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# Medicinal Plants and Phytochemicals Regulating Insulin Resistance and Glucose Homeostasis in Type 2 Diabetic Patients: A Clinical Review

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**Abstract**

Diabetes is a major health problem affecting more than four hundred million adults worldwide. The transition from normal glucose tolerance to type 2 diabetes (T2D) is preceded by increased Insulin resistance (IR), an independent predictor of the development of T2D in high risk (e.g. obese populations, prediabetes) individuals. Insulin deficiency resulting from increased IR results in progressive glucose homeostasis dysfunction. Data has shown that IR is affected by many different factors such as genetics, age, exercise, dietary nutrients, obesity, and body fat distribution. One of the most important factors is diet, which plays an essential role in addressing T2D and metabolic syndrome. Nutraceuticals and medicinal plants have been shown to have efficacy in preventing chronic diseases like cancer, non-alcoholic fatty liver disease (NAFLD), cardiovascular disease, diabetes mellitus and metabolic syndrome, likely through the anti-inflammatory properties found in nutraceuticals. However, the effect of these compounds, including traditional plant medicines, herbal formulations or their extracts on IR have not been systematically investigated. The objective of this review was to assess the reported effects of medicinal plants and bioactive natural com-

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pounds on IR. The findings confirm that most of the herbal bioactive compounds including resveratrol, garlic, curcumin, cinnamon, ginger, nuts, berberine, anthocyanin, soybean, flaxseed, vegetable oils, and soluble fibers have benefit in their efficacy for decreasing IR, fasting blood sugar (FBS), fasting insulin and HbA1c.

**Keywords**

Type 2 diabetes · Metabolic syndrome · Insulin resistance · Medicinal plants

## 13.1 Introduction

Diabetes is a major health problem affecting more than four hundred million adults worldwide [1]. The prevalence of T2D has been increasing steadily and it is thought that nearly 600 million people will be affected by 2035 [2]. More than 80% of diabetic patients suffer from T2D with both macrovascular and microvascular complications leading to an increasing burden on healthcare systems [3]. In addition, T2D is also affecting an increasing number of children, adolescents and young adults [4]. Evidence indicates that the development of T2D is a result of genetics and the environment [5] (Fig. 13.1). The transition from normal glucose tolerance to type 2 diabetes (T2D) is preceded by increased insulin resistance (IR), an independent predictor of the development of T2D in high risk (e.g. obese populations, pre-diabetes) individuals [6, 7]. Insulin deficiency resulting from increased IR results in progressive glucose homeostasis dysfunction. Mutations within the peroxisome proliferator activating receptor gamma (PPAR-γ) receptor gene contribute a key role in T2D [8] and hyperglycemia alters the functional phenotype of monocytes, macrophages, neutrophils, NK cells, and CD8+ T cells [9]. Results from the British Whitehall II study showed that IR precedes diabetes development indicating lowered insulin sensitivity (IS) and reduced β-cell function in the pre-diabetic stage [10]. IR can increase the progression and development of diabetic cardiomyopathy that is a specific form of cardiomyopathy [11]. Diabetic cardiomyopathy may be distinguished by the presence of impaired myocardial insulin signaling and mitochondrial dysfunction [12] leading to systolic heart failure [13]. Hyperglycemia is one of the main causes of T2D [14] as hyperglycemia promotes reactive oxygen species (ROS) production [15, 16] that in turn increases oxidative stress leading to injured cellular organelles and increased lipid peroxidation [17]. These pathways can affect insulin activity, function and secretion contributing to the progression to T2D [18]. In experimental models it has been shown that α-lipoic acid (LA), an anti-

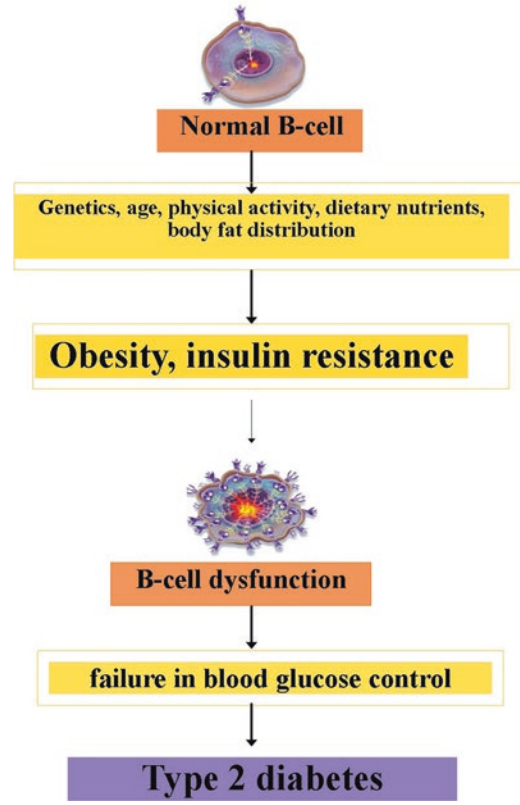


**Fig. 13.1 Effect gene and environmental factors on B-cell dysfunction and progression of Type 2 diabetes.** Genetics, age and environmental factors (physical activity, dietary nutrients, body fat distribution) are responsible for obesity and insulin resistance. Impairment in the function of pancreatic B cells-cells producing insulin causes failure in blood glucose control and development of type 2 diabetes

oxidant, may increase insulin sensitivity [19]. Obesity is another major cause of increased IR and T2D [20] as adipose tissue releases increased amounts of non-esterified fatty acids, glycerol, hormones and adipokines contributing to increased IR [21]. Impairment in the function of pancreatic B cells, responsible for producing insulin, leads to increased glucose dysregulation c [20, 22]. Dysfunction in β-cells is therefore important in determining the risk and development of T2D [20]. Current studies have identified various T lymphocyte subtypes in obese adipose tissue of humans and mice [23, 24]. In obesity, adipose tissue TH1 lymphocytes may help to attract macrophages into adipose tissue leading to increased tissue inflammation and enhancing IR [25].

