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Hypoglycemic Property of Ginger and Green Tea and their Possible Mechanisms in Diabetes Mellitus

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Abstract: Diabetes mellitus disease is increasing rapidly and the incidences in 2010 were about 285 million people worldwide. This is projected to increase to 438 million in 2030. The conventionally used drugs possess many side effects. In addition, the cost of modern antidiabetic drugs is beyond the reach of most people with a low income. Because of this, the need for alternatives that are effective, cheap, and safe is very common.

Plants and many plant derived preparations have long been used as traditional remedies for the treatment of diabetes in many parts of the world. Recently, ginger (*Zingiber officinale*) and green tea (*Camellia sinensis*) have been widely studied to assess their beneficial effects in treatment and prevention of diabetes mellitus. *In vitro* and *in vivo* studies evidenced the potential of ginger and green tea to normalize blood glucose level in diabetes mellitus. In this article we reviewed the various mechanisms through which ginger and green tea exert their hypoglycemic effect. Their pharmacokinetics and safety were also discussed. Results from previous studies revealed that ginger and green tea share some mechanisms of action to reduce blood glucose level in diabetes mellitus. Pharmacokinetics studies provided ample information about their absorption, distribution, and metabolism. Toxicological data exhibited their safety as complementary antidiabetic agents; therefore, a study on the administration of these two herbs simultaneously may be needed as they may exhibit a potential hypoglycemic action due to their synergistic or additive mechanisms of action in diabetes mellitus.

Keywords: Ginger, green tea, hypoglycemic action.

INTRODUCTION

Diabetes Mellitus

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by a high blood glucose concentration (hyperglycemia) caused by insulin deficiency which is often combined with insulin resistance. Diabetes is classified into two types; type 1(insulin dependent diabetes mellitus IDDM) which accounts for 5-10% of cases and usually strikes children and young adults, and type 2(Noninsulin dependent diabetes mellitus NIDDM) which accounts for 90-95% of all diagnosed cases and occurs more frequently in older people. Various complications develop as a consequence of the metabolic derangements in diabetes, often over many years. Mortality & morbidity in diabetes are due mainly to the associated chronic complications [1]. DM diseases increasing rapidly and the incidences in 2010 were about 285 million people worldwide, and are projected to increase to 438 million in 2030 [2].

DM can be treated by using drugs including insulin, biguanides, sulfonylureas, and thiazolidindiones. Treatment should be accompanied by appropriate diet, increased physical activity, and behavior modification to ensure long term compliance [1].

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Plants and many plant derived preparations have long been used as traditional remedies and in folklore medicine for the treatment of diabetes in many parts of the world. One screening study mentioned that 99 plants from 45 families have anti-diabetic activity [3]. Among the plants that have been scientifically evaluated to have beneficial effects in diabetes are spices such as cinnamon, cloves, ginger, garlic, cumin and green tea [4-7].

The efficacy of plants in diabetes requires confirmation; therefore, the WHO (world health organization, 1980) recommended the need for assessment of traditional plant treatment for diabetes mellitus [8].

AIM OF ARTICLE

The aim of our review is to summarize the mechanisms of ginger and green tea in lowering the glucose level in both types of diabetes mellitus, in addition to reviewing their safety and pharmacokinetic based on data available in previous studies.

Ginger Plant

Ginger is an underground rhizome of plant *Zingiber officinale* belonging to the family Zingiberaceae. The genus Zingiberacea comprises some 80-90 species which are perennial aromatic herbs with fresh rhizomes and tuberous roots [9]). The plant was named by an English botanist William Roscue (1753-1831) in 1807 [10]. It is a perennial plant with narrow, bright green grass-like leaves and

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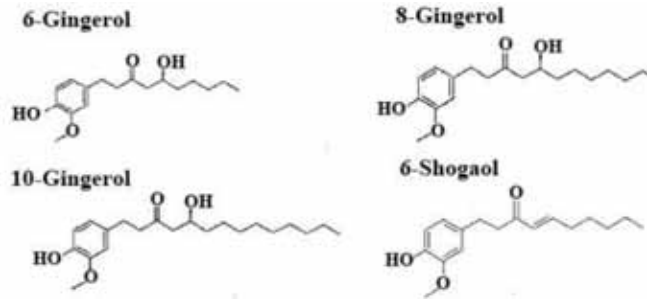


Fig. (1). Chemical structures of some important active constituents of ginger.

yellowish green flowers with purple markings [8]. Ginger plants have been used for cooking and treating a host of ailments throughout Asia, especially in India and China, for over 5000 years. It can be consumed as a fresh or dried root and is often prepared in teas, soft drinks, and breads. According to European Pharmacopoeia 2011, ginger consists of the whole or cut rhizome of *Zingiber officinale* Roscoe with the cork removed, either completely or from the wide, flat surfaces only [11].

Phytochemistry of Ginger

Ginger plants contain volatile oil 1-4%. According to the European Pharmacopeias, more than 100 different compounds have been identified in ginger, most of them terpenoids and sesquiterpenoids (zingiberine, bisabolene, and zingibrol) and small amounts of monoterpenoids (camphene, cineole, geraniol, curcumene, and borneol). The pungent principles, the gingerols (4-7.5%), are a homologous series of phenols (Fig. **1**). The principal one of these is 6-gingerol. Gingerols with other chain-lengths *e.g*. 8-gingerol and 10-gingerol, are present in smaller amounts. During drying and storage, gingerols are partly dehydrated to the corresponding shogaols which may undergo further reduction to form paradols. Other constituents are starch up to 50%, lipids 6-8%, proteins, and inorganic compounds [11].

