Review:

Flavonoids as Antidiabetic Agents

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Abstract: *Flavonoids are polyphenol compounds that exert many potential health benefits, including diabetes type-II, which is the third most common disease that causes death, right after cancer and cardiovascular diseases. The excessively high level of blood glucose has been believed to trigger type II diabetes. The aim of this review is to describe the flavonoid's ability as an alternative treatment for diabetes type-II patients. This paper addresses several aspects in which flavonoids may impart a pivotal role in starch digestion, such as the interaction of flavonoids with enzymes involved in starch hydrolysis, the role of flavonoids in inhibiting glucose absorption, as well as the interaction of flavonoids with starch to form a complex resistant to hydrolysis. Further studies, however, are suggested to extensively carry out, particularly the ones dealing with the intervention study using human volunteers to reveal the role of flavonoids in the real applications. The data on human intervention studies are still rare and can further be exploited using meta-analysis to have firmer results. Flavonoids in the food matrix are more realistic to perform to reveal the effect of interaction with other compounds, which may affect the mechanism of flavonoids interaction or their bioavailability.*

Keywords: *antidiabetic; flavonoids; interactions of flavonoids; starch digestion*

■ INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease caused by a chronic failure of metabolic function in the human body as a result of lack of insulin secretion and a decreased insulin tissue response to metabolize carbohydrates, proteins, and lipids. This disease is featured by an increase in blood glucose levels as well as an increased risk of vascular complications such as cancer [1]. Diabetes mellitus has two types. Type I diabetes is characterized by pancreatic β cell destruction because of autoimmune disease. This leads to the patients dependency on exogenous hormones. Conversely, in type II diabetes, the body becomes resistant to the effects of insulin and/or does not produce enough insulin [2]. The most common case of diabetes is type II diabetes. Diabetes can increase the risk of cancer, heart disease, and other complications. [3]. The prevalence of diabetes in 110 countries is projected to increase from 366 million in 2011 to 552 million in 2030 for the 20–79 year age group. Most diabetics live in low and middle-income countries [4].

Insulin injection is one of the most common treatments for diabetics. However, some people refuse insulin injections due to psychological factors (feeling afraid of the pain caused by daily injections), the formation of addictive effects, the occurrence of hypoglycemia, and the occurrence of insulin resistance in the body that occurs in the jejunum [5-6]. A number of studies have been conducted to address the diabetic problem, including flavonoids that have been believed to exert health benefits, including antidiabetic agents [7-9].

This paper describes the likely mechanisms of flavonoids as antidiabetic agents particularly related to starch digestion. In general, the antidiabetic effect of flavonoids may be related to their role in glucose metabolism or as an antioxidant against oxidative stress. The former is the focus of the review of this paper, while

the latter is out of the scope of this paper. In terms of the role of flavonoids in glucose metabolism, the antidiabetic properties of flavonoids result from the inhibitory effect against digestive enzymes [10-11]. Other mechanisms may be linked to the effect on glucose absorption through small intestinal cells [12] and the interaction of flavonoids with starch to form resistant starch [13]. The fact that flavonoids consist of vastly different compounds, it is important to begin the discussion with flavonoids classification followed by the starch hydrolysis process.

■ FLAVONOIDS

Flavonoids are one of the secondary metabolites included in the group of polyphenols found in plants. The compounds have a carbon framework of C6-C3-C6. The two group rings of C6 (benzene rings) A and B are connected by 3 carbons (Fig. 1). Flavonoids can be classified into 6 groups (Fig. 2), including flavonols, flavan-3-ols (flavanols), flavones, anthocyanins, isoflavones, and flavanones [14]. Flavonoids can be naturally found in foods such as cereals, vegetables, fruits, and nuts, serving as protectors for these plants [15]. The compounds are also responsible for giving color to fruit and flower. In addition, flavonoids exhibit health benefits such as anti-cardiovascular, antidiabetic, obesity, and anticancer in humans [7-9,16].

Flavonols

Flavonols are the main compounds of the flavonoids group, which have an important role in plant growth, development, and resistance, such as damage due to UV irradiation and insect pest [17]. Meanwhile, in the human body, flavonoids, especially quercetin, exhibit antimicrobial and antioxidant activities so that they play a role in preventing cancer, cardiovascular, and anti-inflammatory. In addition, flavonols possess an antihistamine effect, which is used as an antiallergic drug.