The mechanism(s) that underlies the progress of IR in humans remains unclear. What has become clear is that IR is controlled by many different factors such as genetics [25], age [26, 27], exercise [28], dietary nutrients [29], obesity [30, 31], and body fat distribution [32, 33]. Aging is correlated with a reduction in the body's responsiveness to carbohydrate (19, 20). Exercise effects are more complex because exercise has both acute and chronic effects (21). However, in one study, exercise reduced the intra-abdominal fat area by 25% and improved in IR by 36% [5, 34].

The development and treatment of T2D could be addressed in part with lifestyle changes, including maintaining a healthy body weight, having a healthy diet, staying physically active, not smoking and not drinking alcohol [35]. The most important factor is a healthy diet, which plays an essential role in reducing T2D and metabolic syndrome [36]. Among the dietary components, nutraceuticals and medicinal plants have an important role in preventing chronic diseases like cancer, non-alcoholic fatty liver disease (NAFLD), cardiovascular disease, and T2DM and metabolic syndrome [25, 37–42]. There is a need for therapeutic agents that can decrease the risk of IR, and the number of nutraceuticals compounds with potential therapeutic properties to treat T2D patients continues to increase [25]. The expressed anti-inflammatory properties of nutraceuticals may be very important for the treatment of such diseases [25]. For instance, some of these natural agents have been found to repress the expression of PAI-1 by inhibiting the transcription factor early growth response, which has been associated with IR and obesity [43]. However, the effect of these compounds, including traditional plant medicines or herbal formulations or their extracts on IR have not been systematically reviewed. Therefore, the objective of this review is to detail the effects of medicinal plants and bioactive natural compounds on IR. The main findings of previous studies are summarized in Table 13.1.

## 13.2 Resveratrol

Resveratrol has the properties of being an antioxidant and anti-inflammatory factor that may decrease or limit the progress of many diseases including cancer, hypertension, cardiovascular diseases (CVD), T2DM and other metabolic diseases [98–100]. In a meta-analysis study of 11 randomized control trials, a total of 388 subjects were included and results showed that resveratrol significantly decreased fasting blood sugar (FBS), hemoglobin A1C (HbA1c) and IR by evaluation of homeostasis model of assessment for insulin resistance (HOMA-IR) in participants with T2DM though it had no significant effect on subjects without diabetes [101]. In a double-blind clinical trial study, 21 patients with T2DM were asked to take 480 mg/day resveratrol (intervention group) for 4 weeks and 22 individuals with diabetes without any treatment were considered as a control group. At the end of the study there was a significant reduction in fasting insulin and HOMA-IR levels observed in the intervention group compared with the control group. There was no significant difference in fasting blood glucose and TG (triglyceride) between intervention and control groups [44]. In a double-blind study, 19 male patients with T2D were recruited into two groups: patients in the resveratrol group to take oral resveratrol 10 mg/day and nine patients to placebo as a control group, and the intervention was conducted for 4 weeks. At the end of the

**Table 13.1** The effects of medicinal plants and bioactive natural compounds on Insulin resistance and glucose hemostasis in type 2 diabetic patients

| Author, year | Agent | Dose per day | Treatment duration | Subjects | Main outcomes |
|---|---|---|---|---|---|
| Zare Javid A et al. 2017 [44] | Resveratrol | 480 mg/day | 4 weeks | Patients with diabetes | Significant decreases in fasting insulin and HOMA-IR levels weere observed in intervention group compared with control group |
| Brasnyó P et al. 2011 [45] | Resveratrol | 10 mg/day | 4 weeks | Patients with T2D | No effect |
| Movahed A et al. 2013 [46] | Resveratrol | 1 g/day | 45 days | Patients with diabetes | There were significant reductions in fasting blood glucose, HbA1c, insulin, and HOMA-IR in resveratrol supplementation. |
| Bhatt JK et al. 2012 [47] | Resveratrol | 250 mg/day | 3 months | Patients with diabetes | HbA1c had a significant decrease in the group supplemented with resveratrol. |
| Bo S et al. 2016 [48] | Resveratrol | 500 and 40 mg/day | 6 months | Patients with diabetes | No effect for both doses of resveratrol. |
| Talaei B et al. 2017 [49] | Cinnamon | 3 g/day | 8 weeks | Patients with diabetes | No effect |
| Solomon TP et al. 2009 [50] | Cinnamon | 3 g/day | 14 days | Healthy male | Cinnamon diminished the glucose, and also decreased insulin and developing insulin responsiveness |
| Akilen R et al. 2010 [51] | Cinnamon | 2 g/day | 12 weeks | Patients with diabetes | Cinnamon significantly reduced HbA1c compared to placebo. There was no significant effect on fasting plasma glucose in the cinnamon group |
| Vanschoonbeek K et al. 2006 [52] | Cinnamon | 1.5 g | 6 weeks | Postmenopausal women with T2D | No effect |

(continued)

**Table 13.1** (continued)

| Author, year | Agent | Dose per day | Treatment duration | Subjects | Main outcomes |
|---|---|---|---|---|---|
| Mozaffari-Khosravi Hello et al. 2014 [53] | Ginger | 3 g/day | 8 weeks | Patients with diabetes | Fasting blood sugar, fasting insulin concentration and HOMA-decreased significantly between 2 groups. The QUICKI rose significantly in two groups, but differences of this index were significantly higher in ginger group |
| Shidfar F et al. 2015 [54] | Ginger | 3 g/day | 3 months | Patients with diabetes | The levels of glucose, fasting insulin, HOMA-IR, Hb1AC were significantly lower in the ginger group compared with the placebo group |
| Mahluji S et al. 2013 [55] | Ginger | 2 g/day | 2 months | Patients with diabetes | There were significant reductions in the level of insulin, HOMA-IR raised the QUICKI index in the ginger group compared with the control group |
| Arablou T et al. 2014 [56] | Ginger | 1600 mg | 12 weeks | Patients with diabetes | Ginger significantly lowered the levels of insulin, fasting plasma glucose, HbA1c, HOMA-IR in comparison to the control group |
| Yin J et al. 2008 [57] | Berberine | 1500 mg/day | 3 months | Patients with diabetes | There were significant reductions in HbA1c, fasting blood glucose and postprandial blood glucose in the berberine group in two levels A and B, and fasting plasma insulin and HOMA-IR were diminished only in level B |

