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Research Article

Therapeutic Effect and Possible Herb Drug Interactions of Ginger (*Zingiber officinale* Roscoe, Zingiberaceae) Crude Extract with Glibenclamide and Insulin

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ABSTRACT: **Background:** *Zingiber officinale* aqueous extracts have traditionally been used by diabetic patients in Jordan. **Objective:** The present study aims to evaluate the hypoglycemic and antihyperglycemic effects of ginger crude extract (GCE) in normoglycemic- and streptozotocin (STZ)- diabetic- rats and to assess the possible herb-drug interactions with glibenclamide and insulin. **Materials and Methods:** Oral glucose tolerance test (OGTT) was determined for GCE at concentrations 25, 50 and 100 mg/kg body weight (BW). GCE was administered to normoglycemic rats as a single dose (1 day) and as a daily dose for 1 week. STZ diabetic rats were treated with the same GCE concentrations (25, 50 and 100 mg/kg BW) together with glibenclamide (5 mg/kg BW) or insulin (1.2 IU/kg BW). **Results:** Single administration of GCE showed a significant decrease in blood glucose level (BGL) in normoglycemic rats at 1 and 2 h (50 mg/kg BW; $p<0.001$) while one week administration of GCE did not improve BGL. In STZ- diabetic rats GCE (25 and 50 mg/kg BW) decreased non-fasting BGL (N-FBGL) significantly ($p<0.001$) at 1.5, 2.5, 3.5 and 4.5 h. The combinations of Glibenclamide (5 mg/kg BW) and GCE at doses (25 or 50 mg/kg BW) exhibited after 4.5 h a significantly reduction in the N-FBGL 26.3% ($p<0.001$) and 25.1% ($p<0.01$) respectively; while glibenclamide alone exhibited 7.9% reduction. Also co-administration of GCE (50 mg/kg BW) with insulin caused a significant reduction in the N-FBGL at 2.5 ($p<0.001$) and 3.5 h ($p<0.01$) compared to insulin alone. **Conclusions:** The observed interaction of ginger with glibenclamide and insulin appears to be promising in reducing blood glucose levels and needs further evaluation.

KEY WORDS: Diabetes, ginger, herb–drug interactions, OGTT, STZ- diabetic rats.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder of the endocrine system. It has been recognized as a clinical syndrome since ancient times, and remains a crippling global health problem. According to World Health Organization (WHO) projections,[1] the number of people with DM is rapidly increasing worldwide and is currently affect up to 6% of the world population.[1-3] Although the exact cause of type 1 DM is unknown, it is widely accepted that the body's own immune system mistakenly destroys the islets of the pancreas whilst in type 2 DM a malfunction or reduction of insulin secretion from the pancreas islets is observed. Type 2 DM is the most common form of diabetes.[4,5]

One of the key strategies in treatment of patients with type 2 DM is the maintenance of normal blood glucose level (BGL). Dietary modification, physical exercises and healthy life style are considered as adjuncts to the therapeutic measures. Currently available therapeutic agents in the treatment of type 2 DM have limitations of their own, such as side effects, decreased efficacy over time, ineffectiveness against some long-term diabetic complications and low cost-effectiveness. Oral anti-diabetic agents, which include insulin releasers, insulin sensitizers and α-glucosidase inhibitors, have modest efficacy. Therefore, discovery and development of novel drugs for diabetes is still needed.[6]

Since ancient times, plants have been an exemplary source of medicines. Herbal drugs have served as a major source

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of medicines for the prevention and treatment of diseases including DM.[5,7,8] In Jordan, numerous plant species are used for the treatment of diabetes, mainly in form of their crude aqueous extracts. The plants used ethnopharmacologically include many food plants such as pumpkin, wheat, celery, wax guard, lotus root as well as many medicinal plants, indigenous to Jordan or imported from different parts of the world.[9-11]

The antidiabetic researches conducted in last decades on many plants - used traditionally for the treatment of DM - have shown anti-diabetic property. *Acacia arabica*, *Allium cepa*, *Allium sativum*, *Artemisia herba-alba*, *Momordica charantia*, *Opuntia cactus* and *Panax ginseng* are a few species with established antidiabetic activities. Moreover, for many plant -derived compounds, antidiabetic activity has been established.[2,12,13]

In traditional medicine, patients might use herbs in addition to their orthodox drug therapy. Hence attention should be given to herb-drug interactions. Interactions between herbs and drugs may increase or decrease the pharmacological or toxicological effects of either component. Synergistic therapeutic effects may complicate the dosing of long term medications. It has been reported that herbs, traditionally used to decrease glucose level in diabetes, may precipitate hypoglycemic shock if taken in combination with conventional drugs.[14,15]

