Chapter 8

Functional and Biological Potential of Bioactive Compounds in Foods for the Dietary Treatment of Type 2 Diabetes Mellitus

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Abstract

Type 2 diabetes mellitus (T2DM), or noninsulin-dependent diabetes, is a complex disease characterized by the alteration of oxidoreductive and proinflammatory mechanisms, which leads to disorders in the insulin receptor and consequent chronic hyperglycemia. The hypoglycemic, insulinomimetic, and lipid-lowering potential of food is a reality given the advances in understanding of the role of food in nutrition. Besides its nutritional content, food exerts a biological function in the organism, and this demonstrates the importance of redirecting therapeutic strategies as well as related prevention policies of T2DM. The present review evaluates the effect of food on T2DM treatment. Particular attention is paid to the consumption of nopal, soy, and oats for their hypoglycemic functions, as well as the consumption of omega-3 fatty acids, which are associated with the control of metabolic alterations of this disease.

Keywords: antioxidant, anti-inflammatory, functional foods, bioactive compounds, diabetes

1. Introduction

Type 2 diabetes mellitus (T2DM), also called noninsulin-dependent diabetes, is a complex and multifactorial disease. This review describes T2DM in the framework of oxidative stress and the inflammatory process, since its main etiological factor is obesity. These mechanisms can lead to various metabolic alterations, which have been proposed to be part of their chronicity and complexity [1].

According to the World Health Organization (WHO), there are 350 million people with diabetes worldwide, whereas the International Diabetes Federation (IDF) estimates that by 2013, 382 million people worldwide were diagnosed with some type of diabetes. This figure is expected to increase to 592 million by 2035 [2].

As a response to the increase in diseases related to the modern lifestyle, functional foods, such as soybean, nopal, oats, and foods with high antioxidant and omega-3 content, were developed in Japan in the 1980s, and these have become important alternatives for improving nutrition and public health. Hence, research into the benefits or effects of functional foods on T2DM is crucial and can determine whether these can be a true alternative for the prevention and control of this pathology, as well as for associated metabolic effects.

2. Physiopathogenesis of T2DM: oxidative stress and the inflammatory process

The alteration of some cellular biochemical processes is mainly caused by factors such as over-nutrition and decreased physical activity in the individual, as for glucose metabolism, specifically hyperglycemia, which in turn triggers:

- Cell overload of free fatty acids
- Endothelial dysfunction
- Insulin resistance in muscle
- Impaired insulin secretion in the beta cells of the pancreas.

T2DM includes several alterations in metabolism, including hyperglycemia, insulin resistance, dyslipidemia, and chronic low-grade inflammation, and these alterations arise from oxidative stress [3].

Oxidative stress is defined as the biochemical imbalance caused by the overproduction of reactive species (RS) and free radicals (FR) that cause oxidative damage to membrane lipids, carbohydrates, proteins, and DNA. In people with T2DM, free radicals are found in high concentrations, causing damage to various organs, such as the heart and blood vessels. This has been described as a risk factor for the development of complications in this disease [4].

As mentioned above, the excess of FR leads to the oxidation of macromolecules, which in turn leads to lesions at the cellular level; among them, the following effects are described:

- Lipids: During lipid peroxidation, unsaturated fatty acids react (in chains) with molecular oxygen and hydroperoxides are formed, which are degraded into various products, such as conjugated dienes, alkanes, aldehydes, and isoprostanes, among others. Damage from oxidation can affect both the lipids in cell membranes and those contained in plasma lipoproteins. In the first case, this would cause inadequate cellular functioning, which is presumed to be one of the causes of premature aging experienced by some individuals with diabetes [5].

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In the case of plasma lipoproteins, damage to these in all known cases is derived from the oxidation of their lipids. Alterations of high density lipoproteins (HDL) and very low density lipoproteins (VLDL) can affect reverse cholesterol transport and clarification of plasma triglycerides, respectively [6].

On the other hand, the peroxidation of low-density lipoproteins (LDL) constitutes the major contribution of FR to the genesis and aggravation of atherosclerosis. Oxidative modifications of LDL confer greater atherogenic power on this macromolecule [6, 7].

It is also known that in diabetic patients with unacceptable metabolic control, there is greater susceptibility of LDL to oxidation and more oxidized LDL than in those with optimal control [6, 7].

- Protein: The mechanisms of damage in each radical-generating system may be different and may also vary depending on the affected protein. Oxidative modification of proteins increases their degradability and susceptibility to proteolysis, probably due to their increased hydrophobicity, which implies more rapid ubiquitination and degradation by the lysosomal pathway. Likewise, the alteration of free radical proteolysis is manifested both in intracellular protein catabolism and in extracellular protein systems, especially in proteins of the extracellular matrix [8].

  One protein that can undergo oxidative damage in people with T2DM is insulin. Oxidative damage causes chemical and structural changes in this hormone and, as a consequence, a loss of its biological function. It has been shown that human adipose tissue in the presence of oxidized insulin does not use glucose with the same efficiency as with native insulin [9].