Beneficial Effects of Ginger

Ginger has a long history of use as a herbal medicine to treat many ailments. The major pharmacological activity of ginger appears to be due to gingerol and shogaol. The principal use is to treat nausea due to motion sickness, morning sickness, general anesthesia and chemotherapy [12]. The anti-inflammatory and antioxidant properties in ginger help to relieve various inflammatory disorders like gout, osteoarithritis and rheumatoid arithritis. It also has analgesic and hypoglycemic actions [13]. Experimental studies demonstrated that ginger in a crude or standardized extract has cardiotonic, antiplatelets, antiemetic, antimicrobial, antifungal actions andantidiabetic, antidyslipidemia; anti-obesity, anticancer activity [14]. It also has hypotensive, vasodilator effects and verapamil like effects on the heart [15].

Toxicological Data Available Regarding Ginger and its Constituents

Toxicological studies on animals determined the acute toxicity of methanolic and aqueous ginger extracts when used orally or by intraperitoneal routes of administration. The LD50 of methanolic extract was 10.25 g/kg and for aqueous extract was 11.75g/kg when given orally to mice [16]. The LD50 for the ethanolic extract was 1551+-75 mg/kg when given intraperitoneally to mice [13]. A single dose of ginger in a dose 2500 mg/kg can be toxic by causing severe hypotension and bradycardia with induction of prenecrotic changes in cardiac tissue. The hypotensive and bradycardia effects of ginger may be partially due to induction of vasodilation by increasing nitrous oxide release or synthesis and partially due to a calcium channel blocking effect [15]. Concerning repeated dose toxicity, Rong *et al.*, 2009 [17] evaluated the safety of powdered ginger by conducting a 35 day toxicity study in rats. The results demonstrated that oral administration of up to 2g/kg of ginger did not cause any mortality or abnormal changes of the general condition or heamatological parameters in male or female rats. Other studies demonstrated that ginger, at 500 mg/kg when administered to rats intraperitoneally, for 28 days is slightly toxic when investigated for haematological parameters, liver enzymes, and systemic toxicity (liver and lung tissues) [18].

Pharmacokinetics of Ginger

Several studies were conducted to demonstrate the absorption, metabolism, distribution and excretion of the ginger components. After oral administration of ginger as a single dose (300 mg) to rats, 8-gingerol, 10-gingerol and 6-shogaol were detected in the plasma as the free forms. The pungent principle 6-gingerol mainly existed as a glucoronide with a Cmax of 3.86 microgram/ml and a free form at 0.93 microgram/ml about 1.2 hours after dosing [19]. In clinical studies 6,8,10 gingerol and 6-shogoal were also identified as glucoronide metabolites [20, 21]. Several studies have been conducted on the pharmacokinetics of pungent 6-gingerol. Incubation of 6-gingerol with NADPH-fortified rat hepatic microsomes gave rise to eight metabolites [22]. The gut flora and liver enzymes play an important role in its metabolism [23]. Another study on rats aimed to clarify the plasma pharmacokinetics and distribution profile of 6-gingerol in rats after oral administration. It demonstrated a rapid absorption into the plasma of 6-gingerol and the maximal concentration was achieved after 10 minutes of oral dosing of 240 mg/kg of ginger extract. The Cmax of 6-gingerol was seen in the majority of tissue at 30 minutes. The highest value was in the stomach followed by the intestine. Concerning its distribution study, it was shown that it had a high tissue partitioning and extensive distribution and its concentration in tissue was higher than plasma after 0.25 hr of dosing [24].

Animal Models used for Assessment the Alterations Observed in Diabetes Mellitus

Injection of strepotozotocin (STZ) or alloxan [25-28] which destroy pancreatic β-cells were well established methods for induction of type 1 DM, while fructose-rich diets (which induce obesity and insulin resistance) were used to induce type 2 DM [6, 29].

Hypoglycemic Effects of Ginger in Diabetes Mellitus

Recently, several animal based researches and some human studies suggested that ginger or its components has

hypoglycemic effects and decreases the complications of diabetes mellitus. In these studies, ginger extract and its components were used in various doses for different periods and in diverse routes of administration in both types of DM. Several experimental studies reported that long term administration of ginger extract significantly decreased blood glucose level in type1 induced diabetic animals [8, 30-33]. Ginger has a dose dependent antihyperglycemic effect [34]. One acute study indicated that administration of ginger (4 and 8 gm/kg) intraperitoneally for rats after 30 minutes of diabetes induction also exhibited hypoglycemic effect and this effect was more pronounced after 2 hours [35]. Results from a number of animal studies supported the hypoglycemic effect of ginger extract in type 2 DM [6, 36, 34].

The main component 6-gingerol also exhibited hypoglycemic property when administered to diabetic mice [37], and improved impaired insulin signaling in arsenic intoxicated mice [38].

In normal animals, it was seen that ginger exerted hypoglycemic effect in normal rats [4, 13], mice [39], rabbits [40] and broiler chick [41].

Clinical trials revealed that ginger supplementation lowered blood glucose in patients with type 2DM when administered for a long period [42]. In addition, it improved insulin sensitivity and lipid profile [43].

Possible Mechanisms Related to Hypoglycemic Effects of Ginger

In vitro, studies revealed that ginger and its components enhanced insulin sensitivity and improved diabetes as a result of increasing glucose uptake in gingerol treated L6 myotubemice cells [44] and L6 cultured rat skeletal muscle cells [45]. This action was attributed to increase in Glut-4 protein expression. It was also reported that 6-gingerol promoted glucose uptake in responsive 3T3-LI adipocytes [46].

It was reported that ginger and its components also have an effect on digestive enzymes to reduce glucose absorption. This effect was exhibited by ethyl extract of ginger which inhibits the activity of amylase and glucosidaseenzymes [44]. Another study reported that the antihyperglycemic effect of ginger is due to its effects on the activities of glycolytic enzymes [34]. In addition, ginger extract could reduce the absorption of glucose from intestines [35].

In arsenic-induced type 2 diabetic rats, 6-gingerol showed a protective effect on pancreatic beta cells and restored the plasma insulin level [38].