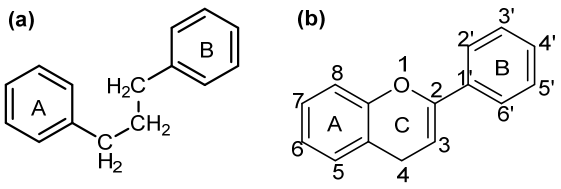


Fig 1. (a) Flavonoid framework; (b) Numbering system

Flavonols can be used to reduce high blood pressure in people with hypertension and improve the barrier function of human intestinal cells so that it does not cause diarrhea [18-20]. In another study, it was found that the aglycone form of flavonols in lotus leaf charcoal increased hemostatic effects [21]. The most common flavonols are kaempferol, quercetin, and myricetin (Fig. 2), with the main flavonols, quercetin 3-*O*-glycoside [22-23].

Flavones

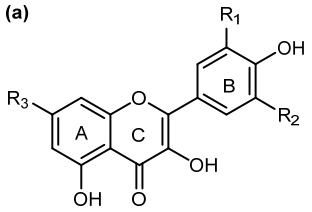
Flavones have a structure consisting of 2 benzene rings (rings A and B) connected by 3 carbon chains forming a closed pyranone ring (ring C) that joins ring A (Fig. 2) [24]. This structure is closely related to flavonols, but in terms of the occurrence in plants, flavones are found in smaller quantities than flavonols. Examples of flavone compounds are luteolin, apigenin, and chrysin [16].

Flavones in the form of C-glycoside, demonstrate an important role in plants, including as an antioxidant and pigment for UV absorption. In addition, flavones are also used to regulate the interaction of plants with microbes and insects in defense of the plants [25]. Flavones are non-essential nutrient compounds that provide additional nutraceutical effects in food [26]. Flavones have several health benefits, including anticancer properties. This effect is related to the ability of flavones to interact with human estrogen receptors in cancer prevention through a mechanism similar to tamoxifen that is often used medically. As such, flavones are often classified as phytoestrogen [27]. In addition, flavones exhibit antifungal and antidiabetic properties [24,28]. Flavones are also known to be used as antioxidants because they can inhibit the action of the xanthine oxidase enzyme from producing Reactive Oxygen Species (ROS). This inhibition can prevent endothelial damage during acute inflammation and restore the function of the mitochondria [29].

Flavan-3-ols (Flavanols)

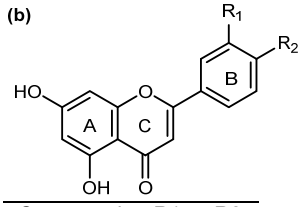
Flavan-3-ols, or often referred to as flavanols, are the most complex group of flavonoids based on their structure (Fig. 2). The compounds include catechins in

(a)



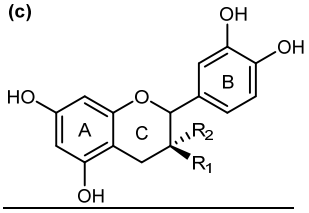
Compound	R1	R2	R3
Quercetin	OH	H	OH
Kaempferol	H	H	OH
Myricetin	OH	OH	OH

(b)



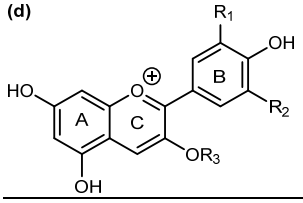
Compound	R1	R2
Luteolin	OH	OH
Apigenin	H	OH
Chrysin	H	H

(c)



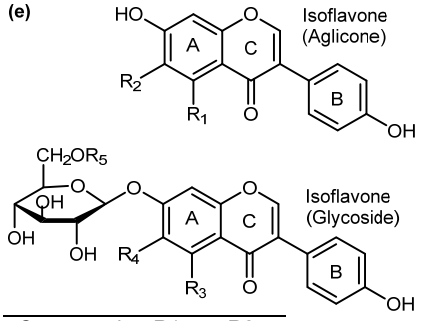
Compound	R1	R2
(+)catechins	OH	H
(-)epicatechins	H	OH

(d)



