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## Functional foods-based diet as a novel dietary approach for management of type 2 diabetes and its complications: A review

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### Abstract

Type 2 diabetes is a complicated metabolic disorder with both short- and long-term undesirable complications. In recent years, there has been growing evidence that functional foods and their bioactive compounds, due to their biological properties, may be used as complementary treatment for type 2 diabetes mellitus. In this review, we have highlighted various functional foods as missing part of medical nutrition therapy in diabetic patients. Several *in vitro*, animal models and some human studies, have demonstrated that functional foods and nutraceuticals may improve postprandial hyperglycemia and adipose tissue metabolism modulate

carbohydrate and lipid metabolism. Functional foods may also improve dyslipidemia and insulin resistance, and attenuate oxidative stress and inflammatory processes and subsequently could prevent the development of long-term diabetes complications including cardiovascular disease, neuropathy, nephropathy and retinopathy. In conclusion available data indicate that a functional foods-based diet may be a novel and comprehensive dietary approach for management of type 2 diabetes.

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**Key words:** Type 2 diabetes; Insulin resistance; Functional foods; Whole grain; Legumes; Nuts; Fruits; Herbs or spices; Vegetables; Prebiotics; Probiotics

**Core tip:** Medical nutrition therapy (MNT) is a main part of type 2 diabetes management. Apparently the therapeutic and medicinal properties of foods maybe a missing step during MNT process, and could enhance the effectiveness of dietary management of type 2 diabetes.

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### INTRODUCTION

Type 2 diabetes is a metabolic disorder characterized by hyperglycemia, developing insulin resistance,  $\beta$ -cell dysfunction and impaired insulin secretion<sup>[1,2]</sup>. Multiple metabolic disorders including impaired lipid and lipoprotein metabolism, oxidative stress (over production of free

radicals and defect in endogenous antioxidant defense system), sub-clinical inflammation, vascular endothelial dysfunction and hypertension are commonly accompanied by type 2 diabetes<sup>[3-5]</sup>; these metabolic disorders lead to long-term pathogenic conditions such as micro- and macro-vascular complications including neuropathy, retinopathy, nephropathy, and a decreased quality of life and an increased mortality rate<sup>[6,7]</sup>.

Despite availability of many pharmacological interventions including oral hypoglycemic agents and insulin therapy for diabetes management, current evidence shows an alarming rising trend in the occurrence of undesirable complications among these patients<sup>[1]</sup>.

Medical nutrition therapy (MNT) is also a main part of type 2 diabetes management; estimation of energy and nutrients requirements, carbohydrate counting as well as glycemic index and glycemic load, recommendation for dietary fats and cholesterol and protein intakes, explanation the foods exchange list for patients and common important recommendations for a healthy diet are the main components of diet planning in type 2 diabetic patients<sup>[8,9]</sup>; however it is not clear whether this approach *per se* is sufficiently adequate for prevention of long-term complications of diabetes. Administration of various supplements, including antioxidant vitamins, fibers, ω<sub>3</sub> fatty acids, numerous nutraceuticals, and herbs has also been proposed for glycemic control but data available supporting these recommendations for diabetic patients are insufficient<sup>[10-14]</sup>. Apparently the therapeutic and medicinal properties of foods maybe a missing step during MNT process, and could enhance the effectiveness of dietary management of type 2 diabetes.

During the past two decades, the concept of functional food is fast expanding; functional foods beyond the basic nutritional functions have potential benefits to promote health and reduce the risk of chronic diseases and have hence been given much attention<sup>[15,16]</sup>. In recent years, researchers have focused on properties of the bioactive compounds of functional foods in the control of various aspects of diabetes mellitus; some protective effects of these compounds and food sources have been investigated *in vitro* and *in vivo*, and several clinical trials have even confirmed these advantages in diabetic patients<sup>[17-19]</sup>.

Here, based on the multiple biological properties of functional foods and their bioactive compounds, a functional foods-based diet has been hypothesized as a novel and comprehensive dietary approach for management of type 2 diabetes and prevention of long-term complications.

## RESEARCH

The evidence cited in this review was obtained through searches in PubMed, Scopus, and Google scholar using the following key words: “Type 2 diabetes or hyperglycemia”, “insulin resistance”, “cardiovascular disease”, “obesity”, “metabolic syndrome”, “oxidative stress”, “inflammation”, “long-term diabetic complications” in combination with “functional foods”, “nutraceuticals”, “bio-

active food compounds”, “fiber”, “polyphenols”, “whole grain”, “legumes”, “nuts”, “fruits”, “herbs or spices” “vegetables”, “prebiotics”, “probiotics”, and “bioactive peptides”. Relevant articles of acceptable quality were used. Briefly, in this article we tried to highlight some of the following important functional foods including whole grains, phytochemical-rich fruits and vegetables, legumes, nuts, dairy products, green tea and some spices, as required components of a health-promoting diet for diabetic patients.

