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Nutraceutical in the Management of Diabetes Mellitus: A Review

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Abstract

Objective: Diabetes mellitus (DM) is recognized as one of the most critical health issues and leading causes of death worldwide. This disease is associated with macro-vascular and micro-vascular complications. The prevention of DM and its complications is always essential. In recent years, due to the known biological properties of some foods, the tendency to consume these foods has increased. This narrative review showed the effect of cinnamon, ginseng, thyme, sesame oil, fenugreek, saffron, aloe vera, garlic, ginger, turmeric, and green tea on improving insulin sensitivity, reducing blood sugar, blood lipid, and blood pressure, and regulating metabolism. Therefore, it is suggested that these nutraceuticals could be considered in the special food formulation of diabetic patients. It seems that the anti-diabetic properties of nutraceutical interest of diabetic persons specify their potential role in improving insulin sensitivity, lowering blood sugar, blood lipid, and blood pressure, and regulating metabolism.

Keywords: Nutraceutical, Diabetes mellitus, Blood sugar, Blood lipids, Blood pressure, Insulin sensitivity

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Introduction

Diabetes mellitus (DM), as one of the most important health issues, has become a worldwide concern. The 10th edition of the International Diabetes Federation (IDF) Atlas estimated that 1 in 10 people aged 20-79 have diabetes, equivalent to 537 million people in the world (1). It was estimated that the number of diabetic patients will globally increase to 640 million by 2040 (2). This metabolic disorder has been noted due to its complications including increased blood sugar, blood lipid and blood pressure (3). The prevalence of micro-vascular complications of diabetes, including neuropathy, nephropathy and retinopathy, are reported higher than its macro-vascular complications such as cardiovascular disease, stroke and peripheral arterial disease (4).

Unhealthy diet and lifestyle, obesity and genetic factors are risk factors of type 2 diabetes (5). Hence, in these years, attempts have been made to reduce the spread of the disease and its complications with medicinal plants (6). The potential anti-diabetic activity of alkaloids, glycosides, terpenoids, phenolic compounds and flavonoids has been shown in various experiments (7). Studies have indicated that about 800 plants may have anti-diabetic potential and beneficial effects in treating or preventing the complications of diabetes (8). Therefore, using new strategies, including functional foods such as whole or fortified and enriched foods will increase the effectiveness of diabetes management. The word "Nutraceuticals" includes "nutrients" and "medicines". They have a medicinal effect on human health (9).

Cinnamon

Cinnamon is a bushy evergreen tree of the Lauraceous family (10) and is known as an antioxidant, anti-fungal, and anti-inflammatory agent. The start of its utilization as a medicine goes back to about 2800 BC (11). Cinnamon effectively treats diabetes, heart disease, hyperlipidemia, and hypertension (12). C. Zeylanicum is an effective species to reducing cholesterol and glucose levels (13). Polyphenols in cinnamon can increase insulin sensitivity, that associated with lower blood pressure (12). On the other hand, these molecules have various properties, such as antioxidant and anti-obesity (14). The hypoglycemic activity of this substance may be mediated by several mechanisms, including the stimulation of insulin secretion and insulin receptor signal, activation and regulation of enzymes involved in carbohydrate metabolism, glycolysis and gluconeogenesis, stimulation of cellular glucose uptake and glycogen content, and increased expression of Glucose transporter type 4 (GLUT-4) and peroxisome proliferator-activated receptors (PPARs) (15).

Anderson et al. showed that supplementation of 500 mg of cinnamon water extract for two months was associated with decreased blood glucose, fasting insulin, total cholesterol, low-density lipoprotein cholesterol (LDL-C) and increased insulin sensitivity in people with high blood glucose (16). Qin et al. have shown that cinnamon can significantly reduce blood glucose and lipid levels, and prevent obesity, especially abdominal obesity (17). Another clinical trial showed that intervention with cinnamon (120 and 360 mg/day) and gliclazide for three months could significantly reduce fasting blood glucose (FBG) and HbA_1c levels (18).

Inconsistent results were also reported in some clinical trials. Cinnamon has not appeared to improve FBG, HbA_1c or lipid parameters in diabetic patients in a meta-analysis of randomized controlled trials (19). Therefore, further investigations seem to be necessary to evaluate the therapeutic potential of cinnamon (20).

Ginseng

Ginseng is traditional herbal medicine in East Asian countries (21). This low-growing perennial plant has fleshy roots from the

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family Araliaceae and is usually related to the Panax species. The main active ingredients of ginseng are ginsenoside panaxadiol, protopanaxadiol and compound K and been classified as a functional food (22).

Ginseng has many medicinal properties, including antioxidant, glycemic lowering, lipid lowering, antimicrobial, anti-inflammatory, anti-stress, and anti-cancer activities, and protecting the nervous system, heart, and liver (22,23). Ginseng anti-glycemic mechanisms can effectively inhibit protein-tyrosine phosphatase 1B (PTP1B) via PPAR and insulin signaling pathways (IRS-AMPK, PI3K/Akt, GSK-3β). These mechanisms are associated with increased glucose uptake, glycogen synthesis, inhibition of gluconeogenesis, and impaired intestinal glucose uptake (3).

