

# The role of isoflavon in reducing blood glucose levels

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## ABSTRACT

Plants provide excellent sources of medicinal compounds. Over 5000 flavonoids have been isolated and identified from plant sources. Flavonoids are polyphenolic compounds mainly recognized as pigments which produce the colors found in flowers, fruit and leaves. Dietary polyphenols are commonly found in plants and are abundant in fruit, vegetables, chocolate, and nuts. These polyphenols also found in beverages including tea, coffee, wine, and soy milk. Flavonoids are known to lower glucose levels, decrease cholesterol and triglycerides, and increase liver enzyme levels most likely by stimulating pancreatic insulin release. By activating cell-signaling pathways involved in controlling blood glucose levels, flavonoids aid in carbohydrate digestion, and adipose deposition. Flavonoids containing isoflavones, flavanols, flavanones, flavonols, flavones, and anthocyanins have been studied from clinic study until pre clinic study. However, not all of the studies conducted had adequate results. Isoflavone is one of the potential flavonoids that still can be explored for future research. Research on isoflavone supplementation in animals and humans in reducing blood glucose levels is still limited. Short-term supplementation did not improve blood glucose levels in postmenopausal women, while other studies suggest that the long-term isoflavone supplementation can reduce postmenopausal blood glucose levels. These findings found that isoflavone is a component of flavonoids that have potency in reducing blood glucose levels.

## ABSTRAK

Tanaman merupakan sumber senyawa obat yang bagus. Lebih dari 5000 flavonoid telah di isolasi dan di identifikasi dari tumbuhan. Flavonoid merupakan senyawa polifenol terutama dikenal sebagai pigmen yang bertanggung jawab terhadap beberapa warna bunga, buah dan daun. Polifenol diet merupakan senyawa kimia yang berasal dari tumbuhan yang banyak terdapat dalam buah, sayuran, coklat, dan kacang, juga terdapat pada minuman seperti teh, kopi, anggur dan susu kedelai. Flavonoid dapat menurunkan kadar glukosa darah, kolesterol dan trigliserida plasma secara bermakna dan meningkatkan aktivitas glukokinase hepar dengan meningkatkan pelepasan insulin dari sel beta pankreas. Flavonoid mengatur pencernaan karbohidrat, deposisi jaringan adiposa, pelepasan insulin, dan ambilan glukosa dalam jaringan yang merespon terhadap insulin melalui beberapa jalur signaling sel. Flavonoid terdiri dari isoflavon, flavanol, flavanon, flavonol, flavon, dan antosiani telah dikaji mulai dari uji pre klinik sampai klinik. Namun, tidak semua penelitian yang dilakukan menunjukkan hasil yang sesuai. Salah satu flavonoid yang mungkin memberi harapan untuk penelitian masa depan adalah isoflavon. Penelitian tentang suplementasi isoflavon pada hewan dan manusia dalam menurunkan kadar glukosa darah masih terbatas. Suplementasi isoflavon jangka pendek tidak memperbaiki kadar glukosa darah pada wanita postmenopausal, sedangkan penelitian lain menunjukkan bahwa suplementasi isoflavon jangka panjang dapat menurunkan kadar glukosa darah wanita postmenopausal. Oleh karena itu isoflavon sebagai komponen flavonoid telah terbukti dapat menurunkan kadar glukosa darah.

**Keywords:** flavonoid – isoflavone - blood glucose level - G-6-Pase enzyme - PEPCK enzyme

## INTRODUCTION

Plants are excellent sources of medicinal compounds. Over 5000 flavonoids have been isolated and identified from plant sources. Flavonoids are polyphenolic compounds mainly recognized as pigments which produce the colors found in flowers, fruit and leaves. Beginning more than 20 years ago many studies have focused on polyphenol compounds derived from plants because they are beneficial for human health.<sup>1</sup> The World Health Organization (WHO) recommends evaluating traditional medicinal plants because they are effective, non-toxic, and have few or no side effects so that they are excellent candidates for oral treatment.

Recently, the flavonoid rich fraction of pomegranate (PGFF) was shown to decrease fasting blood glucose significantly in streptozotocin (STZ) induced diabetic rats.<sup>2</sup> Treatment with O-prenilated flavonoid constituents in *Melicope lunu-ankenda* at dose 10mg/kg BW given to diabetic rats significantly reduced blood glucose levels after 2 weeks returning it very close to normal values.<sup>3</sup> Jiang *et al.*<sup>4</sup> treated diabetic rats with fenugreek flavonoids at dose 0.5 g in 10 mL water intragastrically for 28 days and found significantly decreased levels of fasting blood glucose (FBG).