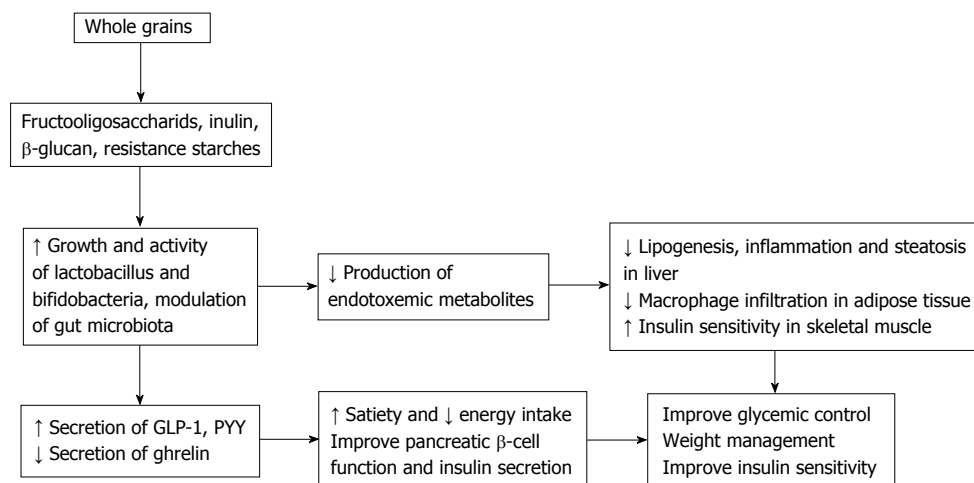
### Whole grains

Grains and cereal-based products are the basic sources providing energy and carbohydrate in human diets. Since the dietary carbohydrate sources in type 2 diabetic patients play a determining role in glycemic and insulin secretory response, the use of functional grains including whole grain cereals, and bakery products prepared using whole wheat, rye, oat, and barley is the first step in planning of a functional foods-based diet.

Some previous studies report that dietary carbohydrate modification in patients with metabolic syndrome resulted in favorable metabolic consequences especially increased insulin sensitivity, decreased adipocyte cell size, and modulated expression of adipose tissue genes involved in insulin signaling pathways (insulin-like-growth-factor binding protein-5, insulin receptors, hormone-sensitive lipase<sup>[20,21]</sup>).

Compared to refined grains, whole grains (WGs) have more non-digestible complex polysaccharides including soluble and insoluble fibers, inulin, β-glucan, and resistant starches, as well as non-carbohydrate functional components including carotenoids, phytates and phytoestrogens, phenolic acids (ferulic acid, vanilic acid, caffeic acid, syringic acid, *P*-cumarinic acid), and tocopherols. The most well-known protective effects of whole grain-based products against obesity, type 2 diabetes, cardiovascular diseases, hypertension, metabolic syndrome and various types of cancer, have been attributed to these bioactive compounds<sup>[22-25]</sup>. Among the several mechanisms available in current data regarding the beneficial effects of WGs and cereal-based products in diabetic patients, some of the more important are that bioactive compounds of WGs could effectively regulate glycemic response, increase insulin sensitivity, improve pancreatic β-cell functions and increase insulin secretion<sup>[26,27]</sup>. High contents of inulin and β-glucan, main soluble and fermentable fibers in WGs, in addition to their hypolipidemic and hypoglycemic effects, act as prebiotics in the gut and modulate gut microbiota *via* stimulation of growth and activity of bifidobacteria and lactic acid bacteria<sup>[28,29]</sup>, effects leading to more metabolic responses (Figure 1).

Long-term follow-ups of diabetic patients indicate that higher consumption of whole grain, cereal fiber, bran, and germ were associated with decreased all-cause and cardiovascular disease-cause mortality<sup>[30]</sup>. Epidemiological studies also confirmed that regular consumption of WGs products could modify the main risk factors of atherosclerotic diseases including triglyceride and LDL-C



**Figure 1** Role of prebiotic compounds of whole grains and cereal-based products in modulation of gut microbiota and consequent metabolic effects could lead to better glycemic control.

levels, blood pressure and serum homocysteine levels, as well as vascular functions, and oxidative and inflammatory status<sup>[31]</sup>.

Rye, a widely used grain especially in Northern and Eastern Europe, is considered a functional grain. The high fiber content of rye products decreases digestion and absorption of dietary carbohydrates, and increase metabolites derived from colonic fermentation of the soluble fiber of rye products, including propionic and butyric acids which effectively stimulate secretion of insulin from  $\beta$ -cells; studies have indicated that the bioactive compounds of rye (phenolic acids, tannins, benzoic acid, phenylalanine) derivatives have a similar efficacy with anti-diabetic drugs in insulin secretion<sup>[26,32]</sup>. In one study, the consumption of rye products in the breakfast meal increased colonic fermentation, decreased ghrelin levels and satiety rating in the late postprandial phase after breakfast as well as energy intake at a subsequent lunch meal, and improved acute glucose and insulin responses<sup>[32]</sup>.