Several studies demonstrated that ginger improved lipid profiles and it had antiobesity effects and subsequently reduced insulin resistance [36, 47].

Recently, one clinical trial also indicated that ginger increased insulin sensitivity in type 2 DM patients [43]. Several reports have demonstrated that serotonin receptor (5-HT3) may be involved in hypoglycemic effect of ginger. Serotonin receptors mediate suppression of insulin release and ginger can antagonize this suppression effect [48, 49]. A long term administration of ginger extract to diabetic rats indicated that the antidiabetic effect of ginger is due to inhibition of oxidative stress and its anti-inflammatory activity [33]. The hypoglycemic activity of ginger in diabetic rats was explained by its effect on carbohydrates metabolism that caused the normalization of carbohydrates profile [31]. In a combined high-fat diet and STZ induced type 2 diabetic animal model, ginger was observed to enhance serum insulin concentration and improved glucose tolerance [6]. In another study the pungent component 6-gingerol also improved the glucose tolerance in type 2 diabetic mice [14]. Other possible mechanisms are that ginger extract may act by increasing peripheral utilization and inhibition of proximal tubule re-absorption mechanism of glucose in the kidney [50].

Green Tea Plant

Tea is from the plant (*Camellia sinensis*, which is a member of the Theaceae family). The plant is an evergreen scrub or tree and can grow to heights of 30 feet, but is usually pruned to 2-5 feet for cultivation. The tea plant is considered native to south China and now is cultivated in other countries. The major tea-production countries are China, India, Srilanka, Indonesia and central African countries [51].

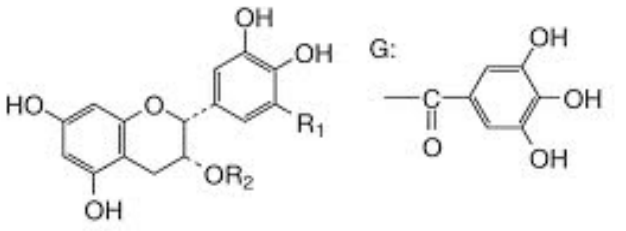
More than 300 different kinds of tea are produced from the leaves of *Camellia sinensis* by different manufacturing processes. Generally, they are divided into two types: green tea (non-fermented), oolongtea (semi fermented) and black tea (fermented). To produce green tea, freshly harvested leaves are immediately steamed to prevent fermentation, yielding a dry, stable product. This steaming process destroys the enzymes responsible for breaking down the color pigments in the leaves and allows the tea to maintain its green color during the subsequent rolling and drying processes. These processes preserve natural polyphenols with respect to the health- promoting properties [7].

Phytochemistry of Green Tea

The chemical composition of green tea is complex. The fresh dry weight of green tea contains protein (15-20%), amino acids (1-4%), carbohydrates (5-7%), minerals and trace elements (5% dry weight), fibers (26%), lipids(7%), pigments (2%), and phenolic compounds (30%) [7]. The polyphenols found in tea are known as flavonols or catechins. The main catechins are epigallocatechingallate (EGCG), epigallocatechin(EGC), epicatechingallate (ECG), and epicatechin (EC) (Fig. **2**). One 200 ml cup of green tea supplies 140, 65, 28, and 17 mg of these polyphenols, respectively [52]. Green tea leaves extract is more stable than EGCG because the extract has other antioxidant substances [7].

Beneficial Effects of Green Tea

In recent years green tea has been widely studied to assess its beneficial effects and medicinal properties in the treatment and prevention of many diseases. The health benefits of green tea are related to its catechins, particularly EGCG [7]. Green tea polyphenols have demonstrated significant antioxidant, anticarcinogenic, anti-inflammatory, and antimicrobial properties in humans, animals, and *in vitro* studies [53, 54]. Moreover, consumption of green tea was associated with a reduced risk for type 2 DM in humans [55].



	R_1	R_2
(-)Epicatechin (EC)	H	H
(-)Epigallocatechin (EGC)	OH	H
(-)Epicatechin-3-gallate (ECG)	H	G
(-)Epigallocatechin-3-gallate (EGCG)	OH	G

Fig. (2). Chemical structures of the major polyphenols found in green tea.

Other studies demonstrated that administration of green tea to diabetic rats promoted blood glucose reduction, hypolipidemic response, antioxidant effect, improved kidney functions, and had cardiac protection effect [2, 56, 57].

Safety of Green Tea

A study on healthy individuals showed that it is safe to take green tea polyphenol products in an amount equivalent to the EGCG content in 8-16 cups of green tea once a day or in divided doses twice a day for 4 weeks [58]. High doses administered for a long time *i.e* 90 days to female and male rats demonstrated safety of green tea. Hematological and histopathological observations revealed no toxicological changes and there was no mortality among these rats. The no observed adverse effect level (NOAEL) of green tea was estimated to be 764 mg/kg/day for males and 820 mg/kg/day for females [59]. Nevertheless, over consumption of green and black tea may cause harmful effects which are due to three main factors;

1. Its caffeine content (should not be taken by patients with cardiovascular problems)
2. The presence of aluminum (can be accumulated in patients with renal failure, resulting in neurological disorders)
3. The effect of polyphenol on bioavailability of iron from diet [7].

An *in vitro* study on hepatic cells suggested that high concentration of green tea extract can exert acute toxicity in rat liver cells [51]. Another study reported that side effects of green tea had increased when taken on an empty stomach, and high doses may cause liver toxicity. Recently, regulatory agencies in France and Spain suspended market authorization of a weight loss product containing green tea extract because of the hepatotoxicity concerns [60].

Pharmacokinetics of Green Tea

A clinical study demonstrated that a single dose of green tea (20 mg/kg) reached its peak in 1.3-1.6 hr., and the time of excretion is 8 hrs. EGCG was mostly present in the free form, whereas EGC and EC were mostly in conjugated forms [61].