Compound	R1	R2	R3
Cyanidin	OH	H	Glucose, galactose, or arabinose
Pelargonidin	H	H	
Peonidin	OCH_3	H	
Delphinidin	OH	OH	
Petunidin	OCH_3	OH	
Malvidine	OCH_3	OCH3	

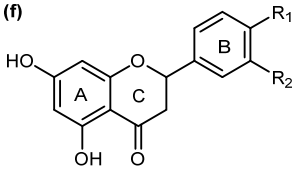
(e)



Compound	R1	R2
Daidzein	H	H
Genistein	OH	H
Glycitein	H	OCH

Compound	R3	R4	R5
Daidzin	H	H	H
Genistein	OH	H	H
Glycitein	H	OCH_3	H

(f)



Compound	R1	R2
Hesperetin	OCH_3	OH
Naringinin	OH	H

Fig 2. Types of flavonoids (a) Flavonols; (b) Flavones; (c) Flavanols; (d) Anthocyanins; (e) Isoflavones (aglycone and glycoside); (f) Flavanones

the form of monomers and epicatechins as their isomers found in nature. In addition, there are monomers whose distribution is more limited such as epiafzelekin, theaflavins, proanthocyanidin as oligomers, and a polymer form known as tannin [30]. These compounds are a group of polyphenol present significantly in tea leaves, such as catechins in green tea [31]. In the human body, the reducing effect on blood glucose levels following the consumption of this compound is suggested to result from its effect on inhibiting digestive enzyme activity such as α-amylase and α-glucosidase [32]. In addition, flavanols are known to reduce blood pressure or hypertension, thereby reduction in the risk of cardiovascular disease, especially in the elderly [33-34].

Flavanols also possess antioxidant effects, antidepressant properties, and an impact on body weight loss, thereby reducing the effect on obesity [35-37]. Flavanols rich food intake can reverse vascular dysfunction in diabetics. Therefore the compounds are a potential alternative to treat patients with cardiovascular disease [38].

Flavanones

Flavanones are the first product of the flavonoid biosynthesis pathway, where there is a chiral C in C2. In addition, these compounds do not have a C2-C3 double bond so that the structure is very reactive (Fig. 2) and can undergo hydroxylation, glycosylation, and *O*-methylation reactions [23]. The antioxidant properties of flavanones are believed to be related to their chemical structures [39]. The most commonly found flavanones are naringenin, hesperidin, and hesperetin [40]. In addition, other types of flavanones are also found, such as pinocembrin, pinostrobin, and alpinetin [39]. Flavanones and their derivatives exhibit antioxidant and anti-inflammatory properties in the human body by inhibiting the formation of nitric oxide (NO) from macrophage cells induced by lipopolysaccharides (LPS). Flavanones are also reported to play a role as an anticancer [41-42].

Isoflavones

The structure of isoflavones is shown in Fig. 2 [23]. The aglycone forms of isoflavones are genistein, daidzein, and glycitein [43], whereas isoflavones available in the form of β-glycosides are daidzin and genistin, and glycitin [44].

The role of isoflavones in a plant is to protect plants from pathogenic microbial attack [45]. While in the human body, isoflavones show their role in preventing and alleviating several diseases, including osteoporosis in women [46], diabetes, heart disease, Kawasaki, and Alzheimer disease, and exhibit antitumor, antiaging properties [47-48]. In addition, isoflavones also provide a protective effect against breast cancer in postmenopausal women [49].

Anthocyanins

Anthocyanins are commonly found in fruits and flower tissues, which provide colors ranging from pink to orange to red, purple, and also blue [50]. The function of anthocyanins in plants is to attract insects in the pollination process. Anthocyanins also protect the plant from the absorption of excess light. The most common anthocyanins are pelargonidin, cyanidin, peonidin, delphinidin, maldivine, and petunidin [51]. The difference in these compounds can be seen in Fig. 2.

In the human body, anthocyanins show health benefits and can suppress postprandial glycemia because the compounds inhibit digestive enzyme activity in the intestine. These interactions are influenced by several environmental factors, such as pH, temperature, and chemical structure [52]. Anthocyanins also inhibit insulin secretion in the body and glucose absorption (2-deoxy-D-glucose (2DG)) [53-55]. In addition, anthocyanins demonstrate antiobesity and anticancer properties [56-57]. Anthocyanins are reported to have low bioavailability [58]. This low bioavailability may lead to low effectiveness of anthocyanins as antioxidants but sufficient to modulate gene expression.