Oat meal products have also been investigated as healthy carbohydrate sources for diabetic patients; they are rich sources of soluble fiber especially  $\beta$ -glucan, antioxidants and bioactive compounds including carotenoids, phytic acid, phenolic acids (hydroxycinnamic acids, caffeic acid, ferulic acid), flavonoids and phytosterols<sup>[33]</sup>. Studies show that consumption of oat products improves glycemic, insulinemic, and lipidemic responses in diabetic patients, and act as active ingredient reducing postprandial glycemia<sup>[34,35]</sup>. In diabetic animal models, oat products attenuated hyperglycemia-induced retinal oxidative stress, increased glycogen content of liver, decreased plasma free fatty acids and succinate dehydrogenase activity and inhibited pancreatic  $\beta$ -cell apoptosis as well<sup>[36]</sup>.

The beneficial effects of barley and its by products for diabetic patients are mainly attributed to its high content of  $\beta$ -glucan; Administration of barley  $\beta$ -glucan extract in pre-diabetic subjects improved glucose tolerance and insulin resistance index<sup>[27]</sup>. In addition, barley may use as base of a meal; the use of barley combined

with refined grains such as white rice maybe a practical way to attenuate their undesirable effects on glycemic control; in a randomized crossover study, combination of cooked barley with white rice dose-dependently reduced the area under the curves of plasma glucose and insulin concentrations, suppressed postprandial decrease of plasma desacyl ghrelin levels and consequently increased satiety<sup>[37]</sup>. The hypolipidemic properties, antioxidant and anti-inflammatory activities of barley products have also been investigated<sup>[38,39]</sup>. In animal diabetic models, barley improved some features of fatty liver, decreased lipid content of the liver, increased fatty acid oxidation and adiponectin levels<sup>[40]</sup>.

Several positive effects of whole wheat and its byproducts on carbohydrate and insulin metabolism have also been reported; wheat bran and whole wheat products are rich sources of dietary fiber, magnesium (main cofactor of enzymes involved in glucose metabolism and insulin secretion), potassium, phenolic acids,  $\alpha$ -tocopherols, carotenoids and antioxidants<sup>[41]</sup>. It is believed that the majority of beneficial effects of whole wheat grain are related to bran and germ fractions; wheat bran is a main source of fiber, lignans, phenolic acid and alkylresorcinol, and beyond the health promotion of gastrointestinal tract and weight management, could improve postprandial glycemic response, glycosylated hemoglobin, lipid disorders and other cardiovascular risk factors in diabetic patients<sup>[42]</sup>. Studies showed that alkylresorcinol of wheat bran inhibited platelet activity and aggregation, decreased triglyceride de novo synthesis, and decreased cardiovascular disease risk factors<sup>[43]</sup>. Wheat germ is rich in non-digestible oligosaccharides, phytosterols, benzoquinone and flavonoids that play a potent role in induction of antioxidant and anti-inflammatory properties and modulation of immunity responses<sup>[44]</sup>. Avemar, fermented wheat germ extract, had interesting properties in the treatment of cardiovascular disease, and improved metabolic abnormalities including hyperglycemia, lipid peroxidation and abdominal fat gain<sup>[45]</sup>.

Brown rice and its byproducts is another grain investigated as a functional food. Compared to white rice, brown rice has lower glycemic load and glycemic index, and higher content of fiber, vitamins and minerals, phytic acids, polyphenols, tocopherols, tocotrienols, and other bioactive compounds<sup>[46]</sup>; consumption of brown rice has benefits on glycemic control, dyslipidemia, endothelial function, abdominal obesity and liver functions in type 2 diabetic patients<sup>[47]</sup>. Studies show that  $\gamma$ -orizanol found in brown rice modulates high-fat diet induces oxidative stress, improves  $\beta$ -cell function, enhances glucose-stimulated insulin secretion and prevents the development of type 2 diabetes<sup>[48]</sup>. Germinated and pre-germinated brown rice, as more interesting functional foods, have unique components including  $\gamma$ -amino butyric acid, and bioactive acylated steryl glucosides with potent anti-diabetic properties; these bioactive components attenuate oxidative-induced peripheral nervous system, prevent diabetic neuropathy, inhibit oxidative-induced pancreatic  $\beta$ -cell apoptosis and enhance insulin secretion<sup>[49-51]</sup>. Bran rice, a byproduct of brown rice, contains within 31% fiber (mainly insoluble fiber),  $\beta$ -glucan, pectin, tocopherols, orizanol, ferulic acid, lutein, xanthine, vitamin K, thiamin, niacin, pantothenic acid,  $\alpha$ -lipoic acid, coenzyme Q<sub>10</sub> and other nutraceuticals; administration of bran rice in diabetic patients reduced glycosylated hemoglobin, LDL-C and total cholesterol as well as increased HDL-C<sup>[52]</sup>.