  Also, carbonyl stress can also affect insulin receptors, and the molecules involved in the cellular response are appropriate to insulin stimulation [9].

- Deoxyribonucleic acid (DNA): There are many phenomena, associated with mutations and carcinogenesis, which are caused by damage to DNA. These include loss of expression or synthesis of a protein by damage to a specific gene, oxidative modifications of bases, fragmentations, stable interactions of DNA-proteins, chromosomal rearrangements, and demethylation of cytokines of the DNA that activates genes. The damage may be effected by such alterations; for example, via inactivation or loss of tumor suppressor genes, which may lead to the initiation, progression or both of carcinogenesis [10].

The above-described conditions are causes of metabolic alterations characteristic of T2DM. Also, oxidative stress present in people with T2DM is associated with the chronic hyperglycemia that characterizes this disease. Meanwhile, an excess of circulating glucose activates several metabolic pathways not very common in the organism, which leads to the generation of other metabolites, among which are oxygen FR [1, 4].

Regarding the sorbitol pathway, given the high circulating glucose levels in the blood, the metabolic pathway of the aldose reductase enzyme is followed: it is of low affinity to normal glucose concentrations, generates sorbitol from glucose and uses NADPH (nicotinamide adenine dinucleotide phosphate) as a cofactor. Because the antioxidant potential of glutathione

depends on the NADPH supply (because glutathione requires it for regeneration), the flow of this cofactor by another route, such as that of sorbitol pathway, shifts the oxidant-antioxidant balance toward oxidative stress [11].

In turn, it has been shown that sorbitol affects the physiology of cells that do not use insulin-mediated transporters to take glucose (and which contain the enzyme aldose reductase), such as neurons, red blood cells, and the nephrons that undergo osmotic changes. In addition, the permeability of these cells may be altered due to the increase of sorbitol, leading to complications typical of T2DM [11].

Likewise, sorbitol has been linked to oxidative stress with low insulin levels in diabetic patients, since it has been shown that the beta cells of the pancreas are not immune to damage by FR. In this way, in patients who already have the disease, it is possible that symptoms worsen, since insulin secretion in the pancreas decreases because of interference of FR to the normal process of insulin production and secretion [1].

In addition to the increase in free radicals, there is also an increase in metabolic stress, which is the result of change in energy metabolism, in the level of mediators of inflammation and in the state of the antioxidant defense system. Therefore, the inflammatory process is also altered in patients with T2DM. Systemic inflammation is one of the most representative features of this type of diabetes, characterized by high systemic levels of pro-inflammatory cytokines damaging DNA and causing endothelial dysfunction, which causes microvascular and macrovascular complications in T2DM [1].

3. Mechanisms of antioxidant defense in T2DM

An antioxidant is a chemical entity that, at low concentrations and compared to the oxidant, retards or prevents the oxidation of a substrate, which includes lipids, proteins, carbohydrates, and DNA [12].

Antioxidants have been classified in different ways, of which the most used establish differences in chemical structure and biological function, dividing them into enzymatic and nonenzymatic [13].

- Exogenous: These come from the diet and include vitamin E, vitamin C, and carotenoids (beta carotenes, lycopenes, and xanthines). Vitamin C is the most abundant water-soluble antioxidant in the blood, whereas vitamin E is the major lipophilic antioxidant. Selenium, the most toxic mineral included in our diet, acts together with vitamin E as an antioxidant [13].

- Endogens: Antioxidant defenses consist of avoiding the univalent reduction of oxygen by enzymatic or nonenzymatic systems. A group of enzymes specialized in inactivating the reactive oxygen species (ROS) by different mechanisms has been described, such as catalase (CAT), glutathione peroxidase (GPX), and superoxide dismutase (SOD). Nonenzymatic antioxidants recognize amino acids, such as glycine, taurine, and the tripeptide glutathione [13].

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In T2DM, a series of changes occur that indirectly indicate the existence of marked oxidative stress, due to the increase in formation of oxygen free radicals and the decrease of the plasma and intracellular levels of the antioxidants [4].

Carmeli et al. [14] confirmed that in people with T2DM, there is significantly decreased activity of the SOD enzyme as a consequence of high levels of hydrogen peroxide produced during the reaction, which inhibit the enzyme by negative feedback. Indeed, it was observed that an increase of SOD initially occurs in response to the high generation of the superoxide anion in the cell and its elimination by the enzyme. However, the intense production of this radical for a prolonged time exhausts the stimulation of enzymatic activity, since the product of the reaction can inhibit it.

With respect to the concentration of minerals (Cu^{2+} and Zn^{2+}), Devi et al. [15] found that patients with T2DM had significantly higher serum and erythrocyte copper levels. In addition, plasma copper levels have been reported to be higher in patients with complications. In this sense, it has been hypothesized that alterations in copper metabolism contribute to the progression of pathologies related to diabetes, because glycosylated proteins have a higher affinity for transition metals such as copper.

