported into enterocytes lining the wall of the small intestine and then from the enterocytes into the portal vein by the glucose transporters sodium-dependent glucose cotransporter 1 (SGLT1) (brush-border membrane facing the lumen) and glucose transporter 2 (GLUT2) (basolateral membrane facing the bloodstream), respectively [25]. The rise in glucose in the portal vein (drains directly into liver before entering general circulation) induces glucose uptake facilitated by GLUT2, followed by phosphorylation of glucose to glucose-6-phosphate by glucokinase (GK) in the liver [26], hence increasing glucose clearance and storage by the liver before it reaches the circulation [27]. The activation of GK is accompanied by inhibition of a key gluconeogenic enzyme, glucose-6-phosphatase (G6Pase), which is responsible for the last step in gluconeogenesis and glycogenolysis by dephosphorylating glucose to its free form [28]. Consequently, the rate of hepatic glucose production is suppressed [29]. Meanwhile, pancreatic β -cells sense increased circulating glucose and subsequently elevate glucose influx into the cells via GLUT2, which is the only glucose transporter expressed in β -cells. GLUT2 has a low substrate affinity, and mobilization of GLUT2 to the plasma membrane is insulin-independent, which may be necessary for ensuring efficient and high glucose uptake into the cells [30]. It is well characterized that glucose induces insulin secretion through glycolysis and mitochondrial oxidation in the cells, which increase intracellular adenosine triphosphate/adenosine diphosphate (ATP/ADP) ratio, sequentially leading to closure of K_{ATP} channels, depolarization of voltage-gated L-type Ca^{2+} channels on the plasma membrane, Ca^{2+} influx, and ultimate activation of exocytosis of insulin-containing granules [31–33].

After insulin travels from pancreatic β -cells into the portal vein, it then rapidly acts on tissues like the liver to increase glycogen synthesis and reduce glycogenolysis while simultaneously inhibiting gluconeogenesis [34,35]. Skeletal muscle tissue makes a major contribution to insulin-dependent glucose uptake, accounting for about 30% of total glucose clearance as compared with about 39% by splanchnic tissues, primarily by the liver [36]. Glucose uptake is mediated by the combined influence of glucose concentrations (concentration-dependent facilitated diffusion via transporters) and insulin signaling (leading to increased membrane localization of transporters like glucose transporter 4, GLUT4) [37]. Intracellular glucose is phosphorylated by hexokinase in the muscle myofibers [38] and is then routed to different destinations such as glycolysis, oxidation, or glycogen synthesis [39,40]. In the fasting state however, glycogen in the liver is hydrolyzed to release glucose, and gluconeogenesis is increased, in order to maintain glucose homeostasis [41]. When blood glucose levels are low, the secretion of glucagon from pancreatic α -cells increases, which leads to increased glucose production and thus glucose output into the blood [42]. Glucagon acts to enhance the rate of glycogen breakdown and gluconeogenesis in the liver through modulating the transcription and activity of key glucogenic enzymes such as G6Pase and phosphoenolpyruvate carboxykinase (PEPCK) [43]. The liver is the

primary supplier of glucose during fasting and is responsible for about 90% of the overall produced glucose, while the kidneys produce the remaining percentage [44]. Although the muscle stores glycogen [45], it cannot be released to the circulation as free glucose due to the lack of G6Pase [46]. However, peripheral tissues including skeletal muscle and adipose tissues can supply the liver with glucogenic precursors such as amino acids and glycerol, pathways that are blocked in the presence of insulin [47].

Insulin acts on target tissues such as muscle, liver, and adipose tissues [9]. It binds to its plasma membrane receptor, a tyrosine kinase receptor, which then triggers a chain of events that eventually affects many processes in the short and long term including glucose and lipid metabolic homeostasis [48]. However, IR in peripheral tissues such as skeletal muscle reduces glucose uptake, utilization, and storage [49]. Moreover, IR in the liver can result in excessive hepatic glucose production because of increased gluconeogenesis and glycogenolysis, which make a significant contribution to fasting and postprandial hyperglycemia, the hallmarks of T2D [50–52]. Likewise, IR may impair the function of the kidneys [53], thereby contributing to the development of hyperglycemia in T2D, as kidneys also play a role in regulating glucose homeostasis [54]. In normal subjects, kidneys act similarly to the liver in maintaining glucose homeostasis through glucose uptake and production in the fed [55] and fasting state [56], respectively. There is a reciprocal relationship between liver and kidneys to maintain glucose homeostasis referred to as hepatorenal glucose reciprocity [57,58]. In animal models of T2D, glucose transporters in kidneys are upregulated [59], which results in increased glucose reabsorption [60]. Similar findings were reported in T2D patients suggesting that the increased activity of glucose transporters in kidneys might make substantial contribution to hyperglycemia in T2D [61].

2.1. IR and T2D

The underlying mechanisms that lead to the development of IR are still an active area of investigation. Many genetic and environmental factors are involved in the development of IR [62]. One of the biggest difficulties in investigating IR is the accompanying metabolic abnormalities referred to as IR syndrome (IRS), or more commonly metabolic syndrome (MetS) [63], which also increases the risk of developing T2D [64]. Elevated plasma free fatty acids (FFAs) associated with obesity [65] or independent of obesity, i.e., consumption of a large amount of dietary fat, may impair the insulin signaling pathway leading to IR in the muscle and liver [66,67]. Other factors that play a role in inducing IR are genetic polymorphisms, abnormal cytokine and adipokine production, and endothelial dysfunction [65], which will be discussed in more detail in this review.

2.1.1. IR in Muscle and Development of T2D

There is strong evidence suggesting that IR in skeletal muscle is a primary risk factor for T2D [68,69]. For glucose uptake, storage and utilization in the muscle, insulin activation of the insulin receptor substrate (IRS)-1/phosphatidylinositol (PI)-3 kinase (PI3K)/kinase B (or Akt) pathway is required [70]. However, this pathway was reported to be impaired in subjects that were genetically predisposed to developing T2D [71], and in T2D patients [72]. Due to this defect in signaling, IR develops in the muscle leading to a decrease in glucose uptake and utilization (mainly in glycogen synthesis) [73].