Methylation, glucuronidation, sulfation, and ring-fusion metabolism represent the major metabolic pathways for tea catechins [51].

One study in human volunteers revealed that 90% of EGC and EC were excreted in 8 hrs after administration of 1.5, 3 and 4.5 gm / 500 ml of decaffeinated green tea. The half-life of EGCG was 5 hrs and for EC and ECG was 2.5-3.4 hrs. [62].

The absorption of flavonol was enhanced when tea polyphenols were administered as a green tea supplement in capsule form and led to a significant increase in plasma antioxidant activity compared to when tea polyphenols were consumed as black tea or green tea [63].

Bioavailability of green tea was affected by many factors when it was given to rats orally. These factors include membrane permeability, transporter mediated intestinal secretion, or gut wall metabolism [64]. The availability of free EGCG was increased by 60% after chronic administration of green tea at a high bolus dose [65].

Hypoglycemic Effect of Green Tea in Diabetes Mellitus

Several studies suggested that administration of green tea or its main constituents by different routes, in various doses, and in different length of time lowered the blood glucose level in type 1 induced diabetic animals [41, 56, 66-69].

Consumption of green tea extract for a long period of time by type 2 induced diabetic animals also exhibited hypoglycemic effect [70, 71].

A study in normal rats also noticed a decrease in fasting blood glucose after a long term of green tea administration [72].

In one short term study, green tea promoted hypoglycemic effects in healthy humans and in diabetic mice 2-6 hrs after administration [73]. Indeed, the drinking of green tea by the Japanese might be a factor in preventing the onset of type 2 DM [74].

Possible Mechanisms Related to Hypoglycemic Effects of Green Tea

Findings from *in vitro* and *in vivo* studies suggested different mechanisms by which tea and its components may normalize glucose level in diabetes mellitus.

EGCG was observed to protect pancreas cells by ameliorating cytokine- induced β-cell damage *in vitro* [49] and by preventing the decrease in islet mass induced by treatment with multiple doses of STZ *in vivo* [69]. ECG was also indicated to have a protective effect on pancreatic cells against exposure to STZ in both *in vitro* and *in vivo* tests [75]. EGCG is possibly playing a role in controlling the dietary glucose uptake in the intestinal tract by its action as SGLTI (glucose transporter) an antagonist like molecule [76, 77]. Tea catechins may also affect glucose production. This was suggested by Walter *et al.*, 2002 [78]. A study provided *in vitro* evidence that EGCG repressed the glucose

production of H4IIE rat hepatoma cells and decreased the expression of genes that control gluconeogenesis. Reduced hepatic glucose production and enhanced pancreatic function in type 2 DM was also suggested by Wolfram *et al.*, 2006 [79] after consumption of ECGC. The antihyperglycemic activity of green tea was also ascribed to enhance insulin release. This was demonstrated by a study in which green tea and its polyphenol significantly increased basal and insulin-stimulated glucose uptake of adipocytes [72].

It has been reported that the insulin like action of polyphenols was involved in the mechanism by which green tea lowered the blood glucose level [80]. Green tea and its components were also indicated to enhance insulin sensitivity and decrease oxidative stress in diabetic animals [71]. In healthy humans, green tea has been shown to improve insulin sensitivity and glucose tolerance [81]. Anderson *et al.*, 2002 [82] demonstrated that tea contains *in vitro* insulin-enhancing activity (increase insulin activity > 15 fold) and the predominant active ingredient was EGCG. The positive effect of green tea extract on insulin activity suggested a possible role of this plant in improving glucose and insulin metabolism [83]. It was suggested that green tea ameliorated insulin resistance in fructose fed-rats and this action was associated with the increase in the expression of Glut-4 [29]. One study by Tsuneki *et al.*, 2004 [73] reported that a certain serum protein may be involved in the antihyperglycemic effect of green tea. The study also showed evidence of improvement in glucose metabolism in diabetic mice and healthy humans upon green tea consumption.

Chen *et al.*, 2005 [84] suggested that there is a direct connection between antioxidant activity and the hypoglycemic activity of green tea. In addition, tea catechins appeared to have antiobesity effects in type 2 DM by modulating lipid metabolism, and consequently decreasing insulin resistance [85, 86].

SUMMARY

Findings from *in vitro* and *in vivo* studies and clinical trials revealed that ginger and green tea have effective hypoglycemic property in both types of diabetes mellitus.

Toxicity studies demonstrated the wide margin of their safety as a complementary hypoglycemic agent in diabetes. Pharmacokinetics studies provided information about the absorption, distribution and metabolism of ginger, green tea and their principle constituents.

Previous studies suggested different mechanisms by which ginger, green tea, or their components may lower the glucose level in type 1 and 2 diabetes mellitus. These mechanisms can be summarized as the following

1. Reduction of glucose absorption from digestive system by their effect on enzymes (↓ activity of α glucosidase and α amylase).
2. Protective effect on pancreatic β cells from damage and restored the plasma insulin level.
3. Enhancing insulin sensitivity and glucose uptake in peripheral adipose and skeletal muscle tissues.
4. Reduction of insulin resistance by improving lipid profile.

CONCLUSION

We conclude that *Zingiber officinale* (ginger) and *Camellia sinensis* (green tea) plants share some possible mechanisms to lower glucose levels in type 1 and 2 of diabetes mellitus. The mechanisms underlying their actions are associated with the reduction of glucose absorption, increasing glucose uptake in peripheral tissues, enhancing insulin sensitivity and release, and decreasing its resistance by its effect on lipid profile. Toxicity studies have demonstrated their wide margin of safety; therefore, a study on a combination of these two medicinal plants in prevention and protection against diabetes mellitus may be needed, as they may exhibit a potential hypoglycemic action due to their synergistic or additive mechanisms of action.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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REFERENCES

[1] Rang, H.D.; Dale, M.M.; Ritter, JM.; Moor, P.K. Pharmacology. 5th ed, Churchle Living strong, **2003**.

