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Functional Foods in the Therapeutic Management of Diabetic Gastroenteropathy

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1. Abstract

Diabetic gastroenteropathy is one of the main morbidities in long-term diabetic patients, which causes several symptomatic manifestations, such as heartburn, abdominal pain, nausea, vomiting and even constipation, diarrhea and fecal incontinence. Its pathophysiology differs for each organ and may be caused by neuropathy of the autonomic nervous system, by loss of interstitial cells in Cajal, as well as by oxidative stress resulting from hyperglycemia. Its main therapeutic interventions include maintaining glycemic control.

In such context, nutritional therapy based on functional foods might emerge as an alternative treatment for diabetic gastroenteropathy due to the presence of bioactive compounds that assist the glycemic control, improving the quality of life of patients. Therefore, this study aimed to investigate, in the scientific literature, functional foods that have a role in glycemic homeostasis and the diabetic complications of the gastrointestinal tract. Cinnamon, oats, guava, yacon potatoes, pumpkin, flaxseed and avocado were among the functional foods studied here.

2. Keywords: Diabetic gastroenteropathy; Glycemic control; Functional foods

3. Introduction

Diabetes mellitus (DM) is a condition characterized by hyperglycemia, resulted from defects in the action and / or secretion of insulin. The global prevalence of DM is increasing, with 429.9 million patients in 2017 and that number is estimated to increase to 628.9 million by 2045 [1].

Diabetic gastroenteropathy (DGE) is one of the most common complications in diabetic patients and corresponds to a dysfunction in the motility of the gastrointestinal tract (GIT). In the stomach, dysmotility is known as gastroparesis, one of the most common diabetic complications of GIT [2]. Gastroparesis promotes a delay in gastric emptying, which contributes to the onset of gastroesophageal reflux and, consequently, symptoms related to the disorders such as heartburn, nausea and vomiting [3]. In the intestine, rectum and anus, dysmotility causes impaired intestinal transit, which may speed up or slow down the passage of the bolus or the fecal matter, causing abdominal pain, diarrhea, constipation and even fecal incontinence [4].

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The pathophysiology of DGE involves: impairment of the motility of the gastrointestinal tract by autonomic neuropathy; loss of Cajal's interstitial cells; and oxidative stress caused by chronic hyperglycemia. DGE clinical manifestations significantly impair quality of life, as well as increase the morbidity of patients [4,5]. Therefore, early treatment of DGE is important in order to stabilize blood glucose control and provide symptom relief.

The treatment of DGE is largely based on drugs with prokinetic and / or antiemetic effects; however, currently-available treatments have major limitations [2]. Current therapeutic strategies include blood glucose control and dietary modifications [6]. In this context, functional foods stand out for the presence of natural compounds with beneficial effects on DGE, such as anti-hyperglycemic and antioxidant activity [7]. Thus, this study aimed to search in the literature for functional foods with action on glycemic homeostasis as a strategy to reduce hyperglycemia and the DGE-associated symptoms, with a focus on researches in the evaluation of the effects on health and mechanisms of action of cinnamon, oats, guava, yacon potatoes, green tea, pumpkin, flaxseed and avocado.

4. Epidemiology

The great prevalence of GDE in diabetic patients was identified in both Type 1 [8] and Type 2 Diabetes [9]. Assessing the prevalence of gastrointestinal symptoms in type 1 and 2 diabetic individuals, have demonstrated that constipation was the most prevalent symptom (24.5%), followed by reflux (14.4%), dyspepsia (14, 1%), abdominal pain (8.7%), fecal incontinence (6.7%) and diarrhea (2.5%) [10]. However, many patients with gastrointestinal symptoms remain undiagnosed and untreated. This may be due to the lack of attention and knowledge of health professionals in identifying such complication. Although gastrointestinal symptoms are generally not considered to be an important cause of morbidity or mortality in patients with DM, these symptoms can influence health-related quality of life and affect productivity and employment [11].

5. Pathophysiology

The pathophysiology of GDE involve several factors, including autonomic neuropathy and interstitial Cajal cell (ICC) injury [12,13]. The process starts in the presence of chronic hyperglycemia, which induces the synthesis of advanced glycation end-products (AGE) or the exacerbated mitochondrial production of free radicals, which, together with inadequate antioxidant defense in DM, promote neural deleterious effects, known as autonomic neuropathy, which can affect both the sympathetic and parasympathetic nervous system, as well as the enteric nervous system [14,15]. ICC are mesenchymal cells found throughout the GIT that play an important role in the motility control, acting in the control of myogenic activity and in the mediation or amplification of the motor neurons effects in the smooth muscle system through the propagation of slow waves [16]. Studies have shown that hyperglycemia causes damage to ICC, which impairs motility coordination and induces gastrointestinal symptoms [17,13].

