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Effect and Mechanism of Herbal Ingredients in Improving Diabetes Mellitus Complications

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Abstract

Context: Diabetes mellitus is the most common endocrine disease worldwide and its prevalence is increasing. The development of drugs with fewer side-effects is required when treating this disease. Thus, the objective of this study was to evaluate the use of traditional medicine and medicinal plants in this regard. The various mechanisms by which isolated extracts and herbal compounds exert their effects on different diabetes mellitus factors was investigated.

Evidence Acquisition: Databases such as PubMed, Science Direct, and Web of Science (from 1990 until the present) were searched, using a detailed list of terms related to the effects and mechanism of herbal ingredients on diabetes mellitus complications.

Results: The presence of secondary metabolites, such as phenols, flavonoids and alkaloids in plants, have been used as a source of medication for the treatment of many diseases, including diabetes mellitus. Following an extensive review of the literature, it was found that the secondary metabolites of plants have a wide range of anti-diabetic effects.

Conclusions: Plant compounds should be isolated and their effects on diabetes mellitus and its complications examined in order to treatment for diabetes mellitus.

Keywords: Diabetes Complications, Diabetes Mellitus, Flavonoids, Mechanism, Phenols

1. Context

Diabetes mellitus is one of the most common diseases in the world. It is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced. The disease has a considerable economic and social impact (1). In 2009, diabetes mellitus was ranked as the fifth cause of death worldwide and its prevalence increases every day (2). In 2010, it was reported that the number of 20- to 69-year-old people with diabetes mellitus equated to 285 million and it was estimated that this number would reach 439 million in 2030 (3). A poor lifestyle, lack of exercise, eating high-fat food, and obesity are risk factors for the development of diabetes mellitus. It is estimated that in regions such as Asia and Africa, the rate of diabetes mellitus is two or three times more than that in other areas (4).

An increased blood glucose through the involvement of the polyol pathway and sorbitol production, the production of protein glycosylation [advanced glycation end products (AGE)], a reduction in nitric oxide (NO) production, and the activation of protein kinase C leads to neuropathy, nephropathy retinopathy, and cardiovascular disease (5). In addition, hyperglycemia stimulates the production of reactive oxygen species and the extension of oxidative reactions (6). Exercising, changing to healthier eating habits, and the use of glucose-lowering drugs can reduce complications of this disease (7).

Herbal medicinal compounds are used worldwide owing to the perception that they are less toxic than mainstream drugs. Thus, there is incentive to use them to treat various diseases (8). In response to demands for the inclusion of compounds from medicinal plants in medications, manufacturers of these products have had to ensure the addition of high-quality extracts using optimal separation methods (9).

Plant compounds can influence the biological pathways associated with diabetes mellitus complications. However, this is a previously held view and one that is not necessarily held in the present. Plant compounds, such as *Galega officinalis* L, have previously been used to treat low blood sugar and diabetes mellitus. Metformin was obtained from this plant (10).

Although the effect and mechanism of most plants compounds in diabetes mellitus treatment has not been adequately identified, but their effects can be by glucose intestinal absorption, metabolic insulin-dependent processes, and the antioxidant effects of these processes (11, 12). Here, the effects and mechanisms of isolated extracts and plant compounds on different factors of diabetes mellitus were reviewed investigated in this paper.

2. Evidence Acquisition

Plants were classified according to their mechanism of action in this study. For this purpose, databases such as PubMed, Science Direct, and Web of Science were used, in conjunction with a detailed list of terms that related to the effect and mechanism of herbal ingredients on diabetes mellitus complications. Thereafter, The content of 80 articles was studied.

