

Effect of Ginger (*Zingiber officinale*) Supplementation on Diabetes: An Update

Araujo AJS¹, Jesus-Lima JCR²,
Otoch JP¹ and Pessoa AFM^{2*}

Abstract

Diabetes Mellitus (DM) is a metabolic syndrome with multifactorial etiology that has a considerable impact on health and its costs, especially in developing countries. It is postulated that oxidative stress plays an important role in the secondary complications of diabetes. Antioxidant supplements from the diet are considered alternatives for the treatment of DM, with ginger (*Zingiber officinale*) being one of them. Its therapeutic effects have action on insulin sensitivity and protect the body from complications caused by diabetes. However, few articles synthesize the beneficial effects of administration of *Z. officinale* on diabetes. For this purpose, a bibliographic research was carried out on the scientific production of the antidiabetic effect of ginger supplementation. The results show that ginger has hypoglycemic potential and reduce diabetic complications and should, therefore, be considered in the treatment of this disease.

Keywords: Ginger; *Zingiber officinale*; Diabetes mellitus; Insulin resistance; Oxidative stress; Anti-inflammatory; Antidiabetic

Received: November 26, 2018; **Accepted:** December 03, 2018; **Published:** December 09, 2018

Introduction

Diabetes mellitus (DM) represents a heterogeneous group of metabolic alterations that present in common hyperglycemia, resulting from defects in insulin action, insulin secretion or both [1]. According to the American Diabetes Association (ADA) [2], it is estimated that the world's population with diabetes is close to 387 million and reaches 471 million in 2035. Moreover, approximately 80% of these diabetics are known to live in developing countries, where infectious diseases are still at risk, affecting younger age groups [2]. Chronic hyperglycemia, a basic characteristic of diabetes mellitus, results in oxidative stress [3], which plays an important role in the development of secondary complications of diabetes, such as heart disease due to atherosclerosis [4] or myocardial hypertrophy [5]; systemic arterial hypertension and endothelial dysfunction [6]; cataract [7], diabetic retinopathy [8]; sexual dysfunction [9]; neurological damage [10] and difficulty in wound healing [11]. Despite having new therapeutic modalities [12], DM is still considered a challenging disease. The use of dietary supplements for the treatment of DM, which has always been encouraged by antique physicians and traditional medicine, has gained considerable attention from researchers in recent years to discover the biopharmaceutical activities of such dietary components, naturally rich in various phytochemical components

[13]. Ginger (*Zingiber officinale*) is a world-known spice and has been used for over 2500 years in traditional Chinese medicine for the treatment of respiratory diseases (rhinitis, asthma), inflammation (rheumatism), heart disease (hypertension, palpitations, cardiopathies), gastrointestinal tract (diarrhea, constipation, vomiting, poor digestion) and metabolic diseases (diabetes) [1]. The aim of the present article was to present the effects of ginger on diabetes and its secondary complications. Although several reviews have been written that focus on specific aspects of *Z. officinale* (including anti-cancer effect [14] and anti-emetic effect [15]), few of them synthesized the beneficial effects of *Z. officinale* administration on diabetes. Thus, we will briefly describe the phytochemical properties of *Z. officinale* as well as the possible mechanisms of herb's action on diabetes and the associated complications and discuss the latest experimental studies/clinical trials available in the scientific literature to evaluate the beneficial effects of *Z. officinale* on diabetes and its complications.

Literature Review

Botanical classification and composition

- 1 Institute of Biomedical Sciences, University of Pernambuco, Pernambuco, Brazil
- 2 University of Sao Paulo Medical School, Sao Paulo, Brazil

*Corresponding author: Pessoa AFM

✉ anabiorq@usp.br

University of Sao Paulo Medical School, Sao Paulo, Brazil

Tel: 551130617345

Citation: Araujo AJS, Jesus-Lima JCR, Otoch JP, Pessoa AFM (2018) Effect of Ginger (*Zingiber officinale*) Supplementation on Diabetes: An Update. Am J Phytomed Clin Ther Vol.6 No.3:13

Zingiber officinale, commonly known as ginger, belongs to the *Zingiberaceae* family that originates in Southeast Asia. *Z. officinale* is an edible rhizomatic herb that is often used as seasoning throughout the world. The ginger rhizome is elongated, reasonably flattened, and its coloration ranges from golden yellow to bright brown, containing longitudinal grooves [16]. The literature reports that ginger contains many chemical constituents, and that these vary according to the place of origin or the form of presentation (dry or fresh form), since the drying leads to the alteration of its composition. Ginger can also be presented in powdered, crystallized form or in solution, which promotes further changes in its composition [17]. The chemical components of ginger can be volatile or non-volatile, the latter being responsible for the characteristic smell and taste of ginger. Among the volatile compounds are sesquiterpene hydrocarbons, such as zingiberene (35%), curcumene (18%) and farnesene (10%) [16]. The non-volatile compounds give the ginger the spicy taste, these being zingerone derivatives, although other non-volatile substances are also recognized for their pharmacological properties, such as gingerols, shogaols and paradols [4,18]. Both gingerols and shogaols are very important phenolic components, since they have pharmacological properties that are beneficial to health [1].

Antidiabetic effects of ginger in experimental studies

Experimental models have played important roles in the investigation of many therapeutic agents [6,19]. To evaluate the antidiabetic effects of *Z. officinale*, streptozotocin- (STZ) or alloxan-induced animal models have been extensively studied [7-10]. STZ stimulates the production of reactive species, which leads to the destruction and disjunction of β (beta) cells from pancreatic islets [20]. According to Eleazu et al. [19], STZ-induced animal models are able to mimic many of the acute and chronic complications of diabetes, besides being easily reproducible. In turn, alloxan has specific cytotoxicity for β -cells of the pancreas, causing damage to pancreatic islet blood vessels, cell death, and clinical picture of type 1 diabetes mellitus [21]. In the following subsections, we briefly discuss the antidiabetic effects of *Z. officinale* which were evaluated using various experimental animal models.

Neuroprotective effect

One of the mechanisms involved in neuronal injury in diabetes is the increase in the generation of reactive species due to the high intracellular concentration of glucose, and lipid peroxidation [22]. Oxidative stress results in the depolarization of the internal mitochondrial membrane, release of cytochrome C into the cytosol and, ultimately, induction of apoptosis by caspase-3 (CPP32) [23]. Recent studies indicate that the administration of ginger showed a neuroprotective effect in STZ-induced diabetic rats, probably because the root is a fount of antioxidants, including gingerols and shogaols [10,22]. In the study conducted by Shanmugam et al. [10], STZ significantly decreased antioxidant enzyme levels and increased the level of malondialdehyde (MDA) in the mitochondrial fractions of the cerebral cortex, cerebellum, hippocampus and hypothalamus of STZ-induced diabetic rats compared to controls. Continuous treatment with ethanolic

extract of ginger (200 mg/kg body weight) for 30 days was able to decrease the activity of antioxidant enzymes and helped to reduce the level of MDA in different parts of the brain compared to STZ-induced diabetic rats untreated [10].

