The Protective Effects of Ginger against Hyperglycemia and Diabetes Mellitus: A review

Younis Muftah Al-zaedi [1], Fathi Salem Hadoud [2]
[1] Department of Biology, Faculty of Education Al-kums, El-mergib University.
[2] Department of Biology, Faculty of Education Tarhuna, Azzaytuna University.
younis68zagloom@gmail.com

Abstract:

Diabetes mellitus is one of the major metabolic disorders, and it is characterized by high blood glucose level resulting from dysfunction of pancreatic beta cells and insulin resistance.. Many traditional plant treatments exist as a hidden wealth of potentially useful natural products for diabetes treatment. *Zingiber officinale* (Ginger) is a traditional medicine against various disorders including diabetes mellitus. Ginger exhibits the beneficial effects due to presence of gingerol and shogaol. Experimental research in animals both *in vitro* and *in vivo* has shown that ginger can have effects on carbohydrate metabolism, insulin sensitivity and lipids. In this review, we provide an overview of the recent literature describing ginger's potential for preventing the diabetes mellitus, and its hypoglycemic activities.

Key words: *Ginger, Diabetes mellitus, Hyperglycemia, Blood glucose, Insulin.*

الملخص:

داء السكري أحد الإضطرابات الأيضية الرئيسية، والتي تتميز بارتفاع مستوى جلوكوز الدم الناتجة عن الاختلال الوظيفي في خلايا بيتا البنكرياسية ومقاومة الأنسولين. هناك العديد من العلاجات النباتية التقليدية ظلت مخفية كثروة من المنتجات الطبيعية المفيدة لعلاج داء السكري. الزنجبيل علاج تقليدي ضد الاضطرابات المختلفة من ضمنها داء السكري. للزنجبيل تأثيرات مفيدة وذلك بسبب وجود المواد الفعالة مثل (gingerol ، shogaol). أظهرت البحوث التجريبية في الحيوانات (سواء خارج الجسم أو داخل الجسم) بأن الزنجبيل له تأثيرات على أيض الكربوهيدرات والدهون وحساسية الأنسولين. في هذا البحث، قدمنا نظرة عامة من الدراسات الحديثة التي تصف أو تشرح إمكانية الزنجبيل في منع داء السكري ونشاطاته في تخفيض مستويات جلوكوز الدم.

الكلمات المفتاحية: *الزنجبيل ، السكري ، ارتفاع السكر في الدم ، جلوكوز الدم ، الأنسولين.*

Introduction:

Diabetes is a metabolic disorder and major global health problem worldwide. It is caused by abnormality of carbohydrate metabolism which is related to low blood insulin level or insensitivity of target organs to insulin (Dhanik, 2017).
Diabetes mellitus is characterized by chronic hyperglycemia resulting from impaired insulin action/ secretion (Talaei et al., 2017), and is classified into two major categories, type 1 and type 2. Type 2 diabetes accounts for >90% of diabetes and is associated with metabolic disorder of lipid and carbohydrate. Effective control of hyperglycaemia in

diabetic patients is critical for reducing the risk of micro- and macrovascular disease (Li et al., 2012). The International Diabetes Federation (IDF) estimates that 285 million people, 6.4% of the world population, suffered from diabetes in 2010 and this prevalence will increase to 439 million people, 7.7% of the world population by 2030. Over 90% percent of diabetic patients are diagnosed with type 2 diabetes (T2D (Chang et al., 2013).

In response to this global health challenge, the WHO Expert Committee on diabetes mellitus recommended further evaluation of the folkloric methods of managing the disease because of high mortality and morbidity arising from its attendant complications and draw-backs associated with the use of conventional anti-diabetic drugs (Adeneve & Agbaje, 2008).

Recent scientific investigations have confirmed the efficacy of some of these herbal preparations; elucidating their mechanisms of action, side effects and phytochemical components. More than 1200 plant components have been tested for their ability to lower blood sugar, and many of them have been found to contain chemical components possessing hypoglycaemic effect (Udia et al., 2016). The growing interest of researchers in traditional medicine has led to discovery and establishment of biological activity of many potent phytochemicals possessing hypoglycemic activity (e.g. glycosides, flavonoides, terpenes, steroidal saponins, alkaloids, polysaccharides) (Aggarwal, 2011). The judicious and liberal use of medicinal plants in treatment of various human diseases has always been supported by the ancient medicinal literature worldwide (Aggarwal, 2011). Medicinal plants are known for their hypoglycemic effects; and among which is ginger (*Zingiber officinale*) (Al-Qudah et al., 2018).