3. Results

3.1. The Role of Antioxidants

Oxidative stress occurs due to an imbalance between the production of free radicals and the antioxidant system. An increase in free radicals damages the cellular components. A long-term increase in blood glucose leads to the imbalance that is found in diabetes mellitus (13). Glucose is able to oxidized automatically and can bind to proteins non-enzymatically, resulting in the formation of AGEs or polyol pathway involvement, together with the activation of aldose reductase. Ultimately, it results in the depletion of nicotinamide adenine dinucleotide phosphate and an increase in nicotinamide adenine dinucleotide. In addition, hyperglycemia occurring during diabetes mellitus leads to an increase in NO synthase and xanthine oxidase activity (14).

Crocus sativum contains compounds, such as carotenoids, one of which is crocin, an antioxidant, which could be used in the treatment of diabetes mellitus as its potential has been demonstrated in various studies. The effect of crocin on diabetic rats was investigated and it was shown that it caused a significant reduction in blood glucose, lipid profile, and glycated hemoglobin (15). The anti-diabetic effect of saffron was also confirmed in another study, probably owing to its antioxidant properties (16).

It was demonstrated in a study by Barari et al. that the antioxidant properties of a substance in milk thistle (*Silybum marianum*), especially a flavonoid called silymarin, were reduced by inflammatory agents such as tumor necrosis factor-α and interleukin-6 (17). To evaluate the antioxidant effect of silymarin, it was injected into alloxan-induced diabetic rats. Superoxide dismutase, glutathione peroxidase, and catalase activity was examined at the end of the treatment period and the results showed a significant increase in the enzyme activity therein. Thus, silymarin plays an important role in the body's defense against free radicals (18). Antioxidants, useful in treating diabetes mellitus, are found in green and sour tea.

The effects of antioxidants on patients with type 2 diabetes mellitus were examined in another study. It was shown following an evaluation of factors such as blood glucose, insulin, lipid profile, and antioxidant levels, that both plants were effective in reducing antioxidant levels and the lipid profile (19).

Celery (*Apium graveolens*) is an antioxidant herb and contains flavonoids, such as apigenin and apiin. The antioxidant properties of this herb lead to an increase in the fertility and improvement of sperm performance (20, 21). It was shown that the antioxidant activity of hydro-alcoholic leaf extract of celery decreased the lipid profile in rats on a high-fat diet (20). It was also reported in another study (22) that a reduction in blood glucose and activity increased the enzyme activity of superoxide dismutase, catalase, and glutathione reductase. However, a significant increase in alanine transaminase and aspartate transaminase levels in diabetic rats treated with n-butanol extract of celery was not found (22).

3.2. Effect on Adiponectin Releasing

As an endocrine tissue, adipose tissue plays a role in energy balance in the body through the release of active ingredients, such as resistin, adipsin, leptin, and adiponectin (23). Two human adiponectin receptors are found in the skeletal muscles. They intermediate the effect of globular and full-length adiponectin. An increase in the expression of these receptors is associated with an increase in insulin sensitivity (24). Adiponectin affects the gluconeogenesis process and fatty acid oxidation through 5' adenosine monophosphate-activated protein kinase (AMP)-dependent protein kinase and peroxisome proliferator-activated receptor (PPAR) in the liver. Moreover, it increases glucose uptake in the peripheral tissues and stimulates insulin secretion, ultimately leading to a regulation of the body's energy (25). The interaction between adiponectin and adapter proteins, such as adaptor protein containing PH domain, phosphotyrosine-binding domain, and leucine zipper, is important in the adiponectin signaling pathway and for an increase in insulin sensitivity (26).

The biological activity of flavonoids is frequent and it has been observed that they are effective in adiponectin secretion from the adipose tissue (27). Tiliroside increases the level of serum adiponectin in obese-diabetic (KK-Ay) mice (28). It was confirmed in a study on the aqueous and hydro-alcoholic extracts of *Momordica charantia* that an aqueous extract at a concentration of 0.2 mg/mL, along with 0.5 nM insulin, increased glucose absorption (61%) and adiponectin secretion (75%) in the 3T3-L1 cells, while 0.4 mg/mL of ethanol extract increased glucose uptake only in the presence of 50 nM insulin. In fact, the compounds of aqueous extract are effective in adiponectin secretion and glucose uptake in very low insulin concentrations (29).

