



## Review

# Modulation of Glucose Transporter Protein by Dietary Flavonoids in Type 2 Diabetes Mellitus

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## Abstract

Diabetes mellitus (DM) is a metabolic diseases characterized by hyperglycemia due to insufficient or inefficient insulin secretory response. This chronic disease is a global problem and there is a need for greater emphasis on therapeutic strategies in the health system. Phytochemicals such as flavonoids have recently attracted attention as source materials for the development of new anti-diabetic drugs or alternative therapy for the management of diabetes and its related complications. The antidiabetic potential of flavonoids are mainly through their modulatory effects on glucose transporter by enhancing GLUT-2 expression in pancreatic  $\beta$  cells and increasing expression and promoting translocation of GLUT-4 via PI3K/AKT, CAP/Cb1/TC10 and AMPK pathways. This review highlights the recent findings on beneficial effects of flavonoids in the management of diabetes with particular emphasis on the investigations that explore the role of these compounds in modulating glucose transporter proteins at cellular and molecular level.

Key words: Glucose transporter protein, insulin, type 2 diabetes mellitus, flavonoids, glucose uptake.

## Introduction

Diabetes mellitus (DM) is a metabolic disease marked by a high level of blood glucose due to insufficient or inefficient insulin secretory response [1, 2]. This disease has been considered as the fast growing epidemic worldwide. It is estimated that the number of people with DM will rise from 381.8 million in 2013 to 591.9 million in 2035 [3, 4]. Genetic condition (e.g., monogenic and polygenic mutations) and environmental factor (e.g., overweight, obesity, and inactivity), and their complex interaction can contribute to development of DM. Type 2 DM (T<sub>2</sub>DM) or non-insulin-dependent diabetes mellitus (NIDDM) is one of the most common types of DM, accounted for 90-95% of the diabetic cases worldwide. This common disease mainly occurs at the age over 40, caused by either deficiency in insulin secretion in the pancreatic

beta cells or insulin resistance in the body [5, 6]. T<sub>2</sub>DM affects several major organs, including heart, blood vessels, nerves, eyes and kidneys leading to disabling or even life-threatening complications such as cardiac dysfunction, atherosclerosis, and nephropathy [7]. Hence, T<sub>2</sub>DM is a global problem which needs to a greater emphasis on its prevention and therapeutic strategies in the health system.

Although T<sub>2</sub>DM cannot be cured, it can be treated successfully. A healthy lifestyle such as diet, exercise and weight control can provide the foundation for managing of T<sub>2</sub>DM, however anti-diabetic agents are required to regulate blood glucose levels in the serious conditions. These drugs can cause side effects for instance, weight gain which consequently increases the risk of insulin resistance leading to a

further enhance in drug dose. Administration of neutral anti-diabetic drugs derived from plants has broken this scenario. These medicinal herbs have been traditionally used for the treatment of T<sub>2</sub>DM since 1550 BC. Approximately, 80% of the people around the world rely on traditional medicinal plants to meet their primary health care needs. Amongst the phytochemical compounds, flavonoids and their derivatives are more under attention due to their hypoglycemic activity [8]. Flavonoids have antioxidative properties which protect the body against the deleterious effects of hyperglycemia in T<sub>2</sub>DM, through acting on the biological targets such as  $\alpha$ -glucosidase, glucose co-transporter or aldose reductase. These antioxidants have been proposed as potential anti-diabetic drugs by acting as biological targets involved in T<sub>2</sub>DM development.

In this review, we have focused on the structure and function of the flavonoids. Moreover, we highlighted the anti-diabetic effects of the flavonoids in the management of T<sub>2</sub>DM, through modulating glucose transporters, with particular emphasis on the investigations and recent findings.

## Type 2 diabetes

Type 2 diabetes is a progressive disease characterized by hyperglycemia with antecedent phase of insulin resistance. However, insulin resistance alone does not lead to diabetes and the disease develops when the insulin resistance is associated with deficit  $\beta$ -cell function. In fact, insulin resistance and defects in insulin release are considered as key pathophysiological abnormalities in development of T<sub>2</sub>DM [9-10].

## Insulin resistance

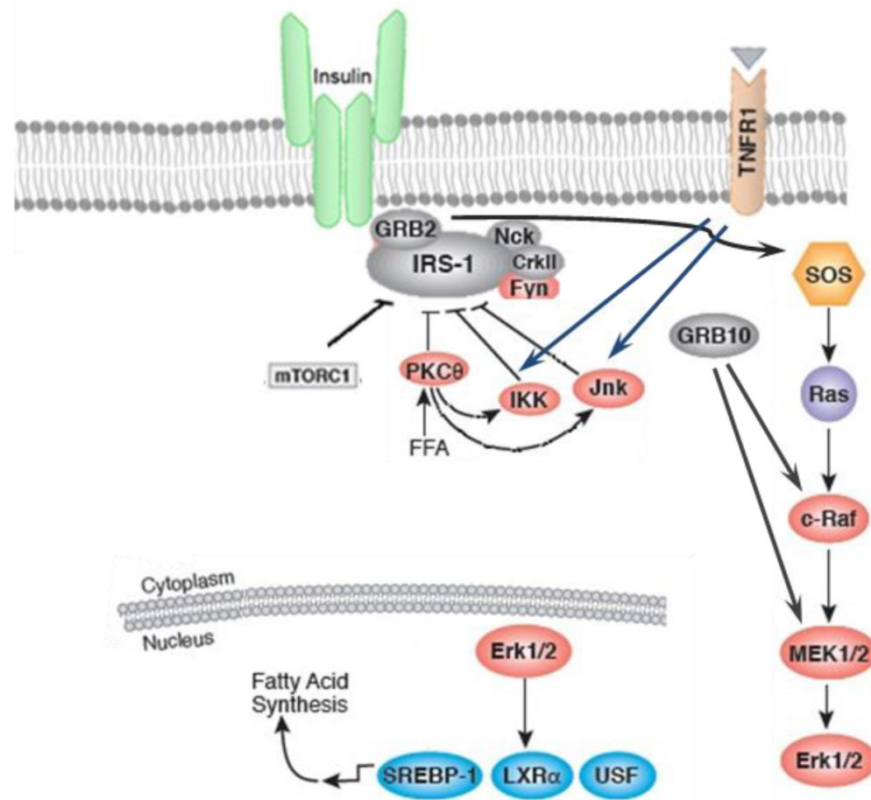
Resistance to insulin or less sensitivity of  $\beta$ -cell to insulin is caused by several different metabolic abnormalities including obesity which more or less affects the function abnormalities to the pancreas. The primarily metabolic abnormality in insulin-resistant type 2 diabetics is the defect in glucose uptake due to defective regulation of glucose transporter-4 (GLUT-4) protein [11]. The defect in translocation of GLUT-4 protein takes place due to the inhibition of tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1). This follows serine phosphorylation IRS-1 which inhibits binding and activation of phosphatidylinositol 3-kinase (PI3K) and initiation of downstream signaling events [12].

It has been proven that exposure of cells to pro-inflammatory cytokine such as tumor necrosis factor alpha (TNF- $\alpha$ ) or high levels of free fatty acids (FFAs) has inhibitory effect on phosphorylation of IRS-1 which inhibits downstream signaling and insulin action [13-15]. Metabolic stresses originated from

intracellular and extracellular signaling molecules, leads to activation of inflammatory signaling pathways. Enormous evidence suggested that obesity activates inflammatory signaling pathway by mediating functional capacity of the endoplasmic reticulum (ER) and induction of ER stress. The change caused to the inflammatory signaling pathway then contributes to insulin resistance [16-20].