[2] Fiorino, P.; Evanggelista, F.S.; Santos; Magri, F.M.M.; Delorenzi, J.C.M.; Ginoza,M.; Farah,V. The effect of green tea consumption on cardiometabolic alterations induced by experimental diabetes. *Exp. Diabetes Res.*, **2011**, *2012* Article ID 309231, 7 pages.

[3] Bnouham, M.; Ziyyat, A.; Mekhfi, H.; Tahri, A.; Legessyer, A. Medicinal plants with potential antidiabetic activity- A review of ten years of herbal medicine research. *Int. J. Diabetes Metab.*, **2006**, *14*, 1-25.

[4] Ugwuja, E.I.; Nwibo, A.N.; Ugwa, N.C.; Aloke, C. Effect of aqueous extract of spices mixture containing curry, garlic and ginger on plasma glucose & lipids in alloxan induced diabetic rats. *Pak. J. Nutr.*, **2010**, *9*(12), 1131-1135.

[5] Kar, A.; Choudhary, B.K.; Bandyopadhyay, N.J. Comparative evaluation of hypoglycemic activity of some Indian medicinal plants in alloxan induced diabetic rats. *J. Ethnopharmacol.*, **2003**, *84*(1), 105-108.

[6] Islam, S.; Hoi, H. Comparative effects of dietary ginger (*Zingiber officinale*) and garlic (*Allium sativum*) investigated in a type 2 diabetes model of rats. *J. Med. Food*, **2008**, *11*(1), 152-159.

[7] Chacko, S.M.; Thambi, P.T.; Kuttan, R.; Nishigaki, I. Beneficial effects of green tea: A literature review. *Chin. Med.*, **2010**, *5*, 13.

[8] Al-Amin, Z.M.; Thomson, M.; Al-Qattan, K.K.; Shalaby, R.P.; Ali, M. Antidiabetic & hypolipidemic properties of ginger in streptozotocin induced diabetic rats. *Br. J. Nutr.*, **2006**, *96*, 660-666.

[9] Corrigan, D. *Zingiber officinale. Adverse effects of herbal drugs*, Springer-Verlag: London, **1997**, vol. 3, pp. 215-228.

[10] El-Bushuty, D.H.; Shanshan, N.M. Effect of natural herbs of marjoram and ginger on hypercholestorlemic rats. Managing knowledge and intellectual in higher education institutions in Egypt and Arab world (11-12 April) **2012**.

[11] Ovesen, M.L. Assessment report on *Zingiber officinale* Roscoe, rihzoma. European medicines agency, **2012**, 27 march.

[12] Kemper, K.J. Ginger *(Zingiber officinale*). Longwood herbal task Force, **1999**, http:www.mcp.edu/herbal/default.htm

[13] Ojewwole, J.A.O. Analgesic, anti-inflammatory and hypoglycemic effects of ethanol extract of *Zingiber officinale* (Roscoe) rhizomes(Zingiberecea) in mice and rats. *Phytother. Res.*, **2006**, *20*(9), 764-772.

[14] Singh, A.; Duggal, S.; Singh, J.; Katekhaye, S. Experimental advances in pharmacology of gingerols & analogues. *Int. J. Comp. Pharm.*, **2010**, *1*(2), 12.

[15] Elkhishin, I.A.; Awwad, I.A. A study of the cardiovascular toxic effects of *Zingiber officinale* (ginger) in adult male albino rats and its possible mechanism of action. *Mansoura. J. Forensic Med. Clin. Toxicol*., **2009**, *27*(2), 109-125.

[16] Shalaby, M.A.; Hamowieh, A.R. Safety and efficacy of *Zingiber officinale* roots on fertility of male rats. *Food Chem. Toxicol*., **2010**, *48*(10), 2920-2924.

[17] Rong, X.; Peng, G.; Suzuki, T.; Yang, Q.; Yamahara, J.; Li, Y. A 35 day gavage safety assessment of ginger in rats. *Regul. Toxicol. Pharmacol.*, **2009**, *54*(2), 118-123.

[18] Al-naqeeb, M.A.; Thomson, M.; Al-Qattan, K.K.; Kamel, F.; Mustafa, T.; Ali, M. Biochemical and histopathological toxicity of an aqueous extract of ginger. *Kuwait J. Sci. Eng.*, **2003**, *30*, 35-48.

[19] Wang, W.; Li, C.Y.; Wen, X.D.; Li, P.; Qi, L.W. Simultaneous determination of 6-gingerol, 8-gingerol,10-gingerol and 6- shogaol in rat plasma by liquid chromatography mass spectrometry: application to pharmacokinetics. *J. Chromatogr. B. Analyst. Technol. Biomed. Life Sci*., **2009**, *877*(8-9), 671-679.

[20] Yu, Y.; Zick, S.; Li, X.; Zou, P.; Wright, B.; Sun, D. Examination of the pharmacokinetics of active ingredients of ginger in humans. *BMC Biology*, **2011**, *13*(3), 417-426.

[21] Zick, S.M.; Djuric, Z.; Ruffin, M.T.; Litzinger, A.J.; Normolle, D.P.; Alrawi, S.; Feng, M.R.; Brenner, D.E. Pharmacokinetics of 6-gingerol, 8-shogoal, and 6-shogoal and conjugate metabolites in healthy human subjects. *Cancer Epidemiol. Biomarkers Prev.*, **2008**, *17*(8), 1930-1936.

[22] Pfeiffer, E.; Heuschmid, F.F.; Kranz, S.; Metzler, M. Microsomal hydroxylation and glucuronidation of 6-gingerol. *J. Agr. Food Chem*., **2006**, *54*(23), 8769-8774.

