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Review

Role of different nutraceuticals in the management of type 2 diabetes mellitus (T2DM): a literature review

Md Shahedul Islam*[1]

Molua Akter Moly[1]

Md. Abdus Samad Azad[2]

Mohammad Ariful Islam[3]

Sofiul Alam[1]

Imam Hossain[2]

[1] Department of Food Technology and Nutrition Science, Noakhali Science and Technology University, Noakhali-3814, Bangladesh

[2] Department of Applied Chemistry and Chemical Engineering, Noakhali Science and Technology University, Noakhali-3814, Bangladesh

[3] Department of Biochemistry and Molecular Biology, Noakhali Science and Technology University, Noakhali-3814, Bangladesh

*Corresponding author:
Md Shahedul Islam

shahed.ftns.nstu@gmail.com

Abstract

The objective of this research was to evaluate current knowledge of the role that some nutraceuticals play in the administration of type 2 diabetes mellitus (T2DM) treatment strategies. The information was compiled via an online search of the databases of PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and Google Scholar. Nutraceuticals play a significant part in the prevention and treatment of a wide variety of illnesses and disorders and, as a result, enhance general health and longevity. This article summarises and discusses some of the most notable studies on nutraceuticals used as anti-diabetic agents for T2DM. Table 1 summarises 18 studies involving approximately 21 nutraceuticals. Most of the studies cited suggest that the consumption of various nutraceuticals (such as L-carnitine, myo-inositol, d-chiro, and folic acid twice daily, mulberry flavonoids, and mulberry alkaloids) significantly decrease fasting blood glucose and HbA1c ($p<0.05$). Only a small number of nutraceuticals, including alpha-lipoic acid and resistant dextrin, have been demonstrated to reduce fasting plasma glucose, haemoglobin A1c, and C-reactive protein levels in people with T2DM ($p<0.05$). To better understand the function of diverse nutraceuticals and support evidence-based therapy recommendations, which have already been proven to have a considerable influence on T2DM, further clinical trials with larger sample sizes and appropriate methodologies are required.

Keywords: Nutraceuticals, T2DM, glycaemic control, probiotics, glucose level

Introduction

Although the use of nutraceuticals has a long history, it is only recently that scientifically proven nutritional and clinical evidence has prompted nutraceuticals to appear as potentially beneficial to health [1]. Diabetes mellitus (DM) is characterized by chronic hyperglycaemia and impaired carbohydrate, lipid, and protein metabolism due to inadequate insulin secretion and/or action [2]. Type 2 diabetes mellitus (T2DM) is characterized by two main symptoms: impaired insulin secretion by pancreatic cells and the incapability of insulin-sensitive tissues to respond to insulin [3]. T2DM is the most prevalent type of diabetes, accounting for 90–95% of all incidences [4]. It is anticipated that the number of people living with T2DM will rise to 439 million by the year 2030 [5]. Diabetes is a global epidemic. In 2000, diabetes was estimated to affect 2.8% of the global population; by 2030, it is expected that 4.4% of the population will have diabetes due to demographic ageing and a slow increase in obesity [6]. In 2014, the universal cost of treating diagnosed diabetes was projected to be US$825 bn per year [7].
The worldwide increase in diabetes is mainly a result of the increasing prevalence of T2DM.

Recently, there has been a shift in emphasis towards the use of bioactive chemicals and nutraceuticals as potential preventative measures for degenerative illnesses [7–9]. Nutraceuticals can be derived from any organic food source and can be categorised as one of 24 different types, including fibre, probiotics, prebiotics, antioxidant vitamins, polyphenols, herbs, and polyunsaturated fats [10]. Berries are an excellent source of biologically active chemicals and berry consumption has been investigated in terms of its potential impact on T2DM glucose control in human participants [11–14].