Inflammation and stressful stimuli activates protein kinase C $\theta$  (PKC- $\theta$ ) and I $\kappa$ B kinase (IKK) which results in inhibition of insulin signaling [21]. These serine/threonine kinase, particularly IKK and c-jun amino terminal kinase (JNK), are also activated in obesity which highlights the overlap of metabolic and immune pathways [16-18]. As shown in figure 1, IKK and JNK pathways are activated in response to stimuli during metabolic dysregulation including ligands for TNF- $\alpha$ , interleukin-1 (IL-1), Toll, or advanced glycation end products receptors (RAGE), intracellular stresses including reactive oxygen species (ROS) and ER stress, ceramide, and various PKC isoforms [22, 23]. Upon activation of both JNK and IKK, IRS-1 phosphorylation takes place on Ser307 and Ser302 which results in impairment of insulin action [15, 16, 24-26]. JNK and IKK pathways lead to the production of additional inflammatory mediators via transcriptional regulation of inflammatory genes by phosphorylating activator protein-1 (AP-1) and nuclear factor -kappa B (NF- $\kappa$ B), respectively [27]. IKK $\beta$  activates NF- $\kappa$ B by phosphorylation of NF- $\kappa$ B inhibitor and consequently stimulates production of multiple inflammatory mediators, including TNF- $\alpha$  and IL-6 [28].

On the other hand, lipids-regulated transcription factors, e.g. peroxisome proliferator-activated receptor (PPAR) and liver X receptor (LXR) families) are promoter of nutrient transport and lipid metabolism thereby moderating inflammatory response. However, it has been demonstrated that the expression of fatty acid-binding proteins (FABPs) is antagonist to these transcription factors and promotes a more inflammatory environment [23]. It has been reported that the PPAR- $\gamma$  activation by insulin sensitizers, enhance the expression and translocation of GLUT-1 and GLUT-4, which results in increased glucose uptake in adipocytes and muscle cells and subsequent reduction in plasma glucose levels [29]. Insulin action can be disturbed by other inflammatory kinases, PKC- $\theta$ . Activation of PKC- $\theta$  and increased Ser307 phosphorylation of IRS-1 is correlated with lipid infusion and rise in levels of intracellular fatty acid metabolites, such as diacylglycerol (DAG) and fatty acyl CoAs. PKC- $\theta$  may also cause insulin resistance by activation of IKK $\beta$ , or JNK [30, 31]. The role of other PKC isoforms in inhibition of insulin signaling has also been reported [32].



**Figure 1.** The insulin action can be inhibited by inflammatory signaling pathways. Inflammation and stressful stimuli activates c-jun amino terminal kinase (JNK), IκB kinase (IKK), and protein kinase Cθ (PKC-θ) which result in inhibition of insulin signaling. The activation of sterol regulatory element binding protein-1c (SREBP-1c), upstream stimulatory factor 1 (USF1), and liver X receptor (LXR) induces fatty acid synthesis.

## Defects in Insulin Release

The pathogenesis of T<sub>2</sub>DM is characterized by alteration in β-cell function and mass in the presence of hyperglycemia and relatively constant insulin resistance. In response to insulin resistance β-cells compensate with increased insulin production to maintain euglycemia. The increased insulin production is accompanied by increased islet size and pancreatic proportion of β-cells [33]. At this stage, β-cells weaken the insulin secretion and gradually the over worked β-cells and their mass diminished.

Decreased β-cells mass is due to apoptosis of β-cells mainly caused by glucotoxicity, lipotoxicity, and deposits of islets amyloid polypeptide (IAPP) [34-36]. The islet in T<sub>2</sub>DM is characterized by amyloid deposit that derived from islet amyloid polypeptide is co-stored and co-secreted with insulin by pancreatic β-cells. It has been proven that in addition to extracellular IAPP deposit, IAPP toxic oligomers are present intracellularly in β-cells of type 2 diabetic patients which induces β-cells apoptosis [37].

Clinical and experimental animal studies have documented the deleterious role of chronic hyperglycemia in β-cell function and induction of cell apoptosis. The mechanisms involved include mito-

chondrial dysfunction caused by production of ROS, ER stress, and elevated levels of intracellular calcium [38-40]. In addition, increased FFAs has been demonstrated to induce pro-apoptotic effects on β-cells through ER stress, suppression of the mitogen activated protein kinase (MAPK cascade) [41, 42]. Moreover, intracellular accumulation of triglycerides due to the activation of the sterol regulatory element binding proteins (SREBP) may also contribute to β-cell dysfunction [43].

## Role of glucagon, incretin hormones and oxidative stress in the pathogenesis of T<sub>2</sub>DM

In addition to insulin, secretion of glucagon by pancreatic α-cells has a critical role in glucose homeostasis. These hormones have opposite effects on glycaemia where low blood glucose level induces α-cell secretion while β-cells release insulin in high blood glucose levels. In diabetic condition glucagon secretion is not suppressed at high glucose level and the secretion is inadequate at low glucose level [44-46].

Moreover, the impact of gut on insulin or glucagon secretion by giving rise to a number of peptide hormones such as glucagon-like peptide 1 (GLP-1), gastric inhibitory polypeptide (GIP) and gastrin has

been demonstrated. The secretion and insulinotropic action of the two major incretin hormones, GIP and GLP-1, are markedly decreased in T<sub>2</sub>DM. The reduced incretin action can precede the onset of hyperglycaemia in patients with T<sub>2</sub>DM [47-49].

Another factor that can lead to insulin resistance,  $\beta$ -cell dysfunction, impaired glucose tolerance and eventually T<sub>2</sub>DM is oxidative stress. Oxidative stress is defined as imbalance between formation and removal of highly reactive molecules, e.g., reactive oxygen species (ROS) and reactive nitrogen species (RNS) [50]. In oxidative stress condition reactive oxygen species such as superoxide ( $O_2^-$ ), hydroxyl ( $\cdot OH$ ), peroxy ( $\cdot RO_2$ ), hydroperoxyl ( $\cdot HRO_2^-$ ) and reactive nitrogen species such as nitric oxide ( $\cdot NO$ ) are responsible for lipid and protein modifications [51]. For instance the role of ROS such as  $O_2^-$  and  $H_2O_2$  in stimulation of stress-related signaling mechanisms including NF- $\kappa B$ , p38-MAP and janus kinase signal transducer and activator of transcription (JAK-STAT) has been well documented [52]. In T<sub>2</sub>DM, such activation of stress-sensitive pathways and elevations in glucose and free fatty acid (FFA) levels lead to both insulin resistance and impaired insulin secretion [53]. The production of ROS combined with a decreased antioxidant enzymes level leads to development of diabetes complications [50]. Many studies shown the key role of dietary antioxidants to neutralize or trap reactive oxygen species (ROS); therefore, antioxidants can act as antidiabetic agents [54-56]. Many studies have shown that oxidative stress increases the progression of the disorder, whereas an antioxidant-rich diet reduces the risk of diabetes [57, 58].

## Dietary Flavonoids

Flavonoids represent a biologically active class of secondary metabolite plant compounds that constitute an important part of the human diet. Till date, about 8,000 different members have been identified in a wide variety of fruit, vegetables and other plant-based food and beverage products [59]. The basic structure of flavonoids consist of 2 phenyl rings (A and B rings) linked by a 3-carbon unit that forms an oxygenated heterocyclic ring (C ring) (Figure 2). Based on differences in generic structure of the C ring, functional groups on the rings and the position at which the B ring is attached to the C ring flavonoids are classified into six subgroups; namely anthocyanidins, flavan-3-ols, flavanones, flavones, flavonols and isoflavones [60, 61]. The chemical structures and individual compounds along with the dietary source

of these subgroups are shown in Table 1.

The antidiabetic properties of flavonoids are mainly through their effect on a number of molecular targets and regulation of several pathways such as reducing apoptosis, improving proliferation of pancreatic  $\beta$ -cell and promoting insulin secretion; regulation of glucose metabolism in hepatocytes and subsequent improvement of hyperglycemia; decreasing insulin resistant, inflammation and oxidative stress in adipocytes and skeletal myofibers; enhancing glucose uptake in skeletal muscle and adipose tissues. Some epidemiological studies have suggested some undesirable effects on the consumption of flavonoid-rich diets and development of certain ailments [62, 63]. However, many *in vitro* and *in vivo* studies on animal have shown convincing evidences regarding beneficial effects of flavonoids on glucose homeostasis [64].