(continued)

**Table 13.1** (continued)

| Author, year | Agent | Dose per day | Treatment duration | Subjects | Main outcomes |
|---|---|---|---|---|---|
| Zhang Y et al. 2008 [58] | Berberine | 1.0 g/day | 3 months | Patients with diabetes and dyslipidemia | Berberine had significant improvements in fasting plasma glucose and 2-h OGTT plasma glucose, HbA1c, and HOMA-IR decreased |
| Shidfar F et al. 2012 [59] | Berberis vulgaris fruit extract | 3 g/day | 3 months | Patients with diabetes | There were significant reductions in serum glucose and insulin and HOMA-IR between two groups |
| Atkin M et al. 2016 [60] | Aged garlic extract | 1200 mg/day | 4 weeks | Patients with diabetes | No effect |
| Ghorbani A et al. 2019 [61] | Garlic | 300 mg/day | 12 weeks | Patients with diabetes and dyslipidemia | The levels of HbA1c decreased significantly in the intervention group though no effect on fasting blood glucose |
| Li D et al. 2015 [62] | Anthocyanin | 320 mg/day | 24 weeks | Patients with diabetes | Significant reductions in plasma fasting plasma glucose and HOMA-IR levels were observed in the anthocyanins group compared with the placebo group |
| Moazen S et al. 2013 [63] | Freeze-dried strawberry | 50 g/day | 6 weeks | Patients with diabetes | The level of HbA1c reduced significantly in the intervention group and there was no significant difference in serum glucose concentrations between two groups |
| Banihani S et al. 2014 [64] | Fresh pomegranate juice | 1.5 mL/kg body weight | Blood samples were obtained after 12 h of fasting, 1 and 3 h after the ingestion of the juice. | Patients with diabetes | HOMA-IR reduced between diabetic patients after 3 h of pomegranate juice ingestion |

(continued)

**Table 13.1** (continued)

| Author, year | Agent | Dose per day | Treatment duration | Subjects | Main outcomes |
|---|---|---|---|---|---|
| Liu C-Y et al. 2014 [65] | Green tea extract | 1500 mg/day | 16 weeks | Patients with diabetes and dyslipidemia | There was a significant reduction in triglyceride and HOMA-IR |
| Hua C et al. 2011 [66] | Decaffeinated green tea extract | 500 mg/day | 16 weeks | Patients with diabetes | No effect |
| Fukino Y et al. 2005 [67] | Green tea extracts/ powder | 544 mg/day | 2 months | Patients with diabetes | No effect |
| Ryu O et al. 2006 [68] | Green tea | 9 g/day | 4 weeks | Patients with diabetes | No effect |
| MacKenzie T et al. 2007 [69] | *Camellia sinensis* (eg, green, oolong, and black tea) | 0, 375, or 750 mg of 40% catechins from green tea (150 mg) | 3 months | Patients with diabetes | No effect |
| Ahn HY et al. 2018 [70] | Fermented soybean powder mixture | 19.45 g/day | 12 weeks | Patients with impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or newly diagnosed T2D | The level of fasting glucose, glucose at 60 min, HOMA-IR decreased in intervention group |
| Kim J-I et al. 2005 [71] | Soybean-derived pinitol | 600 mg/day | 13 weeks | Patients with diabetes | The levels of fasting plasma glucose, insulin, fructosamine, HbA1c, and HOMA-IR diminished significantly |
| T Sathyapalan et al. 2017 [72] | Soy protein | 15 g/day | 3 months | Male patients with diabetes | A significant linear correlation between the decrease of βCTX in the SPI group with a decrease of HbA1c and HOMA-IR. |
| J Konya et al. 2019 [73] | Soy protein | 15 g/day | 8 weeks | Patients with diabetes | The level of HbA1c improved in the soy protein group compared with the placebo group. |
| V Jayagopal et al. 2002 [74] | Soy protein | 30 g/day | 12 weeks | Postmenopausal women with T2D | There were significant reductions in the levels of insulin resistance, fasting insulin, HbA1c, HOMA-IR. |
| S González et al. 2007 [75] | Soy protein | Soy that included 132 mg isoflavone capsules | 12 weeks | Postmenopausal women with T2D | No effect |

(continued)

**Table 13.1** (continued)

| Author, year | Agent | Dose per day | Treatment duration | Subjects | Main outcomes |
|---|---|---|---|---|---|
| Soleimani Z et al. 2017 [76] | Omega-3 fatty acids from flaxseed oil | 1000 mg/day | 12 weeks | Patients with diabetic foot ulcer grade 3 | Omega-3 fatty acids reduced significantly serum insulin, HOMA-IR, HbA1c and increased significantly QUICKI compared with the placebo group |
| Zheng JS et al. 2016 [77] | Flaxseed oil, fish oil, corn oil | 2.5 g/day of alpha-linolenic acid | 180 days | Patients with diabetes | No effect |
| Soleimani A et al. 2017 [78] | Omega-3 fatty acids from flaxseed oil | 1000 mg/day | 12 weeks | Patients with diabetic nephropathy | Omega-3 fatty acids significantly reduced the level of insulin, HOMA-IR and increased QUICKI compared with the placebo group |
| Foster M et al. 2014 [79] | Zinc and flaxseed oil | Flaxseed oil (2 g/day) | 12 weeks | Women with diabetes | No effect |
| Panahi Y et al. 2018 [80] | Curcuminoids | 500 mg/day with piperine 5 mg/day | 3 months | Patients with diabetes | Serum levels of insulin, HbA1c, and HOMA-IR reduced significantly in both groups, whereas serum levels of glucose and HbA1c reduced significantly after curcuminoids group compared with the placebo group |
| Na LX et al. 2013 [81] | Curcuminoids | 300 mg/day | 3 months | Patients with T2D that was overweight or obese | Fasting blood glucose, HbA1c, HOMA-IR diminished significantly after curcuminoids supplementation |
| H Hodaei et al. 2019 [82] | Curcumin | 1500 mg three times daily | 10 weeks | Patients with diabetes | Curcumin had a significant reduction in FBS but did not affect HOMA-IR, HbA1c and insulin. |

(continued)