6. Functional Foods in the Management of Diabetic Gastroenteropathy

Studies that assess the nutritional management of GDE are scarce. In general, it is recommended to split the diet into smaller portions (4 to 6 meals a day). Patients with gastroparesis should eat a diet low in fat and fiber, as they can slow gastric emptying and impair symptoms. Smoking, alcohol consumption, spicy and acidic foods can also delay gastric emptying and should be avoided or excluded [6]. In constipation, a diet rich in fiber can help this complication [18].

As gastrointestinal symptoms are associated with worsening glycemic control [8], functional foods can contribute to the treatment of GDE, as they assist in glycemic homeostasis [19]. Below, the beneficial effect of functional foods and their possible mechanisms of action in GDE therapy are

summarized in Table 1.

Cinnamon

Cinnamon (Cinnamomum cassia) is used as a spice to flavor dishes, but it is also recommended in Ayurvedic and Chinese medicine, possibly due to its tannin content. Cassia cinnamon is rich in cinnamaldehyde, coumarin, cinnamic acid, cinnamyl alcohol and eugenol and has been extensively studied due to the benefits in diabetes [20-24].

Table 1: Overview of functional foods for the prevention and control of diabetic gastroenteropathy.

Functional food	Bioactive compounds	Likely effects	Mechanisms of action
Cinnamon	Cinnamaldehyde, coumarin, cinnamic acid, cinnamyl alcohol and eugenol	Decreases fasting glycemia, glycated hemoglobin and oxidative stress	Insulin-receptor auto-phosphorylation, GLUT-4 synthesis and translocation, PPAR-γ activation, reduction of gluconeogenesis and inhibition of intestinal glycosidases
Oats	Beta-glucan	Reduces glucose absorption and relieves constipation	Slows gastric emptying and reduces the action of digestive enzymes
Guava	Phenolic compounds, e.g. protocatechuic acid, ferulic acid, quercetin	Antioxidant, anti-diarrheal and helps in glycemic control	Increases glycogen storage, reduces oxidative damage, restores antioxidant enzymes, inhibits α-glucosidase and α-amylase
Linseed	Lignins, lignans, α - tocopherol, vitamin E, and omega-3	Reduces glycated hemoglobin and improves constipation	Improves insulin sensitivity, reduces oxidative damage and increases fecal bolus
Yacon potato	Fructooligosaccharide (FOS)	Promotes glucose homeostasis, antioxidant effect and aids in constipation	Stimulates the growth of beneficial bacteria and satiety, reduces MDA, increases the production of GLP-1 and glutathione
Pumpkin	D-chiro inositol	Favors glycemic control, antioxidant effect and improves diarrhea	Promotes glucose transport (GLUT-4) and glycogen synthesis, and increases glutathione levels
Avocado	Polyphenols, carotenoids, oleic acid and fibers	Glycemic and antioxidant control	Inhibition of α-amylase and α-glucosidase enzymes and neutralization of ROS

A blind study using three different amounts of cinnamon (1 g, 3 g or 6 g) for 40 days showed that

cinnamon significantly reduced fasting blood glucose and that the effect persisted after 20 days [24]. In another blind randomized study, cinnamon extract from C. cassia decreased fasting glycemia after 4 months of treatment [23]. In Chinese diabetic patients taking gliclazide simultaneously, cinnamon extract caused a decrease in glycemia and glycated hemoglobin [21]. Yet, another study showed that cinnamon extract reduced fasting glycemia and oxidative stress over a 12-week period [22].

The hypoglycemic activity mechanisms of cinnamon have already been identified. They involve: increased autophosphorylation and reduced dephosphorylation of the insulin receptor, as it increases insulin sensitivity [25]; stimulating the translocation of the glucose transporter type 4 (GLUT-4) via signaling of protein kinase activated by adenosine monophosphate (AMPK) [26]; activation of the peroxisome proliferator-activated gamma receptor (PPAR-γ) [27]; inhibition of gluconeogenesis by reducing the activity of pyruvate kinase and phosphoenolpyruvate carboxykinase [28]; and reduction of intestinal α-glucosidase and pancreatic α-amylase [29]. Thus, whole cinnamon or its aqueous extract has beneficial effects in the prevention and treatment of GDE.