[23] Nakazawa, T.; Ohsawa, K. Metabolism of 6 gingerol in rats. *Life Sci*., **2002**, *7*(18), 2165-2175.

[24] Jiang, S.Z.; Wang, N.S.; Mi, S.Q. Plasma pharmacokinetics and tissue distribution of 6 gingerol in rats. *Biopharm. Drug Dispos.*, **2008**, *29*(9), 529-537.

[25] Abu-Abeeleh, M.; Ismail, Z. B.; Alzaben, K.R.; Abu-Halawa, S.A.; Al-Essa, M.K.; Abu-Abeeleh, J.; Alsamady, M.M. Induction of diabetes mellitus in rats using intraperitonial streptozotocin. A comparison between two strains of rats. *Eur. J. Scientific Res.*, **2009**, *32*(3), 398-402.

[26] Akbarzadeh, A.; Norouzian, D.; Mehrabi, M.R.; Jamshidi, Sh.; Farhangi, A.; Verdi, A.A; Mofidian, S.M.; Rad, B.L. Induction of diabetes by streptozotocine in rats. *Indian J. Clin. Biochem.*, **2007**, *22*(2), 60-64.

[27] Junod, A.; Lambert, A.E.; Stauffacher, W.; Renold, A.E. Diabetogenic action of streptozotocin: relationship of dose metabolic response. *J. Clin. Invest*., **1969**, *48*(11), 2129-2139.

[28] Elshater, A.A.; Salman, M.M.A.; Moussa, M.A. The effect of green tea consumption on levels of blood glucose, lipid profile & kidney functions in Alloxan induced diabetic rats. *Egypt. Acad. J. Biology. Sci*., **2008**, *1*(2), 125-134.

[29] Wu, L.Y.; Jaun, CC.; Ho, L.T.; Hsu, Y.P.; Hawng, L.S. Effect of green tea supplementation on insulin sensitivity in Sprague-Dawely rats. *J. Agr. Food Chem.*, **2004**, *52*(3), 643-648.

[30] Elshater, A.A.; Salman, M.M.A.; Moussa, M.M.A. The effect of ginger extract consumption on levels of blood glucose, lipid profile & kidney functions in Alloxan induced diabetic rats. *Egypt. Acad. J. Biol. Sci.*, **2009**, *2*(1), 153-162.

[31] Shanmugam, K.R.; Ramakrishana, Ch.; Mallikarjuna, K.; Reddy, K.S. The impact of ginger on kidney carbohydrates metabolic profiles in STZ induced diabetic rats. *Asian J. Exp. Sci.*, **2009**, *23*(1), 127-134.

[32] Jafari, S.A.; Abbas, S.; Qassim, M. Hypoglycemic effect of ginger in Alloxan induced diabetic rats. *Pak. Vet. J*., **2011**, *31*(2), 160-162.

[33] Morakinyo, O.A.; Akindele, A.J.J.; Ahmend, Z. Modulation of antioxidant enzymes and inflammatory cytokines. Possible mechanism of anti-diabetic effect of ginger extracts. *Afr. J. Biomed. Res*., **2011**, *14*(3), 195-202.

[34] Abdulrazaq, N.B.; Cho, M.M.; Win, N.N.; Zaman, R.; Rahman, M.T. Beneficial effects of ginger (Zingiber *officinale*) on carbohydrate metabolism in streptozotocin – induced diabetic rats. *Br. J. Nutr.*, **2011**, *108*(7), 1194-1201.

[35] Kalejaiye, O.F.; Iwalewa, E.O.; Omobuwajo, O.R.; Oyedapo, O.O. Hypoglycemic effects of Nigerian *Zingiber officianal* rhizome on experimental diabetic rats. *Nig. J. Nat. Prod. Med.*, **2002**, *6*.

[36] Nammi, S.; Sreemantula, S.; Roufogalis, B.D. Protective effects of ethanolic extract of *Zingiber officinale* rhizome on the development of metabolic syndrome in high fat diet rats. *Basic Clin. Pharmacol. Toxicol*, **2009**, *104*(5), 366- 373.

[37] Singh, A.B.; Akanksha, N.; Singh, N.; Maurya, R.; Srivastava, K. Antihyperglycemic, lipid lowering and anti-oxidant properties of (6) gingerol in db/db mice. *Int. J. Med. Med. Sci*., **2009**, *1*(12), 536-544.

[38] Chakraborty, D.; Mukherjee, A.; Sikdar, S.; Paul, A.; Gosh, S.; Rahman, A.; Bukhsh. K. [6]- Gingerol isolated from ginger attenuates sodium arsenite induced oxidative stress and plays a corrective role in improving insulin signaling in mice. *Toxicol. Lett.*, **2012**, *210*(1), 34-43.

[39] Hussain, M.A. Effect of ginger aqueous extract on some biochemical parameters & kidney functions in male mice. *Kufa Med. J*., **2012**, *15*(1), 273.

[40] Heimes, K.; Feistel, B.; Versphohl, E.J. Impact of 5-HT3 receptor channel system for insulin secretion and interaction of ginger extracts. *Eur. J. Pharmacol*., **2009**, *624*(1-3), 58-65.

[41] Sabu, M.C.; Smitha, K.; Kuttan, R. Antidiabetic activity of green tea polyphenols and their role in reducing oxidative stress in experimental diabetes. *J. Ethnopharmcol*., **2002**, *83*, 109-116.

[42] Andallu, B.; Radhika, B.; Suryakantham, V. Effect of aswagandha, ginger and mulberry on hyperglycemia and hyperlipidemia. *Plant Foods Hum. Nutr*., **2003**, *58*(3), 1-7.

[43] Mahluji, S.; Atarri, V.E.; Mobasseri, M.; Payahoo, L. Ostadrahimi, omplicatcAonslevel, HbA1c & insulin sensitivity in type 2 diabetic patients. *Int. J. Food Sci. Nutrit.*, March 18, posted online.