Another study in humans showed extract of cocoa (EC) and cocoa polyphenolic extract (CPE) can improve insulin sensitivity of HepG2 cells induced with high glucose levels. Beneficial effects were demonstrated for liver function and involved mitigating the signaling pathways for insulin while modulating production and uptake of glucose.<sup>5</sup> Similarly, research by Ferguson *et al.*<sup>6</sup> showed soy products rich in isoflavones could lower fasting insulin in European soy consumers and lower glucose levels post-OGTT significantly compared to non-soy consumers.

Research by Yun *et al.*<sup>7</sup> indicated that soy isoflavones reduced body weight and improved glucose metabolism significantly in non-Asian postmenopausal women.

Furthermore, the longer the treatment with soy isoflavones, the greater the decrease in blood glucose levels. This review article comprehensively describes the main categories of the bioflavonoid family, with particular emphasis on the efficacy of polyphenols such as isoflavones which can be used in oral supplementation for control treatment to decrease blood glucose levels.

## DISCUSSION

### Flavonoids

Flavonoids are polyphenolic compounds mainly recognized as pigments which produce the colors found in flowers, fruit and leaves and contain many health benefits. Their salutogenetic effects range from treatments for arteriosclerosis and heart disease to hepatic dysfunction and insulin insensitivity. As chemical compounds, most polyphenols are poorly soluble in water containing a 15-carbon (C6–C3–C6) skeleton. They consist of two benzene rings joined together by a short chain of three carbon atoms. Dietary polyphenols are commonly found in plants and are abundant in fruit, vegetables, chocolate, and nuts. These polyphenols also occur in beverages including tea, coffee, wine, and soy milk.<sup>8,9</sup> Flavonoids are known to lower blood glucose levels, decrease cholesterol and triglycerides, and increase liver enzyme levels most likely by stimulating pancreatic insulin release. By activating cell-signaling pathways involved in controlling blood glucose levels, flavonoids aid in carbohydrate digestion, and adipose deposition. Under oxidative stress conditions, research showed the negative effects of the accumulation of free radicals such as reactive oxygen species (ROS) and reactive nitrogen species (RNS). ROS and RNS are cellular by-products of human metabolism and contribute to a variety of life-threatening diseases such as coronary heart diseases, Type 2 diabetes mellitus (T2DM), obesity and cancers.<sup>10</sup> Our previous study demonstrated that the flavonoids from *Swietenia macrophylla* King seeds can lower

blood glucose levels by down regulating the hepatic enzyme, phosphoenolpyruvate carboxykinase (PEPCK).<sup>11</sup>

Flavonoids are absorbed by active transport. There are two compartments involved in the metabolism of flavonoids. The first compartment includes the small intestine, liver, and kidneys. The second compartment is the colon. Before absorption flavonoids are held in hydrolysis by lactase phlorizin hydrolase (LPH) that catalyzes some glycosides and cytosolic  $\beta$ -glucosidase (CBG) that are involved intracellularly with broad specificity.<sup>12,13</sup> After absorption, flavonoids undergo three main processes: methylation, sulfation and glucuronidation.<sup>8,14,15</sup> In the small intestine, some flavonoids are not absorbed while most absorbed are then secreted with bile in the large intestine. This process of biliary secretion is not well-understood in humans, while nearly 40% of absorbed (p)-catechin was secreted with bile back into the rat small intestine.<sup>16</sup>

## Classification of flavonoid

### Flavanols

Rich in flavanols (FIGURE 1), green tea extract taken orally has been found to have many health benefits and to be a significant source of monomeric flavan-3-ols. These beneficial flavanols include epicatechingallate (ECG) and epigallocatechin gallate (EGCG), which can prevent glucose absorption from intestinal lumen. The beneficial effects of (-)-catechin enhanced insulin-dependent glucose uptake in differentiated adipocytes in T2DM cases.<sup>17</sup> Epigallocatechin 3-gallate acts like insulin, and as a supplement, the drug candidate enhances tyrosine phosphorylation of the insulin receptor and insulin receptor substrate-1 (IRS-1), as well as PI3K activity, while reducing phosphoenolpyruvate carboxykinase gene expression mediated by PI3K.<sup>18</sup> The (-)-epicatechin gallate, myricetin, quercetin, apigenin, (-)-epigallocatechin gallate, and (-)-epigallocatechin are known to reduce

glucose absorption by competitive inhibition of sodium dependent glucose transporter-1 (GLUT-1).<sup>19</sup>