Nsonwu et al. [16] found that serum zinc levels were significantly lower in people with T2DM. This apparent hypozincemia may be the result of urinary loss, decreased intestinal absorption of this mineral or both conditions.

4. Inflammatory process and insulin resistance

Inflammation is a response of the body to exposure to infectious agents, antigenic stimuli or physical injury involving the nervous, vascular, and immune systems. Initially, it has a homeostatic function of protection or defense that is characterized by flushing, pain, swelling, edema, and lack of function in the affected area; however, if the process is inefficient and chronic, it becomes a pathophysiological process that favors the increase in FR and consequently oxidative stress [17].

In T2DM, there is a pathophysiological relationship with the chronic inflammatory process (CIP) by two mechanisms: one linked to obesity and the endocrine activity of adipose tissue, and the other involving the development of the immune response stimulated by generated AGEs because of the nonenzymatic glycosylation reaction of proteins [11].

The chronic inflammatory process is an alteration linked to obesity and T2DM, considering that adipose tissue, besides being an energy reserve, acts as a high activity endocrine gland, producing a wide variety of substances with effects at different levels in the body, including proinflammatory cytokines. In addition to secreting hormones, such as leptin, adiponectin, resistin and ghrelin, adipocytes synthesize and secrete cytokines associated with inflammation, such as IL-6 and TNF-α [18].

The mechanism by which the chronic process is linked to the development of diabetes mellitus occurs at the molecular level and implies insulin resistance. Briefly, the mechanism is as follows: when insulin binds to the extracellular alpha subunit of its receptor, it causes a conformational change that allows the binding of ATP to the intracellular beta subunit of the receptor. This promotes autophosphorylation of insulin and confers tyrosine kinase activity, which initiates tyrosine phosphorylation of intracellular proteins called insulin receptor substrate (IRS). IRS have a conserved region that, once activated, allows them to interact with other intracellular proteins, promoting the translocation of the glucose transporter (GLUT) to the cell membrane, with the subsequent entry of glucose [1, 19].

TNF-α causes an inhibition of the autophosphorylation of tyrosine residues of the insulin receptor and also causes the phosphorylation of a serine of the insulin receptor substrate (IRS). This in turn promotes the phosphorylation of a serine of the insulin receptor and inhibits the phosphorylation of tyrosine that is required to promote the cascade of signals for the capture of glucose; thus, this translates into insulin resistance. Also, it has been reported that IL-6 inhibits the signal of insulin transduction in the hepatocyte, which also causes insulin resistance [19].

Vozarova et al. [20] showed that markers of inflammation correlate with diabetes. The total leukocyte count is an indirect marker of inflammation and, specifically a higher neutrophil count than normal, is related to the insulin resistance characteristic of T2DM and cardiovascular diseases.

Inflammation of beta cells of the pancreas as a result of an autoimmune phenomenon has been recognized in type 1 diabetes mellitus and is increased in the pathogenesis of T2DM. Such inflammation is one of the pathways of the pathogenesis of T2DM and its complications [21, 22].

The main cell involved in the inflammatory process and in the insulin resistance of T2DM is the adipocyte, since insulin regulates glucose uptake and storage of triglycerides through these. Adipokines in turn also affect secretion and insulin resistance [23].

In particular, leptin, adiponectin, and resistin contribute to the dysfunction of the beta cells of the pancreas increasing insulin resistance. The adipose tissue also secretes dipeptidyl peptidase-4 (DPP-4) improving the degradation of glucagon in peptide 1 (GLP-1), which has an insulinotropic effect on beta cells [24].

On the other hand, the circulation of proinflammatory cytokines directly and indirectly affects the function of beta cells, increasing inflammation of the adipocyte. Cytokines such as TNF-α, beta-interleukin (IL-1β), and gamma interferon (IFN-γ) alter the regulation of intracellular calcium in beta cells and thus release insulin. In addition, TNF-α increases the expression of amyloid peptide (IAPP) in beta cells leading to accelerated death, which leads to insulin resistance [24].

Glucotoxicity, particularly lipotoxicity, increases fatty acids locally in the islets, and long chain fatty acids, especially palmitic acids, cause oxidative stress and the activation of N-terminal c-Jun kinases. These increase the secretion of adipokines, initiating a cycle that induces the dysfunction of the beta cells of the pancreas, which consequently increases inflammation [25].

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5. New trends in the treatment of T2DM: functional foods and bioactive compounds

The World Health Organization (WHO) estimates that 50% of patients with T2DM do not comply with experts' recommendations regarding lifestyle and eating habits. In response to this problem, the science of nutrition faces a challenge: the search for new foods and/or food components that ensure health and reduce the risk of certain diseases. In addition, it could reduce future costs derived from the treatment of these diseases. At this point, the food industry plays a significant role, since it is the main producer and distributor of food [26, 27].

The concept of "functional food" was born as a convenient and economical solution for chronic health problems, being influential in many branches of science. Since 1984, the meaning of "functional food" has changed according to country and culture and has been defined and redefined over the past 30 years. A food may be considered "functional" if it has been satisfactorily demonstrated that, in addition to its nutritional effects, it beneficially affects one or more functions of the organism in a way that improves the state of health or well-being or reduces the risk of disease [27].