Uptake of glucose by the cells is an important phenomena in maintain the blood glucose level and there are convincing evidences regarding beneficial effects of flavonoids on peripheral glucose uptake in both insulin sensitive and non-insulin sensitive tissues (Table 2). A study conducted by Prabhakar and Doble [1], showed comparable performance of phenolic compounds to common hypoglycemic drugs in enhancing glucose uptake. In line with the phenolic compounds, epicatechin has been known to possess antidiabetic effects by reducing blood glucose levels [65, 66] and improving the insulin sensitivity and secretion [66-69]. Similarly, the protective effect of epigallocatechin gallate (EGCG), the major polyphenol in green tea, on diabetes and obesity has been extensively studied. It has been indicated that EGCG possess insulin-potentiating activity on the utilization of glucose [70-74]. Many studies on polyphenolic flavonoid, quercetin have identified it as a natural immunity booster and showed to possess  $\alpha$ -glucosidase inhibitory activity *in vitro* [75, 76]. In addition, administration of quercetin has been found to attenuate fasting and postprandial blood glucose level in diabetic mice and rats [77].

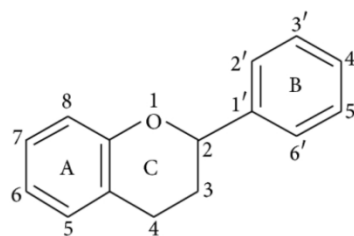
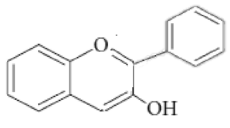
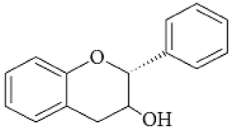
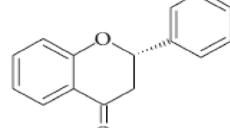
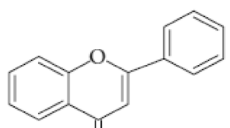
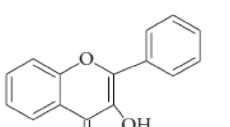
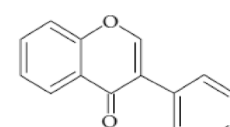


Figure 2. Basic structure of flavonoid.

**Table 1.** The chemical structures and classification of the flavonoids dietary sources.

Group of Flavonoid	Dietary sources	Compounds	Chemical formula	References
Anthocyanidins 	Fruits (e.g., Cherry and berries) vegetables and red wine	Cyanidin Delphinidin Malvidin Pelargonidin Peonidin Petunidin	C <sub>15</sub> H <sub>11</sub> O <sub>6</sub> C <sub>15</sub> H <sub>11</sub> O <sub>7</sub> C <sub>17</sub> H <sub>15</sub> O <sub>7</sub> C <sub>15</sub> H <sub>11</sub> O <sub>5</sub> C <sub>16</sub> H <sub>13</sub> O <sub>6</sub> C <sub>16</sub> H <sub>13</sub> O <sub>7</sub>	[164, 169-171]
Flavan-3-ols 	Tea, Fruits, Cocoa and Chocolate	Catechin Epicatechin Procyanidins	C <sub>15</sub> H <sub>14</sub> O <sub>6</sub> C <sub>15</sub> H <sub>14</sub> O <sub>6</sub> C <sub>30</sub> H <sub>26</sub> O <sub>12</sub>	[172, 173]
Flavanones 	Citrus fruits (e.g., grapefruits, lemons, and oranges)	Naringin Naringenin Hesperidin	C <sub>27</sub> H <sub>32</sub> O <sub>14</sub> C <sub>15</sub> H <sub>12</sub> O <sub>5</sub> C <sub>28</sub> H <sub>34</sub> O <sub>15</sub>	[110, 174-176]
Flavones 	Fruit skins, red wine, buckwheat, red pepper, and tomato skin, celery, parsley and many herbs	Apigenin luteolin	C <sub>15</sub> H <sub>10</sub> O <sub>5</sub> C <sub>15</sub> H <sub>10</sub> O <sub>6</sub>	[170, 171, 177, 178]
Flavonols 	Onion, red wine, olive oil, berries, and grapefruit.	Fisetin Isorhamnetin Kaempferol Myricetin Quercetin	C <sub>15</sub> H <sub>10</sub> O <sub>6</sub> C <sub>16</sub> H <sub>12</sub> O <sub>7</sub> C <sub>15</sub> H <sub>10</sub> O <sub>6</sub> C <sub>15</sub> H <sub>10</sub> O <sub>8</sub> C <sub>15</sub> H <sub>10</sub> O <sub>7</sub>	[170, 179]
Isoflavones 	Soyabean, leguminous plants and Chinese herb medicines	Daidzein Genistein	C <sub>15</sub> H <sub>10</sub> O <sub>4</sub> C <sub>15</sub> H <sub>10</sub> O <sub>5</sub>	[179-181]

**Table 2.** List of flavonoids targeting signaling pathways in diabetes.

Flavonoids	Glucose transporter isoforms	Pathways/target molecules	Experimental model	Targets	Comments	References
<b>Anthocyanins</b>						
Anthocyanin	GLUT-4	IRS1, PI3k/ AKT pathway, Anti-inflamtroly pathway	HFD-treated mice	Liver	Suppressed reactive oxygen species, restored the impairment of PI3k/ AKT pathway, suppressed the JNK, NF- κB and IKKβ activation.	[78]
Anthocyanin	GLUT-4	AMPK pathway, glucose uptake	<i>In vitro</i>	Adipocyte 3T3-L1, C2C12 muscle cells and β TC-tetcells	Enhanced glucose uptake, insulin-like activities, insulin-sensitizing properties, PPARγ agonist activity, increased insulin secretion.	[182]
Anthocyanin	GLUT-4	Glucose uptake	STZ-induced diabetic rats	Heart, skeletal muscle, pancreatic tissues and serum	Antioxidant activity, prevent pancreatic apoptosis, decreased glucose levels, Increased insulin secretion, activated insulin receptor phosphorylation and increased GLUT-4 expression.	[163]
Anthocyanin	GLUT-4	AMPK, insulin sensi-	diabetic mic	White adipose	hyperglycemia and insulin sensitivity <i>via</i> activa-	[164]