In conclusion, replacement of whole grain and cereal-based products with refined grains in diet planning may be an effective and practical strategy for MNT in type 2 diabetic patients; this approach beyond the improvement of glycemic control, leads to more benefits for management of other aspects of diabetes, attenuation of diabetes-induced metabolic disorders, and prevents long-term complications especially atherosclerosis and cardiovascular disease.

## PHYTOCHEMICAL-RICH FRUITS AND VEGETABLES

Fruits and vegetables are rich sources of dietary fiber (soluble and insoluble fiber), vitamins, and various phytochemicals and play a vital role in health promotion and prevention of chronic disease<sup>[53]</sup>. Dietary modification based on fruits and vegetables certainly is a definitely important strategy for management of type 2 diabetes and prevention of its complications; several studies indicate that regular consumption of various fruits and vegetables in diabetic patients can lead to an improved glycemic control, reduced HbA1c and triglyceride levels, enhanced antioxidant defense system, attenuated oxidative stress and inflammatory markers, decreased risk of diabetic retinopathy, and a lower burden of carotid atherosclerosis<sup>[54-57]</sup>. Since various fruits and vegetables provide many different micronutrients and bioactive compounds, consumption of varied fruits and vegetables is mainly recommended; it should be noted that the color of fruits and vegetables reflects predominant pigmented phytochemi-

icals, and considering the colors in selection of these food groups provide a wide range of nutraceuticals. In Table 1, some phytochemical-rich fruits and vegetables, their bioactive compounds and favorable effects on diabetic related conditions are reviewed. Studies showed that tomato and its by products, as main sources of lycopene,  $\beta$ -carotene, flavonoids and other bioactive components, could attenuate blood pressure and dyslipidemia, decrease cardiovascular risk factors and enhance antioxidant defense system; other sources of lycopene and carotenoids such as grapefruit and watermelon have also beneficial properties to regulate lipid and lipoprotein metabolism, blood pressure and vascular function. Anthocyanins-rich fruits including red apple, berries family, grapes, cherries, red cabbage, and pomegranate have mainly hypoglycemic effects ( $\downarrow$  digestion and absorption of dietary carbohydrates,  $\downarrow$  postprandial glycemic response and  $\downarrow$  glycosylated hemoglobin) as well as protective properties against oxidative damages (Table 1).

## LEGUMES

Legumes (peas, beans, lentils, peanuts) are valuable sources of dietary protein, non-digestible carbohydrates including dietary fiber, resistance starches, oligosaccharides, and bioactive compounds such as functional fatty acids (linoleic acid,  $\alpha$ -linolenic acid), isoflavones (daidzein, genistein, glycitein), phenolic acids, saponins, and phytic acid; some polyphenols including pelargonidin, cyanidin, delphinidin, and malvidin are also found in legumes<sup>[134,135]</sup>. Legumes are considered a component of a healthy diet and there is much evidence showing that regular consumption of legumes has protective effects against obesity, type 2 diabetes, and cardiovascular disease<sup>[136]</sup>. Legumes may be considered as an important component of a functional-foods based diet for management of type 2 diabetes.  $\alpha$ -amylase inhibitory peptides are one of the bioactive compounds in legumes and beans that reduce digestion and absorption of dietary carbohydrates, and modulate postprandial glycemic response; other bioactive peptides of grain legumes including the 7S globulin  $\alpha$  chain and conglutin  $\gamma$  have unique properties to regulate lipid metabolism and normalize lipid and lipoprotein levels<sup>[137]</sup>. Low glycemic index, high fiber and phytochemical content of legumes have made them functional food for diabetic patients.

Lentils (*Lens culinaris*), the most consumed legume grains, are rich sources of dietary fiber, slowly digestible starch and resistant starch, tannins,  $\beta$ -glucan, functional antioxidant ingredients, a wide range of phenolic acids including gallic acid, proanthocyanidins, prodelfinidin, procyanidins, catechins, epicatechin, kampferol, quercetin, cinapic acid and apigenin<sup>[138]</sup>. Studies show that bioactive proteins of lentil reduce plasma levels of LDL-C, triglyceride content of the liver, and adipose tissue lipoprotein lipase activity; moreover, polyphenols of lentil could prevent angiotensin II-induced hypertension, and pathological changes including vascular remodeling and