Antiglycant effect

Advanced glycation end products (AGEs) are related to the development of several pathologies associated with DM, including diabetic cataract (diabetic retinopathy), arthritis, atherosclerosis, chronic renal failure, Alzheimer's disease, nephropathy and neuropathy [7]. AGEs form covalent bonds with proteins present in cells and cause changes in the structure and function of cell matrices, basement membranes, and vessel wall components. They also interact with AGEs binding receptors (RAGE) on the cell surface, leading to pro-inflammatory activation [13]. To assess the antiglycant potential of ginger *in vivo*, Saraswat et al. [7] used two different concentrations of ginger powder (0.5 or 3%) for two months in STZ-induced diabetic cataract. The slit-lamp biomicroscopic examination showed that treatment with ginger not only prevented the onset, but also helped to decrease the progression of cataract in STZ-induced diabetic animals compared to untreated STZ-induced diabetic animals. In addition, treatment with ginger also prevented the formation of AGEs, such as carboxymethyl-lysine, and reduced the stress caused by hyperglycemia in the eye lens compared to untreated diabetic animals. Dongare et al. [8] emphasize that formation (and accumulation) of AGEs is one of the metabolic pathways responsible for the inflammatory response in STZ-induced diabetic rats. In these, AGE exposure was associated with increased levels of tumor necrosis factor- α (TNF- α), nuclear Kappa B factor (NF- κ B) and vascular endothelial growth factor (VEGF), and treatment with 6-gingerol for 24 weeks was effective in significantly reducing the three parameters. Considering that chronic low-grade inflammation is associated with the pathogenesis of diabetes, it is likely that the effects of ginger extract may be partially attributed to the direct anti-inflammatory actions of its polyphenols, resulting from NF- κ B signaling and TNF- α suppression [4,8].

Antioxidant effect

Oxidation is a metabolic process that leads to the production of energy necessary for the essential activities of cells. However, the oxygen metabolism in living cells also induces to the production of reactive species [9]. Oxidative stress is the imbalance between the production and the removal of reactive oxygen species (ROS), associated to the decrease of the antioxidant system. Increased oxidative stress contributes substantially to the pathogenesis of diabetic complications [13]. Several studies using diabetic animal models have shown that ginger extracts may enhance the activities of various antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), and improve glucose transport by the GLUT-4 transporter and increase the secretory function of pancreatic β cells [1,10,13]. Kota et al. [24] evaluated the dose-dependent effect of ginger in STZ-induced diabetic rats on markers of protein and lipid oxidative damage and observed a reduction of these in liver and kidney after 30 days of treatment.

Effect on carbohydrate metabolism

Researchers speculate that the hypoglycemic activity of ginger may be associated with normalization of the activity of enzymes that participate in the carbohydrate metabolism [25-27]. Kazeem et al. [25] observed that STZ-induced diabetic rats showed an increase in the synthesis of the enzymes hexokinase and phosphofructokinase, with consequent elevation of hepatic glucose production, and that the administration of *Z. officinale* polyphenols was able to normalize the action of these enzymes at levels comparable to the control group and to the group of diabetic rats treated with glibenclamide. Similar results were demonstrated by Ramudu et al. [28]. In addition, the main enzymes that control carbohydrate metabolism are α -amylase and α -glucosidase. Activation of these enzymes induces hyperglycemia. *Z. officinale* extract was shown to inhibit the activities of α -amylase and α -glucosidase *in vitro* [26].

Androgenic effect

One of the complications of diabetes is infertility or sexual dysfunction, known to affect male reproductive organs at various levels. Some specialists argue that diabetes-induced infertility occurs by overproduction of ROS, and in this way, the ingestion of antioxidants could protect cells from the damaging effects of oxidative stress by improving sperm quality and increasing the efficiency of male reproductive organs [13]. Ghilissi et al. [9] evaluated the protective effect of dietary ginger for 30 days on the reproductive function of male diabetic rats. Ginger supplementation after alloxan treatment resulted in lower glycemia levels, increased weight of reproductive organs (testes, epididymis, prostate and seminal vesicle), and better sperm counts, motility and serum testosterone levels, follicle stimulating hormone (FSH) and luteinizing hormone (LH).

Effect on organ morphology

In the clinical condition of diabetes, the liver may decrease in weight due to catabolic processes, such as glycogenolysis, lipolysis and proteolysis, resulting from lack of insulin in hepatocytes. Conversely, the kidney tends to increase weight due to glucose overload. These changes may lead to severe microvascular complications of the kidney, participating in the pathogenesis of diabetic nephropathy [19]. Ramudu et al. [28] observed severe degeneration of tubular and glomeruli, focal necrosis of tubules, cystic dilatation of tubules and fatty infiltration in diabetic rats. In this study, the authors demonstrated that injury to cells in the diabetic rats recovered by a 30-day ginger treatment. Administration of *Z. officinale* also repaired pancreatic damage caused by STZ, through cell regeneration and subsequent stimulation of insulin secretion [29]. In the study of Ilkhanizadeh et al. [5], structural changes including moderate fibrosis and proliferation of muscle and coronary cells were also detected in the hearts of diabetic rats when compared to the hearts of control group rats. The authors observed a significant improvement in cardiac tissue and biochemical changes in rats treated with ginger extract when compared to rats in the control group. Treatment with *Z. officinale* extract reduced arginase I activity and expression in the retina of STZ-induced diabetic rats, indicating that the **herbal** may have a promising therapeutic potential for treating

vascular disorders associated with diabetes. The protective effect of ginger appears to result from its antioxidant and anti-inflammatory properties. Due to antioxidants contained in ginger, supplementation increases total antioxidant capacity (TAC) and reduces oxidation of lipids and proteins in DM and other oxidative stress conditions [13,19].

Effect on metabolic profile

Considering the experimental data, it is evident that ginger is effective in regulating glycemia in diabetic rats, as well as improving the lipid abnormalities associated with diabetes due to the antioxidants present in its composition, such as gingerols and shogaols [18,25,30,31]. Kota et al. [24] showed that, when administering ginger at different concentrations, such as 0.5%, 1% and 5%, in STZ-induced diabetic rats, serum glucose, cholesterol and triglycerides levels were reduced in a dose-dependent manner.

Antidiabetic effects of ginger in type 2 diabetes

In addition to the various studies that were conducted with *Z. officinale* and/or its constituents in different types of diabetic animals, some studies [1,3,4,6,32-35] were also conducted in humans with type 2 diabetes to assess the antidiabetic effects of ginger. In these studies, the researchers conducted randomized, placebo and double-blind clinical trials, evaluating 58, 204, 63, 81, 45 and 50 patients with type 2 diabetes, and administered 2 grams/day [32-36] of ginger in capsule, 3 grams/day of ginger powder for making tea [1,6,35], or 1.6 grams of ginger in capsule [3,4]. At the end of the respective treatment periods (**Table 1**), several authors were able to observe reduced levels of glucose, insulin, glycated hemoglobin (HbA1c), homeostasis model assessment (HOMA), quantitative insulin sensitivity check (QUICKI), LDL-cholesterol, triglycerides, C-reactive protein (CRP), TNF- α , MDA, apolipoprotein B (ApoB), and increased paroxonase-1 (PON-1) and TAC, when compared to control. The main conclusions of these clinical trials [1,3,4,6,32-36] on the efficacy of ginger in type 2 diabetic patients are consistent with the results of the numerous animal studies discussed above. In addition to these results, a recent study also points to the importance of ginger in the treatment of symptoms associated with diabetes, such as xerostomia [37].