**Table 13.1** (continued)

| Author, year | Agent | Dose per day | Treatment duration | Subjects | Main outcomes |
|---|---|---|---|---|---|
| RN Thota et al. 2019 [83] | Curcumin | 2 × 500 mg tablets | 12 weeks | Patients with diabetes | There was no difference in levels of HbA1c and fasting glucose between all groups. Insulin sensitivity increased significantly in CC group compared with PL. |
| S Asadi et al. 2019 [84] | Nano-curcumin | 80 mg | 8 weeks | Patients with diabetes | HbA1c and FBC reduced significantly in nano curcumin group compared with placebo group. |
| LX Na et al. 2013 [81] | Curcumin | 300 mg | 3 months | Patients with diabetes | There were significant reductions in FBS, HbA1c and HOMA-IR in curcumin group. |
| Rabiei K et al. 2018 [85] | Extract of *Juglans regia* (walnut) leaves | 100 mg/day | 8 weeks | Patients with diabetes | No effect |
| Hosseini S et al. 2014 [86] | *Juglans regia* leaf extract | 200 mg/day | 3 months | Patients with diabetes | Juglans regia reduced significantly levels of fasting blood glucose and HbA1c: There was no effect on insulin levels. |
| Parham M et al. 2014 [87] | Pistachio nuts | 50 g/day | 12 weeks | Patients with diabetes | Fasting blood glucose and HbA1c decreased in the pistachio group but there was no effect on HOMA-IR |
| Hernández-Alonso P et al. 2014 [88] | Pistachio diet | 57 g/day | 4 months | Prediabetic patients | Pistachio diet diminished fasting glucose, insulin, and HOMA-IR. |
| Li S-C et al. 2011 [89] | Almond diet | 20% of calorie intake were almonds | 4 weeks | Patients with diabetes and mild hyperlipidemia | Levels of fasting insulin, fasting glucose, and HOMA-IR were lower in the almond diet |
| Jenkins DJ et al. 2014 [90] | A bread that enriched with canola oil | 31 g canola oil per 2000 kcal | 3 months | Patients with diabetic and hyperlipidemic | The level of Hb1Ac decreased in both groups but the reduction was greater in the test diet |

(continued)

**Table 13.1** (continued)

| Author, year | Agent | Dose per day | Treatment duration | Subjects | Main outcomes |
|---|---|---|---|---|---|
| Sarbolouki S et al. 2013 [91] | Eicosapentaenoic acid (EPA) in intervention group and corn oil in control group. | (EPA) (2 g/day) and corn oil (2 g/day) | 3 months | Patients with diabetes | The levels of fasting plasma glucose, HbA1c, HOMA-IR reduced significantly in the EPA group compared with control group |
| Mostad IL et al. 2006 [92] | Fish oil in the intervention group and corn oil in the control group. | 17.6 mL/day of fish oil and 17.8 ml/day of corn oil | Short-term (1 week) and longer-term (9 week) | Patients with diabetes | The mean blood glucose concentrations and fasting blood glucose concentrations were significantly greater after 8 week in the fish oil group compared with the corn oil group, but at baseline, 1 week, and 9 week there was no changes |
| Jacobo-Cejudo MG et al. 2017 [93] | Docosahexaenoic acid plus eicosapentaenoic acid-enriched fish-oil (FOG) | 520 mg/day | 24 weeks | Patients with diabetes | Hb1Ac decreased and insulin, HOMA-IR raised significantly in both groups |
| Ogawa S et al. 2013 [94] | Liquid diet with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) | Liquid diet with EPA (25 mg/100 kcal) and DHA (17 mg/100 kcal) | 3 months | Patients with diabetes | There were significant decreases in the levels of fasting plasma glucose and HbA1c in the diet with EPA/DHA compared with a diet without EPA/DHA |
| Kamalpour M et al. 2018 [95] | Psyllium powder | 7 g | 2 weeks | Patients with diabetes | There was a significant reduction and increase in fasting plasma insulin and HOMA-IR, respectively |
| Dall'Alba V et al. 2013 [96] | Partially hydrolyzed guar gum (PHGG) | 10 g/day | 4 and 6 weeks | Diabetic patients with metabolic syndrome | HbA1c decreased in the intervention group after baseline, 4 and 6 weeks |
| Abutair AS et al. 2016 [97] | Soluble fiber from psyllium | 10.5 g/day | 8 weeks | Patients with diabetes | Soluble fiber supplementation improved fasting blood sugar, HbA1c, insulin, HOMA.IR and HOMA-β % |

study, there was no significant difference in serum insulin levels and HOMA assessment of b-cell function (HOMA-b) values between the resveratrol and the placebo groups; however, HOMA-IR values significantly reduced in the intervention group compared with placebo [45]. In another clinical trial study, 66 T2DM patients were divided into two groups to receive resveratrol (1 g/day) or placebo group for 45 days. At the end of the study there was a significant reduction in fasting blood glucose, HbA1c, insulin, and HOMA-IR in the resveratrol group compared to their baseline levels [46]. In another study, a total of 62 subjects with T2D were asked to consume resveratrol (250 mg/day) or placebo (control group) whilst using an oral hypoglycemic agent in both groups. After 3 months of intervention, only HbA1c was significantly decreased in the resveratrol group [47]. In a further control trial, 192 patients with T2D were assigned to receive resveratrol 500 mg/day, resveratrol 40 mg/day or placebo for 6-months. Results showed that no significant changes were observed in plasma FBS, HbA1c or insulin between groups for both resveratrol 500 and resveratrol 40 compared with the placebo group [48].