		tivity, PPAR		tissue, skeletal muscle, and the liver	tion of AMPK, upregulation of glucose transporter 4 in WAT and skeletal muscle, suppression of glucose production and inactivation of acetyl-CoA carboxylase in the liver.	
Cyanidin 3-glucoside	GLUT-4	Antiinflamtroty pathway, glucose uptake, GLUT 4 regulation,	KK-Ay diabetic mice	White adipose tissue	Ameliorated hyperglycemia and insulin sensitivity, upregulated the GLUT 4,downregulated the inflammatory adipocytokines (TNF- $\alpha$ and MCP-1).	[183]
Cyanidin 3-glucoside	GLUT-4	Antiinflamtroty pathway, modulating the JNK/FoxO1 signaling pathway	C57BL/Ks db/db	White adipose tissue and blood	Lowered fasting glucose levels, improved the insulin sensitivity, reduced inflammatory cytokines (TNF- $\alpha$ , IL-6, and MCP-1).	[184]
Cyanidin 3-Glucoside	GLUT-4	Glucose uptake	<i>In vitro</i>	Adipocyte 3T3-L1	Insulin-like activities, increased adipocyte glucose uptake, GLUT-4 expression and translocation, increased nuclear PPAR $\gamma$ activity, improve insulin resistance.	[161, 185]
<b>Flavon-3-ols</b>						
Catechin	GLUT-4	Enhanced GLUT4 mRNA and protein expression	STZ-induced diabetic rats	Liver, muscle and blood	Hypo-glycemic, Glucose oxidizing and insulin mimetic activities.	[186]
(-)-epicatechin(EP)	GLUT-4	Glucose uptake, PI3K	<i>In vitro</i>	3T3-L1 adipocytes	Promote the translocation of GLUT-4 through activation of PI3K, increased phosphorylation of PKC $\alpha$ / $\zeta$ .	[187]
(-)-epigallocatechin (EGC)	GLUT-4	Glucose uptake, PI3K	<i>In vitro</i>	3T3-L1 adipocytes	Promote the translocation of GLUT-4 through activation of PI3K, increased phosphorylation of PKC $\alpha$ / $\zeta$ .	[187]
(-)-epigallocatechin n-3-gallate (EGCG)	GLUT-4	Suppressed JNK pathway	<i>In vitro and obese KK-ay mice,HFD-induced obese rats</i>	Adipocytes tissue, 3T3-L1 adipocytes	Decreased JNK phosphorylation and promoted GLUT-4 translocation.	[188]
(-)-epigallocatechin n-3-gallate (EGCG)	GLUT-4	AMPK, insulin signaling pathway	<i>In vivo</i>	Skeletal muscle and adipose tissue	Activated AMPK pathway, improving insulin signaling pathway, decrease oxidative stress, membrane translocation and Ser307 phosphorylation of IRS-1, increase in Ser473 phosphorylation of Akt and GLUT-4 translocation in skeletal muscle and adipose tissue.	[150]
(-)-epigallocatechin n-3-gallate (EGCG)	GLUT-4	PI3K/aPKC $\alpha$ , AMPK and NF- $\kappa$ B signaling pathways	<i>In vitro</i>	H4IIE cells	Stimulates the PI3K/aPKC $\alpha$ , AMPK and NF- $\kappa$ B pathways.	[149]
(-)-epigallocatechin n-3-gallate (EGCG)	GLUT-4	inflammatory response pathway	HFD rats	adipose tissues	Decreasing the levels of toll-like receptor 4, IKK $\beta$ , NF- $\kappa$ B, TNF- $\alpha$ , and IL-6, decreased the level of phosphorylated insulin receptor substrate 1 and increased phosphoinositide-3-kinase and GLUT-4 in adipose tissues of HFD rats.	[189]
(-)-epigallocatechin n-3-gallate (EGCG)	GLUT-4	Glucose uptake and GLUT-4 translocation	<i>In vitro and ratEx vivo</i>	Insulin-resistant L6 myotubes and skeletal muscle of mice	Increased glucose uptake and promoted translocation of GLUT-4 to plasma membrane in skeletal muscle.	[131]
(-)-epigallocatechin n-3-gallate (EGCG)	GLUT-4	IRS1, AMPK	<i>In vitro</i>	HepG2	Attenuates insulin signaling blockade by reducing IRS-1 Ser307 phosphorylation through the AMPK activation pathway.	[139]
(-)-epigallocatechin n-3-gallate (EGCG)	GLUT-4	AMPK, insulin signaling pathway	FFAs-induced peripheral insulin resistance in rats	Skeletal muscle cells and adipose tissue	Decreased oxidative stress and PKC $\theta$ membrane translocation activated the AMPK pathway and improved insulin signaling pathway.	[140]
(-)-epigallocatechin n-3-gallate (EGCG)	-	AMPK pathway	<i>In vitro and BALB/c mice</i>	Mouse hepatoma (Hepa 1-6) cells, rat myotube L6 cells, and 3T3-L1 adipocytes cells and liver of mice	Increased in AMPK and the downstream target acetyl-CoA carboxylase (ACC) phosphorylation.	[151]
(-)-epigallocatechin n-3-gallate (EGCG)	GLUT-4	AMPK and PI3K/ Akt pathway.	<i>In vitro</i>	L6 cells	Improved insulin-stimulated glucose uptake by increasing GLUT-4 translocation to plasma membrane.	[141]
Procyanidins	GLUT-4	signaling pathway (PI3K and p38 MAPK), glucose uptake, glucose transporter-4 translocation	<i>In vitro and STZ-induced diabetic rats</i>	L6E9 myotubes and 3T3-L1 adipocytes, Blood sample	Antihyperglycemic effect, insulinomimetic activity, stimulated glucose uptake, stimulated GLUT-4 expression and translocation.	[147]
<b>Flavanones</b>						
Hesperidin	GLUT-2 and GLUT-4	GLUT 4 expression, increasing hepatic glycolysis and lowering hepatic gluconeogenesis	C57BL/KsJ-db/db mice	Liver and adipocyte	Reduced blood glucose, reduced protein expression of GLUT-2 in hepatocyte, elevated GLUT-4 in adipocyte and hepatocyte.	[80, 110]
Naringenin	GLUT-4	AMPK, glucose up-	<i>In vitro</i>	L6 myotubes	Stimulated glucose uptake, increased AMPK	[132]

		take,			phosphorylation/ activation.	
Naringin	GLUT-2 and GLUT-4	GLUT 4 expression, increasing hepatic glycolysis and lowering hepatic gluconeogenesis	C57BL/KsJ-db/db mice	Liver and adipocyte	Reduced blood glucose, lowered the mRNA expression of PEPCK and G6Pase in the liver, reduced protein expression of GLUT-2 in hepatocyte, elevated GLUT-4 in adipocyte and hepatocyte.	[80, 110]
Naringin	GIUT-4	AMPK-dependent mechanism and Anti-oxidative stress	HFD in C57BL/6 mice	Liver, white adipose tissue and Blood	Regulated of PEPCK and G6pase, improvement of insulin resistance, protective by phosphorylating AMPKa and IRS1.	[152]
Naringin	GLUT-4	AMPK Pathway, glucose uptake	<i>In vitro</i>	L6 myotubes	Stimulated glucose uptake, increased AMPK phosphorylation/ activation.	[132]
<b>Flavones</b>						
Apigenin	GLUT-4	GLUT-4 translocation	STZ-induced diabetic rats	Liver and pancreas	Antioxidant effect, effective control of blood glucose level along, enhanced GLUT-4 translocation.	[190]
Apigenin-6-C- $\beta$ -L-fucopyranoside	GLUT-2	MAPK-PP1 and PI3K-GSK3 pathways, Insulin secretion	<i>In vivo</i> and <i>in vitro</i>	rat soleus muscle, hyperglycemic rats serum,	Stimulated insulin secretion and glycogen synthesis, reduce blood glucose level and insulin mimetic effects.	[158]
luteolin-7-O-glucoside	GLUT-4	Glucose uptake, suppressed gluconeogenic enzymes	STZ-induced diabetic rats	Rat skeletal muscle	Protected pancreatic $\beta$ -cells, stimulated glucose uptake, increased GLUT-4 expression and translocation, suppressed G6Pase.	[191]
Tangeritin	GLUT-4	AMPK, glucose uptake	<i>In vitro</i> and HFD mice	C2C12 myotubes, muscle tissue	Phosphorylated AMPK and AS160, glucose uptake, GLUT4 translocation.	[192]
Tangeritin	GLUT-4	PI3K/Akt1/2, glucose uptake	<i>In vitro</i>	3T3-F442A adipocytes	Increased in glucose uptake.	[193]
<b>Flavonols</b>						
Fisetin	GIUT-4	AMPK	STZ-induced diabetic rats	Liver	Decreased the expression levels of gluconeogenic genes, such as PEPCK and G6Pase.	[194]
Kaempferitrin	GIUT-4	glucose uptake, insulin receptor, PI3K, atypical PKC activity	<i>In vitro</i>	Rat soleus muscle	Stimulated glucose uptake, involved in translocation of GLUT-4, glucose homeostasis, insulin-mimetic role.	[83]
Kaempferol	GIUT-4	Glucose uptake, PPAR $\gamma$	<i>In vitro</i>	3T3-L1 adipocytes	Improved glucose uptake, ameliorated hyperglycemia, PPAR $\gamma$ agonist activity.	[195]
Kaempferol 3-neohesperidoside	GLUT-4	PI3K - GSK-3 pathway and MAPK - PP1 pathway, glycogen synthesis	<i>In vitro</i>	Rat soleus muscle	Stimulated glycogen synthesis.	[196]
Morin	GIUT-4	Insulin receptor, IRS, PI3K/Akt, FOXO1	<i>In vitro</i>	HepG2	Insulin-mimetic effect, increases the phosphorylation of the insulin receptor and Akt, FOXO1 phosphorylation, inhibits gluconeogenesis and enhances glycogen synthesis.	[197]
Myricetin	GLUT-4	IRS1, PI3K/AKT, p85	fructose chow-fed rats	Soleus muscles, plasma	Improved insulin sensitivity through the enhancement of insulin action on IRS-1-associated PI3K and GLUT 4 activity.	[145, 146]
Myricetin	GLUT-2 and GLUT-4	insulin signaling pathway	STZ-Cd induced diabetic nephrotoxic rats	Plasma, Liver, pancreas and skeletal muscle	Increased glycogen phosphorylase, glycogen synthase and G6pase, increased insulin and insulin signaling molecule expression like GLUT-2, GLUT-4, IRS-1, IRS-2 and PKB.	[198]
Pentamethylquercetin	GLUT-4	GLUT 4, PPAR	<i>In vitro</i>	3T3-L1 cell	Increased mRNA levels of GLUT-4, and PPAR.	[129]
Quercetin	GIUT-4	Glucose uptake, PPAR $\gamma$	<i>In vitro</i>	3T3-L1 adipocytes	Improved glucose uptake, ameliorated hyperglycemia, PPAR $\gamma$ agonist activity.	[195]
Rutin	GLUT-4	PI3K, atypical PkC and MAPK pathways	Wistar rats	Isolated soleus muscles from rats	Insulin-mimetic role, stimulated glucose uptake via the PI3K, atypical PKC, CaMKII and MAPK pathways, increased GLUT-4 translocation, stimulated calcium uptake.	[143, 144]
Tetramethylkaempferol	GLUT-4	GLUT-4, PPAR	<i>In vitro</i>	3T3-L1 cell	Increased mRNA levels of GLUT-4, and PPAR.	[129]
<b>Isoflavones</b>						
Genistein	GLUT-2	CaMK II and Ca <sup>2+</sup> signaling, insulin secretion	<i>In vitro</i>	INS-1 rat insulinoma cells	Stimulated insulin secretion via activation of Ca <sup>2+</sup> /CaMK II.	[100]