Ginseng has many therapeutic properties owing to the presence of compounds, such as saponins and ginsenosides. For example, American ginseng or *Panax quinquefolius* contains ginsenosides, such as Rb1 and Rb2 (30). American ginseng acts as a glucose-reducing agent in patients with type 2 diabetes mellitus (31). It was indicated in a study on American ginseng that it led to an increase in the expression of adiponectin and a reduction in lipid accumulation in the 3T3-L1 cells (32).

3.3. The Enhancement of Glucose Uptake Through the Upregulation of Glucose Transporter Type 4

Glucose is transported into cells by a large family of transporters called glucose transporters (GLUT) of which there are different types, such as glucose transporter type 4 (GLUT4), which is regulated by insulin and is found in the skeletal muscles and adipose tissue (33). The overexpression of GLUT4 was shown to be important in reducing blood glucose and its absorption into the muscles and adipose tissue in animal models of diabetes mellitus (C57BL/KsJ-db/db mice) (34).

Berberine is an isoquinoline alkaloid that is found in plants, such as *Berberis vulgaris* and *B. aristata*, leading to the translocation of GLUT4 and an increase in 3T3-L1 adipocytes and L6 myotubes (35). Naowaboot et al. examined the effect of *Morus alba* L. leaf as an anti-hyperglycemic agent. The results showed that glucose uptake increased in the adipocytes. Also, this effect was confirmed when wortmannin, as an inhibitor of phosphoinositide-3-kinase (P13K) and GLUT4 translocation, was used (36).

It was shown in a study that Cinnamomum zeylanicum increased adipocyte growth, decreased adipolysis and increased the entry of glucose into the 3T3-L1 cells. Therefore, it is very effective in blood glucose homeostasis. Also, it was observed in other research that the consumption of cinnamon extract resulted in GLUT4 translocation from the smooth endoplasmic reticulum membranes to the cytoplasm in the C2C12 cells and that it was effective in energy homeostasis (37).

The *Ficus* spp. have different therapeutic effects, including anti-diabetic properties. A study of the effects of 10 species of this genus on glucose metabolism indicated that only the species, F. lutea, has an anti-diabetic effect because its leaf extract affects blood glucose uptake in the peripheral tissue and causes a reduction in blood glucose concentration which is probably due to its influence on GLUT4 (38).

The researchers studied the effects of Panax ginseng on the 3T3-L1cells. They found that the active ingredients in this plant, such as ginsenosides Rg3 and Re, were effective with respect to glucose uptake via insulin-dependent pathways because it increased the expression of GLUT4, insulin receptor substrate 1, and PI3K (39).

Epigallocatechin gallate (ECCG) is a flavonoid that is found in green tea and is active biologically. This compound is used to treat various diseases, including obesity. The inhibition of glucose uptake and a reduction in GLUT4 in the cell surfaces through the insulin-like growth factor (IGF)-I and IGF-II pathways and 67-kDa laminin receptor were demonstrated following an evaluation of its effects on the 3T3-L1 adipocytes. Interestingly, it was increased glucose uptake via GLUT1 (40).

3.4. The Inhibition of Glucose Absorption

Alpha-amylase is secreted from the pancreas and salivary glands, leading to the conversion of starch into maltose, a substrate required for α-glucosidase enzyme activity. Alpha-amylase is located in the brush-border membrane of the intestinal epithelial cells, leading to the hydrolysis of disaccharide into monosaccharide (41, 42). Glucose is a most important monosaccharide in the intestine and is unable to cross the lipid membrane of cells into the small intestine. This work acts through a Na-dependent glucose transporter (43). An increase in blood glucose following a meal is an early indicator of energy homeostasis impairment and indicates the need for diabetes mellitus treatment (44). Hyperglycemia occurs after a meal owing to increased α-amylase and α-glucosidase activity. Therefore, inhibitors of these enzymes might be helpful in moderating blood sugar levels. However, the most commonly used enzyme inhibitors, including acarbose and miglitol, have side-effects, such as abdominal pain and diarrhea (45).

