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Review article

Functional Foods for Type 2 Diabetes

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Abstract: A number of studies have suggested that functional foods such as tea, wheat, nuts, and sweet potatoes have beneficial effects on glycemic control; however, the effectiveness of consuming functional foods for the management of diabetes remains unclear. The aim of this review is to summarize the evidence for functional foods in diabetes maintenance. A PubMed and Cochrane Database of Systematic Reviews search utilizing the indexing terms “functional food” and “diabetes” was performed. A total of 11 randomized controlled trials (RCTs) met the criteria. Resveratrol, wheat albumin, ginger, and wine grape pomace flour all improved glycemic control, insulin sensitivity, blood pressure, and lipid profiles. On the other hand, citrus flavonoids-enriched product, arabinogalactan, low-fat milk, raw red onion, and functional yogurt appear to have no effects on diabetes. As for resveratrol, the results are controversial. Although the underlying mechanism is not clear, the differences in the characteristics of study participants may have an influence on the effectiveness of functional foods. However, the effects of functional foods on diabetes remain inconclusive due to the small number of subjects, short duration, and methodological heterogeneity among RCTs. In addition to the current evidence, further RCTs investigating the effects of functional foods on diabetic complications, mortality, and cost-effectiveness, as well as glycemic control, are required.

Keywords: functional food; resveratrol; glycemic control; type 2 diabetes; randomized controlled trial

1. Introduction

Previously, two systematic reviews of randomized controlled trials (RCTs) assessed the effects of the functional foods sweet potatoes and cinnamon on diabetes. Consumption of 4 g per day of sweet potato for several months may improve glycemic control (mean difference in glycosylated hemoglobin A1c (HbA1c): −0.3%) [1]. On the contrary, an oral preparation of cinnamon seems to have no favorable effects on glycemic control [2]. Evidence to support the use of functional foods for the control of diabetes is insufficient because the quality of the trials is poor and the risk of bias is high. In addition, no study has investigated the effects of functional foods on diabetic complications, health-related quality of life, or mortality. The effectiveness of consuming functional foods for the management of diabetes remains unclear. An international standard for the definition of functional foods does not exit. The concept of functional foods should be clarified [3]. However, functional foods may be defined as, "foods that are consumed as part of the daily diet that have beneficial effects on health and also reduce the risk of chronic disease" from the viewpoint of metabolic disease and cardiovascular disease (CVD) [3]. Recently, the PREDIMED trial (Prevención con Dieta Mediterránea) has confirmed the effect of a Mediterranean diet on reducing the risk of CVD by approximately 30% [4]. However, the Mediterranean diet has various nutritional components, and their individual effects on CVD are unknown. In addition, several reviews show that consumption of functional foods such as fermented dairy food [5], olive oil [6], and nuts [7] has a beneficial effect on CVD risk factors including diabetes and obesity [8]. However, these reviews included not only clinical trials but also epidemiological studies; therefore, no clear conclusion has been reached on this issue. Table 1 shows a list of functional foods that may have a beneficial effect on diabetes. Type 2 diabetes has become a pandemic in recent years, and it poses social, economic, and medical problems for the entire world. More than 415 million people are living with diabetes in the world, and this number is expected to increase to 642 million by 2040 [9]. Because an imbalanced diet and overeating favor the development of type 2 diabetes, dietary practices in daily life should be improved to reduce the risk of diabetes. On the other hand, as mentioned above, the effect of functional foods on type 2 diabetes has not been fully elucidated. Hence, the purpose of this review is to summarize and evaluate the evidence for control of diabetes using functional foods and to provide clinicians with current knowledge on the roles of functional foods in patients with type 2 diabetes.

2. Materials and Method

The author searched the English literature of functional foods and diabetes from the last 15 years, from June 2001 to May 2016, using PubMed/MEDLINE and Cochrane Database of

Systematic Reviews. The search terms were "functional food", "diabetes", "glycemic control or blood glucose", and "randomized controlled trial". The search returned 63 published articles. The references described in these articles were also assessed. Studies were included if they met the following criteria: (1) Randomized controlled trials; (2) Participants' age ⩾ 18 years; (3) Study duration ⩾ 4 weeks. The author excluded studies related to functional foods such as green tea or coffee, of which reviews including systematic reviews have already published (see Table 1). Studies of experimental animals were excluded from this review. The titles and abstracts of the identified articles were reviewed to determine their relevance. If study outcomes were not related to diabetes, the studies were excluded from this review. A total of eleven RCTs met the criteria.

Table 1. Beneficial effects of functional foods on diabetes.