**Table 1 Bioactive compounds and functional properties of some of favorable fruits and vegetables**

Ref.	Possible functional properties in diabetes	Main bioactive components and phytochemicals	Fruits and vegetables
[58-62]	<ul style="list-style-type: none"> <li>↓ Systolic and diastolic blood pressure</li> <li>↑ apolipoprotein a1 and HDL-C</li> <li>↓ LDL oxidation, improve diabetes-induced lipid disorders</li> <li>↓ cardiovascular risk factors</li> <li>↓ aldose reductase activity and cataract</li> <li>↑ antioxidative enzymes activity</li> </ul>	Lycopene, $\beta$ -carotene, flavonoids, anthocyanins, phytoan, phyto flava, quercetin, kampferol	Tomato and its by products
[63-65]	<ul style="list-style-type: none"> <li>↓ Triglyceride levels, enhance endogenous antioxidant defense system, regulation of appetite</li> </ul>	Lycopene, pectin, naringin, hesperidin	Grapefruit
[66-69]	<ul style="list-style-type: none"> <li>↑ Nitric oxide biosynthesis, improve endothelial function</li> <li>↓ blood pressure</li> <li>↑ plasma arginine levels and consequently</li> <li>↓ insulin resistance and adipocyte size</li> </ul>	Lycopene, carotenoids, cytolin	Watermelon
[70-73]	<ul style="list-style-type: none"> <li>↓ Absorption of dietary carbohydrate</li> <li>↓ postprandial glycemia, improve pancreatic <math>\beta</math>-cell function</li> <li>↓ free radical generation</li> <li>↓ lipid peroxidation</li> <li>↑ plasma total antioxidant capacity, prevent vascular damage, improve dyslipidemia</li> </ul>	Soluble fiber, quercetin, catechins, epicatechin, <i>P</i> -cumaric acid, chlorogenic acid, gallic acid, phlorldizin, procyanidins	Red apple, apple peel, apple and its by products
[74-81]	<ul style="list-style-type: none"> <li>Glycemic control, inhibit <math>\alpha</math>-glucosidase and <math>\alpha</math>-amylase activity</li> <li>↓ digestion and absorption of dietary carbohydrates</li> <li>↓ insulin resistance, improve dyslipidemia</li> <li>↓ postprandial oxidative stress</li> <li>↓ lipid peroxidation</li> <li>↑ plasma total antioxidant capacity</li> <li>↓ systolic blood pressure</li> <li>↑ antioxidative enzymes activity</li> <li>↑ adipocytes lipolysis</li> <li>↓ inflammatory processes, modulation of peroxisome proliferator-activated receptors</li> </ul>	Anthocyanins, tannins, ellagitanins, $\alpha$ -carotene, $\beta$ -carotene, lutein, delphinidins, pelargonidins, cyanidins, catechins, hydroxy-cinnamic acid	Berries; cranberry, blackberry, black raspberry, blueberry, red raspberry, strawberries
[82-86]	<ul style="list-style-type: none"> <li>Protective effects on vascular system</li> <li>↓ platelet hyperactivity and aggregation</li> <li>↓ cardiovascular diseases</li> <li>↓ oxidative damage</li> <li>↓ rennin-angiotensin activity</li> <li>↑ production of nitric oxide</li> <li>↓ blood pressure</li> <li>↑ bone-marrow-derived endothelial progenitor cells</li> </ul>	Anthocyanins, resveratrol	Grapes, grape by products
[87-91]	<ul style="list-style-type: none"> <li>↓ Hyperglycemia</li> <li>↓ HbA1c, improve lipid disorders, anti-inflammatory properties (inhibit cyclooxygenase)</li> <li>↓ abdominal fat</li> <li>↓ microalbuminuria, improve metabolic syndrome and fatty liver features</li> <li>↓ oxidative stress</li> <li>↓ production of cytokines, induction of PPAR<math>\gamma</math></li> <li>↓ diabetic neuropathy</li> </ul>	Anthocyanins, quercetin, hydroxy-cinnamic acid, carotenoids, melatonin, phenolic acids, gallic acid, lutein, xanthine, $\beta$ -carotene	Cherries
[92-95]	<ul style="list-style-type: none"> <li>↓ Hyperglycemia, attenuate hyperglycemia-induced metabolic disorders</li> <li>↓ lipid peroxidation, induction of glutathione reductase, glutathione peroxidase, superoxide dismutase, delay progression of nephropathy</li> <li>↓ inflammatory processes, improve dyslipidemia</li> </ul>	Isothiocyanates, anthocyanins (red cabbage), carotenoids, lutein, $\beta$ -carotene	Cabbage, Cauliflower
[96-100]	<ul style="list-style-type: none"> <li>↓ Hyperglycemia</li> <li>↑ endothelial nitric oxide synthase activity, inhibit angiotensin converting enzyme</li> <li>↓ blood pressure, improve vascular function</li> <li>↓ cholesterol and atherogenic lipids</li> <li>↓ lipid peroxidation</li> <li>↓ progression of atherosclerosis</li> <li>↑ plasma total antioxidant capacity, modulate activation of PPAR<math>\gamma</math> and nuclear factor <math>\kappa</math>B</li> <li>↑ activity of paraxonase 1 and HDL-C levels</li> <li>↓ serum resistin levels and ameliorate obesity-induced insulin resistance</li> </ul>	Anthocyanins, tannins, catechins, gallo catechins, punicalagin acid, ellagic acid, gallic acid, oleanolic acid, ursolic acid, uallic acid	Pomegranate and its by products, pomegranate peel and seeds