Oats

Oats (Avena sativa L.) is one of the most effective viscous dietary fibers in reducing postprandial blood glucose [30]. Previous studies have shown that beta-glucan is the compound responsible for such beneficial effect and its mechanism of action occurs through an increase in the viscosity of the stomach contents, which delays gastric emptying and reduces the mixing of food with digestive enzymes, decreasing glucose absorption [30,31].

In a meta-analysis, clinical trials were investigated to quantitatively assess whether oat beta-glucan intake has a favorable effect on type 2 DM (DM2). They found that the intake of 2.5 g to 3.5 g / day of oat beta-glucan for 3 to 8 weeks in patients with DM2 could clearly improve glycemic levels, as well as markedly reduce the concentration of fasting plasma glucose and glycated hemoglobin [32].

In addition, beta-glucans have been described for their potential in improving the human intestinal microbiota and for their laxative effect. Reported that the microbial use of complex polysaccharides (such as beta-glucan) is the main stimulus for the formation of the human intestinal microbiota composition [33]. Thus, the acceleration of intestinal peristalsis by intestinal microorganisms is commonly pointed out as a prominent mechanism for the laxative effect and that can contribute to the management of constipation [34]. Thus, oats can be an important ally in the treatment of GDE.

Guava

Guava (Psidium guajava), a fruit native to Mexico, is found throughout South America, Europe, Africa and Asia [35]. Its main use in traditional medicine is as an anti-diarrheal [36], but the most recent ethnopharmacological studies show that guava is used to treat a number of diseases, such as diabetes [37-39]. The effect of guava peel, leaves and fruits as antidiabetic agents has been studied by several authors. Verified the anti-hyperglycemic activity of the ethanolic extract obtained from the bark of the guava stem in hyperglycemic rats induced by alloxan [40]. In another study, the aqueous extract of guava leaves reduced glycemia by increasing the levels of hepatic glycogen in diabetic rats [38]. Likewise, the fruit was able to reduce blood glucose, protect pancreatic β cells against lipid peroxidation and restore the activities of antioxidant enzymes, including superoxide dismutase, catalase and glutathione peroxidase [41]. Guava bark extract has also been shown to be used in the treatment of DM2 by acting as inhibitors of α-glucosidase and α-amylase and reducing glucose absorption [37].

The phenolic compounds, such as tannins, flavonoids, pentacyclic triterpenoids, guaijaverin and quercetin present in the plant are speculated to explain the hypoglycemic effects of guava [42]. According to

[41], the significant anti-hyperglycemic effect of guava is associated with its antioxidant activity, which contributes to the prevention and treatment of GDE.

Yacon Potato

The yacon potato (Smallanthus sonchifolius) is a vegetable with a high content of fructooligosaccharide (FOS) and expressive functional properties, such as stimulating the growth of beneficial bacteria while reducing pathogenic bacteria, regulating the immune response and promoting glucose homeostasis [43].

Analyzed the syrup of yacon roots in healthy volunteers for two weeks (8.74g of FOS / day) and, due to its high FOS content, satiety has increased, especially in female volunteers and, consequently, it can be useful in controlling DM2 [44]. In addition, the beneficial effects of yacon syrup were evaluated by [45] in 55 women and it was observed that the supplementation altered intestinal function, particularly on constipation, since the frequency of defecation during experimental period increased compared to the control group. Therefore, it can be said that yacon syrup would contribute to the improvement of constipation in diabetic patients, who are often affected by this gastrointestinal complication.

7.4 g supplementation of FOS, as well as lyophilized yacon powder, was able to reduce blood glucose of individuals over 60 years old for 9 weeks, which indicated diabetes-control without side effects, such as bloating, flatulence and intestinal discomfort [46]. Another study evaluating yacon flour supplementation produced a significant reduction in malondialdehyde (MDA) levels and increased levels of glutathione peroxidase and glutathione in both the liver and kidneys in diabetic rats, indicating that yacon root flour is a supplement food with potential antioxidant activity [47].

When evaluating the hydroethanolic extract of yacon leaves on antioxidant, glycemic and inflammatory biomarkers in diabetic rats, have observed that daily-administered 100 mg / kg of yacon extract by gavage for 30 days improved hyperglycemia, reduced insulin, interleukin-6 and malondialdehyde and increased the antioxidant capacity of diabetic rats [48]. Thus, the benefit of yacon extract in GDE can be mediated by improving glycoregulation and improving oxidative stress and inflammation.