■ α-AMYLASE AND α–GLUCOSIDASE AS DIGESTIVE ENZYMES

The α-amylase enzyme is the common name of α-1,4-glucan-4-glucanohydrolase from the glycosidase hydrolase (GH) family. This enzyme is found in saliva and the pancreas [59-60]. α-Amylase can be isolated from several microbes such as *Bacillus atrophaeus* NRC1 [61], Gram-positive bacteria from soil samples [62], plants, animals, and fungi [63]. This enzyme works as a catalyst in the process of breaking down starch molecules, their derivatives, and other carbohydrate polymers into shorter chains (maltose and maltooligosaccharides) by hydrolyzing and cutting the α-1,4 amylose chain glycoside bonds in the digestive system [10,61,64].

Another enzyme that plays a part in the digestive process of starch is α-glucosidase. This enzyme is located in the small intestinal epithelium or on the surface of the "brush border" membrane of small intestinal cells. α-glucosidase is involved in the final step in the process of carbohydrate digestion into monosaccharides that are directly related to the absorption of blood glucose levels in the jejunum [11]. Given its important role in the

absorption of glucose in the digestive tract, inhibiting the activity of this enzyme can result in the reduction of the glucose absorption and prevent postprandial hyperglycemia in patients with type II diabetes mellitus [65]. Therefore, both the α-amylase and α-glucosidase enzymes are targets for the development of antidiabetic drugs.

■ GLUCOSE PRODUCTION IN THE BODY

The α-amylase enzyme produced by the pancreas enters the small intestine and helps the digestive process by hydrolyzing complex carbohydrates. The hydrolysis process by the enzyme requires the role of calcium ions (Ca^{2+}) [60]. Hydrolyzed starches experience further cleavage by α-glucosidase. The mechanism of starch hydrolysis is shown in Fig. 3. α-Glucosidase is an enzyme that catalyzes the final process of carbohydrates digestion in the intestine and plays a direct role in the process of glucose uptake in the blood [11]. When the concentration of glucose absorbed by the blood is high, it leads to an increase in the glycaemic index and may cause diabetes.

■ THE ROLE OF FLAVONOIDS AS ANTIDIABETIC

Flavonoid compounds have been believed to have an anti-diabetic effect because they can inhibit the α-amylase and α-glucosidase enzymes. The inhibition depends on the interaction of hydrogen bonds between hydroxyl groups on flavonoids and enzyme catalytic residues. This interaction between the enzyme and flavonoids leads to reduced digestion of starch and postprandial glycemia [66]. Another role of flavonoids is to interact with starch and form a complex which is difficult to digest (resistant) [13]. Flavonoids can also inhibit the process of glucose absorption by inhibiting glucose transporters [67]. The schematic mechanism of flavonoids on starch digestion and glucose absorption is presented in Fig. 4.

Interaction of Flavonoids with Digestive Enzymes

The enzymes of α-amylase and α-glucosidase are involved in breaking down starch into glucose. The high concentration of glucose present in the blood triggers an insulin response to reduce the blood glucose level. It is associated with type II diabetes when insulin resistance occurs. Therefore, if the activity of the enzyme can be reduced, then the possibility of type II diabetes in humans would decrease [64]. Many compounds, including flavonoids, show inhibitory activity against α-amylase and α-glucosidase. Therefore, these compounds can be used as antihyperglycaemic candidates [68]. Several factors may affect the interaction of the enzyme with flavonoids. The structure of flavonoids has been believed to affect the flavonoid affinity to the enzymes. Substitution of hydroxyl groups (–OH) with glycosides has been reported to render the affinity of glucose binding with the α-amylase decreased [64].