Obesity is a major risk factor for developing T2D, particularly once associated with IR [74]. In obesity, plasma FFAs are chronically elevated [65], which in muscle, can directly inhibit insulin activation of the IRS-1/PI3K/Akt pathway leading to reduced glucose uptake and phosphorylation, and decreased glycogen synthase activity [66,67]. One of the pathways connected to this alteration in insulin signaling is the diacylglycerol (DAG)/protein kinase C (PKC) pathway. Elevation of FFAs was associated with an increase in DAG, which in turn activates PKC- θ , - β 2 and - δ [75]. The activation of these isoforms phosphorylates IRS1 on Ser³⁰⁷, which interferes with insulin-stimulated phosphorylation of IRS1, thus inhibiting insulin signaling [76]. The excess deposition of intramyocellular lipid (IMCL), which is associated with IR in lean and obese subjects [77], may play a role in inducing IR by activating

the DAG/PKC pathway similar to FFAs. However, IMCL activates another PKC isoform, PKC- ϵ , which induces IR [78,79]. Increased activity of these PKC isoforms in muscle was observed in animal models of obesity and T2D [80,81].

Mitochondria generate energy via oxidative phosphorylation of nutrients such as glucose and fatty acids and thus play an important role in the regulation of cellular metabolism [82]. Mitochondrial dysfunction has been implicated in the development of IR. Indeed, defects in glucose uptake in the muscle of T2D subjects was associated with decreased glucose oxidation [83] and impaired fatty acid metabolism [84], indicative of mitochondrial dysfunction. The decrease in glucose uptake and utilization observed in the muscles of IR subjects may be the cause or the result of the mitochondrial dysfunction. For instance, impaired mitochondrial activity in muscles of IR subjects may lead to increased IMCL deposition which subsequently results in the development of IR [85]. Moreover, downregulation of genes encoding key enzymes for mitochondrial oxidative phosphorylation in the muscle is also linked to IR and T2D [86]. However, the cause and effect relationship between IR and mitochondrial function is still elusive. For example, IR increases ROS production leading to impaired mitochondrial function [87]. For more information about the role of dysfunctional mitochondria in developing IR and T2D, please refer to the comprehensive review by Szendroedi et al. [88].

The endothelium is essential for regulating vascular tone, and endothelial dysfunction impairs the release of nitric oxide (NO), thus affecting vascular homeostasis [89]. In particular, dysfunction of the peripheral vascular endothelium plays a role in the pathogenesis of IR [90]. This vascular dysfunction results in reduced expansion of the capillary network in the major target tissues of insulin such as the skeletal muscle, thereby reducing blood flow and supply of insulin to these tissues, which then subsequently impairs glucose and lipid metabolism [91].

2.1.2. IR in Liver and Development of T2D

The liver has a vital role in maintaining glucose homeostasis in both the fed and fasting states with a major contribution to the latter [24]. Increased hepatic glucose production is considered to be one of the early pathological changes leading to T2D in humans [50,92,93]. There is evidence suggesting that such hepatic metabolic abnormalities in T2D are caused primarily by IR [94]. Insulin is involved in the direct and indirect suppression of hepatic glucose production, which is impaired when there is hepatic IR. In healthy subjects, insulin can suppress the flux of the glucogenic precursors from peripheral tissues such as nonesterified fatty acids to the liver, by promoting lipogenesis and inhibiting lipolysis in adipose tissue [95]. Also, insulin inhibits glucagon production and subsequently reduces the expression and activity of glucogenic enzymes such as PEPCK and G6Pase [96]. However, in IR these indirect pathways are not blocked, in part because insulin is unable to adequately regulate the gene expression and function of PEPCK [97] and G6Pase [98], leading to excessive hepatic glucose production through gluconeogenesis and glycogenolysis, thereby contributing to fasting hyperglycemia [50–52]. Increased hepatic gluconeogenesis, in particular, is considered one of the early pathological changes in newly diagnosed T2D subjects [50]. The activation of Akt by insulin contributes to the control of hepatic glucose metabolism [99], reduction in hepatic glucose output by stimulating glycogen synthesis [100,101], and downregulation of PEPCK and G6Pase gene expression [102]. In one report, gene expression of PEPCK and G6Pase was not changed nor was associated with fasting hyperglycemia in T2D subjects [103]. However, morbidly obese patients with T2D had an increase in hepatic glucose production which was associated with IR and an increase in liver G6Pase activity [104], suggesting that the increased gluconeogenic enzymes' activities rather than their expression may play a larger role for gluconeogenesis in IR and diabetic subjects.

The forkhead box O (FoxO) family of transcription factors play important roles in a variety of physiological and pathological processes. Altered FoxO expression was associated with several metabolic diseases including diabetes. FoxO1 plays a role in mediating hormone-induced hepatic gluconeogenesis [105], by activating transcription of genes encoding PEPCK and G6Pase [106]. Liver-specific FoxO1 knockout mice displayed fasting hypoglycemia associated with reduced

expression of gluconeogenic genes [107]. In addition, FoxO3 and FoxO4 enhance FoxO1-induced hepatic glucose production in mice [107], suggesting that these FoxO transcription factors collectively contribute to the control of hepatic glucose production. The action of FoxO1 in the liver is suppressed by insulin-mediated pathways but is augmented by peroxisome proliferative activated receptor-gamma co-activator-1alpha (PGC-1 α), which serves as a transcriptional co-activator for FoxO1, thereby augmenting the expression of gluconeogenic genes. [108]. Interestingly, PGC-1 α expression was upregulated in the liver of T2D subjects [109], which might partially explain the link between PGC-1 α , FoxO1, and glucose production in diabetes. Recently, another FoxO family member, FoxO6 was found to play a similar role as FoxO1 in regulating gluconeogenesis, as increased FoxO6 activity in the liver promoted gluconeogenesis and increased fasting blood glucose levels, whereas FoxO6 deletion in the liver reduced gluconeogenesis, resulting in fasting hypoglycemia. However, unlike FoxO1, the transcriptional activity of FoxO6 is largely inhibited by insulin through activation of the Akt-mediated pathway, which leads to its nuclear exclusion and degradation in hepatocytes [110].

IR in skeletal muscle can cause the development of IR in the liver. In muscle tissues with IR, the failure of insulin to activate glycogen synthesis leads to a repartitioning of energy substrates to de novo lipogenesis in the liver [111], which lead to the accumulation of fat in hepatocytes [112]. Moreover, excess intrahepatocellular lipid (IHCL) accumulation and elevated FFAs may cause a wide spectrum of dysfunctions in the liver, including IR. On the other hand, hepatic IR may precede the development of IR in the muscle. For instance, high fat (HF) overfeeding induced hepatic IR in healthy subjects, along with elevated fasting blood glucose levels and insulin secretion before the development of IR in the muscle [113]. Similarly, short-term HF diet feeding in rats resulted in hepatic IR and hepatic steatosis, which was independent of IR in skeletal muscle. However, it was associated with activation of PKC- ϵ , attenuated insulin-stimulated signaling pathways, increased gluconeogenesis, and decreased insulin-dependent activation of glycogen synthase [114]. The activation of PKC- ϵ by FFAs and IHCL in the liver was consistent with the activation of this isoform in the muscle. In this regard, DAG may play a role in the activation of PKC which then inhibits insulin activation of IRS and subsequently its initiated signaling, thereby leading to the development of hepatic IR and hyperglycemia [111,115]. The accumulation of lipids in the liver and the promotion of fatty acid oxidation may increase ROS production, which then impairs mitochondrial functions and induce abnormalities in liver function [116].