Zingiber officinale Roscoe (Family Zingiberaceae), commonly known as ginger, has been consumed worldwide in cookeries, as a spice and as a flavoring agent. It has been cultivated for thousands of years for medicinal purposes and used extensively in traditional medicine. It is reported that ginger is useful in anorexia, dyspepsia, dropsy, asthma, cough, colic, diarrhea, flatulence, nausea and vomiting. It is also used for the treatment of gastrointestinal ailments such as motion sickness and hyperemesis gravidarum.[16-18] Furthermore anti-arthritic, anti-platelet and COX-1 enzyme inhibitory,[19] anti-migraine, anti-thrombotic, anti-inflammatory, hypolipidemic,[20,21] hypocholsterolaemic and anti-cancer,[22,23] activities have been reported for ginger. Jordan is a country with deep rooted traditions. Medicinal plants are among the main choices in the management of chronic diseases such as diabetes. Several authors have reported the prevalence and risk factors associated with diabetes in addition to the quality of life of patients with diabetes in Jordan.[24-26] Otoom *et al*,[25] discussed the frequency of use of herbal medicines in the managements of DM in Jordan. They reported the percentage of herbal preparation usage to be 31% by a small number of Jordanian diabetic patients (n=310) in the northern districts of the country. Among the patients, 72.9% used the herbs as adjunctive therapy along with their anti-diabetic drugs. In a recent survey conducted on interviewed patients attending the outpatient departments at The National Centre for Diabetes, Endocrine and Genetics (NCDEG), it was found that 16.6% of the diabetes patients interviewed (n=1000) were using herbs.[26] Ginger was found to be one of the common medicinal plants used by the patients with diabetes (n=31,18.7 %).[26] Therefore, this study was designed to evaluate the hypoglycemic and antihyperglycemic effects of the aqueous ginger crude extract (GCE) in normoglycemic- and streptozotocin (STZ)-diabetic rats and to evaluate the possible ginger/glibenclamide and ginger/insulin interactions. Phytochemically major components of the ginger rhizome were isolated and identified.

MARERIALS AND METHODS

Plant material and preparation of GCE

Fresh rhizomes of ginger were purchased from a local supermarket and were macroscopically and microscopically identified using descriptive reference.[17] The identification of ginger was confirmed by one of the authors (F. Afifi). Voucher specimens of the rhizomes were kept in the Department of Pharmacology, Faculty of Medicine, and in the Department of Pharmaceutical Sciences, Faculty of Pharmacy, University of Jordan. Rhizomes were rinsed with tap water and grated using a fine tooth manual stainless steal grater. Cold tap water was added to the grated ginger in a ratio of 2:1 v/w and mixed using electric blender at high speed for 15 min with intervals of 2 min after each 5 min homogenization. The mixture was filtered through double layered cheesecloth. Tap water was used in order to mimic the ethnopharmacological utilization.[27] After preparation of the extract, one ml portions of the filtrate were taken and placed in a flattened glass lens to calculate the dry material weight per ml. The average of dry weight material was 20 mg ± 1.0/ml (n = 20). Different concentrations of GCE (25, 50 and 100 mg/kg of BW) were prepared. The extract was administered orally by gavage needle using constant volume of 1 ml/100 g of BW in all groups of rats in all experiments.

Phytochemical screening and isolation of the major components

Aqueous, ethanol and chloroform extracts were prepared from ginger rhizome in order to detect the presence of terpenoids, flavonoids, coumarins and alkaloids according to Wagner *et al*,[28] For the extract preparation each 10 g of freshly grated rhizome was refluxed with 50 ml ethanol (70%), kept overnight, filtered and examined by thin layer chromatography (TLC) (silica gel GF_{254}, Macherey-Nagel, Germany). Using preparative TLC plates, the main constituents of ginger rhizome were isolated and identified by comparison with authentic samples (Toluene – Ethylacetate (70:30)).

Animals

Male locally inbred albino rats, weighing (180-250 g) were obtained from the animal house of the Faculty of Medicine, University of Jordan. All experimental work was approved by the University of Jordan ethical committee. All animals were housed, fed and treated in accordance with the in-house ethical guidelines for animal protection. Rats were kept for one week for acclimatization before the initiation of any experiment. They were kept and maintained under standard laboratory conditions such as temperature, humidity and light with free access to water and food (standard pellet diet; Hammoudeh Company for dairy Product, Amman, Jordan) *ad libitum*.

Induction of diabetes

Diabetes was induced according to Akbarzadeh *et al*,[29] and Kanda *et al*.[30] Briefly, overnight fasted rats (16 h) were injected intraperitoneally (i.p.) with a single dose of freshly prepared STZ (25 mg/kg BW), dissolved in 0.1 M citrate buffer, pH 4.5. Diabetes was observed after one week.

Drug preparation

Glibenclamide powder (kindly donated from Al-Hikma Pharmaceuticals, Naur, Jordan) and insulin solution (Eli Lilly and Company, Indianapolis, USA) were used as reference drugs. Glibenclamide (5 mg/kg of BW) was freshly dissolved in DMSO and 2% Tween 80 in the ratio of 1:30 (v/v) and administered orally to overnight fasting rats using gavage needle at a volume of 1 ml/100g BW. Insulin was administered at a dose 1.2 IU/kg BW (0.5 ml/rat). Insulin was diluted in 0.9% normal saline and was injected i.p.