Flavonoid compounds show interactions with the α-amylase and α-glucosidase to form complex structures through hydrogen bonds and hydrophobic interactions. The hydrogen bonds occur between hydroxyl and carbonyl groups in the flavonoid structure with the active residue of the enzyme [69]. The different structure of flavonoids results in enzyme inhibition with different

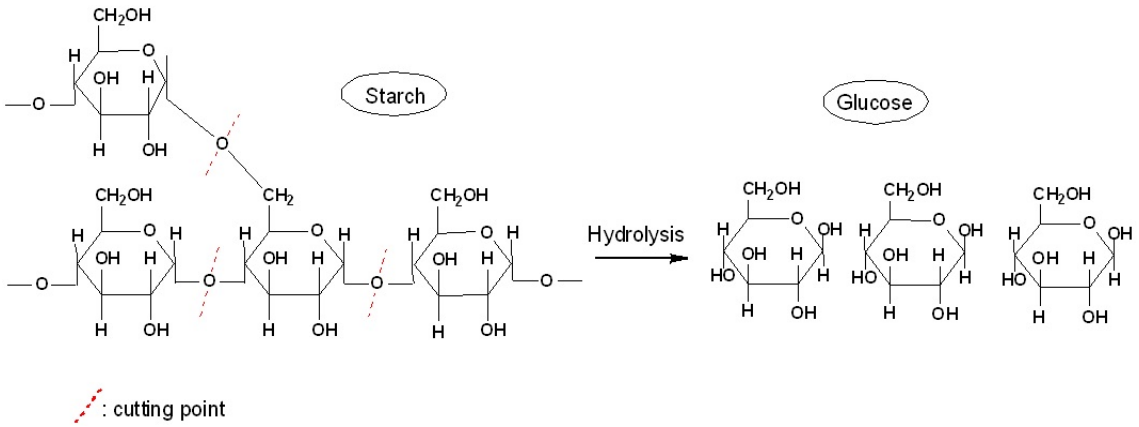


Fig 3. Schematic hydrolysis of starch by amylase enzyme [70]

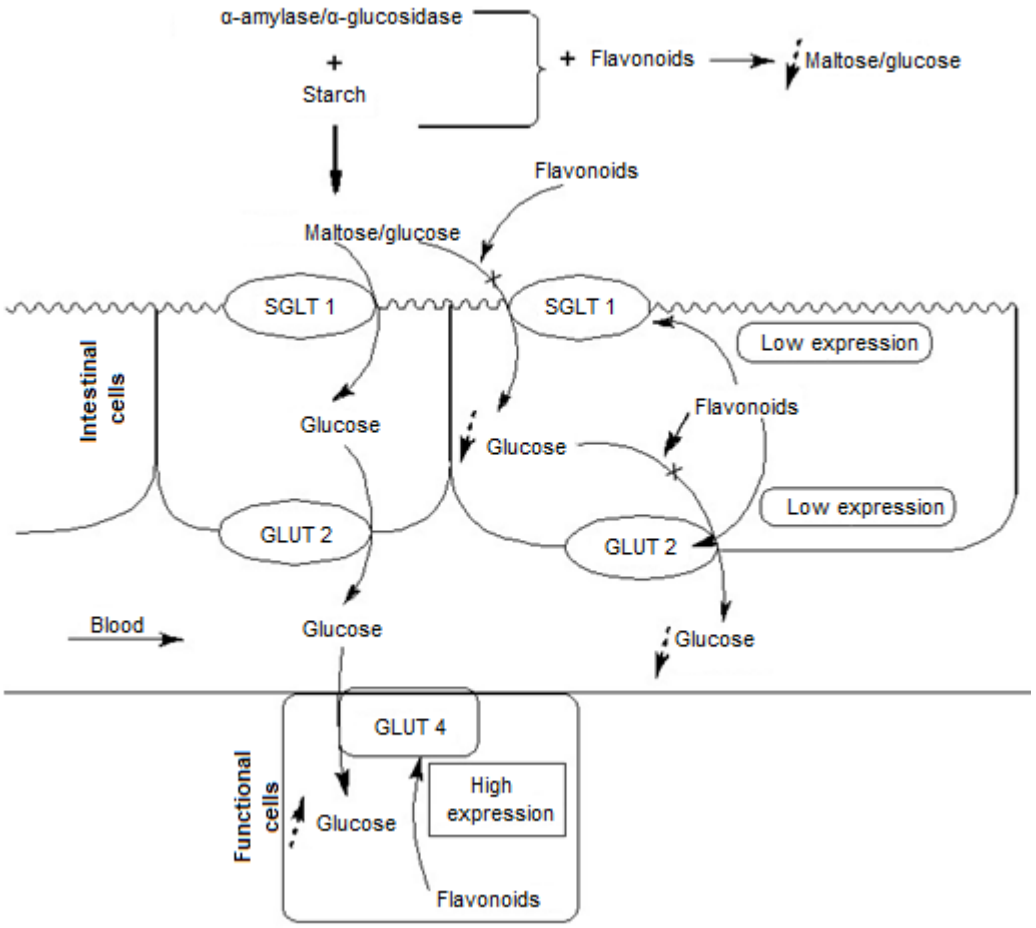


Fig 4. Schematic mechanism of flavonoid effect on starch digestion and its absorption