2.1.3. Relationship between Obesity, Inflammation, IR and Development of T2D

Obesity, a condition of fat accumulation in the body defined as having a body mass index (BMI) ≥ 30 , is a worldwide epidemic that is still increasing globally [117]. Obesity is strongly associated with the development of IR, dyslipidemia, and T2D [118]. It is well recognized that obesity is partly a chronic inflammatory disease. Indeed, studies have suggested a direct connection between obesity and systematic inflammation due to the upregulation of key genes associated with inflammation [119], and the increased secretion of inflammatory markers from white adipose tissue (WAT) [120]. Abdominal obesity, in particular, is associated with many chronic diseases where visceral fat is responsible for the abnormally increased production of various proinflammatory adipokines including tumor necrosis factor-alpha (TNF- α), monocyte chemoattractant protein-1 (MCP-1), and interleukin 6 (IL-6) [121,122]. While WAT contains various other types of immune cells such as dendritic cells, T-lymphocytes, B-cells, and neutrophils during obesity, increased number of macrophages infiltrated into adipose tissue attracted by adipocyte-released chemokines as well as changes in inflammatory phenotype of residing macrophages induced by adipose hypertrophy, adipocyte necrosis, and increased lipotoxicity play a major role in initiating a low-grade systematic inflammation in obesity, which has been reviewed elsewhere [123].

Accumulating evidence shows that inflammation initiated from adipose tissue is one of the major contributing factors for the development of IR and T2D. In particular, TNF- α secreted from adipose tissue [124] and from the infiltrated macrophages in adipose tissue [125] may play an important

role in developing obesity-associated IR. TNF- α expression levels are elevated in obese and diabetic rodent models [126]. Adipocytes exposed to TNF- α impaired insulin-stimulated glucose uptake via reducing insulin activation of IRS-1 [127], whereas neutralization of TNF- α significantly improved insulin-mediated peripheral glucose uptake [126]. Consistently, deletion of TNF- α gene in rodent models of obesity protected them from developing IR [128]. One of the proposed mechanisms by which TNF- α induces IR is through the activation of the c-Jun N-terminal kinase (JNK), and I kappa beta kinase ($I\kappa\beta$ K), which subsequently phosphorylates IRS-1 on Ser³⁰⁷, thereby suppressing IRS-1-mediated insulin action [129]. In addition, TNF- α inhibits the activity of AMP-activated protein kinase (AMPK), which is considered to be a master regulator of whole body energy homeostasis critical for maintaining insulin sensitivity [130]. Activation of AMPK inhibits hepatic gluconeogenesis [131], promotes fatty acids oxidation [132], inhibits fatty acid synthesis [133,134], regulates PGC-1 α -mediated mitochondrial biogenesis [135,136], and increases GLUT4 expression in skeletal muscle [137]. It was demonstrated that the inhibition of AMPK in the muscle by TNF- α lead to the development of IR [138].

IL-6 is another cytokine that could be secreted from adipose tissue and may be associated with IR. IL-6 plasma levels were robustly elevated in obesity [139]. In T2D individuals, IL-6 was independently associated with IR and hyperglycemia [140]. It can induce hepatic production of the inflammatory marker C-reactive protein (CRP) [141], suggesting a role in IR [142]. However, it is still unclear whether IL-6 adversely affects glucose uptake and metabolism. In healthy mice and humans IL-6 can enhance fatty acid oxidation and an insulin-stimulated glucose uptake [143,144]. In T2D subjects, however, insulin-stimulated glucose uptake was not affected by intravenous infusion of IL-6 [145].

Adiponectin is a plasma protein secreted from mature adipocytes and has insulin-sensitizing effect [146]. Unlike other adipokines, circulating adiponectin concentrations are inversely associated with markers of IR and development of T2D [147,148]. Low levels of adiponectin found in obesity were associated with inflammation, whereas a loss in weight increased circulating adiponectin [149]. Adiponectin administration reversed IR in rodent models of obesity [150,151]. Adiponectin binds to its receptors adiponectin receptor protein 1 (AdipoR1) and adiponectin receptor protein 2 (AdipoR2), which are expressed in the liver and skeletal muscle [152] and mediate its various biological effects, including activation of peroxisome proliferator-activated receptor (PPAR)- α [153] and AMPK [154]. Adiponectin may enhance insulin sensitivity via activating the AdipoR1/liver kinase B1 (LKB1)/AMPK pathway, which then suppresses the expression of sterol regulatory element-binding protein (SREBP)-1c [155]. SREBP-1c modulates fat metabolism by upregulating key enzymes on the hepatic fatty acid synthesis pathway such as fatty acid synthase, acetyl coenzyme A (acetyl-CoA) carboxylase, acetyl-CoA synthetase and others. Together, the suppression of SREBP1c and activation of AMPK improve fatty acid metabolism and prevent its accumulation in the liver thereby enhancing insulin sensitivity [156]. Adiponectin may also have functions independent of its receptors. Interestingly, one study showed that adiponectin enhanced insulin sensitivity in mice by inducing the production of IL-6 from macrophages, which then upregulated hepatic IRS-2 expression independent of adiponectin known receptors [157].

2.2. Impaired Insulin Secretion and Development of T2D

It is well known that T2D is characterized by impaired insulin secretion [158]. Both β -cell dysfunction and a decrease in β -cell mass contribute to insulin secretion abnormalities in T2D [159]. There are common mechanisms that regulate both β -cell insulin secretory function and mass [160], suggesting that a combination of β -cell dysfunction and loss of mass is the precipitating factor for impaired insulin secretion in T2D [161]. Progression in β -cell impairment may be at least partially due to increased production of ROS, which results from the abnormal antioxidant status in T2D [162,163]. The increased ROS production in β -cells could be generated from excess amounts of saturated fatty acids (lipotoxicity) and glucose (glucotoxicity) that gradually cause β -cell apoptosis and impair cellular function, thereby contributing to the pathogenesis of T2D [164–167].