Therefore, in functional foods, two very important and different points are integrated. On the one hand, there is the science of nutrition, responsible for investigating and testing new compounds and/or foods that are being developed, and also, there is the industry, responsible for production and distribution of food that will eventually reach consumers [28].

In 1984, the Japanese government allocated funds for the study of functional foods or specific foods with therapeutic uses. Japan was the first country to use the definition of functional food as "fortified foods with special components that have beneficial physiological effects." To be considered as such, there was a legal category of food called FOSHU. In order of importance, the food had to meet three nutritional requirements:

1. It should be constituted by natural ingredients.
2. It should be consumed as part of a daily diet.
3. It should be a food that when consumed presents a particular function in the human body, such as:

- Improvement in biological defense mechanisms.
- Prevention or recovery of some specific diseases.
- Control of physical and mental conditions.
- Aging process delay [28, 29].

Subsequently, the term was adopted by Europe. In the United States, in 1994, the National Academy of Food Sciences and the Nutrition Board defined functional foods as "modified foods or ingredients that can improve health, beyond the nutrients they possess." In 2004,

the American Dietetic Association (ADA) issued an institutional document on functional foods, where they were defined as foods that have potential beneficial effects on health when consumed as part of a varied diet, at effective levels. The definition covers whole, fortified, enriched, or improved (designed) foods [30].

In 2012, FFC (Functional Food Center) announced the new concept of functional food as: "natural or processed foods containing essential or nonessential biologically active compounds, which in specific amounts provide a clinically proven and documented health benefit for the prevention, management, or treatment of a chronic disease." This means that a functional food can be:

- Natural food.
- Food to which a component has been added.
- Foods to which a component has been removed.
- Foods to which the nature of one or more components has been changed.
- Food in which the bioavailability of one or more of its components has been modified.
- Any combination of the above possibilities [31].

At present, these foods are being greatly developed with emphasis on the following functions [31]:

- Regulation of basic metabolic processes: Foods that improve metabolic efficiency are sought. Metabolic efficiency includes glycemia optimization and foods that improve this would produce moderate glucose peaks. This involves developing new ingredients such as hydrogenated carbohydrates or trehalose.
- Defense against oxidative aggressions: The paradoxical relationship (i.e., respiration) is known, and certain toxic or harmful reactions occur, such as those occurring in the presence of reactive oxygen species (ROS) that act as powerful antioxidants. These possibly contribute to the appearance of aging processes, heart disease, cancer, cataracts and degenerative pathologies of the nervous system, such as those that occur in Parkinson's and Alzheimer's. The organic processes that defend against ROS can be complemented by several substances widespread in numerous foods, such as vitamin E, C, and carotenoids, as well as polyphenols of plant origin, which could reinforce the panoply of functional foods against oxidative aggression.
- Circulatory system: Functional foods may play a role in the different predisposing factors of cardiovascular diseases: arterial hypertension, vessel integrity, dyslipidemias, oxidized lipoproteins, elevated levels of homocysteine, increased blood coagulation, and low circulating vitamin K concentrations. Thus, blood lipids can be modified by the presence of certain fatty acids, fiber, and antioxidants, such as flavonoids in the diet. Vegetable components, such as phytosterols, may be able to lower LDL-cholesterol (LDL-C). The overall vascular integrity could also benefit from an increased concentration of folates, vitamin B6 and B12 in the diet, which will reduce plasma concentrations of homocysteine.

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- Digestive system: The balance and variety of the microbial flora in the intestine are important factors in the maintenance of health. Prebiotics, probiotics, and symbiotics are considered as functional foods in this balance of the predominant flora in the intestine.

6. Potential functional foods and bioactive compounds with application in the treatment of T2DM

Currently, several foods with potential roles in the treatment of T2DM are associated. Mainly, the roles of nopal, soy, and oats are recognized because of their hypoglycemic, insulinomimetic and lipid-lowering effects and of bioactive compounds such as antioxidants and omega-3 fatty acids. Oxidative stress and chronic inflammation are present in fresh fruits and vegetables, teas, and blue fish, respectively. The latter, in clinical studies, are treated as compounds characterized as nutraceuticals, given the low bioavailability they possess as part of a food matrix.

6.1. Nopal

The nopal belongs to the family of cactuses, which are fleshy, thickened, and spiny plants, and to the genus *Opuntia*, which is characterized by extended petals with an articulated stem. *Opuntia streptacantha* is the best studied of this genus and is more cultivated in arid and semi-arid zones of the Mexican territory [32].

Scientific evidence on nopal has shown a correlation between ethnomedical uses and experimental results, since people use this food as an alternative or combined treatment with T2DM drugs [32].