Blood sample collection

Blood samples (0.3 ml) were collected from the rat tail under mild ether anesthesia. 0.5-1.0 cm from the tip of the tail was cut and blood drops were collected into Eppendorf tubes. Blood samples were allowed to clot for 10 min and then centrifuged at 3000 rpm for 15 min. The obtained serum samples were frozen at -20°C for determination of BGL.

Determination of blood glucose level (BGL)

BGL was determined spectrophotometrically by Trinder's glucose-oxidase method using Ready Liquid Reagent (Arcomex- Jordan). Briefly, to 1 ml of the testing reagent 10 µl of serum sample was added, mixed and the samples were left for 15 min to equilibrate. Then the absorbance was measured by spectrophotometer, at 500 nm. The standard solution absorbance was measured during the test sample measurements, and used in the calculation of the BGL for these samples.[31]

Experimental protocol

The effect of GCE in normoglycemic rats: Overnight fasted (16 h) normoglycemic male rats - weighing (205-250 g) - were randomly divided into 5 groups with 6 rats in each group. GCE was freshly prepared daily just before administration to the experimental animals.

The effect of single administration of GCE and determination of oral glucose tolerance test (OGTT):

1. At the beginning of the experiment (day 1), overnight fasted rats of each group were treated orally as the following:

   Group 1 (negative control group): Each rat received the vehicle, (DMSO/ 2% Tween 80 in a ratio 1:30 v/v).
   Group 2: Each rat received 25 mg/kg BW GCE.
   Group 3: Each rat received 50 mg/kg BW GCE.
   Group 4: Each rat received 100 mg/kg BW GCE.
   Group 5 (positive control group): Each rat received 5 mg/kg glibenclamide.
2. After 30 min each rat received orally (5 g/kg BW) glucose solution.[30]
3. Blood samples were collected from the tail vein at 0 time and 30 min, 1.0, 2.0 and 3.0 h after glucose administration in order to estimate BGL.

The effect of multiple administration of GCE and determination of oral glucose tolerance test (OGTT): The duration of this experiment lasted for 2 weeks. Administration of GCE, glibenclamide and vehicle (in concentrations as described in the experimental protocol of the effect of single administration of GCE and determination of OGTT) were continued for all rats for one week, and on day 8 the overnight fasted normoglycemic rats received 5 g/kg BW of glucose solution orally. Blood samples were collected at 0 time and 30 min, 1.0, 2.0 and 3.0 h after glucose administration for BGL determination. After that, extract or drug treatment was interrupted for one week. During this period rats had access to pellet diet and water *ad libitum*. On day 14 overnight fasted rats received extract or drug and glucose- as described in single administration experiment- followed by blood sample collection. Subsequently BGL were determined.

The effect of GCE on diabetic rats: STZ-diabetic male rats weighing (200-250 g), were checked for blood glucose on day 3 and 6. Rats showing non-fasting blood glucose level (N-FBGL) 200-300 mg/dl, were selected and divided according to their N-FBGL into 12 groups (6 rats each).

Group 1 (untreated diabetic control): Each rat received vehicle (DMSO/ 2%Tween 80, 1:30 v/v), orally.
Group 2: Each rat received GCE 25 mg/kg BW, orally.
Group 3: Each rat received GCE 50 mg/kg BW, orally.
Group 4: Each rat received GCE 100 mg/kg BW, orally.
Group 5: Each rat received glibenclamide 5 mg/kg BW, orally.

Group 6: Each rat injected insulin 1.2 IU/kg BW, i.p.
Groups 7, 8, 9: At -30 min, each rat was given orally glibenclamide (5 mg/kg BW, orally) followed at 0 time by administration of GCE (25, 50 or 100 mg/kg BW, respectively).
Groups 10, 11, 12: At -30 min, insulin (1.2 IU/kg BW i.p.) was injected to each rat. Then at 0 time GCE (25, 50 or 100 mg/kg BW were given orally, respectively).

Blood samples were collected from the tail vein at -30 min, 0 time, 30 min, 1.0, 1.5, 2.5, 3.5 and 4.5 h after the treatment in order to estimate N-FBGL.

Statistical Analysis: All data were expressed as the mean ± standard deviation (SD). ANOVA test was applied to test the significance of differences between group means, followed by student's *t*-test using version 9.2 of SAS computer software. The results were considered to be significant when the *P* value is less than or equal to 0.05 ($P \leq 0.05$).

RESULTS

Phytochemical screening of GCE

The presence of terpenoids, the pungent principles of ginger rhizomes, was detected after spraying with vanillin-sulphuric acid and heating for 10 min at 100°C. The presence of coumarins was detected after spraying with 10% ethanolic KOH and visualized under UV (365 nm). Flavonoids were visualized after spraying with natural products reagent and UV (365 nm). TLC identification for alkaloids was negative. By preparative TLC, 6-, 8- and 10- gingerol and 6- shagaol were isolated and identified in comparison with the authentic samples (ChromaDex kit, Irvin, CA, USA) by TLC and melting point /mixed melting point determination.