3. Flavonoids

3.1. Discovery and Classifications

Flavonoids are widespread in the plant kingdom [168]. They are synthesized in plants as secondary metabolites from phenylalanine [169]. Many flavonoids have antioxidant capabilities [170] that protect plant membrane from desiccation, oxidation [171], and ultraviolet (UV) damage [172]. Flavonoids are important for the proper development of plants [173], and can improve plant growth [174] and support plant defense systems against microbial invasion [175].

Plants and food products containing flavonoids have been used to treat various human diseases since ancient times [176], although flavonoids were not discovered and characterized until the twentieth century. In the 1930s, Rusznyak and Szent-Gyorgyi extracted a substance containing a mixture of flavonoids from Hungarian peppers that had an action on vascular permeability and named it vitamin P [177]. The advances in flavonoids research in the 1970s led to the discovery of many other flavonoids, clearing the path for characterization of their structures and biological activities [178]. Although flavonoids were classified as semi-essential food components [179] and suggested as a new class of drugs due to their potential in treating many human diseases [168], extensive research on their effects on disease prevention was not started until the middle of the 1990s [180]. Recently, flavonoids have been referred to as nutraceuticals [181], a hybrid term describing a product that combines nutrients and pharmaceuticals [182] and defined as “any non-toxic food extract supplement that has scientifically proven health benefits for both the treatment and prevention of disease” [183].

Over 9000 flavonoid compounds have been identified from plant sources [184] sharing the basic chemical structure of a common three-ring moiety (A-, C- and B-rings) with 15 carbon atoms (C6–C3–C6) (Figure 1). The substitution of a functional group of the heterocyclic ring (C-ring) with a methyl, hydroxyl, glycan, acetyl or other group, along with the C-ring oxidation state determines the classification of various subclasses of flavonoids [185]. Flavonoids in each subclass are further structurally diversified due to different patterns of hydroxylation of the phenolic rings.

Flavonoids are divided into two main groups based on structure, 2-phenylchromans (flavonoids) and 3-phenylchromans (isoflavonoids). The 2-phenylchromans group includes the subclasses of flavanones, flavones, flavonols, flavan-3-ols, and anthocyanidins; whereas the 3-phenylchromans includes the subclasses of isoflavones, isoflavans, and pterocarpanes [186].

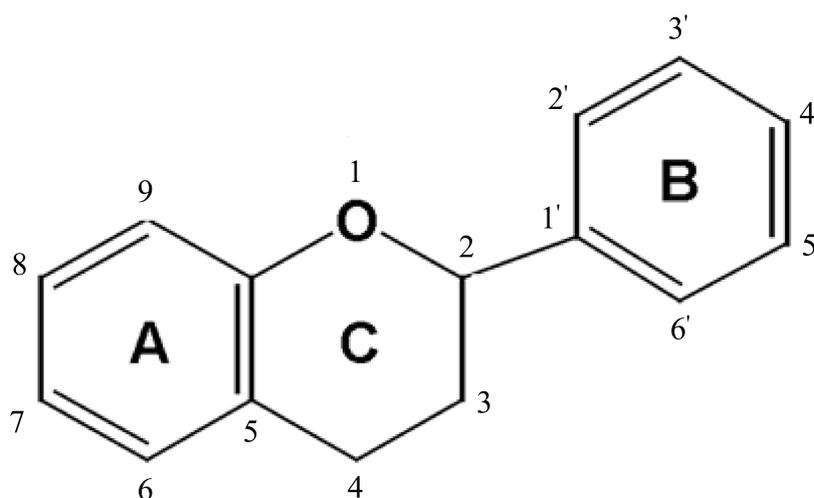


Figure 1. General structure of flavonoids.

The content of flavonoids in plants varies depending on many factors such as plant species, organ, stage of development, and environmental conditions [187]. In addition, food preparation and

processing methods can significantly affect flavonoid content in foods [188,189]. Food databases provide information about food content of some flavonoids from six subclasses of flavonoids and with isoflavonoids separated from other subclasses [190]. According to the United States Department of Agriculture (USDA) database for the flavonoid content of selected foods (Table 1), the flavanones hesperetin, naringenin, and eriodictyol are primarily found in citrus fruits and their juices. Flavones luteolin and apigenin are predominant in aromatic herbs, parsley, celery, and peppers. Flavonols quercetin, kaempferol, myricetin, and isorhamnetin are found in many fruits and vegetables like apples, cranberries, onions, beans, and fennel. The flavan-3-ols (+)-catechin, (–)-epicatechin, (–)-epigallocatechin, theaflavin and their gallate esters are found in large amounts in tea, wine, and cocoa. Anthocyanidins cyanidin, delphinidin, malvidin, pelargonidin, peonidin, and petunidin are present in different varieties of berries, grapes, nuts and some vegetables. The USDA database for the isoflavone content of selected foods shows that the isoflavones daidzein, genistein, and glycitein are found in considerable quantities primarily in soybeans and soy products [191,192].

Table 1. Major subclasses of flavonoids with examples and some of the major dietary sources.

Flavonoid Subclasses	Examples	Dietary Sources
Flavanones	Hesperetin, Naringenin, Eriodictyol, Naringin	Spice (dried oregano), grapefruit, lemon, orange, grapefruit juice, lemon juice, orange juice.
Flavones	Luteolin, Apigenin, Vitexin, Orientin	Spices (dried oregano, celery seed, dried parsley, thyme), celery, parsley, peppers.
Flavonols	Quercetin, Kaempferol, Myricetin, Isorhamnetin, Rutin, Tiliroside, Aromadendrin, Silymarin, Silybin	Capers, spice (saffron), apples, cranberries, arugula, asparagus, broccoli, cabbage, chives, coriander, endive, fennel, ginger, mustard greens, okra, onions, peppers, radish (raw, seeds, leaves), beans, buckwheat.
Flavan-3-ols	(+)-Catechin, (+)-Gallocatechin, (–)-Epicatechin, (–)-Epigallocatechin, (–)-Epicatechin 3-gallate, (–)-Epigallocatechin 3-gallate, Theaflavin, Theaflavin 3-gallate, Theaflavin 3'-gallate, Theaflavin 3,3'- digallate, Thearubigins	Apples, broad beans, pecans, pistachio, wine, cocoa, tea (green, black), soybeans.
Anthocyanidins	Cyanidin, Delphinidin, Malvidin, Pelargonidin, Peonidin, Petunidin	Berries (bilberry, blackberries, blackberry, chokeberry, elderberries, raspberries, blueberry, cranberry, serviceberry), currants, grapes, plum, red cabbage, eggplant, pecans, pistachio, wine, black beans.
Isoflavones	Daidzein, Genistein, Glycitein	Red clover, soybeans and soybean products (milk, flour, yogurt and others).