Ginger *(Zingiber officinale)* belongs to *Zingiberaceae* family. The part of the plant used is rhizome (Tende et al., 2014). Ginger is one of the more commonly used spices in the world as herbal remedies for the treatment of many medical ailments. It has been reported to possess anti-obesity, anti-inflammatory and anti-diabetic activities (Anyakudo, 2019). Ginger contains various potentially bioactive substances such as gingerols, shogaols, zingerone and paradol (Daily et al., 2015). Among gingerols and shogaol the major pungent components in the rhizome are 6-gingerol and 6-shogaol (Daily et al., 2015). Gingerol provides protection to pancreatic β-cells from free radicals-induced stress as well also has effect on blood sugar level, glucose intolerance and gene expression of hepatic enzymes (Mughal, 2018). *In vitro* studies have also shown that extract from ginger and gingerol could increase glucose uptake in muscles and fat cells. *In vivo* studies have shown an increase in plasma insulin levels accompanied by reduced glucose levels (Lindstedt, 2018). Ginger has long been used as an herbal medicine to treat various symptoms including vomiting, pain, and cold symptoms, and it has been shown to have anti-inflammatory, anti-diabetic, anti-clotting and analgesic properties (Daily et al., 2015). Experimental research in animals both *in vitro* and *in vivo* has shown that ginger can have effects on carbohydrate metabolism, insulin sensitivity and lipids (Lindstedt, 2018).

This review will discusses the potential health benefits of ginger with special reference to phytochemical composition and physiological benefits such as anti-diabetic properties.

Chemical composition of Ginger:

Phytochemical studies show that ginger rhizome contains a wide variety of biologically

active compounds which impart medicinal property. *Z. officinale* is reported to possess essential oils, phenolic compounds, flavonoids, carbohydrates, proteins, alkaloids, glycosides, saponins, steroids, terpenoids and tannin as the major phytochemical groups (Dhanik, 2017). The constituents of ginger are numerous and vary depending on the place of origin and whether the rhizomes are fresh or dry. The odor of ginger depends mainly on its volatile oil, the yield of which varies from 1% to 3% (Malipatil et al., 2015). Ginger rhizomes contain a number of pungent constituents and active ingredients (Abdulaziz Bardi et al., 2013). Ginger contains a fusion of an aroma oils both volatile (zingiberene) and non-volatile (oleoresin) oils and phenolic compounds (gingerol and shogaol, zingerone and paradol) (Udia et al., 2016). The main pungent compounds in fresh ginger are gingerols, whereas the pungency of dry ginger is mainly due to shogaols, for example (6)-shogaol, which are dehydrated forms of (6)-gingerols. Most abundant gingerol found in ginger is (6)-gingerol. Other gingerols with different chain lengths are also present in comparatively small quantities (Gunathilake & Rupsinghe, 2015). Gingerol is of the major pungent compounds in ginger and can be altered to shogaols, zingerone, and paradol which takes part in several activities such as hepatoprotective, antiparasitic, antiflarial, antimicrobial, antidiabetic, and radioprotective (Abdulaziz Bardi et al., 2013). In ginger rhizomes, also contains starch, saccharides, proteins, colouring matter and trace minerals that plays a huge role as a spice ingredient. In ginger, starch comprises of 40 - 60 % w/w, protein is 6.2 - 19.8 %, wax or lipid is 5.7 - 14.5 % and crude fiber is 1.1 - 7.0 % and oleoresin approximately 4-7.5% (Pratap, 2017).

Review of Ginger on and Hyperglycemia and Diabetes mellitus:

This review investigates the hypoglycemic property of Ginger and its protective effects in diabetes mellitus and hyperglycemia. Many studies reported the hypoglycemic effect of different forms of ginger in laboratory animals. Several of animal studies support the effectiveness of Ginger in reducing blood glucose in streptozotocin-induced, as well as alloxan-induced diabetes mellitus in mice and rats.