[44] Rani, M.P.; Padmakumar, K.P.; Sankarikutty, B; Cherian, O.L.; Nisho, V.M.; Raghu. K.G. Inhibitory potential of ginger extracts against enzyme linked to type 2 diabetes, inflammation and induced oxidative stress. *Int. J. Food Sci. Nutrit.*, **2011**, *62*(2), 4676-4689.

[45] Li, Y.; Tran, V.H.; Duke, C.C.; Roufogalis, B.D. Gingerol of *Zingiber officinale* enhances glucose uptake by increasing cell surface GLUT4 in cultured L6 myotubes. *Planta. Med*., **2012**, *78*(14), 1549-1555.

[46] Sekiya, K.; Ohtani, A.; Kusano, S. Enhancement of insulin sensitivity in adipocytes by ginger. *Int. Union Biochem. Mol. Bio*. **2004**, *22*(1-4), 153-156.

[47] Goyal, R.K.; Kadnur, S.V. Beneficial effects of *Zingiber officinale* on goldthioglucose induced obesity, *Fitoterapia*, **2006**, *77*(3), 160-163.

[48] Akhani, S.P.; Vishwakarma, L.S.; Goyal, R.K. Anti-diabetic activity of *Zingiber Officianal* in streptozotocine- induced type I diabetic rats. *J. Pharm Pharmacol.*, **2004**, *56*(1), 101-105.

[49] Han, M.K. Epigallocatechin gallate, a constituent of green tea, suppresses cytokine- induced pancreatic beta cell damage. *Exp. Mol. Med*., **2003**, *35*, 136-9.

[50] Ozougwu, J.C.; Eyo, J.E. Evaluation the activity of *Zingiber officinal* (ginger) aqueous extract on alloxan-induced diabetic rats. *Pharmacology online*, **2011**, *1*, 258-269.

[51] Sang, S.; Lambert, J.D.; Ho, C.; Yang, C.S. The chemistry and biotransformation of tea constituents. *Pharmacol. Res.*, **2011**, *64*(2), 87-99.

[52] Smith, T.J. Green tea polyphenols in drug discovery- a success or failure? *Expert Opin. Drug. Discov*., **2011**, *6*(6), 589-595.

[53] Graham, H.N. Green tea composition, consumption, and polyphenol chemistry. *Prev. Med*., **1992**, *12*, 334-350.

[54] Alshuler, L. Green tea: healing tonic. *Am. J. Natur. Med*., **1998**, *5*, 28-31.

[55] Iso, H.; Date, C.; Wakai, K.; Fukui, M.; Tamakoshi, A. The relationship between green tea and total caffeine intake and risk for self – reported type 2 diabetes among Japanese adults. *Ann. Inter. Med*., **2006**, *144*, 554-562

[56] Ramadan, G.; El-Beih, N.M.; Abd-alghffar, E. Modulatory effects of black *v.* green tea aqueous extract on hyperglycemia,

hyperlipidemia and liver dysfunction in diabetic & obese rat models. *Br. J. Nutr*., **2009**, *102*, 1611-1619.

[57] Renno, W.M.; Abdeen, S.; Alkhalaf, M.; Asfar, S. Effect of green tea on kidney tubules of diabetic rats. *Br. J. Nutr*., **2008**, *100*(3), 652-659.

[58] Chow, H.S.; Cai, Y.; Hakim, I.A.; Crowell, J.A.; Shahi, F.; Brooks, C.A.; Dorr, R.T.; Hana, X.; Albert, D.S. Pharmacokinetics and safety of green tea. *Clin. Cancer Res*, **2003**, *9*, 3312.

[59] Takami, S.; Imia, J.; Hasumura, M.; Cho, Y.M.; Onose, J.; Hirose M. Evaluation of toxicity of green tea catechins with 90-day dietary administration to F344 rats. *Food Chem. Toxicol.*, **2008**, *46*(6), 2224-2229.

[60] Sarma, D.N.; Barett, M.L.; Chavez. M.L.; Gardiner, P.; Ko, R.; Mahady, G.B.; Mortes, R.I.; Pecllicore, L.S.; Giancaspro, G.; Dog, T.L. Safety of green tea extracts. *Drug. Saf*., **2008**, *31*(6), 469-84.

[61] Lambert, G.; Mohr, S.; Yang, C.S. Pharmacokinetics of tea catechins after ingestion of green tea and (-) Epigallocatechin-3-gallate by humans. *Cancer Epidemiol. Biomarkers Prevent.*, **2002**, *11*, 1025.

[62] Yang C.S.; Chen, L.; Baletine, D.; Lee, M.J.; Kuo, M.C.; Schantz, S.P. Blood and urine levels of tea catechins after ingestion of different amounts of green tea by human volunteers. *Cancer. Epidemiol. Biomarkers Prevent.*, **1998**, *7*, 35.

[63] Henning, S.M.; Niu, Y.; Lee, N.H.; Tames, G.D.; Minutte, R.R.; Wang, H.; Go, V.L.W.; Herber, D. Bioavailability and antioxidant activity of tea flavanols after consumption of green tea, black tea, or green tea extract supplement. *Am. J. Nutr*., **2004**, *80*(6), 1558-1564.

[64] Cai, Y.; Anvy, N.D.; Chow, H.H.S. Contribution of presystemic hepatic extraction to the low oral bioavailability of green tea catechins in rats. *Drug. Metab. Dispos*., **2002**, *30*(11), 1246-1249.

[65] Chow, H.S.; Cai, Y.; Hakim, I.A.; Crowell, J.A.; Shahi, F.; Brooks, C.A.; Dorr, R.T.; Hana, X.; Albert, D.S. Pharmacokinetics and safety of green tea . *Clin. Cancer Res*., **2003**, *9*, 3312.