## 13.3 Cinnamon

Cinnamon has been used for many years as a herbal Medicine [102]. It has been shown that cinnamon may stimulate insulin secretion, increase insulin sensitivity, and insulin signaling resulting in a decrease in blood glucose and improvement in the lipid profile [103–107]. In one double-blind, randomized, placebo-controlled clinical trial study, 44 patients with T2D were randomly recruited into two groups, placebo or 3 g/day cinnamon supplement daily. After 8 weeks, results showed that there was no significant difference in the level of fasting blood glucose, insulin, HbA1c, HOMA-IR between two groups [49]. In a single-blind randomized cross-over design, 8 healthy males were entered to study, each subject performed two 20-day interventions including control intervention and a cinnamon (3 g/day). Oral glucose tolerance tests (OGTT) were completed on days 0, 1, 14, 16, 18, and 20. Cinnamon diminished the glucose on day 1 and day 14 and also decreased insulin and enhanced insulin responsiveness on day 14 [50]. In a clinical trial, a total of 58 T2DM subjects were asked to take cinnamon (2 g/day) or placebo for 12 weeks. At the end of the study, cinnamon capsules significantly reduced HbA1c compared to placebo, but there was no significant effect on fasting plasma glucose between groups [51]. In another study, 55 postmenopausal women with T2D were enrolled to take 1.5 g of cinnamon or a placebo daily for a period of 6 weeks. At the end of the study, that cinnamon supplementation had no effect on HbA1c, HOMA-IR or oral glucose tolerance [52].

## 13.4 Ginger

Ginger is a pharmaceutical plant that has been utilized for many years as a food spice [108]. Ginger is one of the functional foods that includes essential compounds applicable to gingerol, shogaol, paradol and zingerone [54]. Several health benefits have been ascribed to ginger including immunomodulatory, anti-inflammatory anti-cancer, anti-thrombotic, anti-hyperglycemic and hypolipidemic actions [109, 110].

In a double-blind randomized controlled study, 88 patients with T2DM were randomly recruited into two groups: ginger (GG) and placebo (PG) groups. The GG took 3 g/day for 8 weeks. After the intervention, the results indicated that the median fasting blood sugar, fasting insulin concentration and HOMA-decreased significantly between 2 groups. The QUICKI (quantitative insulin sensitivity check index) as an insulin resistance index rose significantly in both groups, but differences of this index were significantly higher in GG than PG [53]. In another double-blind, placebo-controlled, randomized clinical trial study, 50 T2D patients were asked to consume 3 g of powdered ginger or placebo daily. After 3 months, the level of glucose, fasting insulin, HOMA-IR, Hb1AC was significantly lower in the ginger group compared with the placebo group [54]. In a previous clinical trial study, 64

participants with T2DM were randomised to receive 2 g/day of ginger or placebo for 2 months. At the end of the study there was a significant reduction in the level of insulin, HOMA-IR raised the QUICKI index in the ginger group compared with the control group, and no significant changes were observed in plasma fasting blood glucose [55]. In another study, 70 patients with T2D were assigned to receive 1600 mg ginger or 1600 mg wheat flour placebo every day. After 12 weeks of intervention, ginger supplementation significantly lowered the levels of insulin, fasting plasma glucose, HbA1c, HOMA-IR in comparison to the control group [56].

## 13.5 Berberine

Berberine has several natural activities that may have positive effects on various metabolic disorders including reducing hyperglycemia and dyslipidemia [111–113]. Berberine is an ancient Chinese herb that has been used to treat T2DM and to treat gastrointestinal infections for thousands of years [57]. In a pilot study, 36 individuals with recently diagnosed T2D were asked to take berberine or metformin (500 mg three times daily) in a 3-month trial. After 3 months, there was a significant reduction in HbA1c, fasting blood glucose and postprandial blood glucose in the berberine group in comparison with the metformin group. In another study, 48 T2D patients with poor glycemic control received 500 mg berberine three times daily added to their current medication for a 3 month period. At the end of the study the level of HbA1c, fasting blood glucose and postprandial blood glucose, fasting plasma insulin and HOMA-IR were all decreased [57]. In another study, 116 randomized participants with T2D and dyslipidemia were recruited to consume berberine (1.0 g/day) or placebo for a 3 month period, following which taking berberine had a significant improvement in fasting plasma glucose, the 2-h OGTT plasma glucose and HbA1c. HOMA-IR was decreased in the berberine group, whereas no difference was found in the placebo group [58]. In another double-blind randomized clinical trial study, 31 patients with diabetes were enrolled to receive 3 g/day BVFE (berberis vulgaris fruit extract) or placebo. Comparison of the glycemic indices after 3 months showed that there were a significant reductions in serum glucose, insulin and HOMA-IR between the BVFE and placebo groups [59].

## 13.6 Garlic

Garlic has several active herbal and phytochemicals that may elicit antioxidant activities and has been used for hundreds of years [114]. Garlic has a high amount of organosulfur compounds, such as allicin and flavonoids that may prevent oxidative injury and decrease blood pressure and hyperglycemia, and may be beneficial in the reduction and prevention of CVD and some types of cancers [115, 116]. Preclinical studies showed that garlic has anti-diabetic, anti-obesity, anti-atherosclerotic, anti-carcinogenic and anti-thrombotic properties [117–119]. In a crossover pilot study, 26 participants with T2DM were asked to take 1200 mg of Aged Garlic Extract (AGE) or a placebo daily; however, after 4 weeks, there was no significant difference in HOMA-IR and HbA1c between the two groups [60]. In another recent clinical trial study, 50 diabetic T2DM subjects with dyslipidemia were recruited into two groups: a control group taking a traditional therapy with hypolipidemic and hypoglycemic drugs and intervention group taking traditional therapy and the herbal compound (300 mg garlic). After 12 weeks treatment, the levels of HbA1c decreased significantly in the intervention group, but had no effect on fasting blood glucose [61].

## 13.7 Anthocyanin

Anthocyanin has many bioactive compounds including the flavonoid category of polyphenols seen in berry fruits, including cherry, blueberries, and strawberries [120]. It has been suggested that anthocyanin has multi- health benefits for obesity

and diabetes control, CVD prevention, and recovery of optical and brain functions [120–122]. Anthocyanin, a normal antioxidant, has been considered to lower oxidative stress and to decrease IR and diabetes [62]. In a study, 58 individuals with T2D were assigned to receive 320 mg/day of anthocyanins or placebo for 24 weeks. At the end of the study, a significant reduction in plasma fasting plasma glucose and HOMA-IR levels were observed in the anthocyanins group compared with the placebo group [62]. In a previous clinical trial, 36 patients with T2D were assigned to receive 2 cups of freeze-dried strawberry (FDS) drink (50 g of FDS is equivalent to 500 g of fresh strawberries) or placebo powder with strawberry flavor daily for 6 weeks. The level of HbA1c reduced significantly in the FDS group compared with the placebo group and there was no difference in serum glucose concentrations between two groups [63]. In another study, 85 subjects with T2D were entered to study. The subjects were given fresh pomegranate juice at a dose of 1.5 mL/kg body weight and then blood samples were obtained after 12 h of fasting, 1 and 3 h after the ingestion of the juice. At the end of the study, HOMA-IR reduced in the T2DM patients after 3 h of pomegranate juice ingestion. Response to fasting serum glucose (FSG) was different, patients with lower FSG showed a larger hypoglycemic effect than those with higher FSG [64].