Functional foods	Functionality	References
Tea / Green tea	Fasting serum insulin↓, waist circumference↓	[36]
	Risk of coronary artery disease↓	[37]
Coffee	Fasting plasma glucose↓, Insulin sensitivity↑, anti-inflammatory, antioxidant	[38]
	Risk of type 2 diabetes↓	
Whole wheat	CVD risk factors↓	[39]
	Risk of type 2 diabetes↓	[40]
Oats	Postprandial glucose/insulin response↓, Fasting blood glucose↓, HbA1c↓, anti-inflammatory, antioxidant	[41] [42] [43]
Nuts	Incident of diabetes↓	[44]
Soybeans	No significant effects on fasting glucose, insulin, and HbA1c	[45]
Sweet potato	HbA1c↓	[1]
Cinnamon	No significant effects on insulin, postprandial glucose, and HbA1c	[2]
Chocolate	Risk of CVD and type 2 diabetes↓	[46]
	Insulin resistance↓, anti-inflammatory, antioxidant	[47]
Fenugreek	Fasting blood glucose↓, 2 hour postprandial glucose↓	[48]
Plant sterols (β-sitosterol)	Total cholesterol↓, low-density lipoprotein cholesterol↓	[49]

CVD = cardiovascular disease; HbA1c = hemoglobin A1c

3. Results and Discussion

3.1. RCTs reporting beneficial effects of functional foods on diabetes

The evidence regarding the effect of a single nutritional component on diabetes in humans is sparse. It appears that no RCTs with a large number of subjects (e.g., ⩾ 100 subjects) and a long duration (e.g., ⩾ 6 months) have been performed in patients with type 2 diabetes. However, there are several small scale RCTs investigating the effect of single functional foods on clinical parameters related to diabetes in healthy individuals or in patients with type 2 diabetes and metabolic syndrome.

Bhatt et al. [10] investigated whether oral supplementation with resveratrol, which has been reported to have beneficial effects on diabetes in numerous animal studies, improved glycemic control in patients with type 2 diabetes. Of the 62 subjects enrolled in this trial, 57 subjects completed the protocol. Patients with type 1 diabetes and hepatic and renal dysfunction were excluded. Patients in the intervention group (n = 28) received 250 mg per day of resveratrol via capsule for 3 months, in addition to oral hypoglycemic agents, whereas patients in the control group (n = 29) received only oral hypoglycemic agents. The mean ages of patients in the intervention and control groups were 56.67 ± 8.91 years and 57.75 ± 8.71 years, respectively. Significant differences in changes in fasting blood glucose (−14.39 ± 5.05 mg/dl vs. 13.07 ± 6.34 mg/dl), HbA1c (−0.33 ± 0.04% vs. 0.17 ± 0.10%), systolic blood pressure (−11.78 ± 0.73 mmHg vs. 7.76 ± 1.62 mmHg), diastolic blood pressure (−2.14 ± 0.13 mmHg vs. 7.10 ± 1.72 mmHg), total cholesterol (−14.32 ± 5.31 mg/dl vs. 6.90 ± 0.31 mg/dl), and low-density lipoprotein cholesterol (−12.45 ± 6.95 mg/dl vs. 7.09 ± 0.35 mg/dl) between the intervention group and the control group were found. These results appear at first glance to be promising, but should not be accepted without scrutiny. First, the authors did not describe dietary intake changes during the study period, and patients in the control group did not receive a placebo. Second, glycemic control seems to have been worse in the patients in the intervention group (HbA1c: 9.99 ± 1.50%) than in the control group (HbA1c: 8.75 ± 1.56%) at baseline. It is questionable whether randomization was appropriately performed and whether study participants were well-controlled. Nevertheless, a glucose-lowering effect of resveratrol was noted. The hypoglycemic effect of resveratrol may be induced by its binding effect on sulfonylurea receptors [11]. Resveratrol may block the adenosine triphosphate-sensitive K^+ channels in pancreatic β cell and stimulate insulin secretion [12]. Resveratrol has the potential to ameliorate diabetes. Kodama et al. [13] examined the effects of single and long-term administration of wheat albumin on blood glucose levels and glycemic control. This trial consisted of two studies. One was a randomized crossover study for single administration of wheat albumin in normal subjects, and the other was a double-blinded randomized controlled study in type 2 diabetic patients. Eleven healthy male subjects were recruited in the first study. The mean age, body mass index (BMI), and fasting blood glucose levels were 41 ± 0.7 years, 23.7 ± 0.16 kg/m^2, and 95 ± 0.7 mg/dl, respectively. The peak blood glucose levels in the 0.5 g and 1.0 g wheat albumin consuming groups were significantly lower