Numerous variables of plasma lipids may benefit from zinc supplementation, according to the findings of prior meta-analyses. This includes a large drop in overall cholesterol, as well as a reduction in levels of LDL and triglycerides [15,16]. There have been very few meta-analyses that explore the benefits of zinc supplementation on the control of hyperglycaemia levels alone. However, several studies have demonstrated that zinc supplementation reduces both fasting glucose (FG) and glycated haemoglobin (HbA1c) [17,18]. However, there is not enough research available at this time to determine whether or not taking zinc supplements is beneficial in the management of diabetes or in preventing the condition [19].

The polyphenol present in red wine – resveratrol – is a potent activator of silent information regulator (SIRT1) [20] via AMP-activated protein kinase (AMPK) activation, albeit indirectly [21]. The scientific community has garnered broad acceptance for polyphenols to address a variety of pathological mechanisms associated with diet and inactivity, including T2DM and its associated risk factors [22, 23].

Certain vitamins have insulinotropic effects (promote insulin release from pancreatic beta cells). For example, vitamins A, D, C, E, and biotin are important insulinotropic agents; nicotinamide is also important [24]. Numerous diterpenes have medicinal properties [25]. Phytochemicals, which are found in plants, have been demonstrated to have positive effects on animal biochemistry and metabolism. These phytochemicals include terpenoids, phenolics, alkaloids, and fibre [26].

Recently, there has been a substantial rise in the study of polyphenols as prospective nutraceuticals and additional treatments for a variety of diabetes-related illnesses. These studies have shown that polyphenol and polyphenolic chemicals obtained from dietary plants may manage sugar and fatty acid metabolism, decrease hyperglycaemia, atherosclerosis, and insulin sensitivity, increase the metabolism of fatty tissue and avoid long-term diabetes-related complications [27].

The food and healthcare industries are now faced with new challenges as a direct consequence of the rapid expansion in the use of phytoconstituents in nutraceutical and functional foods. These new challenges include: addressing worldwide health worries about the efficiency and safety of supplements and food products that are presumed to improve health; enacting legislation on safety, labelling, and potential health benefits for products containing phytochemical constituents in government legislation [28].

Methods

Literature data sources

The databases PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and Google Scholar were searched up to June 2020.

Study selection

The focus of this research was to find randomized control studies that are correlated to interventions of various nutraceuticals and their role on T2DM management. One clinical trial, one experimental animal study, one intervention-based pilot study and one systematic article were also included in this research.

Data extraction

Data and information strongly related with the effect of various nutraceuticals on the management of T2DM and their mechanism of action were extracted for this study.

Role of various nutraceuticals in type 2 diabetes management

Table 1: Summary of the function of typical nutraceuticals in the maintenance of T2DM