[101-105]	↓ Hyperglycemia, induce insulin secretion from $\beta$ -cell ↓ blood pressure, inhibit enzyme involved in cholesterol biosynthesis, improve dyslipidemia, prevent atherosclerosis ↓ lipid peroxidation ↓ platelet hyperactivity and aggregation, regulate glycolysis, gluconeogenesis and carbohydrate metabolism pathways ↑ insulin sensitivity	Allyl sulfors, flavonoids, quercetin, dihydroflavonols, anthocyanins (red onion)	Garlic, onions
[106-111]	↓ Endothelial macrophage activation ↓ hyperactivity and aggregation of platelet, improve vascular function ↓ oxidative stress and inhibit stress-sensitive signaling pathways ↓ digestion of dietary lipids, improve dyslipidemia ↓ pro-inflammatory cytokines ↓ lipid peroxidation	Lutein, xanthine, $\alpha$ -cryptoxanthin, $\beta$ -cryptoxanthin, naringenin, hesperidin, $\beta$ -carotene, phytosterols	Citrus fruits
[112-113]	↓ Free radical generation and lipid peroxidation, binding to bile acids ↑ cholesterol excretion, improve lipid profile ↑ plasma total antioxidant capacity	Lutein, betaine, violaxanthine, opioid peptides (rubisculins), <i>P</i> -cumaric acid, ferulic acid	Spinach
[114-115]	Improve glycemic and insulinemic response ↓ systemic inflammation ↓ cardiovascular disease risk factors	Carotenoids, pectin, oleic and linolenic acids	Pumpkin
[116]	Improve hyperglycemia and dyslipidemia ↑ adiponectin, antioxidant and anti-inflammatory effect	Fiber, polyphenols, chlorogenic acid, flavonoids, anthocyanins	Plums
[117-119]	Improve dyslipidemia, anti-inflammatory properties ↓ lipid peroxidation ↑ plasma total antioxidant capacity	Soluble fiber (pectin), $\alpha$ -carotene, $\beta$ -carotene lutein, phenolic acids, stilbenes	Carrots
[120-122]	Inhibit $\alpha$ -amylase ↓ postprandial glycemia ↑ glycogen synthesis, improve dyslipidemia ↓ lipid peroxidation, protective effect against diabetic nephropathy	Carotenoids, quercetin, kampferol, gallic acid, caffeic acid, catechins, tannins, mangiferin	Mango
[123-127]	Regulate carbohydrate metabolism (↑ glucokinase and glucose-6-phosphate dehydrogenase activity ↓ glucose-6-phosphatase activity) ↓ lipid peroxidation ↓ protein carbonylation ↑ antioxidant enzyme activity, improve metabolic syndrome features ↑ insulin sensitivity ↓ carbohydrate absorption ↓ plasma free fatty acid	Anthocyanins, alkaloid compounds (berberine, oxycontin)	Barberry
[128-131]	Protective effects against diabetic neuropathy ↓ lipid peroxidation, induce antioxidant enzymes, protect liver and kidney against oxidative damage	Dietary fiber, polyphenols, acid cinnamic, melatonin	Date fruit
[132-133]	Improve lipid and lipoprotein metabolism ↑ insulin sensitivity ↓ blood pressure	Dietary fiber, pectin, flavonoids, gallic acid, chlorogenic acid, catechins, anthocyanins	Figs

PPAR $\gamma$ : Peroxisome proliferator-activated receptor  $\gamma$ .

vascular fibrosis<sup>[139,140]</sup>.

Beans are also other important legume grains in the human diet with high content of fiber, phytate,  $\omega$ 3 fatty acids, antioxidants, phenolic compounds. The hypoglycemic effect of beans (*via* inhibition of  $\alpha$ -amylase and  $\beta$ -glucosidase activity) has been reported as being similar to those of anti-diabetic drugs<sup>[141-143]</sup>. Including beans (pinto, dark red kidney, black beans) in diet planning for type 2 diabetic patients effectively helps weight management, attenuates postprandial glycemic response, and improves dyslipidemia<sup>[144-146]</sup>.

Soybean, a rich source of unique phytoestrogens (genistein, daidzein, glycitein), is another important functional food which has been considered in diabetes; the isoflavones and bioactive peptides of soybean have

favorable effects on glycemic control and insulin sensitivity, dyslipidemia, and kidney function<sup>[147-149]</sup>. It seems that the anti-diabetic effects of soybean mainly occur through interaction with estrogen receptors (ERs); studies show that soy isoflavones selectively bind to both  $\alpha$  and  $\beta$  estrogen receptors; ER $\alpha$  is considered as key modulator of glucose and lipid metabolism, and regulate insulin biosynthesis and secretion as well as pancreatic  $\beta$ -cell survival<sup>[150]</sup>. Soy protein could induce insulin sensitivity and improve lipid homeostasis *via* activation of peroxisome proliferator-activated receptor and liver X receptors, and inhibition of the sterol regulatory element binding protein-1c<sup>[151]</sup>. Regular consumption of soy products could help diabetic patients in the management of dyslipidemia<sup>[152]</sup>. Soy protein and isoflavones decrease