3.2. Dietary Intake

Several studies attempted to estimate the dietary intake of flavonoids in the U.S. It was estimated in one study that total dietary intake of flavonoids by U.S adults was 190 mg/day [193] while this number was 345 mg/day in another study [194]. These two studies analyzed 24-h dietary recall data from the National Health and Nutrition Examination Survey (NHANES) and used the USDA databases to assess the intake of flavonoids. However, the data used in these studies were from two different time periods, and the databases were from different releases and updates which may explain the difference in the estimated daily intake. Moreover, the highest intake of all flavonoids documented in these studies was from the subclass flavan-3-ols corresponding to a higher intake of tea [193,194]. Recently, USDA expanded flavonoids databases to include 2900 foods with analyzed contents of the five subclasses of flavonoids and the major isoflavones instead of the roughly 500 foods in the original [195]. This expansion is expected to provide researchers with a better tool to estimate dietary

intake of flavonoids and study their effects on populations following exposure to these phytochemicals. Thus, re-analysis of the data from NHANES using the most recent USDA databases is recommended to achieve a more accurate assessment of intake.

3.3. Absorption, Metabolism, and Bioavailability

How well flavonoids are absorbed and to what degree they are metabolized in the human body may determine their potential efficacy for the treatment and prevention of diseases. Starting in the mouth, flavonoids are first released from the plant matrix and some flavonoid glycosides (with sugar moiety) are hydrolyzed to aglycones (without sugar moiety) by saliva [196]. While some flavonoids are absorbed in the stomach [197], most of them undergo enzymatic hydrolysis and further metabolism in the small intestine [198,199]. The hydrolysis involves the deglycosylation of flavonoids, removal of glycosides naturally-bound to flavonoids by beta-glucosidases [200]. The hydrolyzed flavonoids are further metabolized by conjugation with glucuronic acid in the small intestine. The conjugation depends on the flavonoid structure with less predisposition to glucuronidation in flavonoids with a hydroxyl group on the B-ring [201], but more extensive metabolism and/or conjugation to flavan-3-ols [202]. The conjugation pattern is also affected by nutritional status. For example, administration of isoflavones in the fasting state results in more conjugation with sulfates and less glucuronidation than in the non-fasting state in humans [197]. Once absorbed, flavonoids from the small intestine reach the liver where they can be further conjugated with sulfate and/or methyl groups or excreted back with bile components [203–205].

The majority of ingested flavonoids may not undergo hydrolysis or conjugation in the small intestine [206], and are neither absorbed nor excreted from the bile [205]. Instead, these flavonoids pass to the colon where they are degraded by colonic flora into smaller molecules and phenolic acids that can then be absorbed [207,208].

The absorption of flavonoids depends on many factors such as the configuration of their structures and glycosylation [209]. In foods, flavonoids mostly exist in the glycosylated forms [210]. Some flavonoids can be absorbed more readily when attached to glycosides in the small intestine [211], while other flavonoids are absorbed more efficiently as aglycones [212,213]. In addition, the type of sugar moiety (galactose, rhamnose, arabinopyranose) of the glycoside [214], and the plant matrix can affect the absorption of flavonoids [215]. For instance, conjugation of the flavonol quercetin with glucose is associated with a greater absorption rate than the quercetin rutinose irrespective of the glucose position on the quercetin molecule [216,217].

During the past two decades, research has primarily focused on exploring the potential biological and pharmacological functions of flavonoids such as the antioxidant [218], anti-inflammatory [219], and anticancer activities [220]. In this context, many factors that may affect their bioavailability should be taken into consideration to validate their health-promoting effects. Flavonoid bioavailability is influenced by many factors such as absorption rate, metabolism, conjugation, structure, and molecular weight [205,221]. In general, the bioavailability of flavonoids is low, and the majority of flavonoids are detected in the conjugated form in the plasma [222,223]. Among the various classes of flavonoids, isoflavones have the highest bioavailability, whereas anthocyanins have the lowest [224]. Ingestion of 50 mg anthocyanins as aglycone equivalents resulted in a maximal plasma concentration of about 30 nmol/L, while the plasma concentration reached 3 µmol/L after intake of the same amount of isoflavones [225]. Flavonoids can be detected in plasma after 30 min and cleared in several hours after ingestion [226,227], although the half-life for conjugated flavonoids could be as long as 28 h [228]. Other factors that may affect the bioavailability of flavonoids are variation in absorption and metabolism of flavonoids between individuals [229], flavonoid dose [230], and duration of consumption [231].

While conjugation of flavonoids is reported to alter their structure and likely reduce their biological activities [218,232], the microbial metabolism of flavonoids in the gut could generate a variety of metabolites with different biological activities [233]. Results from *in vitro* studies that explore biological roles of some flavonoids using their unconjugated forms should be analyzed with caution because

they may not even be detectable in the plasma. More focus should be given to investigating flavonoid metabolites, which might be more bioavailable [229].

3.4. Potential Adverse Effects and Toxicity

Our daily diet contains considerable amounts of flavonoids, most of which are considered safe [179,234]. Galati and others reviewed the potential toxicity of flavonoids [235], and although one of the proposed actions of many flavonoids is antioxidant activity, in the presence of copper they can become pro-oxidants [218]. Similarly, long-term intake of quercetin may cause mutagenicity [236] and DNA damage that is further enhanced in the presence of copper, suggesting that mutagenesis caused by some flavonoids may be due to their pro-oxidant activity [237,238]. The use of supplements, including non-nutritive supplements, has been on the rise in recent years [239]; however, the purported benefits of flavonoid supplementation are not well justified by research results [240]. Thus, the use of flavonoids as dietary supplements in large quantities should not be encouraged until their biological effects are elucidated [241] and potential adverse effects are better understood [218,242].

4. Flavonoids and T2D

As discussed above, T2D is a result of chronic IR and loss of β -cell mass and function [243,244]. Thus, the search for agents that may promote insulin sensitivity and β -cell survival may provide a more effective strategy to prevent the onset of diabetes [245–248].