Study Reference	Study Site	Nutraceuticals/Intervention	Study Duration	Type of Study Design	Research Findings
[29]	Australia	Curcumin and/or fish oil	12 weeks	Double-blind randomized controlled trial	A decrease in the prospect of development T2DM in those who have prediabetes.
[30]	Iran	500mg propolis, three times/day	8 weeks	Double-blind randomized controlled trial	The scavenging enzymes glutathione peroxidase (GPx) and superoxide dismutase (SOD) increased significantly (p<0.05) after propolis administration.
[31]	US	Vegetarian diet: 10% fat, 15% protein, 75% carbohydrate. Conventional diet: 7% saturated fat, 15–20% protein, 60–70% carbohydrate	74 weeks	Randomized controlled clinical trial	The vegetarian diet was associated with a 13.5mg/dL decrease in LDL cholesterol, whereas the conventional diet was associated with a 3.4mg/dL decrease (p= 0.03).
[32]	Canada	Intervention: flaxseed oil Placebo: safflower oil	3 months	Double-blind randomized controlled trial	Ingestion of flaxseed oil showed no effect on the levels of glucose, insulin, or HbA1c in the blood when fasting.
[33]	UK	Intervention: 250mg/day resveratrol	3 months	Clinical trial	T2DM patients using resveratrol had higher mean A1c haemoglobin (9.99 ± 1.50 vs 9.65 ± 1.54; p<0.05) and total cholesterol (4.70 ± 0.90 vs 4.33 ± 0.76; p<0.05).
[34]	Iran	Control and intervention: 10g/day maltodextrin and oligofructose-enriched inulin, respectively	8 weeks	Randomized controlled clinical trial	The inulin-enriched oligofructose group had no significant differences in interferon-g, high-sensitivity C-reactive protein, or interleukin-10 levels compared with the maltodextrin group.
[35]	German	Intervention: 7.5g insoluble fibre Placebo: 0.8g insoluble fibre twice daily	2 years	Randomized controlled optimal fibre trial	Gender analysis showed that women in the intervention group had a higher drop in glycated haemoglobin and 2-h glucose levels.
[36]	Italy	Intervention: alpha-lipoic food supplement Control Group: placebo	3 months	Randomized controlled clinical trial	The dietary supplement containing alpha-lipoic acid caused in a significant decrease in FPG, LDL-C, Hs-CRP, PPG, and HbA1c compared with the intervention and the placebo (p<0.05).
[37]	China	Intervention: 360mg lignin-derived flaxseed/day Placebo: rice flour equivalent	12 weeks	Double-blind placebo-controlled trial	Supplementation with lignin resulted in CRP increases that were significantly lower than in the placebo group (p=0.021).
[38]	India	G-400 (1000mg/day) polyherbal combination drug to the intervention group	10 weeks	Randomized controlled clinical trial	After 8 weeks of G-400 treatment, patients' dieting and post-prandial blood sugar levels were significantly lower (p<0.05), and diabetic rats displayed consistent safety.
[39]	Iran	300mg of gel aloe vera every 12 hours for the intervention group	2 months	Double-blind randomized controlled trial	Aloe leaf gel significantly reduced fasted hyperglycaemia and glycated haemoglobin (p=0.041 and p=0.023, respectively).
[40]	Iraq	Coenzyme Q10 (150mg/day), and L-carnitine (1g/day) to the intervention group	8 weeks	Single-centre randomized controlled trial	When compared with baseline, L-carnitine administration significantly reduced fasting blood glucose (p<0.05). Q10 did not significantly reduce FBG or HbA1c (p<0.05) compared with the control group.
[41]	Italy	550mg myo-inositol, 13.8mg d-chiro, and 400mcg folic acid twice/day	3 months	Intervention-based pilot study	Fasting blood glucose (p=0.02) and HbA1c significantly decreased after three months of therapy.
[42]	Iran	Control group got 10g/day of maltodextrin, while the intervention group received 10g of resistant dextrin per day.	8 weeks	Randomized controlled clinical trial	The maltodextrin industry did not seem concerned with the decreases in FPG, HbA1c, or hs-CRP, which was shown in resistant dextrin.
[43]	China	An intervention group was administered 600mg/kg mulberry flavonoids (MF), 400mg/kg mulberry polysaccharides (MP), and 200mg/kg mulberry alkaloids (MA)	6 weeks	Experimental animal study	MF and MA had the most hypoglycaemic impact on fasting blood glucose (FBG). MF and MP lowered urine microalbumin/creatinine due to renal damage. MF and MA reduced alanine and aspartate aminotransferases, which indicated liver injury. Mulberry leaf components prevent liver and kidney damage and lower blood sugar.
[44]	Italy	The intervention group was administered 588/108mg Berberis aristata/Silybum marianum, and metformin to the control group for six months	6 months	Double-blind randomized controlled trial	Berberis aristata and metformin lowered glycated haemoglobin (p<0.05). FPG and PPG showed similar results (p<0.05 and p<0.01, respectively). FPI and HOMA-IR decreased (p<0.05). Berberis aristata outperformed metformin on TC, LDL-C, and Tg (p<0.05).
[45]	Egypt	Individuals in the control group were given metformin pills, and Nigella sativa (NS) oil capsules (1350mg/day) were given to the intervention group	3 months	Double-blind randomized controlled trial	NS treatment in recently diagnosed T2DM patients did not reduce FBG, 2hpp, or A1C as well as metformin. NS reduced weight, WC and BMI as well as metformin. Fast insulin, %S, IR, ALT, TC, LDL, HDL, TG, and TAC were similar for NS and metformin. Metformin increased AST and creatinine in NS group alone.
[46]	Brazil	Mixed dosage and variety of berries by oral administration	8–12 weeks	Systematic review	For 8–12 weeks, T2DM patients' glucose control improved with 240mL of cranberry juice and 9.1–9.8mg of blueberry powder anthocyanins.