The effect of GCE on OGTT in normoglycemic rats

The results of the effect of GCE on OGTT were illustrated in figure 1 (A, B & C). At day 1, after loading with glucose, BGL was increased with time and reached the maximum after 1 h. In glibenclamide treated rats a significant decrease of BGL at 30 min ($p<0.05$), 1, 2 and 3 h ($p<0.001$) was observed. On the other hand GCE, exhibited highest activity with the dose of 50 mg/kg at 1 and 2 h from loading of glucose to rats ($p<0.001$) (Figure 1A).

The one-week daily administration of GCE or glibenclamide resulted in a highly significant decrease of FBGL ($p<0.001$) in glibenclamide treated rats but after loading with glucose no improvement of BGL was observed (Figure 1B). After interruption of the treatment of GCE or glibenclamide for one week a clear response appeared after treating rats loaded with glucose. Glibenclamide administration resulted in a significant decrease in BGL at 1 h ($p<0.05$), 2 h and 3 h ($p<0.001$). GCE (50 mg/kg) exhibited the best effect on lowering BGL at 1 h and 2 h ($p<0.01$) (Figure 1C).

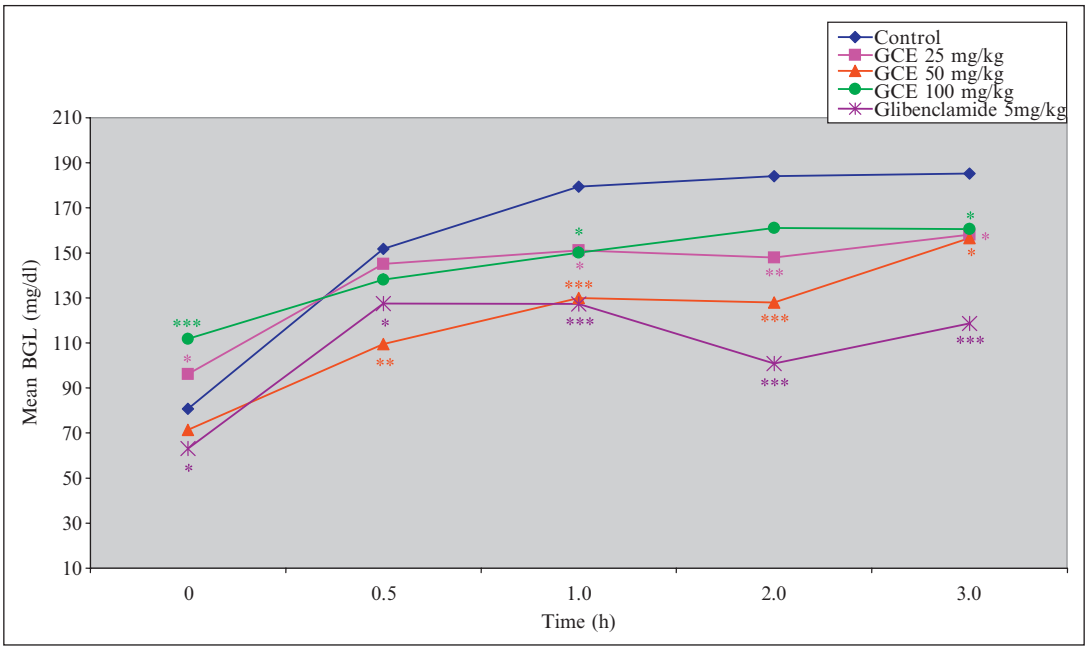

Figure 1A: The effect of ginger crude extract (GCE) on oral glucose tolerance test (OGTT) at day 1. Each value presents means of blood glucose level (BGL) (mg/dl) of 6 rats. *p<0.05; **p<0.01; ***p<0.001 in comparison to values of control at different times.