Consuming Korean red ginseng (5g /12 weeks) reduces FBG, oral glucose tolerance test (OGTT), serum insulin, and C-peptide levels in type 2 diabetic patients (23). Systemic analysis and meta-analysis showed that ginseng supplementation (0.96-13.6 g/daily for 4-20 weeks) improved FBG, postprandial insulin, Cholesterol, Triglyceride (TG), and LDL- cholesterol significantly (24). American ginseng extract supplementation (3g/day, for eight weeks) significantly has reduced FBG, systolic blood pressure SBP, HbA_1c, and LDL-cholesterol compared with placebo in patients with type 2 diabetes (25). However, some studies on this plant still remain obscure due to conflicting results (26).

Thymes persicus

Iranian thyme, with the scientific name of Thymus persicus, is one of the native plants of Iran and belongs to the Mint family. The anti-diabetic, antioxidant, anti-fungal, anti-viral, anti-bacterial, anti-Alzheimer and anti-tumor properties of this plant have been proven (27). Thyme as a source of triterpenoids, has several properties including hypoglycemic activity, anti-hyperlipidemic activity, anti-inflammatory, liver protective, antimicrobial, anti-HIV-1, anti-ulcer and gastrointestinal protection (28).

Zamani et al. (2018) have shown a significant reduction in insulin resistance, serum insulin levels, and blood pressure with consumption of 1400 mg/daily of Zataria multiflora powder for 12 weeks (29). The beneficial effect of Zataria multiflora on insulin resistance in insulin-resistant and high fructose-fed rats was done by three mechanisms, including the direct effect of insulin, an increase of adiponectin and Peroxisome proliferator activated receptor (PPARγ) protein expression. The intragastric injection of thyme extract (1000 mg/kg) for two weeks leads to a significant reduction in blood sugar, serum triglycerides, and insulin resistance (30).

Sesame oil

Sesame oil comprises lignans, minerals, vitamins, phytosterols, unsaturated fatty acids and tocopherols. Sesame oil has been shown the anti-hyperglycemic, anti-hyperlipidemic, anti-hypertensive, antioxidant, anti-cancer properties and immune-regulating activities (31).

The diabetic rats treated with sesame butter (1.25 g/kg) and sesame oil (0.5 g/kg) for six weeks showed lower glucose and higher high-density lipoprotein than the control diabetic rats. Sesame butter supplementation increased total antioxidant capacity and decreased malondialdehyde concentration in diabetic rats (32). In another study, daily consumption of 35g of sesame oil significantly reduced blood pressure, heart rate and arterial stiffness (33). Consuming sesame oil (35 g/daily) leads to an anti-glycemic effect in diabetic hypertensive patients during 60 days (34).

Fenugreek

Fenugreek is one of the annual herbaceous legumes of Fabaceae plants. It can have many therapeutic measures, including anti-diabetic, anti-hyperlipidemic, anti-inflammatory, anti-cancer and antioxidant (3). Fenugreek may exert its anti-hyperglycemic activity by

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improving insulin resistance in fat and liver cells, increasing glucose uptake, increasing the activity of liver enzymes such as glucokinase and hexokinase, increasing serum insulin levels and increasing insulin sensitivity (31). The hypoglycemic activity of fenugreek is mainly determined by active compounds such as galactomannan, saponin and 4-hydroxyleucine (35).

The fasting consumption of fenugreek seed extract supplemented with furostanolic saponins (500 mg/day for 90 days) significantly reduced postprandial blood glucose and HbA_1c compared with placebo in patients with type 2 diabetes (36). Orally consumption of 25g of fenugreek seed solution (two times/daily for one month) has been shown a significant decrease in total cholesterol (TC), TG, LDL levels and an increase in high-density lipoprotein (HDL) levels in type 2 diabetic patients compared to the control group (37).

Saffron

Saffron, the dried stigma of Crocus sativus L, is mainly used as a food coloring and flavoring. The three main secondary metabolites are crocin, picrocrocin and safranal (38). Saffron may attribute to the reduction of oxidative stress and improve diabetes control (39).

The known mechanisms of effects of saffron are stimulating glucose uptake, inhibiting intestinal glucose absorption, and inhibiting the uptake of insulinase activity in the liver and kidneys, inhibiting glucose production, inhibiting the uptake of renal glucose or correction of insulin resistance and stimulation of β-cells (40). The results show that saffron could be a new therapeutic approach in diabetes (39).

Milajerdi et al. reviewed a three-blind randomized study involving 54 patients with type 2 diabetes who accidentally received saffron (15mg saffron hydroalcoholic extracts) two times daily for eight weeks. The results showed that the serum level of fasting blood sugar (FBS) in the saffron group decreased significantly compared to the placebo (41). Saffron powder supplementation (100 mg/daily) significantly reduced FBG and serum TNF-α levels at eight weeks compared with placebo by reducing the expression level of some inflammatory mediators (39).