compared to that of the placebo group (47% and 50% lower, respectively). The AUC of blood glucose levels in both the 0.5 g and 1.0 g wheat albumin consuming groups were also significantly smaller than that of the placebo group. No differences in insulinogenic index and serum insulin levels after consuming the wheat albumin containing soup were observed among the groups. No adverse effects were reported. A total of 18 patients with type 2 diabetes were enrolled in the second RCT. The mean age, BMI, and HbA1c were 55.9 ± 2.23 years, 24.1 ± 0.67 kg/m^2, and 6.8 ± 0.11%, respectively. The duration of diabetes was approximately 2.6 years. HbA1c levels 2 and 3 months after wheat albumin administration significantly decreased from baseline. The reduction was more apparent in patients with higher HbA1c levels (≥ 7.0%) at baseline. No differences in body weight, lipid profile, or liver and renal function between the placebo and wheat albumin groups were observed. One diabetic patient taking wheat albumin reported constipation. Postprandial hyperglycemia might have been suppressed by delaying the absorption of carbohydrates, which was due to strong inhibition of α-amylase activity by wheat albumin. The α-glucosidase inhibitor, one of the oral hypoglycemic agents, has a similar mechanism of action to wheat albumin. It delays disaccharide digestion and absorption, possibly causing abdominal bloating and diarrhea. However, no considerable adverse effects such as gastrointestinal symptoms and hepatic dysfunction were observed in the wheat albumin group. Wheat albumin may be a safe and effective functional food for improving glycemic control. However, all patients in this trial had mild type 2 diabetes; therefore, whether wheat albumin has a glucose lowering effect in patients with moderate to severe type 2 diabetes is unclear. Shidfar et al. [14] reported the effect of ginger (Zingiber officinale) on glycemic indices in type 2 diabetic patients. Among the 50 patients with type 2 diabetes who were randomly assigned to the placebo group and the ginger (Zingiber officinale) supplementation group, 45 patients completed the trial. Patients with obesity (BMI ≥ 30 kg/m^2), chronic diseases such as heart disease, hepatic or kidney dysfunction, insulin therapy, or poor glycemic control (HbA1c > 8%) were excluded. Patients in the ginger group and the placebo group received 3 g per day of powdered ginger capsules and the same dose of placebo capsules for 3 months. No significant differences in medication, physical activity, or dietary intake between the two groups were observed at baseline. After 3-months of the ginger treatment, serum glucose levels (−19.41 ± 18.83 mg/dl vs. 1.63 ± 4.28 mg/dl), HbA1c levels (−0.77 ± 0.88% vs. 0.02 ± 0.16%), insulin levels (−1.46 ± 1.7 μIU/ml vs. 0.09 ± 0.34 μIU/ml), the homeostasis model assessment of insulin resistance (−16.38 ± 19.2 vs. 0.68 ± 2.7), highly sensitive c-reactive protein (−2.78 ± 4.17 mg/dl vs. 0.2 ± 0.77 mg/dl), paraoxonase-1 (22.04 ±24.53 U/l vs. 1.71 ± 2.72 U/l), total antioxidant capacity (0.78 ± 0.71 μU/ml vs. −0.04 ± 0.29 μU/ml), and malondialdehyde (−0.85 ± 1.08 μmol/ml vs. 0.06 ± 0.08 μmol/ml) values in the ginger group were significantly different compared to those in the placebo group. These glycemic, inflammatory, and oxidative stress markers significantly decreased in the ginger group after 3-months of ginger treatment. Similarly, Mozaffari-Khosravi et al. [15] also reported that 3 g daily of ginger supplementation for 8 weeks improved glycemic control and insulin resistance in patients with type 2 diabetes. The compounds of ginger, gingerol and shogaol, inhibit α-amylase and