## 13.8 Green Tea

Green tea has a contains many flavonoids and has been reported to have several potential health benefits including anti-cancer, anti-arteriosclerotic, antioxidant and anti-thrombotic effects, as well as beneficial effects to reduce hyperlipidemia, hypertension and hyperglycemia. The main flavonoids of green tea are catechins that constitute almost 22% of green tea [123–130]. Recent animal studies indicate that green tea has a protective effect on glucose homeostasis, high fat-induced hepatic steatosis, IR and inflammation, and the underlying mechanism may involve the AMPK pathway [131, 132]. In a clinical trial, 92 participants with T2D and dyslipidemia were randomized into 2 groups to receive placebo or 1500 mg green tea extract. After 16 weeks, there was a significant reduction in triglyceride and HOMA-IR [65]. In another study, 68 patients with type 2 diabetes were asked to take 1500 mg of a decaffeinated green tea extract (GTE) or placebo for 16 weeks. At the end of the study, there were no significant difference between the two groups [66]. In a randomized controlled trial study, 66 participants with T2DM were assigned to receive a packet of green tea extracts/powder containing 544 mg polyphenols (456 mg catechins) daily for a period of 2 months at the end of which there were not differences between the green tea and placebo groups, but the level of insulin was related to polyphenol intake in the intervention group [67]. In a clinical trial of 55 T2D participants were asked to take 900 ml water containing 9 g of green tea every day for 4 weeks; at the end of the study, there was no effect on insulin resistance [68]. In a randomized controlled trial, a total of forty-nine T2DM participants were assigned to receive 0, 375, or 750 mg of 40% catechins from green tea (150 mg) and 20% aflavins from black tea for 3 months. At the end of the study, there were no differences in HbA1c or a hypoglycemic effect between the 3 groups [69].

## 13.9 Soybean

Soybeans have bioactive ingredients, including isoflavones, saponins, soy protein and flavonoids that have potential benefits for the prevention and treatment of chronic diseases, such as CVD and T2DM [133–135]. In a study, 60 patients with impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or newly diagnosed T2D were asked to consume 40 g of a Jerusalem artichoke and fermented soybean powder mixture (19.45 g each) every day or placebo. After 12 weeks, the level of fasting glucose, glucose at 60 min, HOMA-IR decreased in those receiving the Jerusalem artichoke and fermented soybean powder mixture [136]. In another study, 30 participants with T2D were asked to consume 600 mg

soybean-derived pinitol or placebo twice daily. After 13 weeks the results showed that the level of fasting plasma glucose, insulin, fructosamine, HbA1c, and HOMA-IR diminished significantly [71]. In another study, 200 male patients with T2D were asked to consume only 15 g soy protein (SP) every day or 15 g soy protein with 66 mg isoflavones (SPI) every day. After 3 months, results showed a significant linear correlation between the decrease of type I collagen crosslinked beta C-telopeptide in the SPI group with a decrease of HbA1c and HOMA-IR [72]. In a recent randomized controlled trial, 84 diabetic patients were assigned to receive only soy protein (SP) 15 g/day, soy protein (15 g) plus isoflavones (32 mg) (SPI), soy protein (15 g) plus cocoa(400 mg) (SPC), soy protein plus isoflavones with cocoa (SPIC) or placebo given twice daily for 8 weeks. At the end of the study, the level of HbA1c improved in the soy protein group compared with the placebo group [73]. In a previous randomized controlled trial, 32 postmenopausal women with T2D were recruited to two groups to consume soy protein (30 g/day) and isoflavones (132 mg/day) or placebo (30 g/day) for 12 weeks, considering 2-weeks washout periods to separate interventions. Results showed that there was a significant reduction in the levels of IR, fasting insulin, HbA1c, HOMA-IR [74]. In one clinical trial study, 32 postmenopausal women with T2D were asked to receive placebo or soy that included 132 mg isoflavones with 4-weeks washout periods to separate the placebo and active phases (12 weeks each). At the end of the study, there was no significant effect on glucose, HbA1c, and HOMA-IR [75].

## 13.10 Flaxseed

Flaxseed is rich in lignans that have both antioxidant and estrogen-like functions [137]. Flaxseed is rich in α-linolenic acid that may have benefits on CVD risk factors, atherosclerosis, diabetes, metabolic syndrome and dyslipidemia [137–141]. In a randomized controlled trial, 60 patients with diabetic foot ulcer grade 3 were recruited to two groups to consume 1000 mg omega-3 fatty acids from flaxseed oil or placebo twice per day. After 12 weeks, omega-3 fatty acids reduced significantly serum insulin, HOMA-IR, HbA1c and increased significantly the QUICKI compared with the placebo group [76]. In another study, 185 Chinese T2D subjects were assigned to receive fish oil (2 g/day of eicosapentaenoic acid + docosahexaenoic acid), flaxseed oil (2.5 g/day of alpha-linolenic acid), or corn oil (control group) for 180 days. At the end of the study, there was no difference between groups for HOMA-IR, fasting insulin, or glucose [77]. In a recent study on 60 subjects with diabetic nephropathy, participants were randomized into two groups with 1000 mg/day omega-3 fatty acids from flaxseed oil or placebo for 12 weeks. At the end of the study, omega-3 fatty acids significantly reduced the level of insulin, HOMA-IR and increased QUICKI compared with the placebo group [78]. In a another randomized, double-blind, placebo-controlled trial, 48 postmenopausal women with T2DM were asked to consume zinc (40 mg/day) and flaxseed oil (2 g/day). After 12 weeks of treatment, Zinc or flaxseed oil had no significant effects on either glycemia or HOMA-IR [79].