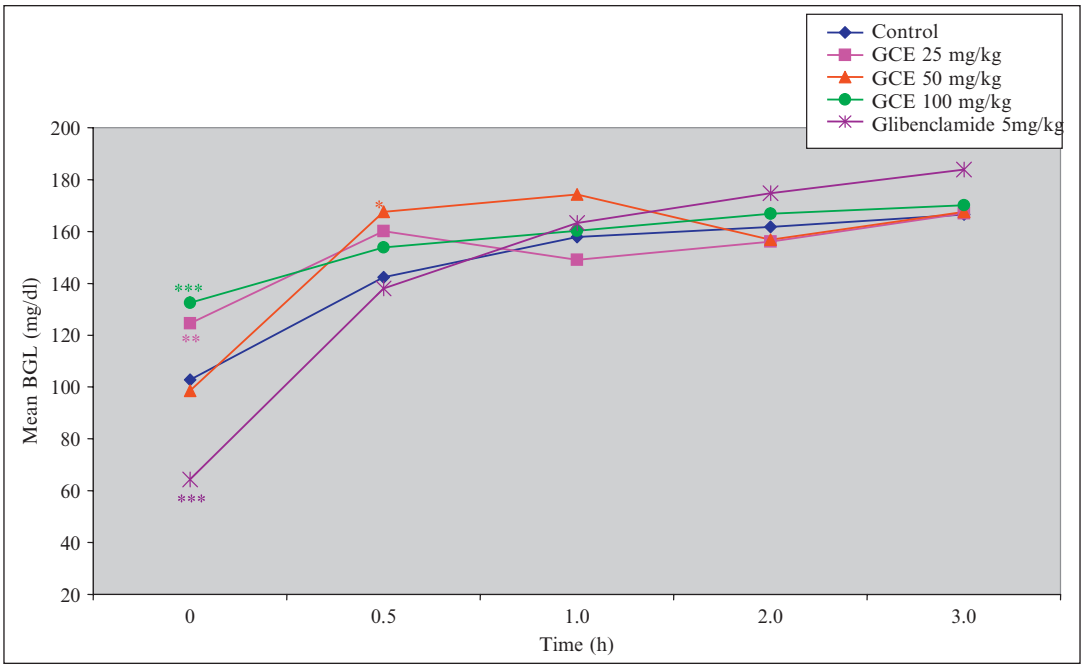

Figure 1B: The effect of ginger crude extract (GCE) on oral glucose tolerance test (OGTT) at day 8. Each value presents means of blood glucose level (BGL) (mg/dl) of 6 rats. *p<0.05; **p<0.01; ***p<0.001 in comparison to values of control at different times.

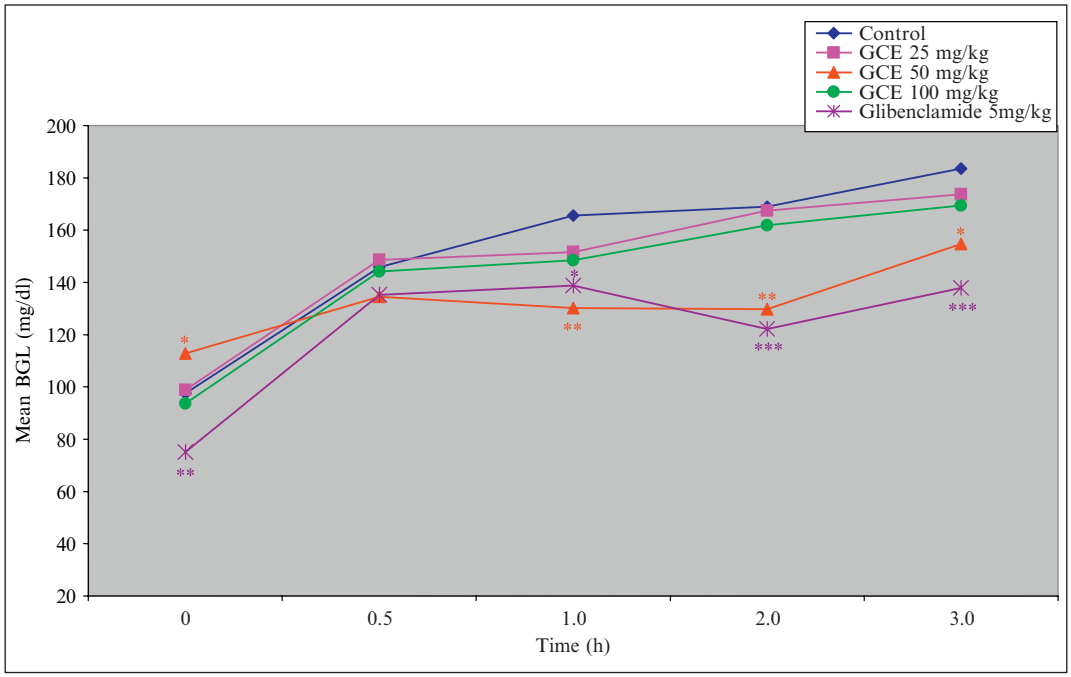

Figure 1C: The effect of ginger crude extract (GCE) on oral glucose tolerance test (OGTT) at day 14. Each value presents means of blood glucose level (BGL) (mg/dl) of 6 rats. *p<0.05; **p<0.01; ***p<0.001 in comparison to values of control at different times.