Type 2 diabetes management using various nutraceuticals

Curcumin with L-Omega-3 PUFA

Curcumin and insulin have been used in separate therapies to lower blood sugar and biochemical markers for liver and kidney damage, improve profiles of lipids and increase levels of hepatocytes antioxidants [47]. Curcumin treatment among diabetic rats was shown to reduce hyperglycaemia and vascular inflammation and lipid peroxidation [48]. Montori *et al.* discovered in a meta-analysis that supplementing with fish oil reduces TG, LDL and cholesterol levels in individuals with T2DM without affecting glycaemic control [49, 50].

Low-calorie food

Traditionally recommended low-calorie diets for treatment of T2DM often have a maximum of 30% of their calories from fat [51]. These low-fat diets were advised to maintain normal body weight. However, they had no effect on plasma triacylglycerol levels or glycaemic control [52, 53]. Excessive consumption of higher-fat dairy products was linked to lower incidences of T2DM; consumption of both low- and high-fat meats was linked to higher incidences of TSDM [54]. When compared with the regulator group, females who followed a low-calorie diet did not have a lower incidence of diabetes [55]. The type of fat consumed is more significant (p<0.05) than overall fat consumption [56].

Vitamin C

Hyperglycaemia and altered glucose metabolism can result from oxidative stress. Therefore, it is scientifically conceivable that antioxidants can prevent diabetes or improve the biomarkers for people with T2DM [57]. According to research, people with T2DM who consume additional vitamin C regularly may benefit from lower blood sugar and lipid levels, which helps to reduce the complications associated with diabetes [58]. Additional research findings point to a preventative function for dietary vitamin C in the onset of T2DM. In studies where the dietary amount of vitamin C was higher, the risk of acquiring diabetes was reduced by approximately 5% [58].

Flaxseed oil

Recent research suggests that replacing fish oil with flaxseed oil may lower insulin sensitivity in people with diabetes and prediabetes and lessen the chance of developing T2DM or type 1 diabetes in vegetarians [59]. Additional research revealed that taking flaxseed supplements reduced insulin resistance. Dramatically, flaxseed supplementation decreased the HOMA-IR index even though plasma insulin levels did not change appreciably [60]. In contrast, separate research indicated that all flaxseed – not just flaxseed oils or flavonoid extract – had a significant effect on glycaemic control [61].

Alpha-lipoic acid supplements

Alpha-lipoic acid (ALA) impacts the primary connections in the aetiology of diabetes problems and is a widely prescribed medication for treating and preventing diabetic complications [62]. Research shows that a nutritional supplement including ALA, L-carnosine, zinc, and group B vitamins improved lipid profiles, anti-oxidative anxiety indicators, and blood glucose control [36]. An earlier investigation found that patients with persistent spinal cord injuries who received 600mg of ALA daily had lower BMI and fasting blood sugar levels [63]. Following the administration of ALA to stroke patients, one meta-analysis revealed noticeably lower serum glucose levels [64]. The peripheral insulin sensitivity of diabetic persons with T2DM was improved by ALA according to the findings of another study [65].

Oligofructose

Previous studies on the consequences of long-term fructo-oligosaccharides intake on plasma glucose and lipid concentrations in individuals with T2DM showed mixed results [66, 67]. Specifically, individuals with T2DM who consumed 15g of fructo-oligosaccharides daily for 20 days did not experience any noteworthy fluctuations in their plasma sugar or cholesterol levels [67]. In line with this, research on administering a daily 20g of fructo-oligosaccharides to individuals with T2DM for four weeks resulted in no changes in their insulin levels, FBG, or basal hepatic glucose production [66]. On the contrary, results showed that FBG and blood total count (TC) levels significantly decreased after consuming 8g of fructo-oligosaccharides per day for 14 days [68].