Aloe vera

Aloe vera is a plant from the Asphodelaceae/ Xanthorrhoeaceae family (3). Aloe vera extract contains polysaccharides, anthraquinones and lectins with anti-diabetic activities (42). Gel derived from the flesh of leaf pulp consumed may cause hypoglycemic effects by stimulating β-cells (8,43). A. Vera has been shown to have many beneficial actions, including antioxidants, hypoglycemic, anti-hyperlipidemic, anti-inflammatory and immune system regulators (44). Possible mechanisms involved in improving blood sugar include positive regulation of insulin signaling pathways, inhibition of glucose uptake (α-glucosidase), delayed gastric emptying and ultimately improving glycemic control (45).

The oral administration of aloe led to blood sugar decrease in diabetic patients (46). The oral administration of aloe vera gel extract (300 mg/kg body weight) significantly reduced fasting blood sugar and improved plasma insulin levels in diabetic rats during 21 days (47).

Garlic (Allium sativum)

Garlic is an aromatic onion product belonging to the Amaryllidaceae Alliaceae / Liliaceae family. Its sulfur compounds are responsible for nutritional and medicinal functions (48). Garlic has therapeutic actions, including anti-hyperglycemic, antioxidant, hyperlipidemic, anti-inflammatory, anti-obesity, anti-atherosclerotic and anticoagulant activities (3). The anti-diabetic effect of garlic acts as both an insulin secretor and as an insulin sensitizer. It also increases glucose utilization by over-regulation of enzymes involved in glycolysis and glycogenesis (49).

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A systematic study and meta-analysis (2019) concluded that garlic could lower blood pressure in hypertensive patients, just like standard blood pressure medications (48). The garlic supplement (1500 mg/day) significantly suppressed FBG and HbA_1c levels relative to metformin in T2DM in 24 weeks (50). The meta-analysis concluded that consuming garlic extract (allicin) significantly reduces blood sugar and lipids over 12 to 24 weeks (51). Therefore, garlic supplementation seems to improve blood sugar in patients with type 2 diabetes and is recommended as an adjunct therapy with conventional anti-glycemic drugs. Few clinical studies showed inconsistent results for the anti-diabetic effects of garlic (52).

Ginger (Zingiber officinale)

Zingiber officinale is a flowering plant of the Zingiberaceae family (53). Zingerone, Shogaol, and Gingerol are essential oils and the main elements of this plant that respond to various biological activities (54,55). Some ginger compounds have been reported to have potent antioxidant, anti-inflammatory properties and free radical scavenging effects (12). It can regulate insulin signaling pathways (AMPK, Akt) related to insulin sensitivity and increase glucose uptake in Gluc4 transport, glucose transport and protection of β-cells (55), insulin release/ insulinotropic activity, inhibition of α-amylase and α-glucosidase synthesis, and inhibition of enzymes related to gluconeogenesis and glycogenolysis (56). It protects against diabetic complications such as retinopathy, neuropathy, nephropathy and liver damage (3).

Shidfar et al. reported that consumption of ginger (3g /three months) was associated with decreased serum glucose, HbAlc, and insulin resistance in patients with type 2 diabetes (57). A systemic analysis and meta-analysis have reported that ginger supplementation significantly reduces blood glucose and lipid levels in type 2 diabetic and hyperlipidemic individuals (56).

Turmeric (Curcuma longa)

Curcuma longa or turmeric has medicinal properties such as anti-stress, anti-depressant, antimicrobial and skin protection (58). The primary active components of turmeric are curcuminoids, including curcumin, desmethoxycurcumin, demethoxycurcumin and bisdemethoxycurcumin, which are responsible for therapeutic properties like anti-diabetic, anti-hyperlipidemic, antioxidant, anti-inflammatory, anti-apoptotic, anti-obesity, anti-atherosclerotic and anti-cancer (3). Turmeric is used to treat diabetic wounds, arthritis, joint pain, anorexia, cough, gastrointestinal disorders and heart disease (12). The anti-diabetic activity of turmeric induces insulin secretion by affecting insulin secretion/ insulinotropic activity and regulating different insulin signaling pathways (AMPK, Akt) (59). Turmeric destroys insulin resistance and inhibits the reabsorption of glucose, α-glucosidase and α-amylase (60).

Administration of curcumin in the form of nano-micelles (80 mg/day for three months) showed a significant decrease in the mean concentrations of FBG, HbA_1c and TG in type 2 diabetic patients (61). The systemic study and meta-analysis concluded that curcumin or combined curcuminoids could significantly reduce FBG levels and HbA_1c in diabetic patients (62). It seems that turmeric and its plant elements can be effective against type 2 diabetes and its complications.

Green tea (Camellia sinensis)

In hypertensive patients, three months of supplementation of green tea extract (379 mg/daily) significantly reduced systolic and diastolic blood pressure compared to the placebo group (63). Clinical evidence suggests that drinking green, black tea and coffee have direct and indirect protective effects for type 2 diabetes and cardiovascular disease (64). The consumption of green tea extract (500 mg, three times daily, for 16 weeks) significantly improves insulin resistance and increases glucagon-like production of peptide-1 (GLP-1) in type 2 diabetes (65). Although contradictory

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results have been reported in studies (66). Table 1 reviews some research.

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Conflict of Interest

The authors declare that there is no conflict of interest in this study.

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