IC_{50} values. In the previous study, it is found that flavonols (quercetagetin) and flavones (eupafolin) exhibit the inhibition with IC_{50} of 10.2 and 48.0 μM, respectively. The maximum inhibition is approximately 97.6% and 99.4% for flavonols and flavones, respectively [66].

Flavonoids extracted from *Artocarpus altilis* also exhibit inhibition activity against α-glucosidase, with the inhibition type being a non-competitive one [71]. Another source of flavonoids, such as Samama plant extract, has been demonstrated to inhibit α-glucosidase activity [72].

The interaction between the hydroxyl group of flavonoids and the residue present in enzymes induces an opening of enzymatic structures by decreasing α-helix and increasing random coils, thus masking the active site. This results in inhibition of substrate binding to the enzyme, and consequently, the enzyme activity decreases. The decrease in the enzyme activity leads to a reduced glucose absorption resulting from starch breakdown [73]. According to an *in silico* study, the structure of flavonoids that shows interactions with enzymes is the hydroxyl (OH) group present in ring A in position C7 and the hydroxyl group in ring B in position C4' [66].

Interaction of Flavonoids with Starch

Interaction of flavonoids with starch through covalent bonds has been reported in another study. This interaction results in resistant starch, which shows a lower digestibility by α-amylase and α-glucosidase [13]. In a study using Surface Plasmon Resonance (SPR), it was demonstrated that those flavanones could bind to starch to form complexes. The ability to form a complex between flavonoids with starch depends on the position of the hydroxyl group, suggesting that the different flavonoids would have different binding capacities [74]. The retrograded starches are known to be resistant to digestion by direct inhibition of the α-amylase enzyme.

Starch retrogradation occurs when polymer chains of gelatinized starch reassociate and recrystallize through hydrogen bonds [74].

The Role of Flavonoids in Inhibiting Glucose Absorption

Glucose cannot pass through cell membranes by passive diffusion due to its relatively large size. It requires a family of specific transport proteins that can carry glucose through the cell membrane. The type of glucose transporter varies depending on the need for glucose in various tissues [75]. Glucose transporters consist of two main types/groups, namely SGLT and GLUT. Sodium Glucose Transporter (SGLT) is also known as an active co-transporter or symporter energized by proton or sodium gradients. SGLT1 is responsible for the absorption of glucose in the intestinal tract by active transport mechanisms. The second type is the Glucose Transporter (GLUT), which acts as a passive diffusion device for glucose to cross the membrane or tissue barriers by energy [67]. Considering the glucose transport across the membrane, alleviating diabetes mellitus can be done by reducing glucose absorption through the inhibition of glucose transporters such as GLUT2 and SGLT1.

According to structural similarity, glucose transporters (GLUT) can be divided into three subclasses, namely class I (GLUTs 1–4), which is a glucose transporter, class II (GLUT 5, 7, 9 and 11) which is fructose transporters, and class III (GLUTs 6, 8, 10, 12 and HMIT1) [76]. Glucose transporter is closely related to the level of glucose in the blood. Therefore many studies are conducted on the interaction of flavonoids with glucose transporters to reduce the risk of diabetes.

Type II diabetes can occur due to high glucose absorption into blood and glucose uptake from blood into functional cells. The uptake involves glucose transporters [77]. GLUT4 is one of the glucose transporters that is closely related to type II diabetes because glucose absorption by muscle and insulin-induced fat is mediated by GLUT4. In muscles, this transporter also takes glucose after muscle contraction [77].

Glucose, which is absorbed through the intestine, will be distributed throughout the body tissues. In the process of distribution, glucose requires a means of transport to cross the cell surface involving a transport protein called GLUT. The protein involved is a polytrophic membrane protein, in which this protein forms a watery pore and crosses the membrane so that glucose can move [76]. GLUT1 and GLUT4 are involved in the transport of glucose through the cell membrane. In diabetic patients, decreased GLUT4 translocation levels can reduce glucose absorption and increase insulin resistance [78]. Reduction in blood glucose levels occurs through three main mechanisms, including (i) increased absorption of glucose by peripheral tissue through GLUT 4 translocation; (ii) inhibition of lipolysis and promotion of lipogenesis, and (iii) increase in storage and utilization of glucose in the liver [78].