Lot of studies on vegetables enrich with flavonoids have been reported to mediate blood glucose levels and are helpful in the management of T<sub>2</sub>DM. One of the examples is purple sweet potato which significantly ameliorates the fasting blood glucose level, glucose and insulin tolerance by blocking oxidative stress and enhancing activity of antioxidant enzymes

[78, 79]. A study conducted by Jung Lee [80], showed beneficial effects of hesperidin and naringin in treatment of diabetes. The improved hyperglycemia was observed in diabetic mice, evidenced by regulation of the activities of the hepatic glucose metabolic enzymes involved in glycolysis and gluconeogenesis.

It has been shown that berberine is effective in

the treatment of diabetes in human by lowering blood insulin level through enhancing insulin sensitivity. A similar study has proven the beneficial effect of berberine by improving insulin secretion in patients with impaired  $\beta$ -cell function [81, 82]. Kaempferitrin has also been demonstrated to possess antidiabetic effects by stimulating GLUT-4 translocation and synthesis in adipocytes [83-85].

## Glucose transporter proteins

One of the most vital cellular nutrient transport in eukaryotic cells is the transport of glucose across plasma membrane which is catalyzed by a family of glucose transporter proteins (GLUT). GLUT family, encoded by SLC2 genes, are integral membrane proteins that mediate transport of monosaccharides, polyols, and other small carbon compounds across the membranes of eukaryotic cells. In human, fourteen GLUT proteins are expressed, named GLUT-1-12 and 14 as well as myo-inositol transporter (HMIT). These proteins are comprised of ~500 amino acid residues and based on their amino acid sequence similarity are characterized into three classes namely Class 1 (GLUTs 1-4, 14); Class 2 (GLUTs 5, 7, 9, and 11); and Class 3 (GLUTs 6, 8, 10, 12, and HMIT) [86, 87].

The fourteen GLUT proteins are composed of 12 transmembrane segments, a single site of N-linked glycosylation, a relatively large, central, cytoplasmic linker domain, and exhibit topologies with both their N and C termini positioned in the cytoplasm [87]. In almost every human cell types, GLUT proteins are expressed. The rate of glucose entry into the cell is determined by tissue-specific expression of one or more GLUT proteins [86]. Among all glucose transporters, GLUTs 1-4 are most widely studied and their roles have been well documented as glucose and/or fructose transporters in different tissues and cell types.

### GLUT-1

GLUT-1, the major membrane protein, was the first purified membrane transporter. This glucose transporter is encoded by SLC2A1 gene, comprising 3-5% of total membrane protein. Gene transcription of GLUT-1 is stimulated by glucose deprivation, as well as most mitogens [87-89]. GLUT is found predominantly at the endothelial of barrier tissues such as blood vessels and the blood-brain barrier (BBB), however, it is expressed in many other tissues such as kidney and colon with minimal expression in the liver [87, 90].

GLUT-1 may express in conjunction with one or more GLUT isoforms. For instant, in adipose tissue, GLUT-1 is expressed along with GLUT-4. Glucose, mannose, galactose, glucosamine, and reduced

ascorbate can be transported by GLUT-1, although glucose is the main physiological substrate of GLUT-1[87]. The activation of GLUT-1 is mainly occurred by the cell stressors such as azide [91, 92], osmotic stress [93, 94], methylene blue [95], and glucose deprivation [96, 97].

Medicinal plants rich in flavonoids have shown promising effects in up-regulation of GLUT-1 expression levels. Berberin, the major active component of *Rhizoma Coptidis*, has been reported to enhance GLUT-1 expression and promotes its activities [98, 99]. In addition, genistein derivatives have been demonstrated promising effects in the treatment of T<sub>2</sub>DM. since the tested compounds significantly stimulated the glucose uptake through elevating GLUT-4 and GLUT-1 mRNA expressions levels in L6 myotubes [100].

### GLUT-2

GLUT-2 encoded by SLC2A2, is predominantly expressed in hepatocytes. However, it is also expressed by kidney proximal convoluted tubule cells, intestinal absorptive cells and pancreatic  $\beta$ -cells [101, 102]. This isoform of glucose transporter is involved in glucose-sensing in pancreatic  $\beta$ -cells, liver, and the hypothalamus as well as triggering the glucose-mediated insulin secretion cascade [103-106]. Among all glucose transporters, GLUT-2 has the lowest apparent affinity for glucose. It has low affinity to other monosaccharaides such as galactose, mannose and fructose. However, glucosamine can be transported with a very high affinity [107].

In recent years GLUT-2 has drawn attentions as a molecule that could be involved in the pathogenesis of diabetes mellitus. Studies have proven that the GLUT-2 expression is down-regulated in pancreatic  $\beta$ -cells [108], while hepatic expression of this glucose transporter is enhanced in diabetic animal models [109]. Hesperidin and naringin have been demonstrated to reduce protein expression of GLUT-2 in the liver of experimental animals [80, 110]. Epicatechin has also been reported to protect HepG2 functionality in high glucose concentration by restoring GLUT-2 expression level and modulating glucose production and uptake [111, 112].

### GLUT-3

GLUT-3 also known as neuron specific glucose transporter, was first characterized by cloning SLC2A3 gene from human fetal skeletal muscle cell line. This glucose transporter is expressed abundantly in mammalian neurons and trophoblasts, with less expression in the cell body [87, 113]. GLUT-3 plays an important role in the alterations of placental function observed in diabetic pregnancies [114].