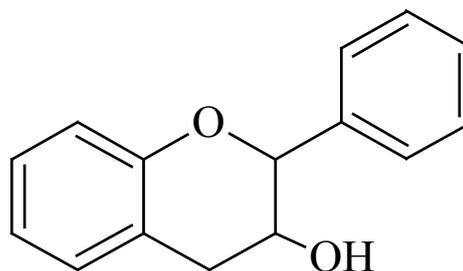


FIGURE 1. Chemical structure of flavanols<sup>20</sup>

### Flavanones

The two major flavanones (FIGURE 2) are naringenin and hesperidin, which are rich in citrus fruits such as grapes, tomatoes, and oranges.<sup>21</sup> *In vivo* studies of *Cochlospermum vitifolium* (Willd.) Spreng containing naringenin was found to decrease blood glucose levels in healthy male Wistar rats.<sup>22</sup> Previous studies showed naringenin supports muscle glucose uptake depending on the dose but independent of insulin.<sup>23,24</sup> One study found treatment of naringenin at a dose of 25 mg/kg BW for 45 days in a diabetic rat model significantly lowered hyperglycemia and hyperinsulinemia, after restoring lipid profiles, decreasing lipid peroxidation, through enhanced antioxidant activities and improved liver function markers.<sup>25,26</sup> Hesperidin in doses of 10 g/kg in the diet was found to lower blood glucose level through changes in glucose regulating enzymes.<sup>27</sup> In a hyperglycemic mice model, hesperidin had beneficial effects on glycolytic and gluconeogenesis enzymes involved in hepatic glucose metabolism.<sup>28,29</sup>

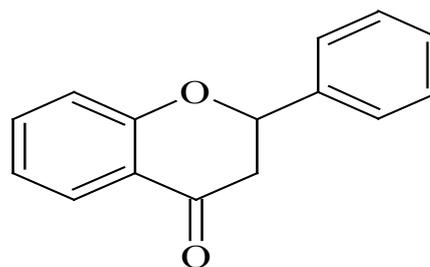


FIGURE 2. Chemical structure of flavanones<sup>20</sup>

## Flavonols

The major flavonols (FIGURE 3) are quercetin, kaempferol, and myricetin. Quercetin and its derivatives in berries considered the primary bioactive components with many health benefits were found to activate AMPK and increase glucose levels in muscle cell uptake. Treatment of quercetin reduced hyperglycemia-stimulating GLUT-4 and hepatic glucokinase (GK). Health benefits included increased liver glucose uptake, and lower hepatic glycogenolysis and gluconeogenesis.<sup>30-32</sup> Oral supplementation of 0.5% quercetin for 2 weeks improved serum insulin level and lowered blood glucose. In the same STZ-induced diabetic mice model, intraperitoneal (IP) injection of quercetin caused lowered levels of hyperglycemia and improved glucose tolerance. Health benefits also included higher liver glucokinase activity and reductions in plasma cholesterol and triglycerides.<sup>33</sup> In an obese diabetic mice model, dietary supplementation of 0.04% quercetin lowered blood glucose and increased insulin resistance.<sup>34</sup> One study in 6-week-old male Wistar rats on a high-fat high-sucrose diet found quercetin supplementation at 30 mg/kg BW per day for six weeks helped to lower basal levels of glucose and insulin.<sup>35</sup> Quercetin has been proven to be effective against obesity and diabetes by blocking digestion of intestinal starch and liver glucose production. Quercetin also increases skeletal muscle glucose uptake, and protects pancreatic islets from damage. Kaempferol extracted from the leaves of the Brazilian orchid tree (*Bauhinia forficata*) has been found to reduce hyperglycemia and increased glucose uptake similar to the action of insulin.<sup>36</sup> Kaempferol caused the increase of glucose uptake in the rat soleus muscle through PI3K and protein kinase C (PKC) pathways and by synthesizing new glucose transporters<sup>37</sup>. As a potent antioxidant kaempferol increased TNF- $\alpha$  and IL-1 $\beta$  expression as well as lipid peroxidation. The resulting benefits improved antioxidant defense.<sup>38,39</sup>