α-glucosidase, stimulate insulin secretion, and decrease reactive oxygen species in pancreatic β cells [16], all of which may result in improved glycemic control. Furthermore, the beneficial effects of ginger could be attributable to peroxisome proliferator-activated receptor-γ agonistic activity and adiponectin secretion [17]. Ginger supplementation may be beneficial for glucose homeostasis in patients with type 2 diabetes. Urquiaga et al. [18] speculated that wine grape pomace flour, which is abundant with antioxidants and fiber, key nutritional components of the Mediterranean diet, conducted an RCT to evaluate the effect of wine grape pomace flour on metabolic syndrome. Thirty-eight male subjects, 13 subjects in the control group and 25 subjects in the intervention group, completed the study. Three subjects in the control group and 6 subjects in the intervention group dropped out of the study. The mean age and BMI of the controls were 43.1 ± 8.4 years and 27.9 ± 3.5 kg/m^2, respectively. The mean age and BMI of the subjects in the intervention group were 44.5 ± 9.3 years and 29.1 ± 3.9 kg/m^2, respectively. No significant differences in clinical characteristics between the groups were observed. Subjects in the intervention group took 20 g of wine grape pomace flour per day, which contained 822 mg of polyphenol and 10 g of dietary fiber. After 16-week administration of wine grape pomace flour, fasting blood glucose levels (from 92.7 ± 5.8 mg/dl to 89.4 ± 7.9 mg/dl) and systolic (from 127.1 ± 11.5 mmHg to 122.8 ± 8.5 mmHg) and diastolic (from 79.7 ± 8.3 mmHg to 74.4 ± 5.6 mmHg) blood pressures significantly decreased in the intervention group, but not in the control group. There were no changes in fasting insulin, postprandial glucose or insulin, insulin resistance evaluated by homeostasis model assessment of insulin resistance, or HbA1c between groups. Serum cholesterol levels also did not change within and between the groups. On the other hand, postprandial insulin levels decreased from baseline in the intervention group in contrast with the increased postprandial insulin levels in controls. In addition, γ-tocopherol (from 1.80 ± 0.74 μM to 2.40 ± 1.36 μM) and δ-tocopherol (from 0.70 ± 0.13 μM to 0.79 ± 0.23 μM) significantly increased, and the carbonyl group in plasma protein significantly decreased (from 0.56 ± 0.18 nmol/mg protein to 0.44 ± 0.19 nmol/mg protein) in the wine grape pomace flour group. The group dependent magnitude of the differences between the initial and final postprandial insulin and γ-tocopherol levels was significant. Wine grape pomace flour contains 52% dietary fiber, and 4.4% of polyphenols have antioxidant capacity of 362.9 ORAC (Oxygen Radical Absorbance Capacity) (μmol TE/g (TE：Trolox Equivalent) dry matter). Previous studies have shown that dietary fiber lowers blood glucose, blood pressure, and obesity and improves the lipid profile and insulin resistance, all of which lead to CVD risk reduction [19–21]. The intake of fiber was estimated to be approximately 30 g per day by supplementation with wine grape pomace flour, which had beneficial effects on blood pressure and glucose homeostasis. Furthermore, the increase in γ-tocopherol by supplementation with wine grape pomace flour suggests that oxidative stress could be attenuated by this product. However, 31 participants reported adverse effects due to consumption of wine grape pomace flour; e.g., increased intestinal gas, constipation, and regularization of intestinal transit. The tolerability of wine grape pomace flour is open to question. Further investigations on the safety and efficacy of wine grape pomace flour for glucose homeostasis in

patients with type 2 diabetes, as well as in subjects with metabolic syndrome, are required. Table 2 summarizes RCTs reporting the beneficial effects of functional foods on diabetes.

Table 2. RCTs reporting beneficial effects of functional foods on diabetes.

Authors, year	Subjects (control vs. intervention)	Functional foods	Adverse effects	Results
Bhatt et al., 2012 [10]	57 patients with type 2 diabetes Age: 56.67 ±8.91 years vs. 57.75 ±8.71 years Sex (Men/Women): 9/20 vs. 12/16 BMI: 24.92 ±3.05 kg/m^2 vs. 24.66 ±3.57 kg/m^2 HbA1c: 8.75 ±1.56% vs. 9.99 ±1.50%	Resveratrol: 250 mg/day for 3 months	No description	Fasting blood glucose↓, HbA1c↓, systolic blood pressure↓, diastolic blood pressure↓, total cholesterol↓, and low-density lipoprotein cholesterol↓
Kodama et al., 2005 [13]	18 patients with mild type 2 diabetes Age: 56.0 ±3.91 years vs. 55.9 ±2.79 years Sex (Men/Women): 4/1 vs. 11/2 BMI: No description (Weight: 66.0 ±2.32 kg vs. 68.7 ±3.89 kg) HbA1c: Not described in detail	Wheat albumin: 0.5 g at three daily meals for 3 months	One subject: constipation	Fasting blood glucose→, HbA1c↓
Shidfar et al., 2015 [14]	45 patients with type 2 diabetes Age: 47.1 ±8.31 years vs. 45.2 ±7.64 years Sex (Men/Women): No description BMI: 29.2 ±3.1 kg/m^2 vs. 29.5 ±2.8 kg/m^2 HbA1c: 7.39 ±1.31% vs. 7.37	Ginger: 3 g/day for 3 months	No description	Serum glucose↓, HbA1c↓, insulin↓, HOMA-R↓, high-sensitive c-reactive protein↓, paraoxonase-1↑, total antioxidant capacity↑, and malondialdehyde↓

	±1.86%			
Urquiaga et al., 2015 [18]	38 male subjects, 23% of subjects in the control group and 32% of subjects in the intervention group had metabolic syndrome Age: 43.1 ±8.4 years vs. 44.5 ±9.3 years Sex (Men/Women): 13/0 vs. 25/0 BMI: 27.9 ±3.5 kg/m^2 vs. 29.1 ±3.9 kg/m^2	Wine grape pomace flour: 20 g/day for 16 weeks	Increased intestinal gas, heartburn, constipation, regularization of intestinal transit, soft stools, increased appetite, dyspepsia, gastroesophageal reflux	Fasting blood glucose↓, systolic blood pressure↓, diastolic blood pressure↓ postprandial insulin↓, and γ-tocopherol↑

RCT = randomized controlled trial; BMI = body mass index; HbA1c = hemoglobin A1c; HOMA-R = the homeostasis model assessment of insulin resistance

3.2. RCTs reporting no significant effects of functional foods on diabetes

The above-referenced RCTs reported some beneficial effects of functional foods on diabetes; however, the other seven trials unfortunately could not find any favorable effects of functional foods on diabetes as their primary outcome.