production of atherogenic apolipoproteins such as apo B, increase biosynthesis of HDL-C, induce LDL-C receptors, increase biosynthesis and excretion of bile acids, decrease gastrointestinal absorption of steroids, induce favorable changes in hormonal status, including the insulin to glucagon ratio, and thyroid hormones which lead to improvement of dyslipidemia<sup>[153,154]</sup>. Recently two bioactive peptides, identified in glycinin (a main soy protein), have unique hypolipidemic properties. These peptides inhibit 3-hydroxy-3-methyl glutaryl CoA reductase, key enzyme involved in cholesterol biosynthesis.  $\beta$ -conglycinin, another main soy bioactive protein with anti-atherogenic properties *via* regulation of lipogenesis, decrease liver lipogenic enzyme activity, inhibits fatty acid biosynthesis in liver, and facilitates fatty acid  $\beta$ -oxidation; other biological activities of soy peptides include antioxidant, anti-inflammatory, and hypotensive effect<sup>[155]</sup>.

Another feature of soybean and soy products as well as other legumes which may highlight them as main part of a functional foods-based diet, is their established effectiveness in weight management; since the overweight and obesity are the common problems in diabetic patients and main contributors in development of insulin resistance, benefit from anti-obesity properties of legumes is considered another key approach in these patients. Thermogenic effects, induction of satiety through some important appetite regulatory gut peptides, mediation in gene expression and secretion of key adipocytokines such as leptin and adiponectin, as well as inhibitory effects on proliferation and differentiation of adipocytes are some of the mechanisms that could explain the role of legumes on weight management<sup>[140,156-159]</sup>. In conclusion, considering the potential benefits of legumes and its by products, regular consumption of these functional foods may be an effective strategy for management of various aspects of type 2 diabetes.

## NUTS

Based on current evidence, nuts may play a protective effect against cardiovascular disease risk factors. Almonds, pistachios, walnuts and hazelnuts are commonly used nuts; these functional foods are considered as rich sources of high-biological value proteins, bioactive peptides, functional fatty acids (mono and poly unsaturated fatty acids), fiber, phytosterols, polyphenols, tocopherols and other antioxidant vitamins; the antioxidative effect of nuts mainly is related to a high content of  $\alpha$  and  $\gamma$  tocopherol, phenolic acids, melatonin, oleic acid and selenium, while the anti-inflammatory effect is related to ellagic acid,  $\alpha$ -linolenic acid and magnesium<sup>[160,161]</sup>.

Most current evidence reveals that consumption of nuts in type 2 diabetic patients other than improving the overall diet quality also has beneficial effects on postprandial glycemic response following high-carbohydrate meals, attenuates postprandial oxidative stress and inflammatory processes, normalizes lipid and lipoprotein levels and decreases lipid atherogenicity, and improves insulin resistance<sup>[162,163]</sup>. Moreover, habitual intake of nuts could help

to effectively manage weight especially in diabetic patients; the anti-obesity effects of nuts investigated in some studies may be attributed to thermogenic effects, induction of satiety, decreased dietary fat absorption, and increased fat excretion; bioactive components of nuts also modulate regulatory appetite neurotransmitters and adipose tissue metabolism, as well as decrease proliferation and differentiation of adipocytes, inhibit lipogenesis and induce fatty acid  $\beta$ -oxidation<sup>[164,165]</sup>. Studies show that consumption of nuts effectively decreases serum levels of high-sensitivity C-reactive protein; a well measure of systemic low-grade inflammation, interleukin 6 (a potent pro-inflammatory cytokine) and fibrinogen while increase plasma concentration of adiponectin, a potent anti-inflammatory cytokine released from adipose tissue; dietary patterns, high in nuts, were also related to lower levels of soluble inflammatory and cardiovascular risk markers including intercellular adhesion molecule 1 and vascular cell adhesion molecule 1<sup>[166,167]</sup>. Another beneficial effect of nuts which is important especially in diabetic patients is favorably influence on endothelial function; high content of L-arginine, a main precursor of nitric oxide, as well as antioxidants and polyphenols could contribute to this effect<sup>[161]</sup>.

In conclusion, it seems that a diet enriched with nuts may be an effective strategy to improve glycemic control and prevent cardiovascular disease in type 2 diabetic patients.

## OTHER BENEFICIAL FUNCTIONAL FOODS AND BIOACTIVE COMPONENTS FOR DIABETIC PATIENTS

Although there are a large number of natural foods, nutraceuticals or bioactive components that could be considered as functional ingredients and have beneficial effects for diabetes management, addressing all these issues is beyond the scope of this article. Table 2 shows some of these potential functional foods including dairy products and probiotics, fish meat, green tea, spices are presented.