Pharmacological research of the nopal as a hypoglycemic agent began in 1964 and was continued in 1979 by the now-extinct Mexican Institute for the Study of Medicinal Plants (IMEPLAM). Researchers at this institute found that different preparations of liquefied raw nopal, administered by a nasogastric tube to rabbits with hyperglycemia induced by pancreatectomy or by administration of aloxane, produced a hypoglycemic effect. Four years later, Ibanez and Meckes (1983) showed that a semipurified fraction of fresh stem juice of *O. streptacantha* given to normoglycemic rabbits or with induced hyperglycemia produced a significant decrease in blood glucose and triglyceride levels [33].

Trejo-González et al. [34] performed a study in rats with streptozotocin-induced diabetes, who were given a simultaneous administration of *O. fuliginosa* (1 mg/kg) and insulin for 7 days. This induced decreased blood glucose and glycosylated hemoglobin to normal values. These values were maintained when insulin was withdrawn and only the cactus extract was administered.

Laurenz et al. [35] found that in pigs with chemically induced diabetes, oral administration of 250–500 mg/kg of *O. lindheimeri* extract maintained blood glucose at normal levels but did not modify the glycemia of nondiabetic pigs.

Frati-Munari et al. [36] administered 100 g of roasted cactus to both healthy and obese subjects with or without T2DM, 20 min before meals three times a day for 10 days, produced a significant decrease in total cholesterol, triglycerides, and total weight in nondiabetic obese subjects and type 2 diabetes obese subjects and in the glycemia of diabetic subjects. These results suggest that the effects observed with nopal are due to their fiber content. The fiber content is a mixture of lignin, cellulose, hemicellulose, pectin, mucilage and gums, which are capable of decreasing the gastrointestinal absorption of various nutrients and, consequently, decreasing blood levels of cholesterol, triglycerides, and glucose due to lack of absorption.

The group of Frati-Munari et al. [37] performed another study in patients with induced hyperglycemia and showed that the same dose as in the previous study of 100 g of roasted cactus, given to healthy volunteers, 20 min before starting the oral glucose tolerance test, prevented blood glucose elevation at 120 and 180 min and decreased blood insulin concentration. To explain this latter effect, a possible inhibitory action of the fiber on the gastric peptide was mentioned. This substance normally increases the sensitivity of the insulin receptor and induces the release of this hormone in the islets of Langerhans. Unfortunately, neither of these hypotheses have been experimentally studied.

In a subsequent study, it was reported that fresh nopal blotch, whose species was not identified, administered orally to healthy individuals, did not modify the basal glucose or blood insulin concentration. In contrast, an antihyperglycemic action was described in healthy individuals with orally, but not intravenously, induced hyperglycemia. These results suggest that liquefied cactus would only have an antihyperglycemic effect if it is ingested prior to food intake; this effect would prevent the complications of T2DM [37].

The same research group also showed that the decrease in blood glucose in individuals with type 2 diabetes is in direct proportion to the administered doses of roasted cactus. This effect which the authors called "acute hypoglycemia" is believed to be independent of that produced by the fiber at the level of the gastrointestinal tract [38].

This group also found that extracts of fresh crude nopal had virtually no "hypoglycemic" effect when given to type 2 diabetic patients under fasting conditions, whereas roasted cactus produced a "hypoglycemic" effect in the same type of patients but not in normoglycemic healthy subjects. These results call into question whether fresh nopal smoothies, which are consumed by much of the Mexican population, have any beneficial effect, especially if consumers are not diabetic [39].

In conclusion, nopal has different effects in the body. However, although it appears that this plant prevents glycemia elevation and has an insulinomimetic effect and lowers blood glucose levels below normal values, these effects only occur under certain conditions, such as the use of large doses (100–500 g) of roasted cactus.

Porrata et al. [40] emphasized the importance of a fiber-rich diet for the control of T2DM. In 6 months, 25 adults with T2DM treated with antihyperglycemic agents and a macrobiotic vegetarian diet with a majority of whole grains, vegetables, legumes, and green tea showed beneficial effects. These were evident in improved blood glucose control, decreased insulin requirements, slowed glucose absorption, increased peripheral tissue sensitivity to insulin, lowered cholesterol levels and triglycerides, controlled body weight and lowered blood pressure.

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It was also observed that insulin has been shown to have a marked lipid-lowering effect in individuals with obesity and dyslipidemia. It has been recommended that 9 g/day of insulin for 4 weeks is sufficient to achieve a favorable effect on the lipid profile [40].

6.2. Soy

Soybean (*Glycine max*) is a species of the leguminous family (*Fabaceae*) cultivated for its seeds, which have medium oil and high protein content. Its composition is based on 40% protein and 20% oil. It is considered as the legume with the highest contribution of protein and its consumption produces hypoglycemic and hypolipidemic benefits, among others [41].

Céspedes et al. [42] conducted a study with 40 patients with T2DM to evaluate the effect of soy protein in this pathology. All patients received three servings of soy protein weekly as a nutritional contribution and performed physical exercises. The effect of the soy protein-enriched diet was highly significant for HDL cholesterol, suggesting that it could participate in the control of plasma concentrations of this lipoprotein by helping metabolic control of dyslipidemia, which is known to be a metabolic alteration characteristic of T2DM.