Evans et al. [50] investigated the efficacy of Diabetinol® (a 525 mg capsule including citrus flavonoids, limonoids, tocotrienols, and vitamin E) as an adjunctive therapy in patients with diabetes. This randomized, double-blind, placebo-controlled, parallel study enrolled fifty subjects. Thirty four subjects completed the trial. Five subjects in the Diabetinol® supplementation group were dropped out because of adverse effects such as diarrhea, liver dysfunction, and gastric complications. After 24 weeks of supplementation, no significant changes in fasting and 2-hour post prandial blood glucose, insulin, and HbA1c levels were observed. The lipid profile in the Diabetinol® supplementation group appeared to be improved compared to the placebo group; however, the difference between the groups was not significant. Citrus flavonoids have anti-inflammatory and antioxidant properties, whose supplementation is expected to be beneficial for the treatment of diabetes [51]. Experimental studies have shown that citrus flavonoids improve dyslipidemia and insulin sensitivity [52], and increase GLUT4 expression [53]. These evidence suggest that Diabetinol® is a promising functional food for the treatment of diabetes; however, it was not effective in a real world setting. Marett and Slavin [22] conducted a 6-month randomized, double-blind, parallel trial to examine the effect of supplementation with arabinogalactan on serum lipids and glucose in healthy individuals. A total of

54 subjects (28 men and 26 women) completed the trial. The mean age of the subjects was 29 years. Subjects were randomly assigned to a larch arabinogalactan group (n = 18), a tamarack arabinogalactan group (n = 19), and a placebo rice starch group (n = 17). Subjects consumed 8.4 g per day of placebo or arabinogalactan for 6 months. No significant differences in age, BMI, diet, kilocalories, nutritive ratio of carbohydrate, protein, fat, cholesterol, or soluble or insoluble fiber among the larch arabinogalactan, tamarack arabinogalactan, and placebo groups were found. After 6 months of intervention, no significant changes in triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, apolipoprotein A, or apolipoprotein B were observed among the three groups. Serum glucose levels significantly decreased compared with the baseline levels in all groups, but all values were within normal ranges. No remarkable differences in adverse effects among the diets were observed, although the occurrence of flatulence increased one month after both larch arabinogalactan and tamarack arabinogalactan administration. Supplementation with arabinogalactan had no effects on weight, blood pressure, serum glucose, lipids, or insulin. The authors stated that the 6–8 week study duration to assess the effect of a treatment on lipid profile might be short. Dietary intervention including supplementation with functional foods may transiently affect serum glucose and lipids; however, the human body adapts to the intervention over time. This statement is highly suggestive. Most clinical studies regarding functional foods and health have a short duration or are completed within a few days because the studies simply examine metabolic responses to the administration of functional foods. Lee et al. [23] assessed the effect of low-fat milk on endothelial function and oxidative stress as well as metabolic risk factors in Korean adults with metabolic syndrome. Subjects who had a history of CVD, were taking hypoglycemic agents, or with HbA1c levels over 7.0% were excluded. Sixty-six subjects were included and randomly allocated to the control (n = 33) or the low-fat milk group (n = 33); however, two subjects dropped out of the low-fat milk group, and 6 subjects were excluded due to not complying with the study rules. Subjects in the low-fat milk group consumed 400 ml per day of low-fat milk for 6 weeks. A total of 58 subjects completed the study protocol. The mean age and BMI of the controls were 45.9 ± 9.0 years and 27.4 ± 3.2 kg/m^2, respectively. The mean age and BMI of the low-fat milk group were 50.4 ± 8.6 years and 28.1 ± 2.6 kg/m^2, respectively. In the low-fat milk group, weight, BMI, and blood urea nitrogen levels significantly increased after 6-week low-fat milk consumption, although no significant changes in blood pressure, glycemic control, or insulin sensitivity were detected. Serum E-selectin, interleukin-6, and oxidized low-density lipoprotein levels increased, but urine malondialdehyde levels decreased. In the control group, waist circumference and urine malondialdehyde levels decreased, whereas serum soluble intercellular adhesion molecule-1 levels increased. The change in blood urea nitrogen levels was significant between groups; however, none of the changes of other parameters showed a significant difference. Supplementation with low-fat milk for 6 weeks did not show a beneficial effect on metabolic health including glycemic control. The authors performed a subgroup analysis and stated that regular intake of low-fat milk may be beneficial for biomarkers of atherosclerosis in subjects with hypertension and hypertriglyceridemia;