## 13.11 Curcumin

Curcumin a brilliant yellow chemical derived from Curcuma longa L. (turmeric) that has been utilized as a food ingredient for flavor and an old herbal medicine [142]. Many studies have shown that curcumin, as a natural polyphenol, is safe and has beneficial health effects including the reduction of hyperlipidemia, anti-cancer, antioxidant, decrease inflammation, lowering IR, antihepatic, anti-atherosclerotic and cardioprotective antithrombotic, antidepressant and antirheumatic activities [143–155]. In a recent study, 100 individuals with T2D were recruited to receive dietary advice with curcuminoids (500 mg/day with piperine 5 mg/day) or placebo. After 3 months of treatment, serum levels of insulin, HbA1c, and HOMA-IR decreased significantly in both groups, whereas serum levels of glucose and HbA1c reduced significantly after curcuminoids group compared with the placebo group

[80]. In a study, a total of 100 patients with T2D who were overweight or obese were asked to consume curcuminoids (300 mg/day) or placebo for 3 months. At the end of the study, fasting blood glucose, HbA1c, HOMA-IR diminished significantly after curcuminoids supplementation versus the placebo group [81]. In another study, 53 diabetic subjects were assigned to consume 1500 mg curcumin or placebo three times daily. After 10 weeks, curcumin had a significant reduction in FBS but did not affect HOMA-IR, HbA1c and insulin [82]. In a recent double-blind randomized controlled study,64 patients with T2D were randomly recruited to four group: (i) placebo, (ii) curcumin (2 × 500 mg) and placebo matching for long-chain omega-3 polyunsaturated fatty acids (LCn-3PUFA), (iii) LCn-3PUFA with placebo matching for curcumin,(iv) curcumin with LCn-3PUFA for 12 weeks. At the end of the study, there was no effect on HbA1c and fasting glucose, but in the curcumin plus placebo matched for LCn-3PUFA (CC) group sensitivity had a significant improvement in triglycerides [83]. In one clinical trial study, 80 patients with T2D were randomized into 2 groups to receive placebo or 80 mg of nano-curcumin for 8 weeks. Results showed that HbA1c and FBC reduced significantly in the nano curcumin compared with placebo group [84]. In another study,100 diabetic patients were asked to consume curcuminoids (300 mg/day) or placebo. After 3 months, the levels of HbA1c, fasting blood glucose and HOMA-IR decreased significantly in the curcumin group compared with the placebo group.

## 13.12 Nuts

It has been shown that nuts contain high amounts of unsaturated fats, soluble fiber, antioxidants and phytosterols that have an effect on serum lipids, blood pressure, blood glucose and inflammation [156]. In a clinical trial, 50 T2DM subjects were randomized into 2 groups to receive 100 mg extract of *Juglans regia* (walnut) leaves or control group for 8 weeks. At post-intervention, there were a significant reductions in the level of postprandial glucose and HbA1c with walnut leaves though there was effect on blood glucose level or HOMA-IR [85]. In another study, 61 participants with T2D were randomized into 2 groups to receive a placebo or 200 mg/day *Juglans regia* leaf extract. After 3 months, Juglans regia reduced significantly the fasting blood glucose level and HbA1c at the end of the study, though there was no significant effect on insulin levels [86]. In a randomized crossover trial, a total of forty-eight T2DM subjects were recruited two groups to consume 50 g pistachio nuts daily or control that did not consume any nuts for a 12 week period, with a 8-week washout periods between interventions. In the first and second phases, fasting blood glucose and HbA1c decreased in the pistachio group, but there was no significant effect on HOMA-IR [87]. In a randomized clinical trial, a total of 54 prediabetic participants randomly recruited into two groups: diet including a supplement of pistachio diet (PD) and a control diet (CD) for 4 months, with a 2-week washout period. The diet for PD included 50% calories from carbohydrate and 35% from fat and containing 57 g/day pistachios, although these percentages for CD were 55% and 30% respectively. At the end of the study, there was a marked reduction in fasting glucose, insulin, and HOMA-IR in the PD compared with the CD [88]. In a crossover clinical trial, 20 Chinese subjects with T2D and mild hyperlipidemia were divided into two groups: an almond diet or control diet for 4 weeks, with a 2-week washout period. At the end of the study, levels of fasting insulin, fasting glucose, and HOMA-IR were lower in the almond diet compared with the control diet [89].

## 13.13 Vegetable Oil

Vegetable oils such as olive oil and canola oil contain a high quantity of Monounsaturated fatty acids (MUFAs) shown to have beneficial effects on blood lipids and inhibition of coronary heart disease, and improvement in insulin sensitivity, lipid peroxidation, and inflammation [157, 158]. In a study, a low-glycemic-load with α-linolenic acid (ALA), MUFA taken as bread that was enriched with 31 g canola oil per 2000 kcal, or a

whole-wheat bread supplement were administrated to 141 T2DM and hyperlipidemic adults for 3 months. Results showed that Hb1Ac decreased in both groups but the reduction was greater in the test diet with canola oil than the control group [90]. In another study, 67 subjects with T2D were asked to take purified eicosapentaenoic acid (EPA) (2 g/day) and corn oil (2 g/day) in the control group. After 3 months of treatment, a significant reduction in plasma fasting plasma glucose, HbA1c, HOMA-IR levels were observed in the EPA group compared with control group [91]. In a double-blind controlled study, 26 T2DM patients were recruited to consume 17.6 mL of fish oil/day in the intervention group and 17.8 ml corn oil/day in the control group. The study examined short-term (1 week) and longer-term (9 week). The mean blood glucose concentrations and fasting blood glucose concentrations were significantly greater after 8 week in the fish oil group compared with the corn oil group. No significant changes were observed in fasting insulin concentrations at baseline, 1 week, and 9 week in both groups [92]. In another study, 54 participants with T2D were asked to consume docosahexaenoic acid (DHA) plus EPA-enriched fish-oil (FOG) (520 mg/day) or placebo for 24 weeks. The result showed that FOG reduced Hb1Ac and insulin; however, HOMA-IR was raised significantly in both groups after the end of the study [93]. In a further study, a total of 30 adults with T2D were randomized into 2 groups to consume a liquid diet enriched with EPA (25 mg/100 kcal) and DHA (17 mg/100 kcal) or liquid diet without EPA and DHA for 3 months. At post-intervention, levels of fasting plasma glucose and HbA1c decreased significantly in the diet with EPA/DHA compared with a diet without EPA/DHA [94].