4.1. Flavonoids and the Prevention and Treatment of T2D

4.1.1. Antioxidant Activity of Flavonoids and T2D

One of the suggested triggers causing β -cell dysfunction and IR that ultimately lead to T2D is excessive ROS production [249], which may be due to the activation of stress signaling pathways [250]. Results from studies using cell cultures and animal models show that flavonoids can directly scavenge ROS [251,252]. Flavonoids can protect and restore antioxidant defense enzymes such as superoxide dismutase, catalase, and glutathione peroxidase [253,254], and inhibit ROS-producing enzymes such as xanthine oxidase [255]. As a consequence, flavonoids can inhibit several ROS-stimulated biological events such as inhibiting oxidized LDL (oxLDL)-induced cell apoptosis, and NF- κ B-mediated transcriptional activity and subsequent inflammation [254]. In humans, the plasma concentrations of flavonoids after dietary intake are typically far less than those used in vitro studies for achieving strong scavenging capabilities, suggesting that these polyphenolic compounds may not have significant antioxidant effect in vivo. Indeed, it was proposed that flavonoids themselves may only have minimal contribution to the antioxidant capacity in humans where the greatest contribution is from other components in flavonoid-rich foods [256]. However, there is the possibility that some flavonoids may exert antioxidant activities in vivo through modulating protein kinases that mediate ROS-induced signaling pathways [257]. Another possibility is that flavonoids might exert antioxidant effects and ROS scavenging capabilities in the digestive tract [258].

4.1.2. Effects of Flavonoids on Postprandial Blood Glucose

The first step in carbohydrate digestion is their breakdown into absorbable monosaccharides in the small intestine. Carbohydrates are digested by enzymes such as α -amylase and α -glucosidase, and after that by small intestinal maltase, sucrase, and lactase [259]. As discussed above, glucose absorption in the small intestine is facilitated via carriers such as GLUT2 and SGLT1. The pharmacological inhibition of the digestive enzymes and/or glucose transporters will reduce glucose absorption, thereby lowering postprandial blood glucose levels [260,261]. The flavonols rutin, kaempferol, and quercetin inhibited carbohydrate digestion and absorption in experimental studies. Rutin inhibited α -glucosidase activity in vitro by directly binding to the enzyme through hydrophobic bonding [262]. In addition, kaempferol inhibited α -glucosidase activity in vitro [263]. Quercetin displayed more inhibitory

activities through the inhibition of both maltase and sucrase activities in vitro and in vivo [264] and the suppression of SGLT1-mediated glucoside uptake in human intestinal Caco-2 cells via interaction with the transporter [265]. Also, quercetin inhibited GLUT2-mediated uptake in vitro (noncompetitive inhibition) and reduced postprandial blood glucose levels in diabetic mice when it was orally administered with glucose compared to glucose only administration [266]. Moreover, tiliroside a flavonol glycoside, reduced glucose absorption by competitive inhibition of the intestinal glucose transporter SGLT1 [267] and inhibited the elevation of blood glucose after an oral glucose load in IR animal model [267]. Flavonoid-rich extracts from *Helichrysum* and grapefruit inhibited the activity of α -amylase and α -glucosidase and suppressed SGLT1-mediated uptake in Caco-2 cells and lowered postprandial blood glucose after the oral administered accompanied with the ingestion of maltose or starch in healthy rats [268]. On the other hand, the flavone luteolin suppressed the activity of α -amylase and α -glucosidase in vitro [269], but had no significant effect on postprandial glucose levels in healthy rats even at a high dose (up to 200 mg/kg) [270].

Tea flavonoids, flavan-3-ols, such as catechin, epicatechin gallate and epigallocatechin gallate (EGCG) reduced glucose absorption by competitive inhibition of the intestinal glucose transporter SGLT1 in vitro [271,272] and showed some ability to delay intestinal absorption of glucose in healthy subjects [273]. Additionally, flavonoid extract from sugarcane reduced the glycemic response to a high glycemic meal in healthy subjects [274].

Proanthocyanin-rich extracts from raspberry and rowanberry inhibited α -amylase activity and acted synergistically with the drug acarbose to inhibit α -amylase activity in vitro [275]. Also, anthocyanins-rich extract from raspberry, blueberry, cranberry, strawberry, and other berries reduced glucose absorption by inhibiting SGLT1 and GUT2 and their expression in human intestinal Caco-2 cells [276]. Moreover, in experimental studies, the oral administration of a flavonoid-rich extract of serviceberry in diet-induced obese and hyperglycemic mice delayed carbohydrate absorption and subsequently ameliorated postprandial hyperglycemia at least partially through inhibiting intestinal α -glucosidase activity [277]. However, in clinical trials, the consumption of a variety of berries had different outcomes on glycemic response in healthy and T2D subjects. Consumption of a berry meal (containing bilberries, blackcurrants, cranberries, and strawberries) sweetened with sucrose, delayed glucose appearance in the blood of healthy subjects [278]. Similarly, in another study, sweetened blackcurrant juice fortified with crowberry powder improved postprandial glycemic control in healthy subjects [279]. On the contrary, the addition of raspberries and blueberries to starch-based food did not reduce blood glucose in healthy subjects [280]. The consumption of a sweetened cranberry juice did not improve the glycemic responses in healthy subjects, but some improvement was noted with unsweetened cranberry juice [281]. The latter finding was consistent with another study in which a cranberry product led to improvement in the glycemic response in T2D subjects when compared with cranberry products that contained more sugar [282].

Findings from the in vitro and animal studies regarding the modulatory effect of flavonoids on carbohydrate digestion and absorption thus postprandial blood glucose levels may have physiological relevance. While the inhibitory action on carbohydrate digestive enzymes of several flavonoids, flavones and flavonols, was suggested to be structure-related [283], some flavonoids such as the flavones from bamboo leaf extract, specifically vitexin, orientin, isovitexin, and isoorientin, inhibited starch digestion by interacting with the enzymes and with the starch molecule itself [284]. However, it is unclear in the clinical trials whether the observed beneficial effects by dietary consumption of flavonoids-rich products are partially or entirely ascribed to flavonoids. More effort should be directed at studying structure-function relationship to assist in predicting the efficacy of flavonoids in inhibiting enzymes involved in glucose digestion and absorption. In addition, long- and short-term studies to test different doses of flavonoids and products on glycemic responses in T2D subjects are needed.

4.1.3. Effects of Flavonoids on Glucose Disposal

Another approach to preventing IR, hyperglycemia, T2D, and subsequent diabetic complications is to enhance glucose uptake by peripheral tissues. Various isoforms of glucose transporters (GLUT), are responsible for most glucose flux into cells [285]. GLUT4, the most abundant glucose transporter in both skeletal muscle and adipose tissue, is primarily regulated by insulin [286]. Insulin stimulation of glucose entry into cells is executed via inducing the translocation of GLUT4 to the plasma membranes of muscle and fat cells [287], which is promoted by a cascade of events including insulin signaling-triggered activation of the PI3K/Akt pathway [288]. In hepatocytes, glucose can be transported into and out of the cells by GLUT2 independent of insulin [289]. Additionally, activation of AMPK, a master regulator of energy metabolism, is considered to be one of the most important insulin-independent targets for improving glucose uptake in both muscle and adipose tissue [290,291].