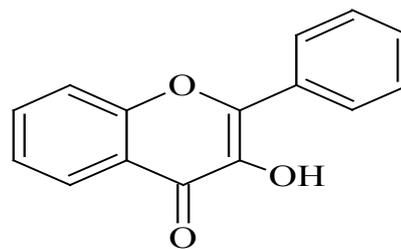


FIGURE 3. Chemical structure of flavonol<sup>20</sup>

## Flavones

The major dietary flavones (FIGURE 4) are apigenin and luteolin.<sup>40,41</sup> Intraperitoneal administration of apigenin significantly acts as an insulin regulating agent with anti-hyperglycemic effects.<sup>22</sup> According to Ding *et al.*<sup>42</sup> luteolin was reported to have insulin potentiate action and increased expression and transcriptional activation of the PPAR gamma target gene. Luteolin positively influenced metabolic pathways in insulin resistance and pathophysiology of diabetes mellitus by inhibiting MCP-1 circulating levels and resistin, among other inflammatory molecules.

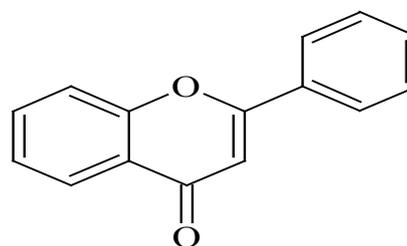
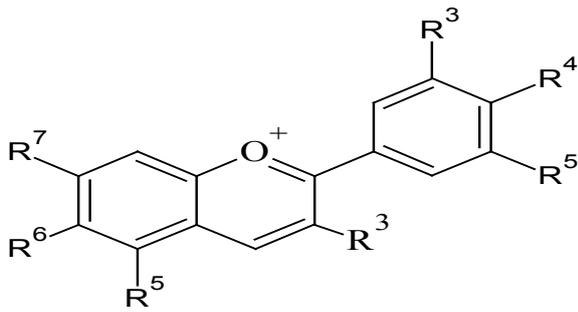


FIGURE 4. Chemical structure of flavones<sup>20</sup>

## Anthocyanins

Bilberries are an abundant source of anthocyanins (FIGURE 5) and bilberry extract (BBE) has been shown to improve hyperglycemia and insulin sensitivity by influencing AMP-activated protein kinase (AMPK), GLUT-4, and metabolic enzymes.<sup>42</sup> Cyanidin also protects hepatocytes from damage triggered by high levels of glucose by reducing the mitochondria-mediated apoptotic pathways and improving antioxidant status by triggering AKT and inactivating JNK.<sup>43,44</sup>

FIGURE 5. Chemical structure of anthocyanins<sup>45</sup>

## Isoflavones

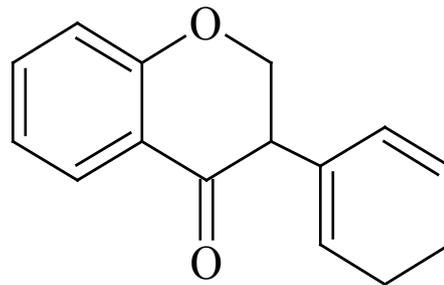
Isoflavones are a type of flavonoids found in legumes, including soybean and soy products. Soy food products contain two main isoflavones: daidzein and genistein.<sup>40</sup> Research has shown isoflavone administration can lower blood glucose levels.<sup>46</sup> Supplementation with isoflavones is known to suppress the activities of gluconeogenic enzymes such as PEPCK and G6Pase. Soy isoflavones were also found to decrease  $\beta$ -oxidation of fatty acids and lipid accumulation while soy dietary supplementation could increase beneficial lipogenesis in the liver.<sup>47</sup>

One study recently found that a soy-supplemented diet could provide a number of overall health benefits. Mice fed 198 ppm daidzein and 286 ppm genistein for their entire life demonstrated better lipid profile and glucose metabolism.<sup>48</sup> Supplementation with soy isoflavones also increased phosphorylation of AMPK. These health benefits included positive metabolic changes, such as improved mitochondrial biogenesis and glucose uptake in the skeletal muscle.<sup>48</sup> There were also a number of reports documenting decreased blood glucose, TGF $\beta$  1, and HbA1C levels.<sup>49,50</sup>

Other research found genistein was beneficial in the treatment of diabetes and could improve plasma lipids<sup>51</sup>, and was shown to increase insulin sensitivity.<sup>52</sup> Genistein could also reduce fasting glucose levels in non-genetic diabetes mice.<sup>52</sup> Supporting these findings, genistein supplementation was beneficial to improve glucose tolerance and hyperglycemia.