GLUT-3 has found to be present in early gestation, proposing its important role in glucose uptake [115]. Among other GLUT proteins present in class I, GLUT-3 has the highest apparent affinity and highest maximum turnover number of glucose. The predominant site of expression of GLUT-3 is brain. However, lower amounts are expressed in placenta, liver, heart and kidney [86, 87]. This tissue distribution is apparently due to the fact that GLUT-3 protein expression occurs more in tissues which exhibit high demand of glucose such as nerve and brain.

The main glucose transporter expressed at the blood-nerve and blood-brain barrier is GLUT-1 while GLUT-3 is responsible for uptake of glucose into the neurons. In fact, GLUT-3 acts in tandem with GLUT-1 to meet the high energy demand of these tissues [116]. In addition, 64% sequence similarity has been reported between GLUT-1 and GLUT-3 proteins [87]. Although GLUT-3 has been proposed to have role in gestation diabetes and alterations of placental function in diabetic pregnancies, there is insufficient information on the expression pattern of GLUT-3 and the role of flavonoids in modulating this glucose transporter isoform.

## GLUT-4

GLUT-4 encoded by *Slc2a4* gene, is mostly expressed in adipocytes, skeletal muscle, and cardiomyocytes. The presence of this glucose transporter has also been identified in the brain and kidney [117-119]. GLUT-4 is unique isoform among glucose transporters due to its insulin-sensitive regulation while exhibiting 65, 54 and 58% protein sequence similarity with GLUT-1, 2 and 3, respectively. The expression of GLUT-4 gene is subject to both tissue-specific and hormonal/metabolic regulation. Muscle and adipose tissue has shown a large similarity in cellular GLUT-4 regulation, although some minor and major differences have been observed. GLUT-4 plays a vital role in glucose-sensing although only 15% of the blood glucose is absorbed by adipose tissue and the remaining 85% by muscle in healthy individuals [120, 121].

GLUT-4 exist in small vesicles in cytoplasm and can be stimulated by both insulin and muscle contraction which induce the translocation of this glucose transporter isoform to the plasma membrane where it serves as portal through which glucose uptake takes place. Impaired translocation of intracellular GLUT-4 to the plasma membrane refers to insulin resistant. Development of insulin resistance in conjunction with impaired insulin secretion and insulin resistance in the liver plays an important role in the pathogenesis of T<sub>2</sub>DM [122, 123].

Numerous studies have suggested the role of

flavonoids and phenolic compound in enhancement of GLUT-4 expression and glucose uptake. Quercetin and procyanidins have been reported to possess anti-diabetic properties by up-regulation of mRNA level of GLUT-4 and its translocation to the cell membrane in adipocytes and skeletal muscle cells [119, 124-128]. Various flavonoids have shown antihyperglycemic effects by increasing mRNA expression levels of GLUT-4 in murine embryonic fibroblast line [129, 130]. EGCG has also been suggested to increase glucose uptake and promote translocation of GLUT-4 to plasma membrane in skeletal muscle cells [131]. Same effects have been observed in adipocyte and skeletal muscle cells by both hesperidin and naringin treatment [80, 110, 132].

## Mechanism of Action of dietary flavonoids on glucose transporter proteins

Insulin-induced translocation of GLUT-4 in fat and muscle cells, takes place by two parallel signaling pathways namely, PI3K/AKT and CAP/Cb1/TC10 pathways as shown in figure 3 and figure 4, respectively. Activation of insulin receptor (IR), leads to phosphorylation of insulin receptor substrate (IRS), which in turn triggers the activation of phosphoinositide 3-kinase (PI3K). PI3k then phosphorylates the lipid phosphatidylinositol 4, 5-bisphosphate (PIP<sub>2</sub>) to yield phosphatidylinositol 3,4,5-trisphosphate (PIP<sub>3</sub>). PIP<sub>3</sub> then activates phosphoinositide-dependent protein kinase 1 (PDK). PDK1-mediated phosphorylation of protein kinase B (Akt), in turn allows phosphorylation of the Rab GTPase-activating protein AS160 and leads to translocation of GLUT-4 from intracellular storage vesicles to plasma membrane and enhances the glucose uptake (Figure 3).

Activation of AKT leads to the inhibition of glycogen synthase kinase-3 (GSK-3), which then phosphorylates and deactivates glycogen synthase (GS). Furthermore, AKT phosphorylates the forkhead box protein O1 (FOXO1), which deactivates the expression of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), and suppresses gluconeogenesis in the hepatocyte [133]. AMP-activated protein kinase (AMPK) is an important regulator of the cellular metabolism which is also represses the hepatic glucose production through the modulation of PEPCK and G6Pase (Figure 5) [134].

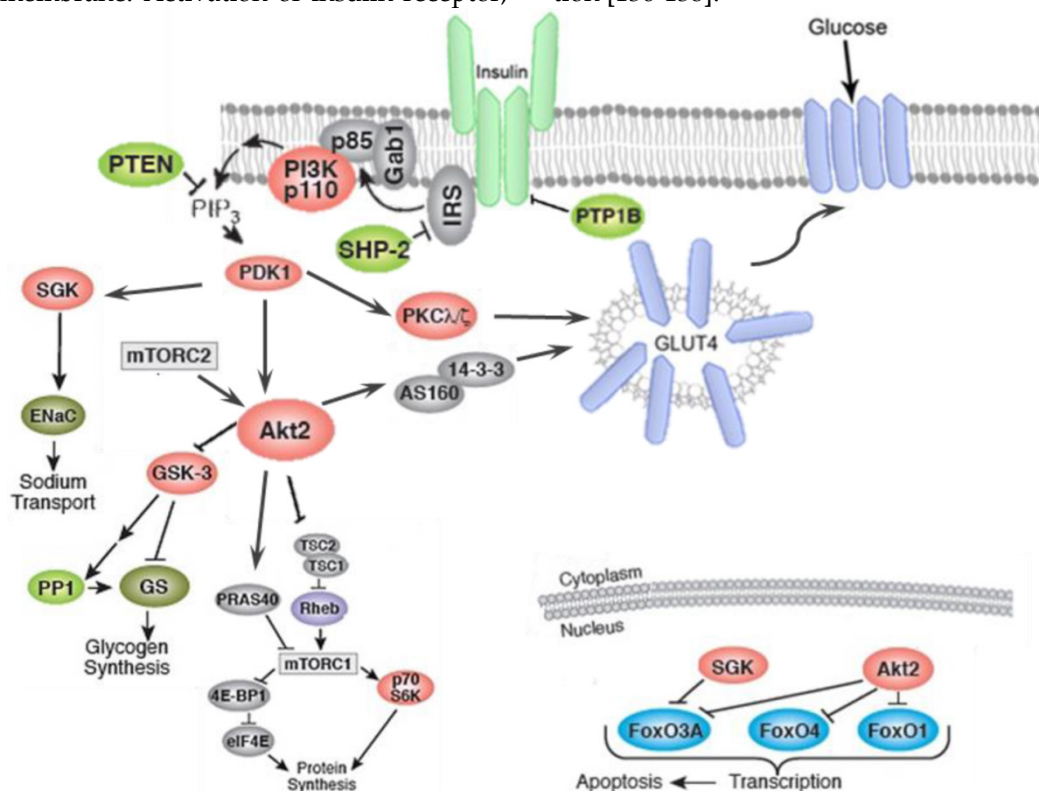
AMPK, a serine/threonine kinase is responsible for regulating anabolic and catabolic processes and maintaining cellular energy balance. The activation of AMPK, is mainly through the cellular energy changes (Figure 5). However, unknown factors from both immune and metabolic tissues/cells can coordinate to regulate this protein kinase [135]. Under high cellular

energy demands, the intracellular ATP is reduced and AMP levels is increased. The increased AMP/ATP ratio activates LKB1:STRAD:MO25 complex which in turn phosphorylates Thr172. The phosphorylation of Thr172 eventually leads to AMPK activation. The alternate pathway to activate AMPK is through activation of Ca<sup>2+</sup>/calmodulin-dependent protein kinase (CaMKKβ) in response to elevation of Ca<sup>2+</sup> level in cell cytoplasm. The Activated AMPK, decrease hepatic glucose production by inhibiting gluconeogenic enzymes phosphoenolpyruvate carboxykinase (PEPCK) and G6Pase and translocates GLUT-4 and GLUT-1 which ultimately increase glucose uptake (Figure 5). Lipid metabolism is also stimulated by AMPK through decreasing malonyl CoA levels in response to inhibition of acetyl CoA carboxylate (ACC) and activation of malonyl CoA decarboxylase (MCD)[133, 135].