Finally, the use of yacon may be useful in the treatment of GDE due to the hypoglycemic property related mainly to FOS, which works by improving insulin sensitivity, due to its ability in increasing the production of glucagon-like peptide-1 (GLP-1), a hormone that stimulates insulin production [49].

Pumpkin

Pumpkin is a vegetable grown worldwide [50] and is used in traditional medicine to treat diabetes, as it has hypoglycemic properties [51], in addition to being anti-inflammatory [52].

Investigated the effects of polysaccharide extracted from pumpkin on diabetic rabbits induced by alloxan [53]. They noted that the administration of 75 mg / kg of the polysaccharide showed benefits over glycemic control in the group of diabetic animals compared to the control group, as well as reduced the levels of glycated hemoglobin. Evaluated the physiological effect of pumpkin seed flour in the intestinal tract of rats and showed that the relevant insoluble fiber content of pumpkin flour influenced the fecal material of the animals, since the experimental group presented feces more compact and with greater volume, which can be advantageous in diarrhea, recurrent in diabetics [54]. Another study with diabetic rats, when carrying out the treatment with pumpkin administration orally, for 30 days, has observed a reduction in glycemia and glycated hemoglobin, in addition to a significant increase in the content of glutathione, demonstrating its antihyperglycemic and antioxidant effect [55].

Pumpkin-associated antihyperglycemic action has been attributed to the compound D-chiro inositol,

which acts as a second messenger in the insulin signaling pathways, with importance in the signal transduction and in the composition of the PIK3 enzyme, involved in the glucose cell-uptake process via insulin for glycogen synthesis or to be used as an energy substrate [56,57].

Linseed

Flaxseed (Linum usitatissimum) has been grown in Asia and Europe [58] and has been studied for its functional properties on the progression of cardiovascular diseases, such as diabetes [59].

When evaluating glycemic control mediated by flaxseed, [60] supplemented 360 mg of flaxseed lignan in diabetic patients. They found that there was a high reduction in glycated hemoglobin levels (0.7% reduction) and resistance insulin (3.4% reduction in the HOMA-IR index) compared to the group that did not receive lignan.

Analyzed the chronic use of flaxseed on constipation of a group of women with constipation who were subjected to the daily use of 1 tablespoon of brown flaxseed seed in half a glass of water in the morning for 6 months, assessing the frequency of defecation each month [61]. It was concluded that there was a considerable improvement in constipation in approximately 75% of the participants after 6 months of treatment. Therefore, it is proven that flaxseed can influence DM-related both hyperglycemia and constipation.

In addition, bioactive compounds (lignins, lignans, α - tocopherol, vitamin E) present in flaxseed also have antioxidant properties, preventing membrane peroxidation and neuronal oxidative damage [62].

Avocado

Avocado (Persea americana) is a fruit native to Mexico and Central America, characterized by its large amount of fat consisting mainly of monounsaturated fatty acids (oleic and palmitoleic acids), with an emphasis on oleic acid which comprises 45% of fatty acids totals [63-65].

Due to the great variety of lipophilic antioxidants and high amount of oleic acid, avocado has played a beneficial role against the effects of DM-related oxidative stress. A study with streptozotocin-induced diabetic rats demonstrated that the consumption of avocado oil was able to neutralize the production of mitochondrial ROS [66].

In addition to the benefits of oleic acid, avocado also has a large amount of fibers, which act in the prevention of DM. A study carried out for investigating the effect of avocado paste in rats on a high-fructose hypercholesterolemic diet showed lower blood glucose levels, which was attributed to its large amount of fiber, in addition to the presence of bioactive compounds such as polyphenols and carotenoids [67].

The beneficial effects of avocado leaf and peel extract on DM2 were also investigated. The avocado peel extract showed the greatest inhibition against the enzymes α-amylase and α-glucosidase, while the leaf extract significantly inhibited α-glucosidase, preventing carbohydrate digestion and reducing the impact of carbohydrate hydrolysis in the bloodstream. Finally, all parts of the avocado can be used for the prevention and / or as an adjunct in the treatment of DM and its complications [68].

7. Conclusion

Before what was exposed in this study, it is concluded that diabetic gastroenteropathy can be prevented and treated by glycemic control through the supplementary use of the evaluated functional foods associated with a healthy diet. However, clinical studies are needed to assess the effect of functional foods in the treatment of gastrointestinal symptoms.

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