Chapter

A Review of the Antidiabetic Activities of Ginger

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Abstract

Diabetes mellitus, a chronic metabolic disorder with major health care burden worldwide, is increasing, with 173 million adults being diabetic and over 8 million deaths recorded annually. Undesirable pathological conditions and high rates of secondary failure limit the use of current antidiabetic agents, thus, the need for more effective antidiabetic agents. Medicinal plants such as spices, rich in bioactive components that promote prevention and treatment of chronic conditions such as heart disease, cancer and Type-2 diabetes, are inexpensive with no side effects. The Zingiberaceae family, of which ginger is a member, consists of many species frequently cited for their antidiabetic and hypoglycemic properties. All important scientific literatures from 2000 to 2018 on the antidiabetic potentials of *Zingiber officinale* were evaluated. According to these studies, ginger exerts its antidiabetic effects through restorative effects on pancreatic β-cells, increasing insulin sensitivity, action and peripheral utilization of glucose. Other mechanisms include increased synthesis of hepatic glycogen through the enhancement of glycogen regulatory enzyme expression in the liver, inhibition of carbohydrate metabolizing enzymes, stimulation of pancreatic insulin release and inhibition of hepatic glucose production. Further studies, especially in humans are needed, more so, since ginger is one of the spices generally regarded as safe.

Keywords: spices, diabetes, ginger, pharmacology, mechanism of action

1. Introduction

Diabetes mellitus (DM) is the most common endocrine disorder that affects more than 100 million people worldwide. It is a heterogeneous group of diseases, all of which ultimately lead to an elevation of glucose in the blood (hyperglycemia) and loss of glucose in the urine as hyperglycemia increases. It is characterized by increased urine production (polyurea) excessive thirst (polydipsia) and excessive eating (polyphagia).

Diabetes mellitus is a chronic metabolic disorder of the endocrine system that is characterized by defects in impaired metabolism of glucose, lipid and protein as well as insulin secretion or insufficiency. Diabetes continues to be a major health care problem worldwide and its prevalence is expected to rise from the current 382–471 million individuals by 2035 [1, 2]. There are three main types of diabetes-Type 1 diabetes (T1D), which is an autoimmune disorder leading to the destruction of pancreatic beta-cells; Type 2 diabetes (T2D), which is much more common and primarily caused by impaired glucose regulation due to a combination of dysfunctional pancreatic beta cells and insulin resistance and gestational diabetes mellitus (GDM).

Different treatments, such as insulin, pharmacotherapy and diet therapies, which exert antidiabetic effects through different mechanisms, are currently used for the management of diabetes. Such mechanisms include stimulation of insulin secretion by sulfonylurea and meglitinides drugs, increase of peripheral absorption of glucose by biguanides and thiazolidinediones, delay in the absorption of carbohydrates from the intestine by alpha-glucosidase and reduction of hepatic gluconeogenesis by biguanides [3–5].

In spite of the appreciable progress that has been made in the management of diabetes through the use of conventional drugs and management strategies, diabetes and its complications continue to be a major medical problem and rising burden of disease. Most synthetic oral hypoglycemic agents available for the treatment of the disease have some disadvantages, including drug resistance, serious side effects, cannot be used during pregnancy, are toxic and also costly [6, 7].

Spices and herbs have played important roles in civilization and history of many nations of the world. Their flavor and pungency makes them indispensable in the preparation of palatable dishes; but beyond adding flavor, spices are reputed to possess several medicinal and pharmacological properties and hence find use in the preparation of a number of medicines. Spices can be the dried leaf (e.g., bay leaf), buds (cloves), bark (cinnamon), rhizome/root (ginger), berries (grains of pepper), seeds (cumin), or even the stigma of the flower (saffron) [8].

The Zingiberaceae plant family consists of many species used as culinary herbs and spices, frequently cited for their antidiabetic and hypoglycemic properties. Ginger (*Zingiber officinale*) belongs to this family, and has a long and wide history of usage both as a culinary spice and in traditional/alternative medicine. This study attempts to update the available scientific information on the antidiabetic and hypoglycemic potentials of ginger.