Jothi *et al.*, study was assessed effects of anti-diabetic and hypolipidemic activity of Zingerone on streptozotocin induced diabetic rats. A total of 30 animals (6 normal and 24 diabetic rats), he rats were divided into the following 5 groups of 6 rats each: Normals control receiving normal saline (Group I); Diabetic control receiving single intraperitoneal administration of streptozotocin (STZ) (40 mg/kg body weight) (Group II). STZ - induced diabetic rats received zingerone (10 mg/kg body weight) orally for 30 days (Group III); and STZ-induced diabetic rats treated with Met (50 mg/bwt) orally for 30 days (Group IV). Normal rats were treated with zingerone (10 mg/kg bwt) orally for 30 days (Group V). The findings substantiated the beneficial effects of zingerone in the treatment of diabetes through exhibiting hypolipidemic effects as well as restoring the function of several organs including the pancreas (Jothi et al., 2016).

Singh *et al.*, study investigated the blood glucose lowering, lipid lowering and antioxidant effect of [6]-gingerol in type 2 diabetic db/db mice. Treatment of db/db mice with [6]-gingerol (100 mg/kg bw) for 12 days significantly ($p<0.05$) lowered fasting blood glucose and improved the glucose tolerance in db/db mice. The results suggest that [6]-gingerol exhibits a significant potential as an anti-hyperglycaemic agent for the treatment of type 2 diabetes (Singh et al., 2009).

Z. M. Al-Amin *et al.*, study investigated the hypoglycaemic potentials of ginger

(*Zingiber officinale*) in rats. An aqueous extract of raw ginger was administered daily (500 mg/kg, intraperitoneally) for a period of 7 weeks to streptozotocin (STZ)-induced diabetic rats. After 7 weeks of treatment with ginger extract, the ginger-treated diabetic rats exhibited significantly reduced glucose levels during the treatment period. The serum glucose levels of the ginger-treated diabetic rats were significantly reduced (52% reduction; P,0.05) in comparison with the control diabetic rats (Al-Amin et al., 2006).

El-kott *et al.*, study was carried out to evaluate the hypoglycaemic potentials of ginger (*Zingiber officinale*) were studied in rats (four groups: control, ginger, diabetics and diabetics treated with ginger). Ginger extract was daily orally administered (400 mg/kg,) for 4 weeks to alloxan-induced diabetic rats (150 mg/kg). Fasting blood serum was analysed for blood glucose. The results demonstrated that the alloxan-induced diabetic rats which treated with *Zingiber officinale* extract, the significant decreased blood glucose levels ($p<0.0001$) was recorded. Ginger was significantly effective in lowering serum glucose (El-Kott et al., 2010).

Shalaby *et al.*, study was designed to assess some pharmacological effects of ginger aqueous extract in obese diabetic rats. The obese diabetic rats were orally given ginger aqueous extract in doses 200 and 400 mg/kg for 6 weeks. At the end of experiment, the results shown significant ($P < 0.05$) decreased blood glucose and leptin hormone and increased insulin serum levels when compared with the positive control group. The findings of study affirm the traditional use of cinnamon and ginger for treating patients suffering from obesity and diabetes (Shalaby & Saifan, 2014).

Neveen S. Ismail, study was evaluated to protective effects of ginger aqueous extract in obese diabetic rats. The obese diabetic rats were orally given ginger aqueous extract in doses 100 and 200 mg/kg for 6 weeks. At the end of experiment, the results shown significant ($P < 0.05$) decreased blood glucose and leptin hormone and increased insulin serum levels when compared with the positive control group. The findings of study affirm the traditional use of cinnamon and ginger for treating patients suffering from obesity and diabetes (Ismail, 2014).

Abdulrazaq *et al.*, study evaluated the antihyperglycaemic effect of aqueous extract of ginger administered orally on a daily basis in three different doses (100, 300, 500 mg/kg body weight) for a period of 30 days to STZ-induced diabetic rats. Results revealed a dose-dependent antihyperglycaemic effect with a decrease of plasma glucose levels by 38% and 68% on the 15th and 30th day, respectively, after the rats were given 500 mg/kg ginger (Abdulrazaq et al., 2012).

Chukwudike *et al.*, study demonstrated the dose-dependent antidiabetic and antiobesity potentials of ginger rhizome. Acute and chronic treatment with aqueous extract of ginger in the doses of 250, 500 and 1000 mg/kg body weight, in diabetic rats showed a significant dose-dependent decrease in the elevated blood glucose level and weight gain effective for good glycemic control and profile. The hypoglycemic effect of aqueous extract of ginger became remarkably appreciated on the 14th day of the study especially in 500 mg/kg and 1000 mg/kg treated rats while the 250 mg/kg treated rats achieved similar value by the 28th day (Anyakudo, 2019).