Materials and Methods

This bibliographic research was developed through a search on the scientific production of the anti-diabetic effect of ginger supplementation. To do so, we analyzed scientific articles published in the period from August 2010 to September 2017, in three scientific databases: LILACS, PubMed and Scientific Electronic Library Online (SciELO). The choice for these databases was due to the content of important national and international journals. The descriptors used in the database searches were "ginger/*Zingiber officinale*", "*Diabetes Mellitus*", "hypoglycemic", "antidiabetic" combined, in Portuguese, English and Spanish. From this initial selection, we found 79 publications.

Inclusion and exclusion criteria

The criteria for screening the articles were to select publications

Table 1 Synopsis of the articles. ALP: alkaline phosphatase; ALT: Alanine aminotransferase; APO: Apolipoprotein; AST: aspartate aminotransferase; BMI: body mass index; CAT: catalase; DHBA: dihydroxybenzoic acid; FBG: fasting blood glucose; FSH: follicle stimulating hormone; GDH: glutamate dehydrogenase; GR: glutathione reductase; GSH: reduced glutathione; GSSG: oxidized glutathione; GPx: glutathione peroxidase; G6PD: glucose-6-phosphate dehydrogenase; HbA1c: Hemoglobin A1c; HDL: high-density lipoprotein; HOMA: homeostasis model assessment; IL: Interleukin; LDH: lactate dehydrogenase; LDL: low density lipoprotein; LH: luteinizing hormone; MDA: malondialdehyde; MDH: malate dehydrogenase; PCNA: proliferation cell nuclear antigen; PCR: C-reactive protein; PGE2: Prostaglandin E2; PON-1: paraoxonase-1; ROS: Reactive oxygen species; SDH: succinate dehydrogenase; sICAM-1: soluble intercellular adhesion molecule-1; SOD: superoxide dismutase; STZ: Streptozotocin; TAC: total antioxidant capacity; TC: total cholesterol; TNF- α : Tumor necrosis factor- α .

Author	Goals	Public	Type of Test	Source	Method	Results
Mozaffari-Khosravi et al. [1]	To determine the effect of ginger powder supplementation on insulin resistance and glycemic indexes in patients with type 2 diabetes.	Type 2 diabetic patients.	Clinical, randomized, double-blind, placebo-controlled trial.	Ginger powder in capsules.	Patients were categorized into 2 groups: ginger (GG) and placebo (PG). GG daily consumed 3 capsules containing 1 gram of powdered ginger, while the other group received capsules with cellulose, both after meals for 8 weeks.	Evaluated 81 patients, all of whom used oral hypoglycemic agents. Daily consumption of 3 g of ginger in capsules decreased FBG, HbA1c, and insulin resistance.
Shidfar et al. [3]	To investigate the effects of ginger on glucose markers, CT, MDA, PCR and PON-1 in patients with type 2 diabetes mellitus.	Type 2 diabetic patients who did not receive insulin, but medications such as metformin, glibenclamide or both.	Randomized, double-blind, placebo controlled.	Ginger powder in capsules.	Participants in the intervention and control groups received 3 grams of ginger powder or placebo (lactose) (in capsules) daily for 3 months.	Evaluated 45 patients. Supplementation with 3 grams of ginger in diabetic patients for 3 months significantly decreased glucose, insulin, insulin resistance, CRP and MDA, and significantly increased PON and TAC compared to the control group.

<p>Arablo et al. [4]</p>	<p>To evaluate the effect of ginger consumption on glycemia, lipid profile and some inflammatory markers in patients with type 2 diabetes mellitus.</p>	<p>Patients with type 2 diabetes, treated with oral hypoglycemic agents, HbA1C between 7% and 10%, BMI between 20 and 35 kg/m²</p>	<p>Randomized, double-blind, placebo-controlled</p>	<p>Capsule containing 800 mg ginger powder</p>	<p>Participants were randomly assigned to two groups receiving ginger or placebo. They consumed 1,600 mg of ginger powder or wheat flour (placebo) (one 800 mg capsule before lunch and one 800 mg capsule before dinner) per day. Participants were instructed not to change their usual diet and physical activity during the study. The intervention lasted 12 weeks.</p>	<p>We evaluated 63 patients. Ginger supplementation significantly reduced FG, HbA1C, insulin, HOMA, triglycerides, total cholesterol, CRP and PGE2 concentrations when compared to the placebo group. There were no significant differences in HDL-cholesterol, LDL- cholesterol and TNF-α concentrations between the two groups.</p>
------------------------------	---	---	---	--	--	---

<p>Ilkhanizadeh et al. [5]</p>	<p>To investigate the effect of ginger extract on apolipoproteins A and B, hyperhomocysteinemia, cathepsin G and leptin alterations, as well as cardiac fibrosis and proliferation of cardiac muscle cells under hyperglycemic conditions <i>in vivo</i>.</p>	<p>Wistar Rats</p>	<p>Experimental, randomized</p>	<p>Ginger extract</p>	<p>The rats were divided into three groups (eight animals each): control (C), non-treated diabetic (NTD), and ginger extract-treated diabetic (GETD) groups Diabetes was induced in 16 rats by a single intraperitoneal injection of STZ (60 mg/kg). In addition to their regular diet, GETD mice received daily 50 mg/kg body weight ginger extract solution intragastric. The control and NTD groups were treated only with vehicle (water). After 6 weeks, blood was collected for biochemical analysis and dissection of the heart for histopathological analysis.</p>	<p>Administration of ginger extract significantly increased the level of apoA compared to the NTD group but remained significantly lower than that in group C. The amounts of cathepsin G and homocysteine in cardiac tissue were lower in the GETD group than in the NTD group. Treatment with ginger extract decreased plasma CRP levels and increased leptin levels in relation to the NTD group. The GETD group reduced PCNA-positive (cardiac myocyte proliferation) indices compared to those found in the NTD group, but the GETD indices remained greater than those in the C group. No significant differences were found between the tissue injury score of the GETD group and group C.</p>
--------------------------------	---	--------------------	---------------------------------	-----------------------	--	---

<p>Azimi et al. [6]</p>	<p>To compare the effects of cinnamon, cardamom, saffron and ginger consumption on markers of endothelial function and blood pressure in diabetic patients</p>	<p>Type 2 diabetic patients, overweight (BMI \geq 25 kg/m²), who did not receive insulin, but medications such as metformin and glibenclamide.</p>	<p>Randomized, double-blind, placebo-controlled.</p>	<p>Powder herbs</p>	<p>All participants went through a 3-week introductory period (run-in) to standardize the consumption of the same tea. Participants were randomized into 4 groups, receiving 3 g of cinnamon, 3 g of cardamom, 1 g of saffron or 3 g of ginger for 1 week. All participants received the amounts indicated for three cups of tea per day. Participants in the control group received three cups of tea without any herb. The intervention lasted 8 weeks.</p>	<p>204 patients were evaluated. There was no significant difference between the various medicinal plants in influencing blood pressure and serum concentrations of sICAM-1. However, consumption of saffron and ginger significantly reduced sICAM-1 concentrations, and consumption of ginger reduced systolic blood pressure compared to baseline.</p>
<p>Saraswat et al. [7]</p>	<p>Investigate the antigenic potential of ginger under in vivo conditions using the STZ-induced diabetic cataract model in rats.</p>	<p>Male Wistar rats at 2 months of age.</p>	<p>Experimental, randomized</p>	<p>Ginger powder</p>	<p>Diabetes was induced by intraperitoneal injection of STZ and the control mice received only the vehicle. While one part of the diabetic animals received AIN-93 diet, another set received 0.5 or 3% ginger in their diet for a period of two months. Progression of cataract was monitored by slit lamp biomicroscope. At the end of two months, the animals were sacrificed to assess non-enzymatic glycation and osmotic stress in the lens of the eye.</p>	<p>The diet with ginger not only delayed the onset, but also the progression of cataract in diabetic rats. Molecular analyzes indicated that the ginger diet significantly inhibited the formation of several advanced glycation products, including carboxymethylisine in the eye lens. In addition, ginger also counteracted the osmotic stress induced by hyperglycemia in the lens of the eye.</p>