The effect of GCE on diabetic rats

The antidiabetic effect of different concentrations of GCE on STZ- diabetic rats were compared to those of known hypoglycemic agents glibenclamide (5 mg/kg BW) and insulin (1.2 IU/kg BW). A considerable reduction in BGL was observed in GCE treated rats (25 and 50 mg/kg BW) at 1.5, 2.5, 3.5 and 4.5 h ($p < 0.001$) when compared to diabetic control. The dose of 100 mg/kg BW exhibited less reduction which was significant at 1.5, 2.5 ($p<0.01$) and 3.5 h ($p<0.05$) post treatment when compared to diabetic

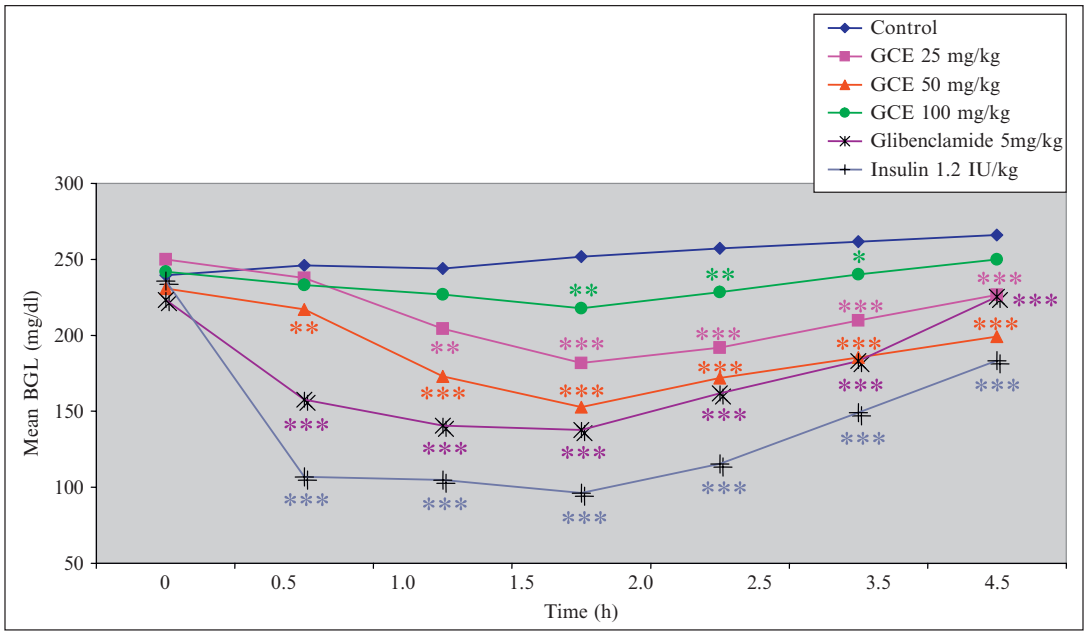

Figure 2A: The effect of ginger crude extract (GCE), glibenclamide and insulin on non- fasting blood glucose level (N-FBGL) of diabetic rats. Each value presents means of N-FBGL (mg/dl) of 6 rats. *p<0.05; **p<0.01; ***p<0.001 in comparison to value of treatment with control.

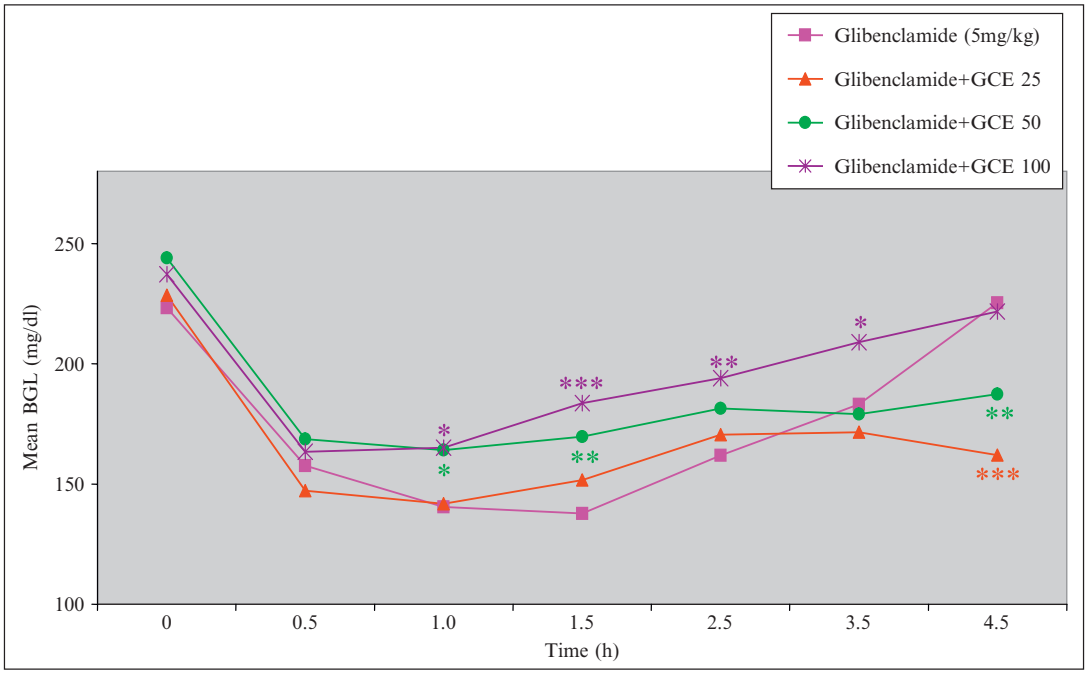

Figure 2B: The combination effect of ginger crude extract (GCE) and glibenclamide on non-fasting blood glucose level (N-FBGL) of diabetic rats. Each value present means of N-FBGL (mg/dl) of 6 rats. At different time intervals, all treatments exhibit significant differences when compared to the control. However, *p<0.05; **p<0.01; ***p<0.001 in comparison to value of treatment with glibenclamide alone.

control. A clear significant reduction in BGL was observed in rats treated with insulin or glibenclamide at 30 min, 1.0, 1.5, 2.5, 3.5 & 4.5 h ($p<0.001$) after administration of both drugs when compared to diabetic control (Figure 2A).