however, this was only a sub-analysis. Low-fat milk does not have a favorable effect on diabetes. Chang et al. [24] developed functional yogurt NY-YP901 (Namyang Dairy Product Co. Ltd and Nutra R&BT Inc.) supplemented with a mixture of Streptococcus thermophilus, Lactobacillus acidophilus, Bifidobacterium infants, and various functional ingredients. They investigated whether this functional yogurt had beneficial effects on blood pressure, blood glucose and lipid profiles. The study design was an 8-week randomized, double-blind, placebo-controlled, parallel study. Subjects with medication such as anti-hypertensive drugs, lipid lowering drugs, oral hypoglycemic agents, or insulin were excluded. Subjects with obesity, apparent hypertension or diabetes were also excluded. A total of 101 subjects completed the study protocol. Fifty-three subjects (16 men and 37 women) in the treatment group consumed the functional yogurt NY-YP901 (150 ml) twice per day for 8 weeks. The mean ages of subjects in the functional yogurt group and the control group were 36.45 ± 9.92 years and 37.16 ± 8.89 years, respectively. Weight (−0.24 ± 1.50 kg) and BMI (−0.10 ± 0.58 kg/m^2) significantly decreased in the functional yogurt group compared to those of the control group. However, no significant differences in blood pressure, fasting blood glucose, or HbA1c within or between the groups were found. After 8-week functional yogurt consumption, low-density lipoprotein cholesterol decreased in the functional yogurt group, and the difference of this change between groups was significant. The cholesterol lowering effect of functional yogurt NY-YP901 is presumed to be due to YQ-2, fibersol-2, and the pine tree leaf extraction solution in the functional yogurt used in this study. However, the functional yogurt did not have a favorable effect on diabetes. Ebrahimi-Mamaghani et al. [25] evaluated the effects of raw red onion on metabolic parameters in overweight or obese women with polycystic ovary syndrome. A total of 54 subjects were randomly assigned to the high-onion-consumption group (n = 27) or the low-onion-consumption group (n = 27). Subjects who suffered from diabetes, hypertension, or endocrine disorders affecting metabolic parameters were excluded before randomization. The high-onion-consumption group received their usual diet plus raw red onions (80-100 g per day for overweight subjects and 100-120 g per day for obese subjects). Subjects in the high-onion-consumption group consumed raw red onions with lunch and dinner for 8 weeks. The control low-onion-consumption group received their usual diet plus fewer raw red onions (20–30 g per day) compared with the high-onion-consumption group for 8 weeks. The dietary intake of subjects in each group was measured using a 3-day food record, and no significant difference between the groups was found. The mean age and BMI of the subjects in the high-onion-consumption group were 26.44 ± 5.93 years and 31.27 ± 3.90 kg/m^2, respectively, whereas those of the low-onion-consumption group were 26.70 ± 5.58 years and 30.83 ± 3.92 kg/m^2, respectively. Four (three in the high-onion-consumption and one in the low-onion-consumption group) out of 54 subjects had impaired fasting glucose. After the 8-week treatment, total cholesterol and low-density lipoprotein cholesterol levels significantly decreased in both the high- and low-onion-consumption groups, but no significant difference between the groups was observed. For fasting blood glucose levels, no significant difference was observed within or between the two groups. However, when a further analysis subdividing subjects into with and without insulin

resistance was performed, total cholesterol (weighted mean difference: −14.87 mg/dl), low-density lipoprotein cholesterol (weighted mean difference: −11.82 mg/dl), high-density lipoprotein cholesterol (weighted mean difference: −4.83 mg/dl), and fasting blood glucose (−5.58 mg/dl) levels significantly decreased in subjects with insulin resistance. Onion has been indicated to be protective against vascular damage through its cholesterol-lowering effects in rats [26]. This trial suggests that raw red onion may also have a cholesterol-lowering effect in humans. On the other hand, the reason why fasting blood glucose decreased in insulin resistant patients with polycystic ovary syndrome after the 8-week treatment was not well described. The authors speculated that failure to show a hypoglycemic effect of onion in this trial was due to normal glucose levels at baseline in the study population. They described that the hypoglycemic effect of onion may appear in patients with diabetes, as referred to in a randomized crossover study over 30 years ago [27], but not in subjects without diabetes. Thus, a further RCT in patients with type 2 diabetes is warranted to reveal the effect of onion on glucose homeostasis in humans. Faghihzadeh et al. [28] evaluated the effects of resveratrol supplementation on CVD risk factors in patients with non-alcoholic fatty liver disease (NAFLD), which is known to be associated with insulin resistance and type 2 diabetes. Of the 127 recruited patients, 50 patients were randomly assigned to the resveratrol group (n = 25) or the placebo control group (n = 25). Patients with diabetes were excluded from this trial. Study participants received 500 mg of pure trans-resveratrol or placebo for 12 weeks. Both groups were advised to have a balanced diet and to perform exercise for at least 30 minutes, three times per week during the study period. Serum glucose and insulin levels and insulin sensitivity index were established as secondary outcomes. No patient complained of considerable adverse effects during the treatment. Plasma levels of alanine aminotransferase and hepatic steatosis were reduced by resveratrol supplementation. BMI, waist circumference, aspartate aminotransferase, bilirubin, and high-density lipoprotein cholesterol were reduced in both groups, but significant differences between the two groups were not found. No significant changes in glucose, insulin, homeostasis model of assessment of insulin resistance, or a homeostasis model of assessment of β-cell function were observed in either group. The results show that 12-week supplementation with 500 mg of resveratrol in addition to lifestyle modification was not beneficial for insulin resistance in patients with NAFLD. However, the results are controversial for clinical studies investigating the effect of resveratrol on diabetes. Previous studies have shown that resveratrol improves glucose metabolism in humans [10] and in mice [29]. Differences in the characteristics of study participants may strongly affect the results. Because favorable effects of resveratrol on metabolic parameters have been reported mostly in individuals with metabolic abnormalities, Yoshino et al. [30] investigated the metabolic effects of resveratrol in non-obese women with normal glucose tolerance. A total of 45 lean and overweight postmenopausal women were recruited. One subject in the placebo group dropped out. Subjects were randomly assigned to the placebo group (n = 14), the resveratrol supplementation group (n = 15), or the calorie restriction group to achieve a 5% weight loss group (n =15). Subjects in the intervention group received 75 mg per day of resveratrol supplementation for 12 weeks. The mean ages of