Garrido et al. [43] stated that soy consumption could confer benefits in the prevention of cardiovascular diseases, risk factors of which are T2DM, obesity, and corresponding dyslipidemias. In 2000, the state agency for the US Food and Drug Administration (FDA) allowed the use of a "health claim" for soy protein, associating consumption of this protein with a low saturated fat diet, with a decreased risk of cardiovascular disease. This measure was based on studies included in a meta-analysis of 38 controlled clinical studies using soy protein from the above, and it was concluded that the substitution of animal protein for soy protein significantly decreased total cholesterol, LDL-cholesterol and triglycerides without affecting HDL-cholesterol (HDL-C), and the effects were higher in subjects with higher basal cholesterol.

Each subject received six randomly tested foods: a standard glucose drink or a commercial low-carbohydrate soy drink (Ades Natural Light and Ades Chocolate Light), peanuts, a high-carbohydrate soy milk, or fiber drink. Before each session, the subjects were weighed and interviewed. Only water was allowed to be consumed during fasting, no caffeinated food was allowed. The subjects did not consume legumes and were not allowed to drink alcoholic beverages. The results showed that soy beverages should contain at least 6.25 g of protein per serving and that four servings per day should be consumed for a long time to see a possible beneficial effect on the blood lipid concentration. It is also recommended that soy products have a low concentration of maltodextrins and, if possible, contain soluble fiber to maintain low glycemic indexes and be usable in obese or diabetic patients. The consumption of soy protein (0.5 g/kg/day) in diabetic patients with renal impairment reduces the excretion of urinary albumin and increases HDL cholesterol, as well as improving glomerular filtration [44].

6.3. Oats

Oat is an annual herbaceous plant, belonging to the grass family. The most cultivated species are *Avena sativa* and *Avena byzantina*. It is rich in proteins of high biological value, fats and a large number of vitamins and minerals. It is the cereal with the greatest proportion of vegetable fat; 54% unsaturated fats and 46% linoleic acid. It also contains readily absorbed carbohydrates

in addition to calcium, zinc, copper, phosphorus, iron, magnesium, potassium and sodium. In addition, it contains vitamins B1, B2, B3, B6 and E and contains a good amount of fiber, which is less important than nutrients, but contributes to good intestinal functioning [45].

Cabrera Llano and Cárdenas Ferrer [46] stated that in the past 30 years, multiple studies have shown that the administration of dietary fiber could reduce blood glucose levels in patients with both type 1 and type 2 diabetes.

The American Diabetes Association (ADA) continues to recommend a fiber intake between 20 and 35 g/day, both soluble and insoluble, to maintain better glycemic and insulin control, with the soluble fraction being the most effective in glycemic control [47].

The mechanisms proposed are delayed gastric emptying; decrease in glucose uptake by being trapped by fiber viscosity and thus less accessible to the action of pancreatic amylase and short chain fatty acid production; and propionate influences gluconeogenesis by reducing the hepatic production of glucose. Butyrate acts by reducing peripheral resistance to insulin by reducing the production of TNFα. Insulin resistance is one of the most important factors involved in the metabolic syndrome [48].

It is also important to take into account that insulin has, in addition to its metabolic action, an effect on vascular endothelium that facilitates the progression of atherogenesis. Therefore, it is proposed that oat hypoglycemic function is important in patients with T2DM and can be an alternative for the treatment of this. However, the hypolipidemic effect of oats is also noteworthy [48].

Regarding the lipid-lowering effect of oats, Kerckhoffs et al. [49] stated that daily consumption of approximately 3 g of soluble fiber can decrease total cholesterol by 0.13 mmol/L in normocholesterolemic and 0.41 mmol/L in hypercholesterolemic drugs, which would be a mechanism of prevention for one of the metabolic alterations of T2DM.

Ruiz et al. [50] carried out a study whose objective was to determine the effect of *Avena sativa* on the lipid profile of patients between 20 and 60 years old with diagnoses of dyslipidemias. Patients consumed 60 g of liquefied oats in water daily for 3 months, and total cholesterol, triglycerides, and LDL were measured at the beginning at 4 and 12 weeks. The results showed statistically significant decreases in total and LDL-C, without major changes in HDL-C and triglycerides.

Furthermore, a study performed by Raasmaja et al. [51] evaluated the effect of drink with symbiotic on the reduction of cholesterol, triglycerides, and glucose control by in vivo analysis with a model of 24 rats with genetic obesity exhibiting similar effects to the metabolic syndrome. These rats were randomly divided into three groups: group 1 control (water), group 2 (symbiotic), and group 3 (malted oats). Measurements of glucose, total cholesterol, and triglycerides in blood plasma were taken for 3 months on six occasions. The results showed that rats that consumed symbiotic beverages had decreased glucose, triglycerides, and weight. However, groups 1 and 3 showed a greater reduction of cholesterol in comparison with group 2. Therefore, it was concluded that the consumption of a symbiotic drink based on malted oats and *Lactobacillus casei* exerted a positive effect on the reduction of glucose and triglycerides in addition to showing a tendency for decreased weight. This type of drink may be a safe alternative for patients with T2DM since, in addition to glucose control, it exerts a lipid-lowering effect and a decrease in body weight.