## 13.14 Soluble Fibers

Soluble fibers have been reported to have several health benefits particularly in obesity, hypertension, diabetes, coronary heart disease, stroke and certain gastrointestinal diseases [159, 160]. It is clear that fiber consumption plays a beneficial role in lessening blood lipids and blood pressure, increasing insulin sensitivity and lowering the prevalence of CVD [161]. In a recent study, thirty-seven T2DM subjects were asked to take diet with medium carbohydrate and low-energy plus 7 g of psyllium powder or a diet with low carbohydrate and low energy plus placebo powder. After 2 weeks, serum fasting plasma glucose and insulin did not change significantly; however, there was a significant reduction in fasting plasma insulin and an increase in HOMA-IR in the intervention group [95]. In another study, 44 T2DM participants with metabolic syndrome were assigned to receive a usual diet plus partially hydrolyzed guar gum (PHGG) in the intervention group or control group with usual diet. The HbA1c decreased significantly in the intervention group after baseline, 4 and 6 weeks; however, no significant changes were observed in fasting plasma glucose in both groups [96]. In a randomized control trial, 40 patients with T2D were randomly recruited into two groups: 10.5 g/day soluble fiber from psyllium in the intervention group and a regular diet in the control group for 8 weeks. At the end of the study, fasting blood sugar, HbA1c, insulin, HOMA.IR and HOMA-β % improved after soluble fiber supplementation versus the control group [97].

## 13.15 Conclusion

This review has comprehensively evaluated the effects of nutraceuticals and some herbal-based bioactive compounds on insulin resistance as well as FBS, HOMA-IR, HbA1c, QUICKI and lipid profiles in human clinical studies. The findings confirm that most of these agents such as resveratrol, garlic, curcumin, cinnamon**,** ginger, nuts, berberine, anthocyanin, soybean, flaxseed, vegetable oils, soluble fibers have beneficial effects on IR and decrease FBS, fasting insulin and HbA1c (Fig. 13.2). However, few studies have shown that green tea has a positive effect on

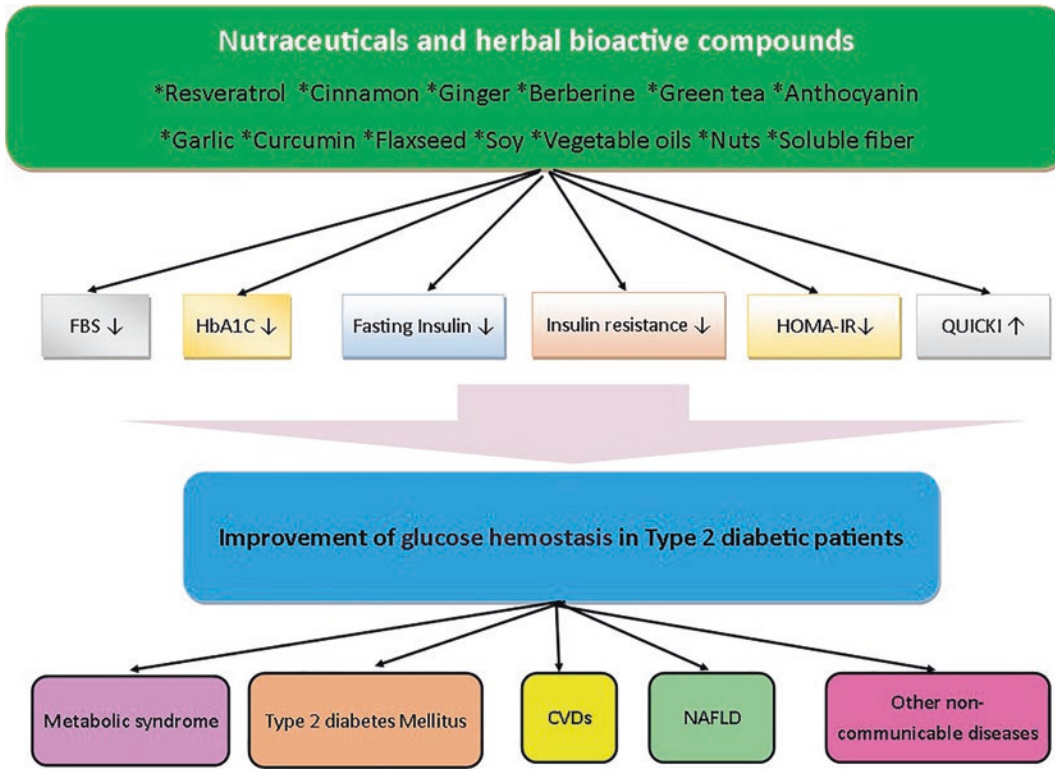


**Fig. 13.2 Schematic summary of pathways depicting the possible effects of nutraceuticals and herbal bioactive compounds on glucose hemostasis in Type 2 diabetic patients and its potential outcomes on non-communicable diseases.** *FBS* fasting blood sugar, *HbA1c* hemoglobin A1C, *HOMA-IR* homeostasis model of assessment for insulin resistance. *QUICKI* quantitative insulin sensitivity check index, *CVD* cardiovascular diseases, *NAFLD* non alcoholic fatty liver disease

IR. However, the data is limited by the number of studies, duration of the intervention and the different dosages and preparations used for each group reviewed. Many of these studies should also be undertaken in those subjects newly diagnosed with T2DM who may have a greater therapeutic response than those with established long standing disease where the response of IR is likely to be less. Therefore, further clinical trials will focus on evaluating the efficiency of other dietary ingredients and nutraceuticals in patients with T2DM with IR, and more definitive studies are needed for the investigation of optimal doses of each the products for their therapeutic effect.

**Conflict of Interests** None

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