2. Methodology

Online published articles from Google Scholar, ScienceDirect, Scopus, ResearchGate, PubMed and SciELO were explored for data collection. For literature search, key words such as spices, diabetes, Zingiberaceae, ginger, in vivo, in vitro, pharmacological, medicinal, hypoglycemic and antidiabetic were used. The study reviewed all important literature from 2000 to 2018.

3. Results

The following sections describe various studies reporting the hypoglycemic and antidiabetic properties of ginger, phytochemical constituents responsible for these properties and its mechanisms of action.

3.1 Ginger (*Zingiber officinale* Roscoe)

The ginger (Zingiberaceae) family consists of 53 genera and over 1200 medicinal plants, typically tropical annuals or perennials, often with large rhizomes. This plant family is well-known for its medicinal values and is distributed widely throughout the tropics, particularly in Southeast Asia.

Ginger (**Figure 1**) has been used for thousands of years for the treatment of numerous ailments, such as colds, nausea, arthritis, migraines and hypertension. Several authors have reviewed the medicinal, chemical, and pharmacological properties of ginger [9–13]. Ginger is recognized by the U.S. Food and Drug

Figure 1.
Zingiber officinale (ginger) rhizomes. Source: www.amazon.com/Culinary-Ginger-Zingiber-Officinalecooking/dp/B01NAJQ6C6 [28].

Administration (FDA) as a food additive that is "generally recognized as safe" [14] and has a long history of use as a culinary spice and in herbal medicine to treat many ailments.

Ginger helps to relieve various inflammatory disorders like gout, osteoarthritis and rheumatoid arthritis; as an analgesic, hypoglycemic, cardiotonic, antiemetic, antimicrobial and antifungal. Other uses include as an antidiabetic, antidyslipidemia, hypotensive, vasodilator, antiobesity and anticancer agent [15–18].

In addition, the spice has shown prominent protective effects on diabetic liver, kidney, eye, and neural system complications [19]. Several experimental studies have reported that administration of ginger extracts significantly decreased blood glucose level in Type 1- and Type 2-induced diabetic animals in a dose-dependent pattern [20–27].

3.2 Antidiabetic properties of ginger

Lamuchi-Deli et al. [29] evaluated the effects of the hydroalcoholic extract of *Zingiber officinale* on arginase I activity and expression in the retina of streptozotocin-induced diabetic rats. The study showed that blood glucose concentration was significantly decreased, arginase I activity and expression was significantly ($P < 0.05$) down regulated and 400 mg/kg of the extract reduced significant elevation in body weight in diabetic rats compared to untreated diabetic controls ($P < 0.01$). Serum insulin was also significantly increased in diabetic rats treated with 400 mg/kg of the extract compared to diabetic controls ($P < 0.05$). The study suggested that ginger could be a promising therapeutic option for treating diabetes-induced vascular disorders.

A recent study by de Las Heras et al. [30] which evaluated the hypolipidemic- and insulin sensitizing effects of hydroethanolic extract of ginger in the liver of high-fat diet (HFD) fed rats, revealed that ginger extract improved lipid profile and attenuated the increase of plasma levels of glucose, insulin, and leptin in HFD rats. Wei et al. [31], also reported that 6-Paradol and 6-Shogaol, the pungent compounds of ginger, promoted glucose utilization in adipocytes and myotubes,

and 6-paradol reduced blood glucose in HFD-fed mice. Al-Qudah et al. [32] reported that aqueous extract of ginger was effective in lowering serum glucose, restoration of hematological indices to normal and repair damaged pancreas in alloxan-induced diabetic rats.