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6.4. Antioxidants

Dietary antioxidants play an important role in the defense against aging and chronic diseases such as T2DM, as these substances inactivate free radicals involved in oxidative stress and prevent its propagation. As previously described, T2DM is characterized by a chronic oxidative state. Therefore, the inclusion of antioxidants in the diet contributes to counteracting the effects of the oxidative state on the organism [52].

Supplementation of the diet with natural antioxidants may have a beneficial effect in improving the morbidity and mortality of diabetic patients, so that they could prevent and delay the development of chronic complications of T2DM [53].

Yusuf et al. [54] performed a study to evaluate the possible effects of antioxidants in the prevention and treatment of T2DM complications. In most studies, vitamin E was isolated or in combination. The doses of vitamin E used were 300–1800 IU/day, generally in the form of alpha-tocopherol. However, there were no significant data demonstrating a beneficial effect of vitamin E in the prevention of T2DM, but a beneficial role of vitamin E in endothelium-dependent vasodilation was observed in subjects with cardiovascular risk, such as diabetes. This directly associates improvement of function of endothelial activity with the reduction of oxidative stress, supporting that the benefit of vitamin E on endothelial function depends in part on its antioxidant effects.

Geohas et al. [55] evaluated metabolic effects of supplementation of chromium in different doses or chromium combined with biotin in a total of 216 type 2 diabetic patients. The study showed a reduction of glycosylated hemoglobin of up to 2%, postprandial glycemia, fructosamine, insulinemia, total cholesterol, HDL/LDL ratio, triglycerides, and atherogenicity index.

In addition, Lu et al. [56] found certain metabolic benefits for patients with T2DM by supplementing the diet with 3000 mg/day of vitamin C in a clinical trial. The metabolic benefits in the vitamin C group were manifested as a tendency to decrease glycosylated hemoglobin and total cholesterol, although there were no changes in the levels of interleukins, C-reactive protein, or in the oxidation of LDL-cholesterol particles.

Moreover, Porrata et al. [40] showed that the consumption of a large amount of green tea in the diet was related to the metabolic control of T2DM, due to the polyphenols it contains. These substances are considered as the main active ingredients in the protection against oxidative damage and in the anti-inflammatory activities of T2DM. They can also increase the activity of insulin, demonstrating an increase of insulin in vitro of more than 15 times. This potentiating activity is attributed to the epigallocatechin gallate contained in green tea.

This study described the benefits of tea on hypercholesterolemia and hypertriglyceridemia, which are metabolic alterations related to T2DM. This antilipemic effect of tea is due to the action of polyphenols leading to a decrease in the absorption of fats, as well as reduced fat storage in the liver and heart [40].

Likewise, Montano et al. [57] conducted a study of 22 patients (nine with T2DM), giving them 100 mg orally of coenzyme Q10 twice a day for 12 weeks. This resulted in a significant decrease in cholesterol and LDL levels, as well as glycosylated hemoglobin levels.

6.5. Omega-3 fatty acids

Long-chain polyunsaturated fatty acids (PUFAs) are dietary components that participate in multiple physiological processes, where they play a structural role in the phospholipids of cell membranes and are substrates for the synthesis of various physiological mediators. Within the PUFAs are two main groups: the omega-3 (ω-3) and omega-6 (ω-6) fatty acids. These are essential fatty acids (EFAs) for humans because the enzymatic machinery necessary to biosynthesize them is absent [58].

The first exponent of omega-3 fatty acids is α-linolenic acid which, via desaturases and elongases, can be transformed into eicosapentaenoic acid (EPA) and subsequently into docosahexaenoic acid (DHA) [59].

Food sources of α-linolenic acid are foods of plant origin, especially oils (soybean, flax, canola, among others) and nuts (almond, walnut, peanut, among others). The nutritional source of PUFAs derived from these is food of animal origin. Arachidonic acid (AA) is found in meats (beef, lamb, and pork). EPA and DHA are found in both marine animals and vegetables, particularly in fish with a high fat content, such as tuna, horse mackerel, and salmon, among others. AA, EPA, and DHA are important structural components of membrane phospholipids and are the substrates for the formation of a series of lipid derivatives called eicosanoids (derived from 20 carbon atoms in the case of AA and EPA) and docosanoids (derived from 22 carbon atoms, in the case of DHA), which exert important actions in cellular metabolism [60, 61].

Clinical and epidemiological evidence from multiple studies allows us to establish that ω-3 PUFAs are ideal therapeutic candidates for the prevention and/or treatment of a number of pathologies, especially those where inflammation plays a major role in its development as T2DM [62, 63].