Flavonoids are effective compounds for glucose absorption in the small intestine. It was indicated in a kinetic study on the effects of flavonoid compounds, such as quercetin-3-glucoside (isoquercitrin) and quercetin-4'-glucoside (spiraeosid), on the inhibition of glucose uptake, that these compounds, such as sodium-dependent glucose co-transporter (SGLT)-1 competitive inhibitors, prevented the absorption of methyl α-D-glucopyranoside (non-metabolizable glucose analogue), while the aglycone forms did not affect glucose absorption (46).

Phlorizin, a type of flavonoid belonging to the isosalipurposide dihydrochalcone group, is found in fruits, such as apples, and could be used in the treatment of type II diabetes mellitus because it reduced SGLT-1 expression and blood glucose levels in diabetic rats (47).

It was shown following an evaluation of the effects of different extracts prepared from the root of Devil's cotton on the activity of purified α-D-glucosidase from

Sacharomyces cerevisiae that only the petroleum ether extract from this plant had a significant effect on the inhibition of this enzyme in vitro and could be used in the composition of diabetes mellitus medication (48).

It was indicated after an assessment of the antioxidant activity of aqueous and methanol extracts prepared from the bark, leaf, and root of mahogany (*Khaya*), that only the root extract had antioxidant activity. In addition, the effect of this extract on the kinetics of the α-glucosidase and α-amylase enzymes was shown to be a competitive inhibitory one for α-glucosidase and a non-competitive inhibitory one for α-amylase (49).

The effects of fenugreek seed extracts on glucose absorption in the small intestine were examined and it was reported that saponin- and sapogenin-rich extracts had a higher effect on glucose absorption than other extracts (50).

The soybean (*Glycine max*) is a plant in the Fabaceae family that has anti-diabetic properties. It was demonstrated that rich extracts of polyphenols and free phenol had an inhibitory effect on α-amylase and α-glucosidase. Therefore, they can be used as effective compounds in the treatment of diabetes mellitus (51).

The effects of Guduchi (*Tinospora cordifoliaon*) leaf extracts on α-amylase activity were examined and it was demonstrated that they inhibited α-amylase enzyme activity (52). It was also shown in a study on green tea poly phenols that compounds, such as epicatechin gallate and EGCG, acted as competitive inhibitors of SGLT-1 in the small intestine in rabbits (53).

3.5. Other Mechanisms

In addition to the previously described mechanisms, there are other ways in which to control diabetes mellitus. These are now described. Following an examination on the effects of an ethanol extract prepared from the bark of Yuzu (*Citrus junos Tanaka*), it was shown that it was effective in regulating glucose uptake and AMPK activity in the C2C12 cells in mice on a high-fat diet (54).

Wax gourd (*Benincasa hispida*), derived from the Cucurbitaceae family, is used in East Asia to treat obesity. Following an examination of its effect on C57BL6 mice, it was confirmed that it decreased PPAR-γ and 3-hydroxy-3-methylglutaryl-CoA reductase expression and improved the lipid profile, resulting in fasting glucose reduction (55).

Loquat (*Eriobotrya japonica*) is a plant in the Rosaceae family. Its aqueous extract is effective in reducing blood sugar through its effect on the pancreas beta cells. Following the isolation of compounds from this extract, it was shown that cinchonain Ib led to insulin secretion from the INS-1 cells after 240 minutes (56). It was shown in a study that the use of methanol extract of *Ocimum sanctum* significantly reduced blood sugar levels by reducing the number of key enzymes in the carbohydrate metabolism pathway (glucokinase, hexokinase, and phosphofructokinase). It also increased glycogen content in the kidney and decreased it in the liver and skeletal muscles (57). It was shown in a study on Dong Quai Japanese (*Angelica acutiloba*) that this herb was effective in reducing insulin resistance. Its root extract decreased the expression of phosphoenolpyruvate carboxykinase and resulted in a reduction in gluconeogenesis pathway activity in the liver, while it increased glycogen content in the liver (58). In addition, following an examination of 13 pentacyclic triterpenoids isolated from the methanol extract of common self-heal (*Prunella vulgaris* L.), it was shown that these compounds had variable degrees of glycogen phosphorylase inhibition (an IC50 range of 30.69 - 68.85 μM (59).