<p>Dongare et al. [8]</p>	<p>To investigate the efficacy of ginger rhizome extract, standardized at 5% of 6-gingerol, in attenuating retinal microvascular changes in rats with STZ-induced diabetes.</p>	<p>Wistar rats of both sexes</p>	<p>Experimental, randomized</p>	<p>Ginger extract</p>	<p>Diabetes was induced by intraperitoneal injection of STZ and the control mice received only the vehicle. Diabetic rats were randomly divided into diabetic control group (DC) and diabetic group receiving ginger extract (n=15; 30 eyes per group). The 6-gingerol treated group received 75 mg/kg/day. The experiment lasted 24 weeks.</p>	<p>Oral administration of ginger extract resulted in a significant reduction of hyperglycemia, as well as attenuation of retinal microvascular changes in diabetic rats through anti-inflammatory and antiangiogenic actions.</p>
<p>Ghlissi et al. [9]</p>	<p>To investigate the effects of dietary intake of ginger in MDA (as an indicator of lipid peroxidation), SOD, CAT and GPx (antioxidant enzymes) in the testes, epididymis, prostate and seminal vesicular organs; at the testicular level of AST, ALT, LDH and ALP (markers of cell damage), serum testosterone concentration, sperm counts and motility and glycemia.</p>	<p>Male Wistar rats</p>	<p>Experimental, randomized</p>	<p>Ginger powder</p>	<p>Experimental type 1 diabetes was induced in rats by intraperitoneal injection of alloxan solution. Rats were divided into three groups (8 mice each). Control (Control) and control (Diab) were fed a standard diet while the second diabetic group (Diab+Z) was fed a diet supplemented with 3% ginger powder for 1 month.</p>	<p>Dietary supplementation of ginger after treatment with aloxane resulted in lower serum glucose levels, increased body weight (testis, epididymis, prostate and seminal vesicle), better sperm and motile counts, and increased serum testosterone levels, hormones FSH and LH when compared to the Diab group. The Diab+Z group demonstrated a significant improvement in the level of MDA and in the activity of antioxidant enzymes (SOD, CAT and GPx) in the testis, epididymis, prostate and seminal vesicle, as well as attenuation of cell injury markers (AST, ALT, LDH and ALP) in testicular tissues.</p>

<p>Shanmugam et al. [10]</p>	<p>Investigate the neuroprotective effect of ginger on oxidative damage in the brain parts of diabetic rats induced by STZ.</p>	<p>Male albino Wistar rats aged 6 months.</p>	<p>Experimental, randomized</p>	<p>Ethanol extract of ginger</p>	<p>Rats were divided into 5 groups, with 6 rats each. Normal control: only received vehicle solution. Treatment with ginger: normal rats receiving ginger extract (200 mg/kg body weight) for 30 days. Diabetic control: induction of diabetes by STZ. Diabetics treated with Ginger: diabetic rats receiving ginger extract (200 mg / kg body weight) for 30 days. Diabetics treated with Glibenclamide: Diabetic rats given 600 mcg/kg of glibenclamide for 30 days.</p>	<p>Treatment with ginger, as well as with glibenclamide, reduced glycemia in diabetic rats when compared to the diabetic control group. Treatment with ginger reversed SOD, CAT and GPx to normal levels in diabetic rats. In addition, there was a reduction of lipid peroxidation and an increase in the action of GR and GSH after treatment with ginger in diabetic rats.</p>
<p>Eleazu et al. [19]</p>	<p>To investigate the potential for improved use of ginger on the relative weight of altered organs of rats with STZ-induced diabetes.</p>	<p>Wistar Rats</p>	<p>Experimental, randomized</p>	<p>Ginger powder</p>	<p>The rats in diabetic condition were divided into 2 subgroups (groups 2 and 3), whereas the non-diabetic group formed the first group as follows: Group 1: Normal rats, who received standard diet (non-diabetic control); Group 2: Diabetic control rats; Group 3: Diabetic rats treated with a diet supplemented with 10% ginger powder for 21 days. The rats were followed for this period and afterwards were anesthetized and had liver and kidneys collected and weighed.</p>	<p>Rats in group 3 presented reduction of glycemia, glycosuria and proteinuria when compared to the other groups. Hepatic weights of the diabetic rats of groups 2 and 3 showed a significant decrease compared to non-diabetic rats, whereas there were no significant differences in the kidneys of the diabetic rats of groups 2, 3 and non-diabetic rats.</p>

<p>El-Akabawy and El-Kholy [22]</p>	<p>Investigate whether ginger has protective effects on neuropathological changes associated with the brain of diabetic rats.</p>	<p>Wistar Rats</p>	<p>Experimental, randomized</p>	<p>Ginger Powder</p>	<p>The animals were randomly divided into four groups: control, control+ginger diabetics and diabetics +ginger. Rats from each of these groups were subdivided into three other subgroups in which the rats were sacrificed at 4, 6 and 8 weeks after the start of the experiment. In diabetic and diabetic+ ginger groups, diabetes was induced by intraperitoneal injections of STZ. Control and diabetic groups were fed the standard technique, while control + ginger and diabetic + ginger mice were fed 500 g/kg/day of ginger.</p>	<p>Treatment with ginger significantly reduced blood glucose levels compared to diabetic rats at all experimental times. Ginger supplementation also reduced oxidative stress, apoptosis, and inflammation. In addition, this study revealed that the beneficial effect of ginger was also mediated by the modulation of the astroglial response to injury, reducing the expression of acetylcholinesterase and improving neurogenesis.</p>
<p>Kota et al. [24]</p>	<p>To evaluate the possible protective effects of dietary ginger on oxidative stress and genotoxicity in rats induced by STZ.</p>	<p>Male Wistar NIN mice, 8-9 weeks of age and weighing 175 g</p>	<p>Experimental, randomized</p>	<p>Ginger powder</p>	<p>Rats were randomly divided into four groups of 12 rats per group. They were divided into different control groups, untreated diabetics and diabetics treated with 0.5%, 1% and 5% ginger powder. The animals were monitored for 4 weeks after administration of STZ.</p>	<p>Diabetic rats, whether or not fed with ginger, progressed with weight loss. However, weight loss was lower in diabetic rats fed ginger. There was a significant reduction in the glucose levels of diabetic rats when compared to the diabetic control group, specifically those who received a diet of 1% ginger and 5% ginger. Furthermore, cholesterol and triglyceride levels of diabetic rats fed ginger were lower than those of diabetics in the control group. An increase in SOD, CAT and GPx activity was observed in the liver of rats fed ginger at 0.5%, 1% and levels of 5%, diabetic or not. SOD activity increased in the kidney of diabetics and non-diabetics fed ginger. There was a reduction in MDA levels in the liver and kidney of rats fed ginger at 0.5%, 1% and 5%, both in non-diabetics and in the diabetic group compared to the respective control groups. The DNA damage of ginger-fed rats was significantly lower than in the control diabetic group. There was a significant reduction in the formation of micronuclei in the diabetic group fed ginger at all levels.</p>