subjects in the intervention and placebo groups were 58.2 ± 4.0 years and 59.8 ± 4.3 years, respectively. No adverse effects of resveratrol were detected during the study. After 12-week resveratrol supplementation, all clinical parameters, including body weight, body composition, plasma glucose, insulin, lipids, adiponectin, leptin, c-reactive protein, interleukin-6, homeostasis model assessment of insulin resistance, blood pressure, and resting metabolic rate, did not change. Although a hyperinsulinemic-euglycemic clamp procedure was performed, no effects on basal glucose, fatty acid kinetics, or insulin sensitivity in the liver, adipose tissue, or skeletal muscle were observed. Furthermore, gene expression of potential resveratrol targets such as AMP-activated protein kinase, NAD^+ biosynthesis, NAD^+-dependent protein deacetylase SIRT1, and peroxisome proliferator-activated receptor γ coactivator-1α [31–34] were measured. No effect of resveratrol supplementation on the expression of these genes in skeletal muscle or adipose tissue was observed. Resveratrol also did not affect the biological pathways associated with mitochondrial function and inflammation. This study showed that daily resveratrol consumption, which is equal to the amount of resveratrol contained in 8 liters of red wine, had no metabolic benefits in postmenopausal women with normal glucose tolerance. It is notable that the authors thoroughly investigated the effects of resveratrol supplementation on the plasma concentrations of resveratrol, on insulin sensitivity in skeletal muscle and adipose tissue via hyperinsulinemic-euglycemic clamp, and on the expression of genes related to the putative mechanism of action of resveratrol in humans. The authors also stated that resveratrol may improve metabolic outcomes in only subjects with obesity and type 2 diabetes, but not in subjects without metabolic disorders. However, in subjects with normal glucose tolerance, resveratrol probably has no effects on metabolic parameters. In any case, further investigations are warranted both in subjects with and without diabetes. Table 3 summarizes RCTs reporting no significant effects of functional foods on diabetes.

Table 3. RCTs reporting no significant effects of functional foods on diabetes.

Authors, year	Subjects (control vs. intervention)	Functional foods	Adverse effects	Results
Evans et al., 2015 [50]	34 patients with type 2 diabetes Age: 57.7 ±7.7 years vs. 58.5 ± 13.0 years Sex (Men/Women): 10/9 vs. 7/8 BMI: 35.1 ±4.4 kg/m^2 vs. 34.5 ±	Diabetinol® (nobiletin (49%), tangeretin (13%), limonoids, tocotrienols, and vitamin E)	Diarrhea (n = 3), liver dysfunction (n = 1), and gastric complications (n = 1)	No effects on glycemic control and lipid profile

	7.8 kg/m^2 HbA1c: 7.06 ± 1.49% vs. 7.03 ± 0.80%			
Marett and Slavin, 2004 [22]	54 healthy individuals (larch arabinogalactan group, tamarack arabinogalactan group, and a placebo of rice starch group) Age: Not described in each group Sex (Men/Women): Not described in each group BMI: Not described in each group	Arabinogalactan: 8.4 g/day for 6 months	Flatulence	No effects on weight, blood pressure, serum glucose, lipids, and insulin
Lee et al., 2016 [23]	58 subjects with metabolic syndrome Age: 49.5 ±9.0 years vs. 50.4 ±8.6 years Sex (Men/Women): 15/15 vs. 14/14 BMI: 27.4 ±3.2 kg/m^2 vs. 28.1 ± 2.6 kg/m^2 HbA1c: 5.7 ±0.3% vs. 5.8 ±0.4%	Low-fat milk: 400 ml/day for 6 weeks	No description	Blood urea nitrogen↑ No effects on glycemic control