Glucagon-like peptide (GLP)-1 is an endocrine hormone produced by the *enteroendocrine* L cells and stimulates beta cell growth, synthesis, secretion, the release of insulin, and glucagon secretion inhibition. It was confirmed in a study on the aqueous extract of wild bitter gourd (*Momordica charantia*) that it led to an increase in GLP-1 and a significant reduction in blood glucose 30 seconds after its administration. In addition, the use of a GLP-1 receptor antagonist, such as exendin-9, decreased hypoglycemia (60). Stereoisomerically, there are nine inositol isomers, of which d-chiro-inositol isomer is very rare and is found in plants. In addition, it is found in the structure of inositol phosphoglycan and is important in the insulin signaling pathway (61). It plays as an anti-hyperglycemic role in the insulin signaling pathway (62). *Cucurbit aficifolia* is a rich source of d-chiro-inositol and is used as a treatment for diabetes mellitus in the Asian region. The consumption of the methanol extract of the *Cucurbita ficifolia* fruit was found to reduce blood sugar and increase total hemoglobin, insulin, and liver glycogen, comparable to the effects of synthetic d-chiro-inositol (63). The use of soluble fiber, such as ß-glucan, can be used to treat diabetes mellitus. It is very effective in combatting hyperglycemia after a meal because it prevents sugar absorption. The effect of polysaccharides prepared from *Rhynchelytrum repens* on blood glucose levels in diabetic rats was examined in a study and it was reported that they significantly decreased them. Furthermore, the presence of high ß-glucan levels was confirmed after hydrolyzing the fresh leaves of *R. repens* with endo-ß-glucanase and conducting high-performance liquid chromatography analysis (64).

4. Conclusion

The effects and mechanism of plant compounds and extracts on a reduction in diabetes mellitus complications

was investigated in this study. It was found that plant compounds and extracts can be used as anti-diabetic agents (Table 1) as many of them have antioxidant properties (such as celery), recommended in reducing hyperglycemia complications, while others (such as soybeans) are effective in lowering blood sugar through the inhibition of glucose uptake subsequent to a meal. Some plants are effective through several mechanisms. For example, American ginseng increases adiponectin expression and also leads to an increment in GLUT4 at the cell surface.

Finally, it was indicated in this study that secondary metabolites of plants have a wide range of effects on diabetes mellitus treatment. Therefore, plant compounds should be separated and their individual effects on diabetes mellitus examined.

Footnote

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Table 1. The Effect Mechanism of Plants in Treatment of Diabetes Mellitus