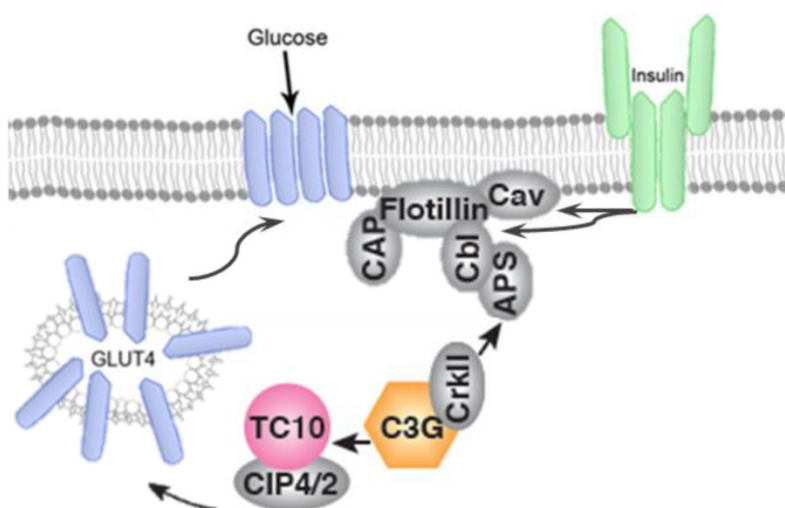
In addition to PI3K/AKT, participation of CAP/Cb1/TC10 pathway has been well documented to have an important role in translocation of GLUT-4 to plasma membrane. Activation of insulin receptor,

recruits the adapter protein APS to the insulin receptor β subunit and subsequently phosphorylates Cb1 proto-oncogene. Cb1 and Cb1-associated protein (CAP) then interact and bind to the lipid raft protein flotillin in the plasma membrane resulting in the recruitment of CrkII. CrkII then binds to the exchange factor C3G which catalyze the exchange of GDP to GTP on the lipid-raft-associated protein TC10. The TC10 downstream effectors are known to translocate GLUT-4 on plasma membrane and facilitate glucose uptake (Figure 4).

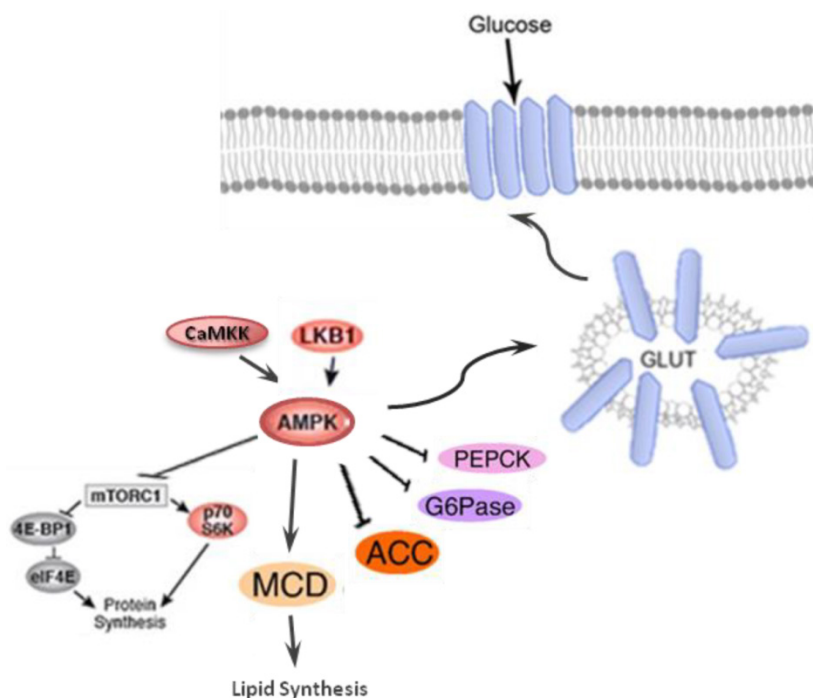
Insulin is secreted from pancreatic β-cells in response to enhanced glucose levels in blood circulation. Glucose is transported into the β-cells through GLUT-2. The increased intracellular concentrations of glucose leads to increase in the production of ATP, and an increase in the ATP/ADP ratio; which ultimately leads to closure of potassium channels on the cell membrane. The membrane depolarizes and leads to voltage-dependent calcium influx. The increased Ca<sup>2+</sup> concentration eventually promotes insulin secretion [136-138].



**Figure 3.** Insulin binding causes activation of the insulin receptor (IR), which phosphorylates different substrate adaptors such as the insulin receptor substrate (IRS). Upon tyrosine phosphorylation, IRS displays binding sites for many signaling partners. Among this signaling pathways PI3K has the main role in insulin function, through the activation of the Akt/PKB and the PKCζ cascades. Activated Akt leads to induction of glycogen synthesis via inhibition of glycogen synthase kinase (GSK-3); protein synthesis through mammalian target of rapamycin (mTOR) and downstream molecules; and regulation of cell proliferation via inhibition of pro-apoptotic agents such as forkhead family transcription factors, bcl-2-associated death promoter (Bad) and GSK-3. The activated Akt eventually leads to translocation GLUT4 to plasma membrane and glucose uptake. In addition to PI3K/Akt pathway.



**Figure 4.** GLUT-4 translocation takes place by IR-mediated phosphorylation of CAP, and formation of the CAP:Cbl:CrkII complex.



**Figure 5.** AMP-activated protein kinase (AMPK) which is the central energy leads to decreases hepatic glucose production via inhibiting the activation of gluconeogenic enzymes phosphoenolpyruvate carboxykinase (PEPCK) and glucose 6-phosphatase (G6Pase); induction of glucose uptake through inducing GLUT-4 and GLUT-1 and stimulation of lipid metabolism via declining malonyl CoA levels by inhibiting acetyl CoA carboxylate (ACC) and activation of malonyl CoA decarboxylase.

## Recent studies on flavonoids modulating glucose transporter proteins

A number of studies hypothesized that some flavonoids may increase GLUT-4 expression and PI3K/Akt activity leading to restore insulin sensitivity and might be a viable therapeutic avenue for treating diabetes. It has been reported that epicatechin reinforce the insulin signaling pathway by activating key proteins, such as IR/IRS, PI3K/AKT pathway and AMPK, and regulates the glucose production through AKT and AMPK modulation in HepG2 cells

[112]. A more recent study on antihyperglycaemic effect of epicatechin, demonstrated that this flavonoid compound reduced the high glucose-induced insulin signaling blockade by preventing the decrease of tyrosine phosphorylated and total IR, IRS-1 and IRS-2 levels, the inhibition of PI3K/AKT and AMPK pathways, and the increase of IRS-1 Ser636/639 phosphorylation values in HepG2 cell line [111]. In addition, it has been reported that EGCG attenuated insulin resistance by increasing IRS-1 serine phosphorylation *in vitro* [139] and *in vivo* [140, 141].