<p>Kazeem et al. [25]</p>	<p>To evaluate the hepatoprotective effects of polyphenols extracted from <i>Zingiber officinale</i> in diabetic mice induced by STZ.</p>	<p>Wistar Rats</p>	<p>Experimental, randomized</p>	<p>Extract of free and bound ginger polyphenols.</p>	<p>A total of 40 rats (8 normal, 32 STZ-diabetic rats) were used. Rats were randomly assigned to five groups of eight animals each. Group 1 comprised normal rats that received the vehicle alone (distilled water) and served as normal controls; Group 2 consisted only of STZ-induced diabetic rats; Groups 3 and 4 comprise STZ-induced diabetic rats receiving 500 mg/kg of free and bound <i>Z. officinale</i> polyphenol extracts, respectively. Group 5 consisted of STZ-induced diabetic rats receiving glibenclamide (0.6 mg/kg). The extract was suspended in distilled water and administered daily for 28 days using orogastric tube. After 28 days of administration, the animals were sacrificed.</p>	<p>Groups of diabetic rats treated with 500 mg/kg free and bound polyphenol showed postprandial glucose reduction compared to the diabetic control group. The animals treated with free polyphenol showed a significant reduction in fasting glycemia when considering the beginning and the end of the treatment. There was a significant increase in the activities of antioxidant enzymes in the animals treated with both polyphenols. Similarly, polyphenols normalized the activities of some carbohydrate metabolic enzymes (hexokinase and phosphofructokinase) in the liver of treated rats and significantly reduced liver enzyme activities (ALT and AST). In addition, the administration of <i>Zingiber officinale</i> polyphenol-free extract reduced the imbalance between the generation of ROS and the activity of antioxidant enzymes in diabetic rats.</p>
---------------------------	---	--------------------	---------------------------------	--	--	---

<p>Abdulrazaq et al. [27]</p>	<p>To determine the efficacy of ginger in the treatment of diabetes mellitus using animal models, investigating its effect on the major enzymes of carbohydrate metabolism.</p>	<p>Male Sprague-Dawley rats</p>	<p>Experimental, randomized</p>	<p>Aqueous ginger extracts</p>	<p>The animals were divided into 5 groups. Group 1 was composed of normal control rats. In group 2 were the diabetes-induced animals that were not treated with ginger. The animals in groups 3 to 5 were diabetic and received different oral doses of the ginger extract (100, 300, 500 mg/kg, respectively) for 30 days.</p>	<p>Administration of 500 mg/kg ginger reduced blood glucose by 68% on the 30th day of treatment. This same dose was also responsible for the significant reduction of kidney weight when compared to the control group. Administration of ginger increased the activity of the enzymes glycoquinase, phosphofructokinase and pyruvate kinase in diabetic rats.</p>
<p>Ramudu et al. [28]</p>	<p>To analyze the changes in the activity of cytosolic and mitochondrial enzymes with the supplementation of ginger in diabetic rats, as well as the effects of this supplementation against renal damage induced by STZ.</p>	<p>Male albino Wistar rats aged 6 months</p>	<p>Experimental, randomized</p>	<p>Ethanollic extract of ginger</p>	<p>Rats were divided into 5 groups, with 6 rats each. Normal control: only received vehicle solution. Treatment with ginger: normal rats receiving ginger extract (200 mg/kg body weight) for 30 days. Diabetic control: induction of diabetes by STZ. Diabetics treated with ginger: diabetic rats receiving ginger extract (200 mg/kg body weight) for 30 days. Diabetics treated with Glibenclamide: Diabetic rats given 600 mcg/kg of glibenclamide for 30 days.</p>	<p>Treatment with ginger for 30 days reversed the activity of G6PD, SDH, MDH and GDH to normal levels. Glomerular and tubular lesions of diabetic rats were recovered after treatment with ginger extract.</p>

<p>Lamuchi-Deli et al. [30]</p>	<p>To determine the effects of the hydroalcoholic extract of <i>Z. officinale</i> on the activity and expression of arginase I in the retina of diabetic rats induced by STZ</p>	<p>Male Wistar rats</p>	<p>Experimental, randomized</p>		<p>Rats (16) were randomly assigned to four experimental groups. The untreated healthy and diabetic controls received 1.5 mL/kg of distilled water. Treated diabetic rats received 200 and 400 mg/kg <i>Z. officinale</i> extract dissolved in distilled water (1.5 mL/kg).</p>	<p>Glucose concentration was significantly decreased in diabetic rats treated with the extract as compared to untreated diabetic controls. Treatment with 400 mg/kg extract reduced the activity and expression of arginase I.</p>
<p>Shalaby and Saifan [31]</p>	<p>To evaluate some pharmacological effects of the aqueous extracts of cinnamon and ginger in diabetic obese rats and to elucidate the possible mechanisms.</p>	<p>Male Sprague-Dawley rats</p>	<p>Experimental, randomized</p>	<p>Aqueous extracts of ginger and cinnamon</p>	<p>Forty-two rats were randomized in 6 groups of 7 rats each. Group 1 was negative control (normal) and the other 5 groups were fed a high-fat diet for 4 weeks to induce obesity. Obese rats were thrashed up with diabetics by subcutaneous injection of aloxane (120 mg/kg) for 5 days. Group 2 was maintained obese diabetic (positive control) and groups 3, 4, 5 and 6 received oral cinnamon extract at doses 200 and 400 mg/kg and ginger extract at the same doses, respectively, for 6 weeks.</p>	<p>The extracts significantly reduced body weight and body fat mass; normalized serum levels of liver enzymes; improved lipid profile; led to decreased glycemia and leptin and increased serum insulin levels in obese diabetic rats. Both extracts also increased the activity of the antioxidant enzymes of the kidneys.</p>