Reference	Plant	Family	Extract or Compound	Description of Effect(s)
Shirali et al. (15)	Saffron (*Crocus sativus*)	Iridaceae	Crocin	An improvement in glucose, lipid profile, and HbA1c levels
Soto et al. (18)	Milk thistle (*Silybum marianum*)	Asteraceae	Silymarin	An increase in SOD, CAT, and GSH-Px activity
Al-Sa'aidi et al. (22)	Celery (*Apium graveolens*)	Apiaceae	n-butanol	A hypoglycemia effect and an increase in SOD, GSH reductase, GSH transferase, and CAT
Yeo et al. (32)	American ginseng (*Panax quinquefolius*)	Araliaceae	Methanol	An increase in adiponectin expression and a reduction in lipid acquisition
Naowaboot et al. (36)	Mulberry (*Morus alba* L.)	Moraceae	Methanol	A stimulatory effect on glucose uptake via GLUT4 translocation
Absalan et al. (37)	Ceylon cinnamon (*Cinnamomum zeylanicum*)	Lauraceae	Hydro-alcoholic extract	An increase in glucose uptake in the 3T3-L1 adipocyte cells
Lee et al. (39)	American ginseng (*Panax quinquefolius*)	Araliaceae	Ginsenosides Rg3 and Re	An increase in the expression of GLUT4, IRS-1, and PI3K
Ku et al. (40)	Green tea (*Camellia sinensis*)	Theaceae	Epigallocatechin gallate	The inhibition of glucose uptake from GLUT4 by suppression of the IGF-I and IGF-II. Stimulation and an increase in glucose uptake by the GLUT1 pathway
Bisht et al. (48)	Devil's cotton (*Abroma augusta*)	Malvaceae	Petroleum ether	α-glucosidase inhibitor
Ibraham et al. (50)	Fenugreek (*Trigonella foenum-graecum*)	Fabaceae	Rich extract of sapogenin and saponin	An inhibitory effect on glucose uptake in the intestine
Ademiluyi et al. (51)	Soybean (*Glycine max*)	Fabaceae	Extract with phenol and without phenol	α-glucosidase and α-amylase inhibitor
Shareef et al. (52)	Guduchi (*Tinospora cordifolia*)	Menispermaceae	Petroleum ether, chloroform, ethyl acetate, and methanol	α-amylase inhibitory activity
Kobayashi et al. (53)	Green tea (*Camellia sinensis*)	Theaceae	Epicatechin gallate	A competitive inhibitor of SGLT-1
Kim et al. (54)	Yuzu (*Citrus junos Tanaka*)	Rutaceae	Ethanol	An increase in AMPK phosphorylation and PPAR-γ activation
Gu et al. (55)	Wax gourd (*Benincasa hispida*)	Cucurbitaceae	Ethanol	Inhibition of PPAR-γ, a reduction in PPAR-γ, mRNA, an improvement in the lipid profile, and a reduction in the fasting blood glucose
Qa'dan et al. (56)	Loquat (*Eriobotrya japonica*)	Rosaceae	Aqueous extract	The stimulation of insulin secretion
Vats et al. (57)	Holy basil (*Ocimum sanctum*)	Lamiaceae	Ethanol	A reduction in GK, HK, and PFK activity
Liu et al. (58)	Japanese Dong Quai (*Angelica acutiloba*)	Apiaceae	Ethanol	A reduction in PEPCK expression
Yu et al. (59)	Common self-heal (*Prunella vulgaris* L)	Lamiaceae	Methanol	The inhibition of glycogen phosphorylase
Huang et al. (60)	Bitter gourd (*Momordica charantia*)	Cucurbitaceae	Water extract	An increase in GLP-1 levels
Xia et al. (63)	Siam pumpkin (*Cucurbita ficifolia*)	Cucurbitaceae	Methanol	Greatly increased D-chiro-inositol and hypoglycemic activity
De Paula et al. (64)	Natal grass (*Rhynchelytrum repens*)	Poaceae	ß-glucan-rich polysaccharides	The prevention of glucose absorption

Abbreviations: AMPK, 5' adenosine monophosphate-activated protein kinase; CAT, catalase; GK, glucokinase; GLP, glucagon-like peptide; GLUT, glucose transporter; GSH, glutathione; GSH-Px, glutathione peroxidase; HbA1c, hemoglobin; HK, hexokinase; IGF, insulin-like growth factor; IRS-1, insulin receptor substrate 1; mRNA, messenger ribonucleic acid; PI3K, phosphoinositide-3-kinase; PEPCK, phosphoenolpyruvate carboxykinase; PFK, phosphofructokinase; PPAR-γ, peroxisome proliferator-activated receptor gamma; SGLT, sodium-dependent glucose co-transporter; SOD, superoxide dismutase.