Aloe vera leaf

Some research reports that aloe vera can improve cells' sensitivity to insulin while lowering blood sugar and insulin levels in serum and may also boost pancreatic beta cells' insulin genetics activity. Aloe gel controls T2DM by reducing insulin resistance and enhancing glycaemic control [69]. A study by Hasani-Ranjbar *et al.* found that aloe gel helps to maintain better glucose control in individuals with T2DM while having no negative effects on lipid profiles, the liver, kidneys or other organ systems [70]. The improved glycaemic control is consistent with the earlier studies [71, 72].

Fibre supplementation

One of the most useful nutritional elements for preventing diabetes is dietary fibre. People with impaired glucose tolerance who received insoluble dietary fibre supplements for one year reported a substantial improvement in their glycated haemoglobin and 2h glucose levels and a 42% reduction in the risk of developing T2DM in females [73]. Large prospective cohort study findings conclusively show that emerging T2DM and insulin resistance (IR) may be reduced by 20–30% by consuming a lot of wholegrain foods or insoluble cereals rich in cereal fibres [74–76].

G-400, polyherbal

Extracts of the herb *Gymnema Sylvestre* have been shown to demonstrate a substantial decrease in sugar levels, glycated matrix proteins, and haemoglobin A1c (HbA1c) in individuals with diabetes, improving glucose metabolism, decreasing insulin resistance, boosting insulin production, and lowering blood glucose levels [77]. Studies show that plasma insulin levels are considerably higher after G-400 treatment compared with diabetes control by FBG [78]. Diabetes-related biochemical alterations, such as blood glucose level, HbA1c, triglyceride profiles, liver and renal function evaluations were improved following eight weeks of G-400 supplementation. HbA1c, also referred to as glycosylated haemoglobin, is used in this study as a measure of long-term glycaemic management [79]. The therapeutic properties of *Phyllanthus emblica* extract as an antioxidant and anti-diabetic in rat studies revealed modifications in the countenance of genes associated to glycolysis and gluconeogenesis, DNA damage, and increased glutathione peroxidase activity. Blood glucose levels were also much lower [79].

L-Carnitine and coenzyme Q10

L-carnitine supplements may help in the management of T2DM by stabilising lipid and glycaemic profiles, decreasing HbA1c levels, triglyceride levels, and FG levels three months after the start of the treatment [80]. However, a comprehensive review involving four trials totalling 284 patients showed no significant changes in triglycerides, lipoprotein(a), or HbA1c after oral L-carnitine therapy for fasting plasma glucose [81].

Coenzyme Q10 may enhance glycaemic control, according to a comprehensive appraisal and meta-analysis of its impacts on individuals with T2DM (decreasing the HbA1c and FBG) [82].

Flaxseed-derived lignin

A supplement containing lignin from flaxseeds was shown to have a positive effect on T2DM by moderately reducing glycated Hb levels [82]. A further study revealed that flax-seed-derived lignan complex supplementation for 12 weeks significantly reduced glycated haemoglobin concentrations in individuals with T2MD – although, the results showed no changes in the homeostasis model, serum glucose, insulin sensitivity or blood lipid profiles [83]. Animal models also showed that the flaxseed lignan secoisolariciresinol diglucoside (SDG) can postpone or stop the onset of T2DM [84, 85]. In the supplemented group who also had a diet high in flaxseed, lignin was linked to decreased fasting blood glucose levels. This finding would suggest that the seed increases glucose absorption by enhancing insulin sensitivity [86].