In another study, Oludoyin and Adegoke [33] investigated the effect of ginger extracts on blood glucose in normal and streptozotocin-induced diabetic rats. The authors reported that the fasting blood glucose in diabetic rats was reduced to normal by both raw and cooked ginger extracts in a manner comparable to glibenclamide. Evaluation of the nutritional and antidiabetic activity of ginger powder, its aqueous and methanolic extract, as well as the essential oil in streptozotocin-induced diabetic rats [34] revealed reduction in levels of alanine and aspartate aminotransferase (ALT and AST), alkaline phosphatase (ALP), liver total lipid and cholesterol of diabetic rats; and increased levels of liver glycogen and triglyceride compared to positive control group. In the study, ginger oil showed the best antidiabetic activity, followed by ginger extracts. Again, another study reported that ginger extract administered at 200 mg/kg/day/kg body weight for 10 weeks to male Sprague-Dawley diabetic rats, exhibited protective activity against insulin resistance [34].

Al-Noory et al. [35] showed that fresh ginger extracts led to decrease in the levels of total cholesterol (TC) and low density lipoprotein (LDL) in the serum of alloxan-induced diabetic rats, compared with the control groups; and previous extracts caused reduction in LDL to levels comparable to normal group and equal to the effect of atorvastatin given at a dosage of 10 mg/day. Similarly, oral administration of aqueous ginger extract to streptozotocin (STZ)-induced diabetic rats for a period of 30 days was reported to give a dose-dependent antihyperglycemic effect, 68% decrease in plasma glucose level at a daily dose of 500 mg/kg body weight, indicating that ginger is a potential phytomedicine for the treatment of diabetes [36]. Iranloye et al. [37] also showed that ginger effectively reduced fasting blood glucose, malondialdehyde levels and enhanced insulin sensitivity in alloxan-induced and insulin-resistant diabetic rats compared to control rats.

Treatment of streptozotocin-induced Type I diabetic rats with *Z. officinale* juice (4 mL kg^{-1}, p.o. daily for 6 weeks) was reported to produce a significant increase in insulin levels, decrease in fasting glucose levels, as well as significant decrease in the area under the curve of glucose in an oral glucose tolerance test [38]. According to Nammi et al. [23], treatment with an ethanolic extract of ginger at doses of 100, 200, and 400 mg/kg for 6 weeks, significantly reduced the marked increase in body weight, serum glucose, insulin, total cholesterol, LDL cholesterol, triglycerides, free fatty acid and phospholipids induced by high-fat diet.

The study conducted by Al-Amin et al. [39] on the antidiabetic and hypolipidemic properties of ginger (*Zingiber officinale*) in streptozotocin-induced diabetic rats revealed that raw ginger at a dose of 500 mg/kg, was significantly effective in lowering serum glucose, cholesterol and triacylglycerol as well as reduction in urine protein (reversal of diabetic proteinuria) levels, of diabetic rats. Ethanolic extracts of *Zingiber officinale* (200 mg/kg) given orally for 20 days was reported to produce significant antihyperglycemic effect ($P < 0.01$) in diabetic rats, while also lowering serum total cholesterol and triglycerides, coupled with increased HDL-cholesterol levels when compared with pathogenic diabetic rats [40].

Hypoglycemic effect of ginger (4 and 8 g/kg), administered intraperitoneally to rats after 30 min of diabetes induction, with the effect being more pronounced after 2 h has been reported. In another study, Otunola and Afolayan [41], showed that aqueous extract of a spice mixture containing ginger at 500 mg/kg body weight extract significantly ($p < 0.05$) lowered the elevated fasting blood glucose, lipid and hematological indices of alloxan-induced diabetic rats at equipotent level with glibenclamide.

Several in vitro hypoglycemic potentials of ginger and its bioactive constituents especially 6-shogaol have been reported (**Table 1**).

The capacity of ginger for hypoglycemic, antidiabetic, insulogenic, better glucose tolerance, increased serum insulin levels, reduction in elevated lipid levels, and prevention of weight loss associated with diabetes in human diabetic patients have also been reported (**Table 2**).

3.3 Phytochemical components of *Zingiber officinale*

GC-MS profiling of diethyl extracts as reported by Koch et al. [46] showed the presence of monoterpenes such as (α-pinene, camphene, myrcene, and α-phellandrene), oxygenated monoterpenes (geranial, citronellal, neral, linalool, borneol, and α-terpineol), and sesquiterpenes (α-and β-farnesene, ar-curcumene, zingiberene, zingiberenol, copaene, or cadinene). The most abundant substances in the extracts were α-zingiberene (37.9%), β-sesquiphellandrene (11.4%), (E,E)-α-farnesene (9.6%), geranial (8.2%), ar-curcumene (6.3%), and γ-terpinene (5.1%).