One of the flavonoids which are known to reduce blood sugar concentration is quercetin extract from berries. This compound is involved in the inhibition of glucose absorption in the intestine [78]. The inhibition of glucose absorption by flavonoids in intestinal cells could occur through at least two mechanisms. The first one is by direct inhibition of glucose transporter of SGLT1 and GLUT2 as observed in a study using strawberry anthocyanins [79]. The other mechanism is by inhibiting SGLT1 and GLUT2 expression by flavonoids, as demonstrated in another study [80]. The inhibition of glucose in the intestinal lumen either by direct inhibition of glucose transporters activity or their expression results in a reduced blood glucose level. The inhibition also leads to an accumulation of glucose products in the intestinal lumen. The glucose product accumulation could inhibit hydrolysis reaction, thereby retarding starch hydrolysis [81]. The decrease in blood glucose level can also occur due to the increase in glucose uptake from the blood by functional tissue cells. Given that the glucose uptake involves glucose transporter of GLUT4, increasing the transporter expression could increase the glucose uptake by cells hence a reduced blood glucose level. Studies reported that flavonoids can increase GLUT4 expression leading to an elevated glucose uptake and a lower blood glucose level [82].

■ FOOD AS SOURCE OF FLAVONOIDS

Flavonoid intake in the body can be obtained from several food sources. Examples of several food sources from each class of flavonoids include flavonols which can be found in daily foods such as apples, onions, broccoli, tea, olives, kale, cranberries, lettuce, beans, and peanut seeds [23,83]. In addition, flavones can be found in celery, parsley, in the form of 7-O-glycosides, as well as in olives and tangerines [23]. Other flavonoid compounds, flavanols, can also be obtained from foods such as nuts, cereals, red wine, chocolate, and apples [33-34,84]. Meanwhile, sources of anthocyanins are found in red fruits such as cherries, plums, strawberries, raspberries, blackberries, grapes, red grapes, and black currants or black grapes. Cyanidin is the most common type of anthocyanin in food [23]. The source of flavanones is found in acidic fruits such as oranges and their preparations [85-86]. Soybeans are the most common food source that contains isoflavones [41,87]. Different types of flavonoids and their content in various food are shown in Table 1.

Table 1. Food Sources of flavonoids

Source	Flavonoid type	Compound	Mean content	Ref
Carica papaya	Flavonols	Quercetin-3-rutinoside	14.54 mg/g	[88]
		Myricetin-3-rhamnoside	9.78 mg/g	
		Kaempferol-3-rutinoside	10.15 mg/g	
Blue Berry	Flavonols	Myricetin-3-*O*-arabinoside	31.2 mg/100 g dry weight	[89]
		Quercetin-3-*O*-arabinoside	18.97 mg/100 g dry weight	
Lingonberry	Flavonols	Quercetin-3-*O*-xyloside	8.9 mg/100 g dry weight	[89]
		Quercetin-3-*O*-arabinoside	7.6 mg/100 g dry weight	
		Quercetin-3-arabino-furanoside	49.3 mg/100 g dry weight	
		Quercetin-3-*O*-(4”-HMG)-rhamnoside	53.1 mg/100 g dry weight	
		Kaempferol-(HMG)-rhamnoside	4 mg/100 g dry weight	
Celery (leaves)	Flavones	Apigenin	152.4 mg/kg fresh weight	[90]
		Luteolin	228.9 mg/kg fresh weight	
Shiso	Flavones	Apigenin-*O*-glycosides	280–920 mg/100 g dry weight	[91]
		Luteolin-*O*-glycosides	30–790 mg/100 g dry weight	
Grape black	Flavanols	(+)-Catechins	8.94 mg/100 g	[92]
		(-)-Epicatechins	8.64 mg/100 g	
		(-)-Epicatechins-3-*O*-gallate	2.81 mg/100 g	
		(-)-Epigallocatechin	0.08 mg/100 g	
Apple	Flavanols	Catechins	1.66 mg/100 g	[93]
		Epicatechins	7.72 mg/100 g	
		Procyanidin B1	2.71 mg/100 g	
		Procyanidin B2	8.58 mg/100 g	
Blueberry	Anthocyanins	Malvidin-3-galactoside	39.1 mg/100 g	[94]
		Delpinidin-3-galactoside	25.6 mg/100 g	
		Malvinidin-3-arabinoside	19.8 mg/100 g	
		Delphinidin-3-arabinoside	15.8 mg/100 g	
		Petunidin-3-glucoside	16.6 mg/100 g	
		Petunidin-3-arabinoside	14.8 mg/100 g	
Purple wheat skin	Anthocyanins	Cyanidin malonyl glucoside	9141.97 mg/100 g	[95]
		Cyanidin-3-galactoside	2393 mg/100 g	
		Cyanidin acetyl galactoside	330.49 mg/100 g	