Khatab *et al.*, study was conducted to evaluate the hypoglycemic, hypolipidemic and antioxidant effect of curcumin, ginger and their mixture in streptozotocin (STZ)-induced diabetic rats. Diabetes was induced by a single intraperitonial injection of STZ (65 mg/kg body weight). Male albino rats (n=35) were divided into two main groups;

first group: negative control (n=7) fed standard diet and second group: diabetic rats (n=28), which divided equally to four subgroups as follows: diabetic untreated rats (positive control), diabetic rats treated with curcumin (0.5 % of diet), diabetic rats treated with ginger (3% of diet) and diabetic rats treated with their mixture. Treatment with curcumin, ginger or their mixture reported very highly significant ($p< 0.001$) improvement in biological evaluation, glucose, insulin, lipid profile when compared with untreated diabetic group. This study demonstrates that the curcumin and ginger mixture possesses significant reduction in hyperglycemic and hyperlipidemic, as well as antioxidant effect in diabetic rats (Khattab et al., 2013).

The results shown from several various studies with diabetic rats and mice support the notion that ginger have hypoglycemic effects.

Mechanism of action of Ginger in hyperglycemia and diabetes mellitus:

The ginger rhizome had a vital role in the treatment or prevention of diabetes in traditional medicinal uses. Many scientific researchers studied on the animals to assess the anti-diabetic action of juice of the plant and various organic extracts (Negi et al., 2019). The mechanisms underlying these actions are associated with the inhibition of key enzymes controlling carbohydrate metabolism and increased insulin release/sensitivity, resulting in enhanced glucose uptake in peripheral adipose and skeletal muscle tissues (Anyakudo, 2019).

The key enzymes controlling carbohydrate metabolism associated with hyperglycemia and type 2 diabetes are α-amylase and α-glucosidase. Ginger extract has *in vitro* been able to inhibit the enzymes α-amylase and α-glucosidase and the inhibiting effect correlated with gingerol and shogaol in the extract. Diabetes mellitus is characterized by defects in insulin release and/or insulin sensitivity. *In vitro* studies have also shown that extract from ginger and gingerol could increase glucose uptake in muscles and fat cells. *In vivo* studies have shown an increase in plasma insulin levels accompanied by reduced glucose levels (Lindstedt, 2018).

In diabetic animals, gingerol has potential to enhance the insulin sensitivity and to decrease hyperlipidemia (Mughal, 2018). Gingerol is of the major pungent compounds in ginger and can be altered to shogaols, zingerone, and paradol which takes part in several activities such as hepatoprotective, antiparasitic, antiflarial, antimicrobial, antidiabetic, and radioprotective (Abdulaziz Bardi et al., 2013).

Recent studies showed that gingerol, its chief active constituent, enhanced cell-mediated glucose uptake via increasing insulin-sensitivity, thus improving chronic disease, as diabetes. The main component 6-gingerol also exhibited hypoglycemic property when administered to diabetic mice and improved impaired insulin signaling in arsenic intoxicated mice (Dhanik, 2017). Ginger has been shown to modulate insulin release. *In vitro*, ginger extract augmented insulin release in the INS-1 rat pancreatic *β*-cell. It is of interest that this effect was more prominent in the presence of exogenous serotonin. *In vivo*, a glucose tolerance test further confirmed that this ginger extract also enhanced plasma insulin levels in conjunction with lowered blood glucose. In arsenic-induced type 2 diabetic rats, (6)-gingerol showed a protective effect on pancreatic *β*-cells and restored the plasma insulin level. The mechanism underlying this action of ginger may involve interaction with the 5-HT3 receptor. It was found that gingerols and shogaol can act on 5-HT3 receptorion channel complex by binding to amodulatory site

distinct from the serotonin binding site, with the potency order (6)-shogaol ≥ (8)-gingerol > (10)-gingerol > (6)-gingerol. The significance of this mechanism remains to be further evaluated (Li et al.,2012).

Conclusion:

From the findings of previous studies, *Zingiber officinale* (ginger) shows effective glycaemic control properties in diabetes mellitus. Ginger exhibits the beneficial effects due to presence of gingerol and shogaol. The mechanisms underlying these actions are associated with the inhibition of key enzymes controlling carbohydrate metabolism and increased insulin release/sensitivity, resulting in enhanced glucose uptake in peripheral adipose and skeletal muscle tissues.

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