[66] Al-Attar, A.M.; Zari, T.A. Influences of crude extract of tea leaves, *Camilliasinensis*, on streptozotocin diabetic male albino mice. *Saudi. J. Biol. Sci.*, **2010**, *17*, 290-301.

[67] Fiorino, P.; Evanggelista, F.S.; Santos, F.; Magri, F.M.M.; Delorenzi, J.C.M.; Ginoza, M.; Farah, V. The effect of green tea consumption on cardiometabolic alterations induced by experimental diabetes. *Exp. Diabetes Res.*, **2011**, *2012* Article ID 309231, 7 pages.

[68] Haidari, F.; Shahi, M.M.; Zarei, M.; Rafiei, H.; Omidian, K. Effect of green tea extract on body weight, serum glucose & lipid profile in STZ- induced diabetic rats, a dose response study. *Saudi. Med. J*., **2012**, *33*(2), 128-33.

[69] Song, E.K.; Hur, H.; Han, M.K. Epigallocatechin gallate prevents autoimmune diabetes induced by multiple low doses of streptozotocin. *Arch. Pharm. Res.*, **2003**, *26*, 559-63.

[70] Babu, P.V.A.; Sabitha, K.E.; Shyamaladevi, C.S. Therapeutic effect of green tea extract on advanced glycation and cross- linking of collagen in the aorta of streptozotocin diabetic rats. *Clin. Exp. Pharmacol. Physiol*, **2006**, *33*, 351-357.

[71] Favier, I.H.; Benaraba, R.; Coves, S.; Anderson, R.A.; Roussel, A.M. Green tea extract decreases oxidative stress and improves insulin sensitivity in animal model of insulin resistance, the fructose fed rat. *J. Am. Coll. Nutr.*, **2009**, *28*(4), 355-361.

[72] Wu, L.Y.; Juan, C.C.; Hwang, L.S.; Hsu, Y.P.; Ho, P.H.; Ho, L.T. Green tea supplementation ameliorates insulin resistance and increases glucose transporter IV content in fructose fed rat model. *Eur. J. Nutr*., **2004**, *43*(2), 116-24.

[73] Tsuneki, H.; Ishizuks, M.; Terasawa, M.; Wu, J.B.; Sasaoko, T.; Kiruma, I. Effect of green tea on blood glucose levels and serum proteomic patterns in diabetic(db/db) mice and on glucose metabolism in healthy humans. *BMC pharmacology*, **2004**, *4*, 18.

[74] Shiria, N.; Suzuki, H. Effects of Western, vegetarian, and Japanese dietary fat model diets with or without green tea extract on the plasma lipids and glucose and liver lipids in mice. A long term feeding experiment. *Ann. Nutr. Metab.*, **2004**, *48*(2), 95-102.

[75] Kim, M.J.; Ryu, G.R.; Chung, J.S.; Sim, S.S.; Min, S.; Rhie, D.J.; Yoon, S.H.; Han, S.J.; Kim, M.S.; Jo, Y.H. Protective effects of epicatechin against the toxic effects of streptozotocin on rat pancreatic islets: *In vivo & in vitro. Pancreas*, **2003**, *26*(3), 292-299.

[76] Kobayashi, Y.; Suzuki, M.; Satsu, H.; Aria, S.; Hara, Y.; Suzuki, K.; Miyamoto, Y.; Shimizu, M. Green tea polyphenols inhibit the sodium-dependent glucose transporter of intestinal epithelial cells by a competitive mechanism. *J. Agric. Food Chem*., **2000**, *48*(11), 5618-5623.

[77] Schimizu, M.; Kobayashi, Y.; Suzuki, M.; Satsu, H.; Miyamoto, Y. Regulation of intestinal glucose transport by tea catechins. *Biofactors*, **2000**, *13*, 61-65.

[78] Waltner-Law, M.E.; Wang, X.L.; Law, B.k.; Hall, R.K.; Nawano, M.; Granner, D.K. Epigallocatechin gallate, a constituent of green tea, repress hepatic glucose production. *J. Biol. Chem.*, **2002**, *277*(38), 34933-34940

[79] Wolfram, S.; Raederstorff, D.; Preller, M.; Wang, Y.; Teixiera, S.R.; Riegger, C.; Weber, P. Epigallocatechin gallate supplementation alleviate diabetes in rodents. *J. Nutr.*, **2006**, *136*, 2512-2518

[80] Hosoda, K.I.M.; Wang, M.F.; Clevidence, B.; Liao, M.L.; Yamamoto, S.; Chuang, C.K. Anti-hyperglycemic effect of oolong tea in type 2 diabetes. *Diabetes Care*, **2003**, *26*, 1714-1718.

[81] Venables, M.C.; Hulston, C.J.; Cox, H.R.; Jeukendrup, A.E. Green tea extract ingestion, fat oxidation, and glucose tolerance in healthy humans. *Am. J. Clin. Nutr.*, **2008**, *87*, 778-84.

[82] Anderson, R.A.; Polansky, M.M. Tea enhances insulin activity. *J. Agric. Food Chem.*, **2002**, *50*(24), 7182-7186.

[83] Boradhurst, C.L.; Polansky, M.M.; Anderson, R.A. Insulin like biological activity of culinary and medicinal plant aqueous extracts *in vitro*. *J. Agric. Food Chem.*, **2000**, *46*(3), 849-852

[84] Chen, H.; Zhang, M.; Xia, B. Components and antioxidant activity of polysaccharides conjugate from green tea. *Food Chem*., **2005,** *90*, 17-21.

[85] Kao, Y.H.; Chang, H.H.; Lee, M.J.; Chen, C.L. Tea, obesity and diabetes. *Mol. Nutr. Food Res*., **2006**, *50*(2), 349-355.

[86] Crespy, V.; Williamson, G. A review of the health effects of green tea catechins in *in vivo* animal models. *J. Nutr*., **2004**, *134*(12), 3431s-3440s.

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