<p>Mahluji et al. [32]</p>	<p>To investigate the effects of daily ginger intake on fasting glycemia levels, HbA1c, lipid profile and insulin sensitivity of type 2 diabetic patients over a 2-month period.</p>	<p>Type 2 diabetic patients with a mean BMI of 29.5 kg/m², with no blood pressure abnormalities in the last 2 years Type 2 diabetic patients with a mean BMI of 29.5 kg/m², with no blood pressure abnormalities in the last 2 years.</p>	<p>Randomized, double-blind, placebo controlled.</p>	<p>Capsule containing 1 g ginger powder.</p>	<p>Patients were allocated into two groups. Each individual received a ginger or placebo capsule (cornstarch) twice daily immediately after lunch and dinner for 8 weeks. Subjects were instructed to maintain their diet and physical activity during the intervention. All patients were instructed to maintain the consumption of their usual medicines, according to the medical orientation.</p>	<p>Fifty-five patients were evaluated. Ginger supplementation was able to reduce insulin, LDL-cholesterol, triglycerides, and HOMA levels compared to the placebo group. However, there were no significant changes in fasting glycemia and total cholesterol between groups.</p>
<p>Mahluji et al. [33]</p>	<p>To evaluate the effects of ginger on proinflammatory cytokines (IL-6 and TNF-α) and the acute phase protein CRP in type 2 diabetic patients.</p>	<p>Type 2 diabetic patients who did not receive insulin.</p>	<p>Randomized, double-blind, placebo-controlled.</p>	<p>Capsule containing 1 g ginger powder.</p>	<p>All patients were randomized into two groups of 32 subjects each to receive either a ginger or placebo capsule (control group) twice a day soon after lunch and dinner for 8 weeks. Patients were instructed to maintain their diet and physical activity during the intervention, in addition to maintaining the consumption of their usual medications, according to the medical orientation.</p>	<p>Fifty-five patients were evaluated. Ginger supplementation significantly reduced levels of TNF-α, IL-6 and CRP compared to the baseline. In addition, covariance analysis showed that the group receiving ginger supplementation significantly reduced TNF-α and CRP concentrations compared to the control group. There were no significant changes in IL-6.</p>

<p>Khandouzi et al. [34]</p>	<p>To evaluate the effects of ginger powder supplementation on serum levels of FBG, HbA1c, apo B, apo AI, Apo B/Apo AI and MDA in type 2 diabetics.</p>	<p>Adult diabetic patients who were not on insulin.</p>	<p>Clinical, randomized, double-blind, placebo-controlled trial</p>	<p>Capsule containing 2 g ginger powder</p>	<p>A total of 41 type 2 diabetic patients were randomly assigned to either ginger or placebo groups (22 in the ginger group and 19 in the control group) and received 2 g/day of ginger or lactose powder supplementation as placebo for 12 weeks.</p>	<p>Ginger supplementation significantly reduced the levels of FBG, HbA1c, Apo B, Apo B/Apo AI and MDA, as well as increasing the level of Apo AI compared to the baseline. Meanwhile, levels of FBG, Apo B, Apo B/Apo AI and MDA increased, and Apo AI decreased in the placebo group during the study.</p>
<p>Azimi et al. [35]</p>	<p>To compare the beneficial effects of cinnamon, cardamom, saffron and ginger on markers of fasting glycemia, lipid profile, oxidative stress and inflammatory mediators in patients with type 2 diabetes.</p>	<p>Type 2 diabetic patients, overweight (BMI \geq 25 kg/m²), who did not receive insulin, but medications such as metformin and glibenclamide.</p>	<p>Randomized clinical trial parallel</p>	<p>Powder herbs</p>	<p>All participants went through a 3-week introductory period (run-in) to standardize the consumption of the same tea. Participants were randomized into 4 groups, receiving 3 g of cinnamon, 3 g of cardamom, 1 g of saffron or 3 g of ginger for 8 weeks. All participants received the amounts indicated for three cups of tea per day. Participants in the control group received three cups of tea without any herb.</p>	<p>204 patients were evaluated. Supplementation with cinnamon, cardamom, ginger or saffron for 8 weeks had a significant effect on total cholesterol, LDL and HDL compared to the control group. However, no intervention had any effect on glycemic control, inflammation and oxidative stress. In the intra-group comparison, ginger supplementation significantly decreased F2-isoprostane concentration and CRP levels.</p>
<p>Arzati et al. [36]</p>	<p>To determine the effect of ginger consumption on glycemia, HbA1c and lipid profile in patients with type 2 diabetes.</p>	<p>Patients with type 2 diabetes, treated with oral hypoglycemic and with BMI between 18.5 and 35 kg/m².</p>	<p>Randomized, double-blind, placebo-controlled</p>	<p>Ginger powder in capsules.</p>	<p>Participants in the intervention and control groups received 2 grams of ginger powder or placebo (wheat flour) (two 500 mg capsules were taken before lunch and 2 before dinner) daily for 10 weeks.</p>	<p>Oral ginger supplementation decreased blood glucose levels, HbA1C and LDL/HDL ratio.</p>

<p>Mardani et al. [37]</p>	<p>To examine the effect of ginger spray on reducing dry mouth in patients with type 2 diabetes.</p>	<p>Patients with type 2 diabetes with xerostomia complaint.</p>	<p>Clinical trial</p>	<p>Oral spray containing 1/3 ginger extract.</p>	<p>Each patient (n = 20) was evaluated at three different times (before treatment, after treatment with placebo and after using the ginger spray). The Schirmer test was performed to measure the saliva flow in patients.</p>	<p>There was a significant increase in the amount of saliva produced after using the ginger spray.</p>
<p>Sani et al. [38]</p>	<p>To evaluate the antioxidant and antidiabetic effects of melam gel, ginger and their combination.</p>	<p>Sprague-Dawley Mice</p>	<p>Experimental, randomized</p>	<p>Ginger and honey extract from Malaysia</p>	<p>60 rats were divided into 2 groups consisting of diabetic and non-diabetic rats. Diabetes was induced with intramuscular STZ (55 mg/kg body weight). Each group was further divided into 4 smaller groups according to the supplements given: distilled water, honey (2 g/kg body weight), ginger (60 mg/kg body weight) and honey + ginger (2 g/kg of body weight of honey + 60 mg/kg body weight of ginger). Body weight and glucose levels were recorded weekly, while orbital sinus blood was obtained after 3 weeks of supplementation to assess the metabolic profile: glucose, TG, SOD, CAT, GPx, GSH, GSSG and MDA.</p>	<p>Treatments of diabetic rats with honey, ginger or their combination did not significantly reduce glucose levels when compared to the diabetic control group. There was a significant reduction of TG in the diabetic group that received both honey and ginger. The activity of the SOD enzyme significantly decreased in ginger treated diabetic rats and the combination of honey + ginger compared to normal rats and the diabetic control group. The treatment of diabetic rats with ginger honey, ginger and their combination managed to cause a significant reduction in CAT activity when compared to the control group and the normal control group.</p>

<p>Ahmadi et al. [40]</p>	<p>To assess the effects of ginger and glibenclamide on the metabolites of DHBA (oxidative stress indicators) in diabetic rats.</p>	<p>Male Wistar rats</p>	<p>Experimental, randomized</p>	<p>Ginger ethanolic extract</p>	<p>The rats were divided into five groups, six rats each, and treated as follows: Group 1: Normal control receiving saline; Group 2: control receiving Dimethylsulfoxide (as solvent of glibenclamide); Group 3: Diabetic control receiving STZ (50 mg / kg); Group 4: diabetics + ginger extract: this group received 200 mg/kg ethanolic extract of ginger intraperitoneally for 30 days. Group 5 diabetic rats received glibenclamide (0.5 m/kg).</p>	<p>After 30 days, supplementation of ethanolic ginger extract with diabetic rats resulted in a more significant decrease in 2,3-DHBA and 2,5-DHBA levels than did diabetic rats receiving glibenclamide.</p>
---------------------------	---	-------------------------	---------------------------------	---------------------------------	--	--