## CONCLUSION

Type 2 diabetes is a complicated metabolic disorder with both short- and long-term undesirable complications as well as various pathogenic conditions including dyslipidemia, vascular dysfunction, oxidative stress, sub-clinical inflammation, and altered signaling pathways. Ineffectiveness of the current medical treatments in management of long-term diabetes complications confirms that other complementary approaches are required; the use of functional foods and bioactive compounds is one of these new approaches. Functional foods and their bioactive compounds could attenuate carbohydrate metabolism and hyperglycemia, improve pancreatic  $\beta$ -cell function and insulin secretion as well as insulin resistance, regulate lipid and lipoprotein metabolism and adipose tissue metabolism, modulate oxidative/antioxidative balance and

**Table 2 Bioactive compounds and functional properties of some of favorable functional foods**

Ref.	Possible functional properties in diabetes	Main bioactive components and nutraceuticals	Functional foods
[168-179]	Improve the features of metabolic syndrome, modulate gut microbiota, regulate satiety and food intake ↑ adiponectin, modulate adipocytokines, induce thermogenesis, lipolysis and $\beta$ -oxidation ↑ dietary fat excretion ↓ adiposity and body weight ↓ oxidative stress and inflammatory markers, hypo-lipidemic and anti-thrombotic effects ↑ insulin sensitivity, modulate immune responses in diabetic patients ↑ total antioxidant capacity ↓ lipid peroxidation ↓ HbA1c	Calcium, vitamin B, bioactive proteins such as casein and whey, immunoglobulines, bioactive peptides ( $\alpha$ - and $\beta$ -lactorphines, lactoferrin, lactoferricin, $\alpha$ -lactalbunin, $\beta$ -lactoglobulin, growth factors), conjugated linoleic acids, lactic acid bacteria and bifidobacteria	Dairy products and probiotics
[180-185]	Improve hypertriglyceridemia and hypertension ↓ cardiovascular disease ↓ insulin resistance and inflammation, improve glycemic management ↓ proteinuria ↓ oxidative stress, inhibit lipogenesis and induce lipolysis, induce PPAR $\alpha$ and PPAR $\beta$ ↓ adiposity and weight management ↑ thermogenesis and energy expenditure, inhibit angiotensin converting enzyme and modulate blood pressure	Bioactive peptides, antioxidant compounds, $\omega$ <sub>3</sub> fatty acids (docosahexaenoic acid, eicosapentaenoic acid), selenium, taurine	Fish and seafood
[186-189]	Regulate cholesterol metabolism ↓ LDL oxidation, protect vascular endothelium against atherogenesis, inhibit platelet aggregation ↓ atherosclerosis development ↓ pro-inflammatory cytokines, activate PPAR $\gamma$ , improve sub-clinical inflammation	Oleic acid, $\omega$ <sub>3</sub> fatty acids, Flavonoids, cinnamic acid, benzoic acid, lignans, cumaric acid, ferulic acid, tocopherols, carotenoids, oleuropein, oleocanthal	Olive oil
[190-193]	Promote endogenous antioxidant defense system, induce superoxide dismutase and catalase ↓ lipid peroxidation, improve glycemic control ↑ insulin sensitivity ↓ gluconeogenesis ↑ glycogen content ↓ glycation of collagen and fibrosis, protect cardiac muscle, regulate lipid metabolism as well as adipose tissue metabolism, inhibit lipogenic enzymes ↓ satiety ↑ thermogenesis ↓ proliferation and differentiation of adipocytes ↓ pro-inflammatory cytokines ↓ monocyte chemotactic protein-1	Polyphenols, phenolic acids, catechins, epigallocatechin-3-gallat, chlorophyll, carotenoids, pectin, plant sterols	Green tea
[194-196]	↑ Insulin sensitivity, improve peripheral uptake of glucose, increase glycolysis and gluconeogenesis, hypoglycemic and hypolipidemic effects, antioxidant and anti-inflammatory properties	Cinnamaldehyde, cinnamic acid, coumarin, catechins, epicatechin, procyanidins B-2	Cinnamon
[197-199]	Inhibit enzymes involved in inflammation including cyclooxygenase-2, lipoxygenase, and nuclear factor $\kappa$ B, inhibit $\alpha$ -glucosidase and $\alpha$ -amylase activity ↓ postprandial glycemic response ↓ proteinuria, activate PPAR $\gamma$ and regulate carbohydrate and lipid metabolism, prevent diabetic cataract	Curcuminoids, stigmasterol, $\beta$ -sitosterol, 2-hydroxy methyl anthraquinone, bioactive peptide turmerin	Turmeric
[200-203]	Attenuate oxidative stress, protective effects against oxidative damage ↓ serum creatinine and urea, improve dyslipidemia ↓ atherogenic lipoprotein levels ↓ lipid peroxidation in renal tissue, inhibit $\alpha$ -glucosidase activity ↓ carbohydrate digestion and absorption, protect liver against diabetes-induced oxidative damage	Tannins, flavonoids, anthocyanins, phenolic acid, gallic acid	Sumac

PPAR: Peroxisome proliferator-activated receptor.

inflammatory processes, improve weight management and prevent micro and macro vascular complications.

Considering the beneficial properties of functional foods, it seems that diet planning based on these healthy foods may be considered an effective strategy for management of various aspects of diabetes and promotion

of health in diabetic patients.

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