The concomitant administration of different concentrations of GCE (25, 50 or 100 mg/kg BW) with glibenclamide or insulin are shown in figure 2B and 2C, respectively. The results exhibited a significant increase in BGL for the combination treatment of GCE with glibenclamide at 1.0 (50 and 100 mg/kg BW; $p<0.05$) and 1.5 h (50 mg/kg BW; $p< 0.01$, 100 mg/kg BW; $p<0.001$) post treatment when compared to the group treated with glibenclamide alone. This increase in BGL with the dose of 100 mg/kg BW of

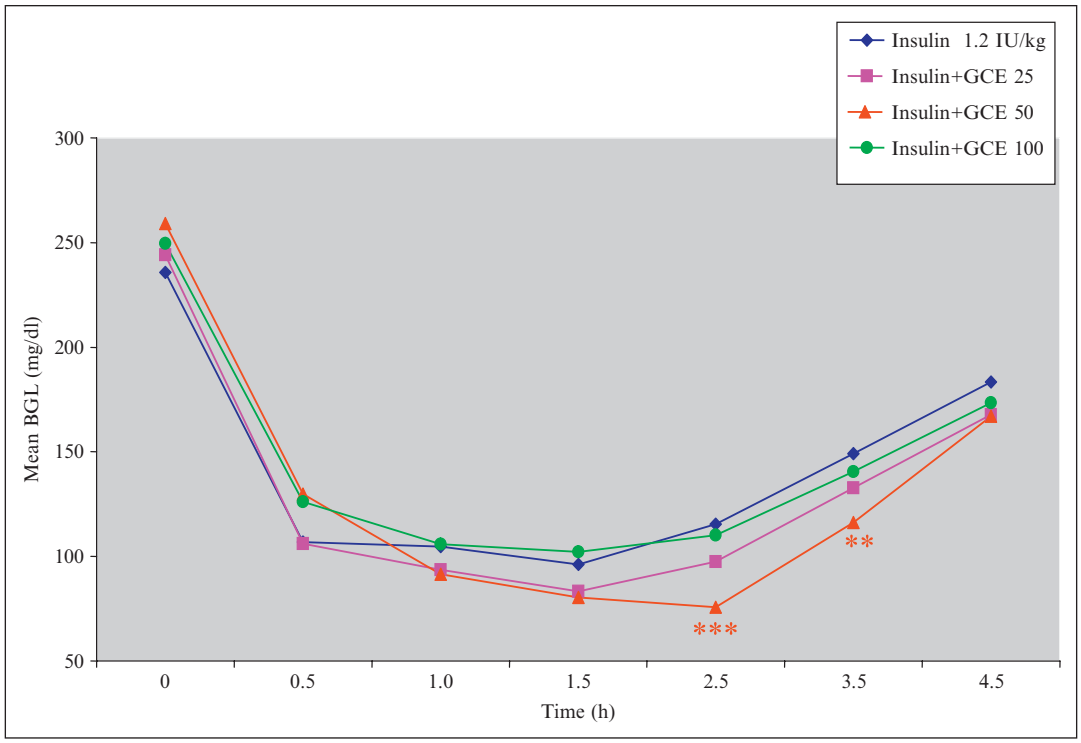

Figure 2C: The combination effect of ginger crude extract (GCE) and insulin on non-fasting blood glucose level (N-FBGL) of diabetic rats. Each value present means of N-FBGL (mg/dl) of 6 rats. At different time intervals, all treatments exhibit significant differences when compared to the control. However, *p<0.05; **p<0.01; ***p<0.001 in comparison to value of treatment with insulin alone.

GCE continued throughout the experimentation period while a significant decrease in BGL occurred with the other two concentrations of GCE (25mg/kg BW; $p<0.001$ and 50 mg/kg BW; $p<0.01$) at 4.5 h post treatment when compared with the group treated with glibenclamide alone (Figure 2B).

During the simultaneous treatment of rats with GCE (25, 50 or 100 mg/kg BW) and insulin, a significant reduction of BGL was detected when insulin was combined with GCE (50 mg/kg BW) at 2.5 ($p<0.001$) and 3.5 h ($p<0.01$) compared to insulin administration alone (Figure 2C).