Similarly, Sharma et al. [47] reported that the essential oil of fresh ginger rhizome was characterized by high percentage of sesquiterpenes (66.66%), monoterpenes (17.28%) and aliphatic compounds (13.58%). The predominant sesquiterpene was zingiberene (46.71%) followed by valencene (7.61%), β-funebrene (3.09%) and selina-4(14),7(11)-diene (1.03%).

3.4 Mechanism of action

Various mechanisms have been proposed for the antidiabetic and hypoglycemic activities of medicinal plants. These include peripheral utilization of glucose, increased synthesis of hepatic glycogen by enhancement of glycogen regulatory enzyme expression in the liver, inhibition of carbohydrate metabolizing enzymes, stimulation of pancreatic insulin release, insulomimetic actions and inhibition of hepatic glucose production [55, 56].

According to Dearlove et al. [57], spices such as cinnamon, cloves, oregano, and allspice possess bioactive compounds that have (1) antiglycation properties which inhibit the formation of AGEs; (2) antioxidant activities that neutralize the

In vitro study	Result/outcome	References
[6]-Gingerol on 3 T3-L1 cells	Enhanced differentiation of 3T3-L1 preadipocytes and insulin-sensitive glucose uptake	Sekiya et al. [42]
[6]-Shogaol or [6]-gingerol on 3 T3-L1 cells	Significant inhibition of TNF-α-mediated adiponectin expression in 3T3-L1 adipocytes. [6]-Shogaol acted as a peroxisome proliferator-activated receptor (PPAR)γ agonist, while [6]-gingerol acted by suppressing TNF-α-induced JNKs signaling	Isa et al. [43]
Ethyl acetate extract of ginger on L6 myotube cell surface	Stimulated glucose uptake and GLUT4 expression in L6 myotube cell surface, reduced lipid content in 3T3 adipocyte, and inhibited protein glycation. Inhibited α-amylase (IC_{50} = 980.2 μg/mL) and α-glucosidase (IC_{50} = 180.1 μg/mL)	Rani et al., [44]
Aqueous extract of ginger at 5, 10, 20, 40 g/L incubated with (PBS), glucose + BSA for 5 weeks	Dose-dependent, antidiabetic activity through inhibition of glucose diffusion and reduced glycation	Sattar et al., [45]

Table 1.
In vitro hypoglycemic potentials of ginger and its bioactive constituents.

Human trials/dosage	Results	References
Type 2 diabetic men (40–60 years) given 3 g/day of dry ginger powder in divided doses for 30 days. Number-8 T2D, 8 placebo	Significant reduction of blood glucose, triglyceride, total cholesterol, LDL and VLDL cholesterol	Andallu et al. [48]
Randomized double-blind placebo-controlled trial, patients with Type 2 diabetes, given 2 g/day of ginger extract supplementation. Number-28 T2D, 30 Placebo	Significantly lowered levels of insulin, LDL-C, TG, HOMA index and increased the QUICKI index; no significant changes in FPG, TC, HDL-C and HbA1c; improved insulin sensitivity	Mahluji et al. [49]
Randomized controlled trial of Type 2 diabetic men between 30 and 70 years given 1.6 g/day of ginger or wheat flour capsule. Number-33 T2D, 30 Placebo	Decreased fasting blood glucose, glycosylated hemoglobin, fasting insulin, homeostasis model assessment-insulin resistance index, total cholesterol and triglyceride. No change in BMI, LDL-C, LDL-C and HDL-C	Arablou et al. [50]
Randomized controlled trial of Type 2 diabetic patients (30–70 years) given either 3 g/day ginger or cellulose microcrystalline capsules for 8 weeks. Number-40 T2D, 41Placebo	Significant reduction in fasting blood glucose and glycosylated hemoglobin; no change in BMI, fasting insulin and homeostasis model assessment-insulin resistance index	Mozaffari-Khosravi et al. [51]
Randomized, double-blind, placebo-controlled, clinical trial where Type 2 diabetic patients received 2 g/day of ginger powder supplement or lactose as placebo for 12 weeks. Number-22 T2D, 19 placebo	Significant reduction of fasting blood sugar, hemoglobin A1c, apolipoprotein B, apolipoprotein B/apolipoprotein A-I and malondialdehyde in ginger group compared to baseline and control group, while increasing apolipoprotein A-I in Type 2 diabetic patients	Khandouzi et al. [52]
Randomized controlled trial of Type 2 diabetic patients (20–60 y) T2DM given 3 g ginger or lactose capsule/day for 3 months. Number-22 T2D, 23 Placebo	Reduced fasting blood glucose, glycosylated hemoglobin, fasting insulin, homeostasis model assessment-insulin resistance index	Shidfar et al. [53]
Double-blind placebo-controlled trials of Type 2 diabetic patients were randomly allocated to 2000 mg/day of ginger or placebo for 10 weeks. Number-25 T2D, 25 placebo	Reduced serum levels of fasting blood glucose, hemoglobin A1C compared to placebo group, reduced ratio of LDL-C/HDL-C; but no significant change in serum concentrations of triglycerides, total cholesterol, LDL-C, and HDL-C	Arzatii et al. [54]