Table 1. Food Sources of flavonoids (*Continued*)

Source	Flavonoid type	Compound	Mean content	Ref
Purple wheat skin	Anthocyanins	Cyanidin di-glucoside	267.60 mg/100 g	
		Pelargonidin-3-glucoside	113.06 mg/100 g	
		Peonidin glucoside	191.09 mg/100 g	
White Grapefruit	Flavanones	Isonaringin	13.42 mg/g dry weight	[96]
		Naringin	160.25 mg/g dry weight	
		Hesperidin	3.23 mg/g dry weight	
		Neohesperidin	3.30 mg/g dry weight	
		Naringenin	8.49 mg/g dry weight	
		Hesperetin	2.93 mg/g dry weight	
		Isosinensetin	3.02 mg/g dry weight	
		Sinensetin	2.10 mg/g dry weight	
		Nobiletin	2.36 mg/g dry weight	
		Tangeretin	2.45 mg/g dry weight	
Orange (Juice)	Flavanones	Naringenin-7-*O*-glucoside	0.6 mg/L	[97]
		Naringenin-7-*O*-rutinoside	363.7 mg/L	
		Hesperetin-7-*O*-rutinoside	274.9 mg/L	
		Hesperetin-7-*O*-glucoside	11.5 mg/L	
		Isosakuranetin-7-*O*-rutinoside	47.9 mg/L	
		Naringenin	0.1 mg/L	
		Hesperetin	0.2 mg/L	
Soybeans	Isoflavones	Malonilgenistin	1.879 μmole/g	[43]
		Malonildaidzin	1.336 μmole/g	
		Malonilglisitin	0.576 μmole/g	
		Daidzin	0.030 μmole/g	
		Genistin	0.057 μmole/g	
		Glycitin	0.018 μmole/g	
Chickpeas	Isoflavones	Ononin (daidzein derivative)	0.06 mg/g	[98]
		Daidzein	0.12 mg/g	
		Sissotrin	0.075 mg/g	
		Formononetin	0.10 mg/g	
		Biochanin A	0.18 mg/g	
		Biochanin glucoside	0.08 mg/g	
		Biochanin A glucoside Malonylated	0.06 mg/g	
		Genistein	0.06 mg/g	

■ CONCLUSION

Diabetes is a disease caused by several factors, one of which is due to an unhealthy lifestyle pattern. Diabetes can be triggered due to high glucose absorption into the blood. This disease can be overcome by insulin injections, but the provision of insulin, in the long run, has side effects on the body. Flavonoid compounds are known to be an alternative for the treatment of diabetes because these compounds can inhibit the activity of the α-amylase and α-glucosidase enzymes. In addition, flavonoids can interact with starch to form covalent bonds resulting in starch resistance to digestion. Flavonoids can also inhibit glucose absorption by modulating the function or the expression of glucose transporters. Therefore, flavonoid compounds are a potential alternative treatment for diabetics. In the future, to expand our knowledge on the effect of flavonoids on diabetes disease, studies on the interaction of flavonoids with

other compounds in the food matrix are suggested, given that such interaction may affect flavonoid bioavailability, which is another important parameter determining the effect of flavonoids in a cellular level. Intervention study using human volunteers to reveal the role of flavonoids in real applications is important to further investigate.

■ AUTHOR CONTRIBUTIONS

Tsani Adiyanti co-wrote the manuscript. Yana Cahyana co-wrote and revised the manuscript. All authors agreed to the final version of this manuscript.

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