<p>Elkirdasy et al. [41]</p>	<p>To investigate the effects of green tea and/or ginger extracts on hematological and immunobiochemical profiles in rabbits induced by Aloxan</p>	<p>Adult male rabbits</p>	<p>Experimental, randomized</p>	<p>Ginger extract and green tea extract.</p>	<p>Fifty adult male rabbits were divided into five experimental groups, with 10 rabbits each: Group 1 (G1): (control group), normal animals without treatment (standard); Group 2 (G2): group of diabetics (aloxan-induced diabetes) with no treatment; Group 3 (G3): diabetic animals treated with green tea extract; Group 4 (G4): diabetic animals treated with ginger extract; Group 5 (G5): diabetic animals treated with combined extract of green tea and ginger. Aqueous green tea extract and/or ginger was given orally (gastric tube) daily at a dose of 1 mL/100 mg body weight for a period of 3 weeks. Control groups (normal and diabetic) received the same volume of isotonic NaCl solution.</p>	<p>G4 was reduced in triglyceride levels compared to G1 and G2. LDL- cholesterol level was reduced when diabetic rabbits were treated with ginger compared to G2. There was improvement in fasting glycemia in G4 compared to groups 1 and 2, however the glucose concentration was still higher than that of G1 and G2. In addition, there was a reduction in lipid peroxidation, TC elevation and reduction of glutathione, CRP and fibrinogen concentration in groups 3,4 and 5 compared to G2. The analysis also revealed an immune stimulating effect and improvement of parameters indicative of hematological disorders in rabbits with alloxan-induced diabetes.</p>
------------------------------	--	---------------------------	---------------------------------	--	---	--

that evaluated the anti-diabetic action of ginger in diabetic-induced animal models and/or human diabetic patients. In this way, scientific articles available as full article was considered, regardless of the language. Reviews, comments, review article, and other texts dealing with only the chemical part of the plant or dealing with other diseases or complications other than Diabetes Mellitus and diabetic complications were discarded. It is worth

mentioning that only the articles repeated in the databases were counted once, since of the 80 articles found in the databases, 1 publication was eliminated because it was duplicitous.

Search, select and analyze procedures

The analysis was performed in three stages. Firstly, the title of the 79 papers was read, selecting papers that included the term

Zingiber officinale or related terms, such as “ginger”, “gengibre” and “jengibre”. In this stage, 27 articles were excluded, as they did not fit the scope of the research, remaining 52 articles. These articles were analyzed by reading the Abstract, and those who mentioned some type of anti-diabetic effect after the use of ginger were chosen. Thus, 25 articles were eliminated, remaining 27, which were read integrally, in order to elect those who evaluated the therapeutic potential of the use of *Z. officinale* against Diabetes Mellitus or its complications. Having established and applied inclusion and exclusion criteria, the scope of this review consisted of 27 articles from the Pubmed database, no articles from the SciELO database and none from LILACS.

Results

From the application of the inclusion and exclusion criteria, the full text of the 27 articles was read. **Table 1** shows the synopsis of articles.

Discussion

Diabetes Mellitus is a chronic and inflammatory disease, characterized by chronic hyperglycemia associated with ROS generation, oxidative stress and lipid peroxidation, and subsequent macro and microvascular complications [20]. Dietary antioxidants are among the most appropriate therapeutic modalities in the prevention of diabetic complications through interaction with oxidative stress [13]. *Z. officinale* contains several phytochemical constituents that have been shown to have antioxidant properties [13]. These compounds combat lipid peroxidation and improve the ability of antioxidant enzymes in the body. Several studies

in animal models and in diabetic humans have confirmed that ginger extracts can enhance the activities of various antioxidant enzymes [22,25,34,38]. Contrary to what was described by most studies, Azimi et al. [35] did not observe the effect of ginger therapy on glycemic control, inflammation and oxidative stress in diabetic patients, probably due to the large sample size and interference of the participants' eating habits over intervention. Thus, it is important to further investigate the issue, considering the interaction between nutrients, the age of patients, and other dosages and times of supplementation. Moreover, it is necessary to highlight the absence of national studies on the subject in recent years. In this context, exploring biodiversity can contribute to the use of medicinal plants as an essential area in the country, considering that there is economic potential in the Brazilian flora [39-41].

Conclusion

Although several therapeutic modalities have been investigated to combat DM, some dietary supplements are considered to be effective alternatives for treating diabetes and clinical changes resulting from this disease. Ginger has been shown to have the potential to reduce diabetes and its complications through interaction with molecular targets including inhibition of various transcription pathways, inflammatory mediators, lipid peroxidation, carbohydrate metabolizing enzymes, and activation of the antioxidant enzyme capacity. We have documented the main findings of the publications that were conducted with *Z. officinale* in the last 5 years. So, we conclude that *Z. officinale* has the potential to treat diabetes, and we suggest that it be recommended in the regular dietary use of diabetic patients.

References

- Mozaffari KH, Talaei B, Jalali BA (2014) The effect of ginger power supplementation on insulin resistance and glycemic indices in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled trial. *Complement Ther Med* 22: 9-16.
- American Diabetes Association (2015) Standards of Medical Care in Diabetes. *Diabetes Care* 54: 1-94.
- Shidfar F, Rajab A, Rahideh T, Khandouzi N (2015) The effect of ginger (*Zingiber officinale*) on glycemic markers in patients with type 2 diabetes. *J Complement Integr Med* 12: 165-170.
- Arablou T, Aryaeian N, Valizadeh M (2014) The effect of ginger consumption on glycemic status, lipid profile and some inflammatory markers in patients with type 2 diabetes mellitus. *Int J Food Sci Nutr* 65: 515-520.
- Ilkhanizadeh B, Shirpoor A, Khadem Ansari MH (2016) Protective Effects of Ginger (*Zingiber officinale*) Extract against Diabetes-Induced Heart Abnormality in Rats. *Diabetes Metab J* 40: 46-53.
- Azimi P, Ghasvand R, Feizi A (2016) Effect of cinnamon, cardamom, saffron and ginger consumption on blood pressure and a marker of endothelial function in patients with type 2 diabetes mellitus: A randomized controlled clinical trial. *Blood Press* 25: 133-140.
- Saraswat M, Suryanarayana P, Reddy PY (2010) Antiglycating potential of *Zingiber officinalis* and delay of diabetic cataract in rats. *Mol Vis* 16: 1525-1537.
- Dongare S, Gupta SK, Mathur R (2016) *Zingiber officinale* attenuates retinal microvascular changes in diabetic rats via anti-inflammatory and antiangiogenic mechanisms. *Mol Vis* 22: 599-609.
- Ghissi Z, Atheymen R, Boujbiha MA (2013) Antioxidant and androgenic effects of dietary ginger on reproductive function of male diabetic rats. *Int J Food Sci Nutr* 64: 974-978.
- Shanmugam KR, Mallikarjuna K, Kesireddy N (2011) Neuroprotective effect of ginger on antioxidant enzymes in streptozotocin-induced diabetic rats. *Food Chem Toxicol* 49: 893-897.
- Pessoa AF, Florim JC, Rodrigues HG (2016) Oral administration of antioxidants improves skin wound healing in diabetic mice. *Wound Repair Regen* 24: 981-993.
- Milech A, Angelucci AP, Golbert A (2016) Guidelines of the Brazilian Diabetes Society. Sao Paulo: A.C. Pharmaceutical.
- Akash MS, Rehman K, Tariq M, Chen S (2015) *Zingiber officinale* and Type 2 Diabetes Mellitus: Evidence from Experimental Studies. *Crit Rev Eukaryot Gene Expr* 25: 91-112.
- Shukla Y, Singh M (2007) Cancer preventive properties of ginger: a brief review. *Food Chem Toxicol* 45: 683-690.
- Chaiyakunapruk N, Kitikannakorn N, Nathisuwan S (2006) The efficacy of ginger for the prevention of postoperative nausea and vomiting: a meta-analysis. *Am J Obst Gynecol* 194: 95-99.
- Butt MS, Sultan M (2011) Ginger and its health claims: molecular aspects. *Crit Rev Food Sci Nutr* 51: 383-393.