Myo-inositol and D-chiro inositol

In animal experiments, the chemical messenger is dependent on myo-inositol modulate blood sugar intake while increasing the function of glucose carrier proteins, whereas chemical messengers based on d-chiro-inositol enhance glycogen formation [41]. After three months of treatment with 2g myo-inositol plus 200µg folic acid twice a day, the results of pilot research were evaluated, including a sequential sample of T2DM patients' fasting blood sugar and HbA1c levels [87]. Myo-inositol dosages were revealed to be particularly effective in lowering the danger of developing diabetes in expecting women with a family history of T2DM [88]. In post-menopausal women, pregnant women, and young females with polycystic ovary syndrome, inositol supplementation has been shown to progress ovulatory function, insulin sensitivity, and fasting blood sugar levels [89, 90].

Blueberry and cranberry consumption

Extracts of blueberry and cranberry were used in a model of T2DM to stimulate the mobilisation of the type 4 glucose (GLUT4) carrier. This resulted in the restoration of glucose utilisation in muscle tissue and adipose cells [91]. According to one review on berries and T2DM, eating berries may reduce insulin resistance [92]. Results showed that consuming blueberries or cranberries lowered fasting blood sugar and glycated haemoglobin in individuals with T2DM but had little to no impact on insulin resistance [46]. According to the findings of another research, the consumption of blueberries and cranberries was beneficial in regulating glucose values in the treatment of T2DM [93].

α-Keto acids

The biological role of 'ammonia shuttle' or 'ammonia catcher' in keto acids (KAs), which are structural analogues of amino acids, allows them to potentially influence ammonia metabolism during physical activity. Using KAs allows individuals with T2DM to exercise longer and more intensely, resulting in a greater training effect and better glucose regulation [94]. KAs help in the management of T2DM by significantly lowering hyperlipidaemia and blood glucose levels. [95].

Mulberry leaves

Mulberry leaves (ML) contain 1-deoxynojirimycin (DNJ), a glucose analogue that inhibits glucosidase to reduce postprandial blood glucose levels [96]. Youl *et al.* demonstrated that the quercetin found in ML increased insulin secretion and decreased oxidative damage in rat pancreatic islets exposed to H2O2 [97].

Similarly, isoquercetin treatment for five weeks decreased levels of glucose in the blood in KK-Ay animal models of noninsulin-dependent diabetes. Oral treatment of ML increased glucose tolerance in db/db animal obesity/T2DM models, demonstrating an influence of ML on insulin production in the pancreas [98].

Berberis aristata

Bioactive constituents in Berberis aristata include alkaloids, such as berberine. Berberine and its in vivo metabolite, berberrubine, upregulate LDL receptors and PCSK9 transcription through the ERK signalling pathway [99]. Many studies have shown Berberis aristata's effects on hyperinsulinemia and insulin sensitivity [100]. After three months of daily intake, Berberis substantially decreased low-density lipoprotein, total cholesterol, fasting plasma glucose, and the homeostasis model assessment score compared with the placebo, but its effects on high-density lipoprotein, triglycerides, and body mass index were not statistically significant [101].

Nigella sativa oil

The extractive of this plant contains thymoquinone (TQ), thymohydroquinone (THQ), dithymoquinon, and thymol [102]. Thymoquinone, a bioactive molecule that protects against diabetes, is responsible for NS's therapeutic actions [103]. Thymoquinone decreased FBG and increased insulin levels in rats, according to previous research [104]. NS considerably lowered FBG in a recent comprehensive review and meta-analysis of randomized controlled trials, however lipid profile alterations were contentious [105].

Conclusion

Nutraceuticals are associated with a reduced development of insulin or with resistance to its action. Plants have historically been used to treat insulin-dependent and non-insulin-dependent diabetes. All the nutrients examined in this research have been shown to have excellent clinical and pharmacological benefits in the treatment of T2DM. This current study confirms these findings. Any adverse effects recorded in the reviewed studies were, for the most part, mild. It would therefore seem appropriate to consider the use of a few distinct nutraceutical agents as supplementary therapy in the management of T2DM. Demand for natural products with anti-diabetic activity is increasing. However, to better understand and improve the function of various nutraceuticals and support evidence-based therapeutic recommendations further clinical tests using substantial sample sizes and adequate methodologies are necessary.

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Conflict of interest

The writers declare no conflicts of interest in their study.

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