Dietary supplementation with EPA and DHA can reduce the production of pro-inflammatory cytokines such as interleukin-1, interleukin-6, interleukin-8, and tumor necrosis factor-α (TNF-α), which are released when macrophages and monocytes are activated. Although these cytokines are potent activators of immune function, the excess activity of these substances contributes to pathological inflammation [64, 65].

Petrova et al. [66] obtained the first data that showed the cardioprotective effects of ω-3 PUFAs. This arose from studies performed in Eskimos (Inuits), who, despite having a high fat intake (more than 30% of energetic requirements), presented a very low incidence of cardiovascular diseases, identifying animals of marine origin (mammals and fish rich in these lipids) as the dietary source of these fats. These results were confirmed in studies carried out in populations with similar diets, which showed a low incidence of cardiovascular diseases.

Manerba et al. [67] conducted a study demonstrating that fish oils lowered plasma cholesterol and TG levels through the inhibition of very low-density lipoproteins (VLDL) and TG biosynthesis in the liver and unchanged biosynthesis of high density lipoproteins (HDL). They also indicated that ω-3 PUFAs have a number of potentially beneficial effects on smooth vascular muscles, by reducing intracellular calcium loss and decreasing smooth muscle cell proliferation (through the inhibition of growth) and increased production of nitric oxide. It is known that one of the main metabolic complications of a patient with T2DM is dyslipidemia, and ω-3 is considered as an alternative treatment for T2DM and, because of this, can be used to treat dyslipidemias.

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Manerba et al. [67] also stated that the beneficial effects on cardiovascular health attributed to ω-3 PUFAs are the result of the following mechanisms: decreased plasma TG and LDL cholesterol, increased HDL cholesterol, decreased blood pressure, reduced platelet aggregation, and decreased incidence of arrhythmias.

Geleijnse et al. [68] noted that the type and form of fish preparation determine the cardioprotective effects of ω-3 PUFAs. The consumption of fish rich in ω-3 PUFAs (tuna, horse mackerel and salmon, among others) produced a significant decrease in the risk of presenting cardiac ischemia. This effect is observed when the fish is consumed roasted or baked, but not when consumed fried.

Nasiff-Hadad and Meriño [69] performed a review of the beneficial and detrimental effects of omega-3 fatty acids in subjects with T2DM, arterial hypertension and dyslipidemias, and their effects on hemostasis and other organs and systems. It was concluded that the ingestion of blue meat fish two or three times a week should be a dietary recommendation for the whole population and that the consumption of fish oils in moderate doses (up to 3 g/day) is beneficial for subjects with T2DM, hypertension and/or dyslipidemias as an adjuvant treatment. In these cases, this diet would also decrease platelet aggregation and reduce the synthesis of chemical mediators of inflammation. However, high doses of fish oils may be harmful to glycemic control, high blood pressure in susceptible persons and serum levels of LDLs and HDLs.

Table 1 shows a summary of the doses of the main foods or bioactive compounds used for the treatment of T2DM and which have updated evidence for their effects.

Food/bioactive compound	Dose	Effect	Reference
Nopal	300 g/day (roasted)	Significant decrease in total cholesterol, triglycerides, body weight, and glycemia	[39]
Insulin	9 g/day by 4 weeks	Improvement of the lipid profile	[40]
Soy protein	0.5 g/kg/day	Reduction of urinary albumin excretion, increase in HDL cholesterol and improve glomerular filtration	[44]
Soluble fiber	3 g/day	Total cholesterol reduction	[49]
	25–30 g/day	Delayed gastric emptying, decreased glucose uptake and short-chain fatty acid production	[47]
Liquefied oats with water	60 g/day	Significant decrease in total cholesterol and LDL	[50]
Vitamin E	300–1800 UI/day (α-tocoferol)	Improvement of endothelial function directly with the reduction of oxidative stress	[54]
Vitamin C	3000 mg/day	Decreased glycosylated hemoglobin and total cholesterol	[56]
Q10 coenzyme	100 mg/day (oral administration)	Significant decrease in the levels of cholesterol, LDL and glycosylated hemoglobin	[57]
Omega-3	3000 mg/day	Decreased platelet aggregation and reduced synthesis of chemical mediators of inflammation	[69]

Table 1. Food and bioactive compounds used in the treatment of T2DM.

7. Conclusion

T2DM is a complex disease with world prevalence, with important oxidative and proinflammatory components, in which lies its chronicity and complication. Nutrition based on the biological effects of food, beyond its nutritional component, is a dietary alternative that has repercussions on the health status and quality of life of patients with T2DM.

A diet based on the use of antioxidants, omega-3, or foods, such as soybean, nopal and oats, contributes to a better status of the metabolic imbalance produced in T2DM, as a product of carbohydrate metabolism, oxidative stress and inflammatory processes, with significant improvement in the biochemical and clinical markers that characterize this disease. In addition, the design of new policies and educational materials for this population should have a new direction, based on the functional potential of food, where studies have shown effective doses to counteract the chronicity and presence of complications.

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