Table 2.
Clinical (human) trials of the antidiabetic potentials of ginger.

effects of ROS; and (3) anti-inflammatory potentials. Some studies associate the antidiabetic action of ginger to its bioactive principles such as gingerol and shogaol which have the capacity to enhance glucose uptake in rat's skeletal muscle cells, and promote increased expression and translocation of GLUT-4 glucose transporter to the plasma membrane of the cells thus clearing excess glucose from the serum [34].

Another mechanism proposed was the inhibition of key enzymes of carbohydrate metabolism-α-glucosidase and α-amylase by phenolic compounds (gingerols and shogaols) present in ginger [23, 45]; while other authors showed that ginger increases muscle and liver glycogen stores by enhancing peripheral utilization of glucose, thus limiting gluconeogenesis in the liver and kidney in a manner similar to insulin [37].

Son et al. [58], posits that-gingerol exerts its antidiabetic effects through multiple mechanisms that include—(1) increased glucose uptake in the absence

of insulin, (2) induction of 5′ adenosine monophosphate-activated protein kinase phosphorylation, (3) promotion of glucose transporter 4 (GLUT4) translocation to plasma membrane, (4) suppression of advanced glycation end product-induced rise of ROS levels in pancreatic β-cells, (5) reduction of fasting blood glucose levels and improved glucose intolerance, (6) regulation of hepatic gene expression of enzymes involved in glucose metabolism toward decreased gluconeogenesis and glycogenolysis, while increasing glycogenesis, thereby reducing blood glucose concentrations.

4. Conclusion

This study presented an update on the antidiabetic potentials of ginger from the Zingiberaceae family. Although several in vivo and in vitro reports were available, there were relatively few clinical (human) trials. The doses and outcomes also varied; as well as the mechanism of action through which antidiabetic effects were mediated. Although these reports are indicative of the anti-diabetic or hypoglycemic potentials of ginger, the doses and outcomes also varied; most importantly, the mechanisms of action through which anti-diabetic effects are mediated were highlighted. Ginger, according to these studies, exerts its anti-diabetic effects through restorative effects on pancreatic β-cells, increasing insulin sensitivity, insulin-like action and peripheral utilization of glucose. Other mechanisms include increased synthesis of hepatic glycogen through the enhancement of glycogen regulatory enzyme expression in the liver, inhibition of carbohydrate metabolizing enzymes, stimulation of pancreatic insulin release, and inhibition of hepatic glucose production. However, further studies, especially in humans are therefore needed and the oral safety of the various extracts under prolonged usage must be confirmed, more so, since ginger is one of the spices generally regarded as safe.

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Conflict of interest

The authors declare no conflict of interest.

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