Various flavonoids demonstrated capabilities of stimulating insulin-dependent and insulin-independent glucose uptake in peripheral tissues in vitro and in vivo. Procyanidins, polymers of the flavan-3-ols catechin and epicatechin, dose-dependently stimulated glucose uptake in L6E9 myotubes and 3T3-L1 adipocytes, which was associated with increased activity of Akt and extracellular signal-regulated kinase 1/2 (ERK1/2), another target of insulin signaling [292,293]. In vivo, the long-term provision of procyanidin extracted from grape seeds improved glucose homeostasis and insulin sensitivity in diet-induced hyperinsulinemic rats, effects that were consistent with the enhanced glucose uptake in cultured 3T3-L1 adipocytes [294]. However, the physiological relevance of these in vitro findings is unclear, because procyanidins might be difficult to be absorbed, given their oligomeric structures. In IR rats, treatment with green tea extract, mainly comprised of epicatechin, epigallocatechin, and their gallates, increased the expression of genes critical for glucose uptake and utilization such as Gsk3beta and Irs2 in the liver and Glut4 in the muscle [295]. Similarly, EGCG, the most abundant catechin in green tea, was shown to enhance insulin-stimulated glucose uptake by increasing GLUT4 membrane translocation in L6 myotubes. In addition, treatment with EGCG inhibited dexamethasone-induced IR via activating AMPK and Akt [296]. Similarly, the isoflavone genistein stimulated glucose uptake in L6 myotubes through activating AMPK and increasing the gene expression of GLUT4 and GLUT1 [297]. Whereas, the flavanone eriodictyol increased glucose uptake in hepatocytes and adipocytes under high-glucose conditions via activating the PI3K/Akt pathway [298]. Flavonoid 7-O-methylaromadendrin treatment stimulated glucose uptake in adipocytes by increasing the gene expression and activity of the transcriptional factor PPAR γ 2, and improved high glucose-induced IR in human hepatocellular liver carcinoma (HepG2) cells through activation of the PI3K/Akt and AMPK dependent pathways [299]. In addition, kaempferol and quercetin can also activate PPAR γ and subsequently improve insulin-stimulated glucose uptake in 3T3-L1 adipocytes [300].

4.1.4. Effects of Flavonoids on Obesity and Inflammation

Some flavonoids can improve dyslipidemia, modulate adipokine secretion, and inhibit adipogenesis, which can thereby ameliorate IR and T2D. Treatment with citrus flavonoids nobiletin and tangeretin increased adiponectin secretion in 3T3-L1 adipocytes while suppressing the production of monocyte chemoattractant protein-1 (MCP-1), a key chemokine involved in monocyte migration and infiltration into fat tissue [301]. Oral administration of naringin, a bioflavonoid from grapefruit, ameliorated dyslipidemia, hyperinsulinemia, hyperglycemia, hepatic steatosis, and IR in T2D rats, which were associated with reduced oxidative stress, upregulated PPAR γ , reduced inflammatory markers, and improved β -cell function [302].

Treatment with flavonoid extracts from *Litsea coreana* (H.) Lev. reduced serum triglyceride, total cholesterol, and LDL-cholesterol, and improved insulin sensitivity in HF diet-fed IR hyperlipidemic rats [303,304]. Oral administration of tiliroside (100 mg/kg/day), a glycosidic flavonoid, ameliorated metabolic disorders in obese diabetic mice, which were associated with activation of multiple signaling molecules important for promoting energy metabolism and insulin

sensitivity, including adiponectin, AMPK, and PPAR α , in skeletal muscle and/or liver [305]. Tiliroside was found to inhibit α -amylase as well as SGLT1 and GLUT2 [267], suggesting that the observed metabolic effects of tiliroside could be partially mediated through inhibitory effects on intestinal carbohydrate digestion and glucose uptake.

4.1.5. Effect of Flavonoids on β -Cell Function

In IR, β -cells compensate for the defects in insulin action by releasing more insulin. T2D only develops when these cells are unable to secrete adequate amounts of insulin to compensate for the decreased insulin sensitivity. The decrease in insulin secretion is largely due to insulin secretory dysfunction and significant loss of functional β -cells [306–310]. Indeed, individuals with T2D always manifest increased β -cell apoptosis and reduced β -cell mass [308,309,311]. There are several proposed mechanisms underlying the β -cell dysfunction including increased generation of ROS, alterations in metabolic pathways, activation of endoplasmic reticulum stress, increases in intracellular calcium, among others [312].

Alloxan and streptozotocin (STZ) have been widely used to induce insulin-deficient diabetic animal models by selectively destroying β -cells [313]. In STZ-induced diabetic rats, intraperitoneal (ip) injection of quercetin improved glucose tolerance and dyslipidemia [314], effects that might be due to protection against β -cell apoptosis via a reduction in oxidative stress [315]. Similar results were observed with ip injection of naringenin 7-O- β -D-glucoside in STZ-induced diabetic rats [316]. Interestingly, treatment with epicatechin improved blood glucose by stimulating regeneration of functional pancreatic β -cells in alloxan-induced diabetic rats [317]. Epicatechin may also preserve β -cell mass and function through protection against oxidative stress [318]. Likewise, other flavonoids such as rutin and apigenin protected the islets against STZ-induced damage, probably due to their antioxidant activity [319].

The potential effects of dietary intake of isoflavones or soy products that are enriched with isoflavones, particularly genistein and daidzein, on diabetes have been extensively studied [320,321]. Dietary supplementation of genistein improved hyperglycemia, glucose tolerance, and blood insulin levels in various diabetic mouse models, including non-obese diabetic (NOD) mice [322,323] and STZ induced lean and obese diabetic mice [324,325], which were associated with improved β -cell proliferation and islet mass and insulin content. At the cellular levels, it has been demonstrated that genistein can directly act on pancreatic β -cells, inducing glucose-dependent insulin secretion and cell proliferation via activating the cAMP and ERK1/2 signaling pathways [324,326]. For more detailed information on the effects of isoflavones on β -cell function, please refer to this recent review article [327].