It was also found to increase islet  $\beta$ -cell expression and prolong the life of mice in a diabetic model induced by STZ.<sup>53</sup> In dietary supplementation, isoflavones, soy protein, or genistein in combination, can have many health benefits, especially for balancing the body's metabolism. In non-obese diabetic mice models, daidzein or genistein can prevent diabetes and improve glucose homeostasis through balancing pancreatic  $\beta$ -cell function.<sup>47</sup>

Daily doses of isoflavones in the form of 100 mg of aglycones for a year were found to improve insulin sensitivity and blood lipid levels of post-menopausal women with T2DM.<sup>54</sup> Oppositely, daily isoflavone doses of 132 mg for 3 months showed no improvement in plasma A1C, blood glucose, nor insulin levels in postmenopausal women with T2DM.<sup>18</sup> While these contradictory results may possibly be due to treatment dosage and duration differences, a number of studies, both *in vitro* and *in vivo* demonstrated health benefits of isoflavone supplementation finding many anti-obesity and anti-diabetic results. Genistein was seen at dose 0.02% to suppress the onset of DM and increased glucose homeostasis through the function of pancreatic beta cell stabilization in non-obese diabetic mice.<sup>47</sup>

FIGURE 6. Chemical structure of isoflavones<sup>20</sup>

## Role of isoflavone in reducing the blood glucose

All members of the bioflavonoid family are important for health due to the ability to control blood glucose levels. Recent research has shown that isoflavones can especially suppress gluconeogenic enzyme activity such as PEPCK and G6Pase, lipid profile, and can increase beta oxidation of

fatty acids and lipogenesis in liver. PEPCK is an essential enzyme for gluconeogenesis so that the enzyme suppression results in the formation of glucose from sources other than dietary carbohydrates and as a result it can reduce blood glucose levels in rat liver.<sup>47</sup> G6Pase is an enzyme that converts G6P to glucose so that suppression of G6Pase also results in a decrease in blood glucose levels. Meta-analysis by Zhan *et al.*<sup>7</sup> reported that soy isoflavone supplementation significantly reduced body weight and improved glucose metabolism compared in non-Asian postmenopausal women.<sup>7</sup> Isoflavones at dose 100 mg for one year in postmenopausal women can improve insulin sensitivity and blood lipid parameter, but low doses for only 3 months cannot improve plasma A1C, blood glucose and insulin levels.<sup>20,54</sup> Soy supplements have been shown to improve lipid profile, metabolism of glucose, increase AMPK phosphorylation and cause favorable metabolic changes and skeletal muscle glucose uptake, while decreasing KGD, TGFβ1 and HbA1C in mice.<sup>48-50</sup> Genistein reduces the expression of PPARs and C/EBP, modulates glucose metabolism and insulin levels, improves lipids so insulin sensitivity increases, and improves glucose tolerance and hyperglycemia.<sup>52,53,55,56</sup> It also increases beta cell proliferation by modulating signaling pathways (activation calmodulin kinase II and Ca<sup>2+</sup> signaling),<sup>57</sup> and suppresses NF-kB, ERK-1/2 and JAK/STAT pathways,<sup>58</sup> in pancreatic beta cells stimulating CAMP/PKA signaling.<sup>59,60</sup>

## CONCLUSIONS

Short-term isoflavone supplementation does not improve blood glucose levels in postmenopausal women, while other studies suggest long-term isoflavone supplementation can reduce postmenopausal blood glucose levels. These findings demonstrate that isoflavones as a component of flavonoids can be used to reduce blood glucose levels by three mechanisms: suppress gluconeogenic enzyme in hepar, increase lipogenesis, and stimulate glucose uptake

and metabolism. Research on isoflavone supplementation in animals and humans in reducing blood glucose levels is still limited.

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