Anthocyanins derived from purple sweet potato

has shown to remarkably restore the impairment of the IRS1/PI3K /Akt insulin signaling pathway in the livers of high fat diet-treated mice [78]. Lou, Zhang [142], claimed that IL-6 and TNF- $\alpha$  are involved in the development of insulin resistance in hepatocytes. The result of this study confirmed that berberine effectively inhibited palmitate-induced IL-6 and TNF- $\alpha$  and attenuated insulin signaling cascade by modification of Serin/Threonine phosphorylation of insulin receptor substrate-1(IRS-1) and downstream Akt. Kaempferitrin and rutin have been identified to stimulate AKT phosphorylation as well as synthesis and translocation of GLUT-4 in adipocytes and skeletal muscle cells [83, 143, 144]. Myricetin has been evaluated to possess promising activities on improving insulin sensitivity by phosphorylation IR/IRS-1 and PI3K/AKT, which subsequently effect translocation of GLUT-4 in soleus muscles of fructose chow-fed rats [145, 146].

In recent years, studies have most often focused on the effect of flavonoids in stimulating CAP/Cb1/TC10 pathway. For instant, an *in vitro* study has demonstrated the effect of gallic acid in elevating glucose up take by activation of Cb1-TC10 pathway in parallel to PI3K/AKT pathway in 3T3-L1 adipocytes [130].

The importance of AMPK pathway in controlling cellular metabolism and regulating energy status has drawn the attention of scientists to target activation of this pathway as a new treatment for obesity and diabetes. For instant, Procyanidins, the oligomers and polymers of flavan-3-ols and consist of epicatechin and catechin subunits, have been reported to effectively increase glucose uptake through activation of this pathway [127, 128, 147]. *In vitro* studies have indicated the role of polyphenolic compounds such as quercetin and resveratrol in increasing glucose uptake in muscle cells and adipocytes by promoting translocation of GLUT-4, mainly via induction of the AMP-activated protein kinase [126, 148]. Epigallocatechin gallate has also been shown to possess beneficial effect on insulin signaling through activation of the AMPK pathway [139, 141, 149-151]. It has been reported that naringin exert hypoglycemic effect in hepatocytes exposed to high glucose by phosphorylating AMPK $\alpha$  and IRS1. The result of the same study also revealed that naringin protected against metabolic syndrome through an AMPK-dependent mechanism in high-fat diet mice [152].

Many studies have demonstrated the ability of berberine to induce Thr-172 phosphorylation of AMPK [81, 99, 153-156]. Berberine has also been reported to be responsible for moderate inhibition of mitochondrial function, decreased oxygen consumption and enhanced glycolysis which lead to increased

AMP/ATP ratio and subsequent activation of AMPK pathway [81, 154, 156]. In a study conducted by Ding and his group [157], myricetin intervention revealed the attenuation for the inhibitory effect of hyperinsulinemia on glucose uptake through increasing AMP-activated protein kinase activity in C2C12 myotubes.

The significant insulin secretagogue effect of flavonoids and their potential role in the treatment of diabetes have been widely studied. For instant, Apigenin-6-C- $\beta$ -L-fucopyranoside and quercetin have been reported to reduce blood glucose level and improve insulin secretion in hyperglycemic rats [158-160].

Antioxidant and anti-inflammatory properties of flavonoids have been well documented, and might be serve as potential therapeutic agents against diabetes by avoiding of insulin resistance. Cyanidin-3-O-b-glucoside and its metabolite protocatechuic acid have been demonstrated to exert insulin-like effects by up-regulating PPAR $\gamma$  activity which results in regulation of adiponectin and translocation of GLUT-4 in human omental adipocytes [161]. In addition, the positive effect of anthocyanins in glucose homeostasis has been investigated *in vivo* and *in vitro* [162-164]. For instant, studies conducted by Zhang et al [78, 165, 166] demonstrated the antidiabetic activity of anthocyanins derived from purple sweet potato through inhibition of JNK and IKK $\beta$  activation caused by oxidative and ER stress in the liver of high-fat-diet mice [166]. Yan Li and colleges [140], suggested the protective effect of epigallocatechin gallate from FFAs-induced peripheral insulin resistance through inhibition of oxidative stress and PKC activity. In addition, the ability of epigallocatechin gallate to improve insulin signaling by decreasing the levels of toll-like receptor 4, IKK $\beta$ , NF- $\kappa$ B, TNF- $\alpha$ , and IL-6 has been reported in high-fat diet rats [129, 149]. Emerging evidence indicated the hypoglycemic effect of naringin by regulation of PEPCK and G6pase as well as anti-oxidative stress property of this flavanone glycoside antioxidant in the improvement of insulin resistance and lipogenesis [152, 167]. It has been reported that naringin and hesperidin attenuate hyperglycemia-mediated oxidative stress and pro-inflammatory cytokines production where, the increased levels of MDA, NO, TNF- $\alpha$  and IL-6 have been reversed in HFD/STZ-induced diabetic rats after administration of naringin and hesperidin [167, 168].

## Conclusion

Diabetes mellitus is now a major global public health problem. Currently available drugs for the management of diabetes are costly and produce adverse effects. Flavonoids have recently attracted at-

tention as source materials for development of new antidiabetic drugs. Emerging evidence from various epidemiological, animal and *in vitro* studies have confirmed the beneficial effects of many dietary flavonoids in the treatment and management of type 2 diabetes and its related complications. Flavonoid mediates glucose metabolism by a number of mechanisms and pathways such as influencing insulin secretion, energy metabolism and insulin sensitivity in peripheral tissues. Not only through antioxidant and anti-inflammatory but different enzyme inhibition, receptor agonist or antagonist activities have shown the protective and curative properties of flavonoids against diabetes. Flavonoid may act through multiple components of signaling cascades to exert their modulatory effects in different cell types. Most of the studies discussed in this review have suggested the important role of flavonoids in enhancing glucose uptake and expression of glucose transporter proteins in particular up-regulation and translocation of GLUT-4. Although to date considerable scientific progress has been made in understanding the mechanism of action of flavonoids, we are still short of having a complete picture of the mechanisms involved in cross-talk based on the insulin action in order to provide new insights into the potential role of flavonoids in the treatment of type 2 diabetes.

## Abbreviations

DM: Diabetes mellitus; T2DM: Type 2 Diabetes mellitus; GLP-1: glucagon-like peptide 1; GIP: gastric inhibitory polypeptide; ACC: Acetyl Co-A carboxylase AMPK: Adenosine monophosphate-activated protein kinase; ATP: Adenosine triphosphate cAMP: cyclic adenosine mono phosphate; ECG: Epicatechingallate; EGC: Epigallocatechin; EGCG: Epigallocatechingallate; ER: Endoplasmic reticulum; FFA: Free fatty acid; GSK-3: glycogen synthase kinase; mTOR: mammalian target of rapamycin; Bad: bcl-2-associated death promoter; SREBP-1C: sterol regulatory element binding protein-1c; USF1: upstream stimulatory factor 1; LXR: liver X receptor; G6Pase: glucose 6-phosphatase; IKK: I $\kappa$ B kinase; FoXO1: Forkhead box protein O1; G6Pase: Glucose-6-phosphatase; GK: Glucokinase; GLUT: Glucose transporter; GSIS: Glucose-stimulated insulin secretion; IR: Insulin receptor; IRS: Insulin receptor Substrate; JNK: c-jun amino terminal kinase MAPK: Mitogen activated protein kinase; NF- $\kappa$ B: Nuclear factor- $\kappa$ B; TNF $\alpha$ : Tumor necrosis factor  $\alpha$ ; PEPCK: Phosphoenolpyruvatecarboxykinase; ROS: Reactive oxygen species; STZ: Streptozotocin; PGC-1 $\alpha$ : Peroxisome proliferator-activated receptor gamma coactivator-1- $\alpha$ ; PKC: Protein kinase C; PPAR: peroxisome

proliferator activated receptor; CaMK II: Calmodulin kinase II; STZ-induced: Streptozotocin-induced; STZ-Cd-induced: Streptozotocin-cadmium-induced; HFD: high-fat diet; FFAs-induced: free fatty acids-induced; NA-STZ-induced: Nicotinamide-streptozotocin-induced.

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## Competing Interests

The authors have declared that no competing interest exists.

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