4.2. Flavonoid Intake and Risk of T2D in Humans

A meta-analysis consisting of 6 cohort studies indicated that total flavonoid intake was associated with a reduced risk of T2D [328]. However, in an observational study, no association was found between dietary intake of flavonoids and the risk of T2D in postmenopausal women [329]. Interestingly, it was found that the flavonoid subclasses flavonols and flavanols are particularly associated with a lower risk T2D [330]. Specifically, there seems to be a reduced risk of T2D with greater intake of the flavonols quercetin and myricetin [331]. Data from several cohort studies demonstrated that tea, coffee, and their products which are rich in flavanols (Table 1), were associated with reduced risk of T2D [332–335]. Consistent with these results, a meta-analysis study concluded that consumption of 4 or more cups of tea derived from *Camellia sinensis* (L.) Kuntze per day may lower the risk of T2D [336]. In a human trial, long-term tea intake was associated with reduced fasting blood glucose and a lower risk of T2D [337]. Similarly, higher intake of anthocyanins or anthocyanin-rich plants like blueberries and grapes was also associated with a lower risk of T2D [338,339]. It should be noted that most of these studies used flavonoid-containing foods that also contain other phytochemicals, which could contribute to the observed health beneficial effects [340], possibly in a synergistic or additive manner [341–343]. Thus,

it is possible that crude extracts or a combination of different pure compounds are more effective than isolated pure flavonoids at an equivalent dose for preventing and treating diabetes.

4.3. Effects of Flavonoids on T2D in Clinical Interventions

Results from clinical trials show different outcomes based on flavonoid subclasses. Supplementation with flavonoids such as silymarin [344] and silybin-beta-cyclodextrin [345] improved glycemic and lipidemic profiles in T2D subjects. Similarly, cranberry juice consumption for 3 months improved glycemic control in T2D subjects [346], where consumption of chokeberry juice for 3 months improved both the glycemic and lipidemic profiles in T2D subjects [347]. Supplementation with grape seed extract improved markers of inflammation and glycemic control in obese T2D subjects [348] and consumption of grapes for 3 weeks lowered plasma LDL-cholesterol and cholesterol in obese subjects [349]. Anthocyanin supplementation improved LDL- and HDL-cholesterol concentrations in dyslipidemic subjects [350] and reduced the inflammatory response in hypercholesterolemic subjects [351]. However, studies with tea catechins have yielded conflicting results. The consumption of green tea (456 mg catechins for 2 months or 9 g of green tea for 1 month) did not exert any beneficial effect in T2D subjects [352,353]. These outcomes were consistent with results from two other reports showing that dietary provision of green and black tea extract mixture (150 mg of green tea catechins and 75 mg of black tea theaflavin for 3 months) in T2D subjects [354] or green tea extract only (500 mg tea catechins for 4 months) in obese subjects with T2D [355]. However, one study found that intake of catechins (582.8 mg of catechins for 3 months) reduced the body weight of obese subjects with T2D, with some improvements in glucose control [356]. In line with this result, another study also showed that consumption of catechin-rich green tea (615 mg green tea catechins for 1 month) improved postprandial glucose in T2D subjects [357]. Collectively, it is still unclear whether tea catechins are effective in the treatment of T2D. Higher doses of tea extract and individual catechins such as EGCG, rather than a mixture, might be more effective in preventing or treating T2D in humans. In addition, the efficacy may depend on the metabolic state of the subjects and the duration of treatment.

5. Conclusions and Limitations

T2D is a progressive metabolic disorder that is increasing in prevalence globally and is a significant healthcare burden. Although the specific causes of T2D still need to be elucidated, there is a considerable body of evidence to support that IR and loss of functional β -cell mass play a major role in the etiology of the disease. Various mechanisms contribute to the development of IR and β -cell impairment and the magnitude of their effects is dependent on a combination of genetic and environmental factors. In the search for naturally occurring compounds to prevent and treat IR and T2D, flavonoids have drawn considerable attention for their potential anti-diabetic activities. Epidemiological studies indicate that higher intake of flavonoids is associated with reduced risk of T2D. Experimental studies have shown that flavonoids may reduce postprandial blood glucose by inhibiting glucose digestion and transport in the small intestine, by increasing glucose disposal in tissues, and by protecting and regenerating impaired β -cells, and/or enhancing pancreatic insulin secretion. As most of previously tested flavonoids only have moderate potency in preventing and treating diabetes, further investigation is needed to identify specific flavonoids with complementary roles in glucose metabolism, and further explore whether combinations of two or more flavonoids could be more effective in preventing and treating T2D.

As discussed above, rodent and in vitro models have been widely employed to determine the potential anti-diabetic mechanisms of flavonoids and flavonoids-enriched extracts. However, Ingested flavonoids from the diets in both humans and animals always undergo extensive transformation in the intestine and the liver [203–205], and thus the majority of flavonoids detected in the plasma (>90%) are in conjugated form [222,223], which are likely less biologically active [218,232]. Thus, the concentrations of the parent compounds in blood are only in the range of nanomoles to sub-micromoles following dietary supplementation. However, most in vitro studies that explored the fundamental

roles of some flavonoids used the unconjugated forms, and the observed results were achieved at pharmacological doses ($>10 \mu\text{M}$) that are well above those physiologically attainable by dietary means ($<5 \mu\text{M}$). Therefore, the physiological relevance of these in vitro findings is still largely unknown.

It was recently reported that microbiota composition is altered in patients with T2D [358–360], suggesting that gut microflora may play an important role in glucose hemostasis and pathogenesis of T2D [361]. Indeed, it was shown that increased *Bifidobacterium* spp. population in the gut is associated with improved glucose tolerance and insulin sensitivity while reduced inflammatory markers [362,363]. Gut microbiota also play a critical role in the biotransformation of flavonoids. The unabsorbed flavonoids in small intestine reach to the colon where they are metabolized by colonic microflora into smaller molecules such as phenolic acids [207,208], some of which might be more bioavailable and biologically active [229]. Meanwhile, some flavonoid metabolites in turn modulate the composition of microbiota by inhibiting the growth of pathogenic bacteria and promoting the growth of beneficial bacteria [364]. Therefore, the target for flavonoids (particularly those poorly absorbed flavonoids) to exert the antidiabetic effects might be restricted to the intestine partially via modulating intestinal microflora, an aspect that has been largely ignored during the past research. In future, it is also important to examine the antidiabetic effects of the major microbial metabolites of flavonoids using physiologically relevant concentrations found in the body. In that regard, it should be noted that there are differences in the intestinal bacterial species and activities for catalyzing and transforming flavonoids between rodent models and humans [365]. These differences need to be carefully considered for designing studies.

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