DISCUSSION

Z. officinale is indigenous to South-East Asia and the fleshy rhizomes are introduced to many parts of the globe because of its aromatic pungent taste. It is a perennial, herbaceous plant of about 1m in height. Commercially, ginger is grown in Africa, China, India as well as in Jamaica and cultivated in the tropics for its edible rhizome.[32]

For centuries ginger has been an important ingredient in Chinese, Ayurvedic and Tibb-Unani herbal medicine. Ginger has been proven to have a broad range of properties and biological and physiological activities.[18,33,34] Ethanol extract of ginger has been reported to have analgesic, anti- inflammatory and anti-hyperglycemic activities in both mice and rats.[18] Kadnur and Goyal [35] demonstrated that the methanol extract of *Z. officinale* was more effective than ethanol extract in reducing fructose- induced hyperlipidemia and hyperinsulinemia in rats. A single oral administration of ethanol extract of *Z. officinale* (200 mg/kg of BW) daily for 20 days also reduced serum cholesterol and triglyceride levels and lowered HDL-cholesterol in diabetic rats maintained with a normal rat pellet diet.[16] Only a few studies have reported the hypoglycemic properties of ginger in animals. Mascolo *et al*,[36] described a significant hypoglycemic activity in normal rabbits using a variety of administration schedules and doses. However, Weidner and Sigwart [37] reported that an ethanol extract of ginger had no effect on BGL in normal rats. Al-Amin *et al*,[33] showed that an aqueous extract of raw ginger, when administered daily (500 mg/kg of BW, i.p.) for a period of 7 weeks to STZ- diabetic rats, was significantly effective in lowering serum glucose-, cholesterol- and triacylglycerol- levels in the ginger- treated diabetic rats compared to the control diabetic rats. In humans, daily consumption of 4 g ginger for 3 months did not change the blood glucose or blood lipid levels in patients with coronary artery disease.[20]

In the present study, several concentrations of GCE were used in normoglycemic and diabetic rats. In normoglycemic

rats, a single administration of 50 mg/kg of GCE, showed a significant reduction of BGL observed 1 and 2 h post glucose loading, while in STZ- diabetic rats, a significant reduction in BGL was detected after administration of GCE (25 and 50 mg/kg BW) started at 1 h and lasted for 4.5 h post administration. These data were in agreement with the earlier reported findings.[36]

GCE and glibenclamide caused slight increases in BGL after glucose loading. In the literature, the phenomenon of decreased activity of sulfonylureas (i.e. glibenclamide) on BGL after chronic administration has previously been reported.[38-41] The exact mechanism for the observed findings is still unclear although several mechanisms have been suggested; such as a decrease in the pancreatic insulin content associated with potent and sustained insulin secretion, desensitization resulting from hyperstimulation of pancreatic ß-cells or decrease of the responsiveness of ß-cells to glucose toxicity under hyperglycemic conditions.[39]

In the present study a single administration of GCE exhibited better results in terms of hypoglycemia compared to one week administration. The daily administration of GCE (25, 50 and 100 mg/kg) or glibenclamide (5 mg/kg of BW) for one week did not cause significant improvement in BGL. In studies with long term treatment with ginger extract, the outcomes were not always in agreement with our findings.[18,33,36,42] But such differences are common and may be influenced by different factors such as source of plant material, methods of drying, methods and solvents used in the preparation of the plant extracts, dose and route of administration, as well as different species/strains of animals used and animal models applied.

In administration of GCE (50 mg/kg of BW) simultaneously either with glibenclamide or insulin, significant decreases in N-FBGL was observed. With the former drug the increase was preceded by an early increase of BGL, but the subsequent decreases were more significant than the drug alone. The percentage of glycemia at 4.5 h for glibenclamide and GCE (25 and 50 mg/kg) were 26.3% and 25.1% respectively, while it was 7.9% for glibenclamide alone (Figure 2B).

When GCE (50 mg/kg of BW) was combined with insulin, a significant decrease in N-FBGL after 2.5 h and 3.5 h post administration was observed. The extents of these apparent decreases in N-FBGL were 73.5% and 67.4% at 2.5 and 3.5 h respectively, compared to 54.4% and 42.6% for insulin alone, indicating a synergistic activity of the drug-plant combination and possible effect of GCE on the release of insulin from the ß-cells of the pancreas (Figure 2C). This may explain the additional reduction in BGL when GCE administered in combination with insulin. Further mechanistic studies are needed to explain the obtained data after concomitant use of GCE with glibenclamide.

CONCLUSIONS

In conclusion, the present study demonstrated the hypoglycemic effect of GCE in normoglycemic- and STZ-diabetic- rats. Low doses of GCE exhibited potential effect in the treatment of hyperglycemia. In animal models, a single administration of GCE exhibited better results in terms of reduction in BGL compared to one week daily administration. Combination of GCE with insulin caused greater reduction of BGL compared to combination with glibenclamide. So, concomitant administration of ginger with these drugs should be used only under supervision of physicians. It is essential to increase the level of awareness among diabetic patients and health care providers regarding the treatment and the possibility of drug-herb interactions. Further studies are needed to evaluate the observed ginger-drug interactions.

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