Chang et al., 2011 [24]	103 healthy individuals Age: 37.16 ±8.89 years vs. 36.45 ± 9.92 years Sex (Men/Women): 15/33 vs. 16/37 BMI: 22.13 ±2.80 kg/m^2 vs. 22.63 ± 3.26 kg/m^2 HbA1c: 5.37 ± 0.27% vs. 5.40 ± 0.32%	Yogurt NY-YP901: 300 ml/day for 8 weeks	No description	Body weight↓, BMI↓ Low-density lipoprotein cholesterol↓
Ebrahimi-Mamaghani et al., 2014 [25]	54 overweight or obese women with polycystic ovary syndrome Age: 26.70 ±5.58 years vs. 26.44 ± 5.93 years BMI: 30.83 ±3.92 kg/m^2 vs. 31.27 ± 3.90 kg/m^2	Raw red onion: 80–120 g/day for 8 weeks	Heart burn (n = 3)	No effects on weight, fasting blood glucose, and lipids in all subjects Fasting blood glucose↓, serum lipids↓ in subjects with insulin resistance
Faghihzadeh et al., 2015 [28]	50 patients with non-alcoholic fatty liver Age: 46.28 ±9.52 years vs. 44.04 ± 10.10 years Sex (Men/Women): 17/8 vs. 18/7 BMI: 28.75 ±3.50 kg/m^2 vs. 28.35 ± 3.49 kg/m^2	Resveratrol: 500 mg/day for 12 weeks	None	Alanine aminotransferase↓ No effects on fating blood glucose and insulin resistance

Yoshino et al., 2012 [30]	29 postmenopausal women with normal glucose tolerance Age: 59.8 ±4.3 years vs. 58.2 ±4.0 years BMI: 24.3 ±2.7 kg/m^2 vs. 24.2 ± 2.8 kg/m^2	Resveratrol: 75 mg/day for 12 weeks	None	No effects on weight, body composition, blood glucose, and insulin sensitivity

RCT = randomized controlled trial; BMI = body mass index; HbA1c = hemoglobin A1c

4. Factors that can Influence Functional Food Consumption

Recently, many consumers believe that functional foods contribute to their health, and the market of functional foods is growing [54]. A cross-sectional study in Belgium showed that higher age, level of education, physical activity, and regular use of vitamin supplements were associated with functional food consumption [55]. This study also suggested that cultural background is one of the predictors of functional food consumption [55]. Ozen and colleagues reported that age, gender, marital status, level of education, BMI, and physical activity were predictors of functional food consumption [56]. In general, older, female, and highly educated individuals are more likely to consume functional foods [55–57]. Moreover, taste is also a main determinant of functional food consumption [54]. Consumers may firstly evaluate functional foods as daily foods. In addition to health benefits, price, product quality, and taste are key factors to increase functional food consumption.

5. Limitation of this Review

Since there is no international standard for the definition of functional foods, searching for the relevant literature using the keyword “functional food” instead of the name of single nutrient may miss a number of published articles. For example, Sauder and colleagues [58] reported that 4-week daily pistachio consumption improved lipid profile in well-controlled type 2 diabetic patients. However, this study was excluded from the review because it was a randomized crossover, not placebo-controlled, trial. The author carefully searched the current literature; however, there is some possibility of missing the relevant studies to review.

6. Conclusion

A number of studies including epidemiological studies and intervention studies have demonstrated that various functional foods are beneficial for the management or prevention of type 2 diabetes. Several RCTs have shown that supplementation with ginger, resveratrol, wheat albumin, or wine grape pomace flour, besides other recognized functional foods, may have beneficial effects on type 2 diabetes. Although controversial results from RCTs exist, a possible explanation is that the effects of functional foods differ depending on study participants' clinical characteristics. Functional foods may have more considerable effects on glucose homeostasis in patients with type 2 diabetes compared to those with normal glucose tolerance. However, the effects of functional foods on type 2 diabetes are still inconclusive because of the small number of subjects ($n < 100$), short duration (< 6 months), high risk of biases, and methodological heterogeneity among studies. Moreover, little evidence is available regarding the cost-effectiveness of functional foods in patients with diabetes. The consumption of effective and safe functional foods has the potential to improve human health, and it also has the potential to be economically beneficial. For example, daily consumption of plant sterol- and stanol-enriched margarine, dairy products, and omega-3 fatty acids was found to be effective in reducing coronary heart disease-related costs [35]. Cost-effective analysis for each functional food and health benefit should be performed. In addition, investigating the effects of functional foods on diabetic complications, health-related quality of life, and mortality is an important issue for the future. Well-designed RCTs with a large number of subjects and a long duration are needed to elucidate the effects of functional foods on type 2 diabetes.

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Conflict of Interest

The author declares no conflict of interest.

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