- 17 Ali BH, Blunden G, Tanira MO, Nemmar A (2008) Some phytochemical, pharmacological and toxicological properties of ginger (*Zingiber officinale* Roscoe): A review of recent research. *Food Chem Toxicol* 46: 409-420.
- 18 Chen CY, Cheng KC, Chang AY (2012) 10- Shogaol, an antioxidant from *Zingiber officinale* from Skin Cell Proliferation and Migration Enhancer. *Int J Mol Sci* 13: 1762-1777.
- 19 Eleazu CO, Iroaganachi M, Okafor PN (2013) Ameliorative Potentials of Ginger (*Z. officinale* Roscoe) on Relative Organ Weights in Streptozotocin induced Diabetic Rats. *Int J Biomed Sci* 9: 82-90.
- 20 Madkor HR, Mansour SW, Ramadan G (2011) Modulatory effects of garlic, ginger, turmeric and their mixture on hyperglycaemia, dyslipidaemia and oxidative stress in streptozotocin–nicotinamide diabetic rats. *Br J Nutr* 105: 1210-1217.
- 21 Silva VD, Nogueira RMB (2015) Diabetes mellitus experimental induzido com aloxana em ratos Wistar. *Rev Ciênc Farm Básica Apl* 36: 9-15.
- 22 ElAkabawy G, ElKholly W (2014) Neuroprotective effect of ginger in the brain of streptozotocin-induced diabetic rats. *Ann Anat* 196: 119-128.
- 23 Gurpınar T, Ekerbiçer N, Uysal N (2012) The effects of the melatonin treatment on the oxidative stress and apoptosis in diabetic eye and brain. *Scientific World Journal* 2012: 1-5.
- 24 Kota N, Panpatil VV, Kaleb R (2012) Dose-dependent effect in the inhibition of oxidative stress and anticlastogenic potential of ginger in STZ induced diabetic rats. *Food Chem* 135: 2954-2959.
- 25 Kazeem MI, Akanji MA, Yakubu MT, Ashafa AO (2013) Protective Effect of Free and Bound Polyphenol Extracts from Ginger (*Zingiber officinale* Roscoe) on the Hepatic Antioxidant and Some Carbohydrate Metabolizing Enzymes of Streptozotocin-Induced Diabetic Rats. *Evid Based Complement Alternat Med*. 2013: 1-7.
- 26 Rani MP, Padmakumari KP, Sankarikutty B (2011) Inhibitory potential of ginger extracts against enzymes linked to type 2 diabetes, inflammation and induced oxidative stress. *Int J Food Sci Nutr* 62: 106-110.
- 27 Abdulrazaq NB, Cho MM, Win NN (2012) Beneficial effects of ginger (*Zingiber officinale*) on carbohydrate metabolism in streptozotocin-induced diabetic rats. *Br J Nutr* 108: 1194-1201.
- 28 Ramudu SK, Korivi M, Kesireddy N (2011) Nephro-protective effects of a ginger extract on cytosolic and mitochondrial enzymes against streptozotocin (STZ)-induced diabetic complications in rats. *Chin J Physiol* 54: 79-86.
- 29 Kazeem MI, Akanji MA, Yakubu MT (2015) Amelioration of pancreatic and renal derangements in streptozotocin-induced diabetic rats by polyphenol extracts of Ginger (*Zingiber officinale*) rhizome. *Pathophysiology* 22: 203-209.
- 30 Lamuchi DN, Aberomand M, Babaahmadi RH (2017) Effects of the Hydroalcoholic Extract of *Zingiber officinale* on Arginase I Activity and Expression in the Retina of Streptozotocin-Induced Diabetic Rats. *Int J Endocrinol Metab* 15: 1-7.
- 31 Shalaby MA, Saifan HY (2014) Some pharmacological effects of cinnamon and ginger herbs in obese diabetic rats. *J Intercult Ethnopharmacol* 3: 144-149.
- 32 Mahluji S, Attari VE, Mobasseri M (2013) Effects of ginger (*Zingiber officinale*) on plasma glucose level, HbA1c and insulin sensitivity in type 2 diabetic patients. *Int J Food Sci Nutr* 64: 682-686.
- 33 Mahluji S, Ostadrahimi A, Mobasseri M (2013) Anti-Inflammatory Effects of *Zingiber Officinale* in Type 2 Diabetic Patients. *Adv Pharm Bull* 3: 273-276.
- 34 Khandouzi N, Shidfar F, Rajab A (2015) The Effects of Ginger on Fasting Blood Sugar, Hemoglobin A1c, Apolipoprotein B, Apolipoprotein A-I and Malondialdehyde in Type 2 Diabetic Patients. *Iran J Pharm Res* 14: 131-140.
- 35 Azimi P, Ghiasvand R, Feizi A (2014) Effects of Cinnamon, Cardamom, Saffron, and Ginger Consumption on Markers of Glycemic Control, Lipid Profile, Oxidative Stress, and Inflammation in Type 2 Diabetes Patients. *Rev Diabet Stud* 11: 258-266.
- 36 Arzati MM, Honarvar NM, Saedisomeolia A (2017) The Effects of Ginger on Fasting Blood Sugar, Hemoglobin A1c, and Lipid Profiles in Patients with Type 2 Diabetes. *Int J Endocrinol Metab* 15: e57927.
- 37 Mardani H, Ghannadi A, Rashnavadi B (2017) The Effect of Ginger Herbal Spray on Reducing Xerostomia in Patients with Type II Diabetes. *Avicenna J Phytomed* 7: 308-336.
- 38 Sani NF, Belani LK, Sin CP (2014) Effect of the Combination of Gelam Honey and Ginger on Oxidative Stress and Metabolic Profile in Streptozotocin-Induced Diabetic Sprague-Dawley Rats. *BioMed Res Int* 2014: 1-9.
- 39 Marmitt DJ, Goettert MI, Rempel C (2016) Analysis of scientific production of *Curcuma longa* L. (saffron) in three databases after the creation of RENISUS. *Rev Pan-Amaz Saude* 7: 71-77.
- 40 Ahmadi R, Pishghadam S, Mollaamine F (2013) Comparing the Effects of Ginger and Glibenclamide on Dihydroxybenzoic Metabolites Produced in Stz-Induced Diabetic Rats. *Int J Endocrinol Metab* 11: 1-4.
- 41 Elkirdasy A, Shousha S, Alrohaimi AH, Arshad MF (2015) Hematological and Immunobiochemical Study of Green Tea and Ginger Extracts in Experimentally Induced Diabetic Rabbits. *Acta Pol Pharm* 72: 497-506.