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In Vivo and *in Vitro* Evaluation of Anti Diabetic and Insulin Secretagogue Activities of *Capparis zeylanica*

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Abstract

Since ancient times, traditional medicines have been in the usage for the treatment of Diabetes mellitus. An edible fruit from traditional medicinal plant *Capparis zeylanica* (CZ) was studied for its anti diabetic, insulin secretagogue activities and mechanisms involved in it. In Streptozotocin induced diabetes rats, oral administration of *Capparis zeylanica* methanolic extract (CZME) (200 mg/kg body weight) for 28 days showed a significant reduction in blood glucose levels by 35.53% and enhanced circulating insulin levels by 81.82% than the diabetic control rats. The insulin secretagogue activity mechanisms of the extract were evaluated by using mouse insulinoma beta cell line (MIN6-*β*). The extract stimulated insulin release in dependent manner of glucose concentration (3 - 16.7 mM) and extract dose (5 - 500 μg/mL). The insulin releasing effect of the extract was significantly enhanced by 3-isobutyl-1-methyl xanthine, glibenclamide, elevated extracellular calcium and K^+ depolarized media. This insulin release was significantly reduced in calcium blocking conditions (by nifedipine and EGTA), in the presence of potassium channel opener (diazoxide). Hence, anti diabetic activity of CZME might be a result of its stimulatory effect on insulin release from pancreatic beta cells via K_{ATP} channel dependent and independent ways. These results indicate that CZ fruits have the potential to use in diabetes therapy.

Keywords

Anti Diabetic, Insulin Secretagogue, MIN6-*β* Cells, K_{ATP} Channel

1. Introduction

Diabetes mellitus is a chronic metabolic disorder manifested with elevated levels of glucose in the body, which

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is an effect of impaired insulin secretion, insulin effect, or both [1]. According to the latest reports, more than 382 million people are affected with diabetes in 2013 and estimated to reach a total of 592 million by 2035. The prevalence of global diabetes in 2013 was 8.3% and expected to reach 10.1% in the year 2035 [2].

The chronic metabolic disorders like diabetes necessitate long term management with oral hypoglycemic agents, which results into adverse effects and drug resistance [3] [4]. This signifies the necessity to focus on research and discovery of new anti diabetic drugs with improved safety and efficacy. From ancient system of medicine, drugs from natural sources were proven to be useful. Therefore, search for the advanced drugs from natural sources may prove to be useful.

Stimulation in insulin release from pancreatic beta cells is one of the major mechanisms of anti diabetic activity by natural products. In reported literature, the *in vitro* studies of *Ficus deltoidea* extracts on BRIN BD11 cells have provided pharmacological evidence for its anti diabetic activity. In the studies, the extracts reported insulin secretagogue activity is dependent on K^+-ATP channel and calcium [3]. In another study, aqueous extract of *Abutilon indicum* is also reported being effective in diabetes by enhancing insulin secretion in diabetic rats and also in INS-1E insulinoma cells [4].

Capparis zeylanica (CZ), Linn. (family: Capparidaceae), which is generally called as Indian caper, is a climbing shrub found throughout India, Bangladesh, Srilanka, Malaysia and some parts of Pakistan [5] [6]. In India, it has been used in the traditional Ayurvedic system of medicine as a cooling agent, cholagogue, bitter stomachic, sedative and anti-hydrotic and is also used in cholera, neuralgia, hemiplegia and rheumatism [7]. The plant also showed anti oxidant activity by aerial parts [8]; anti-microbial [9], anti-inflammatory [10] and analgesic activities [10] [11] were indicated by roots of the plant. Leaves of the plant have shown analgesic, antipyretic [12] and immunomodulatory effect [13]. CZ fruits are used as vegetables to prepare curry [14] and unripe fruits are pickled to eat [15]. These fruits are traditionally used as an antidote in snakebite [16] and ripened fruits are consumed for the treatment of diabetes [6]. So far, no scientific evidence is available on anti diabetic potential of the CZ fruits. Therefore, the present study was aimed to investigate the anti diabetic activity, mechanisms of activity of the methanolic extract of CZ fruits in *in vivo* by using STZ induced diabetes rats model and mouse insulinoma beta cells (MIN6-β) in *in vitro* conditions.

2. Materials and Methods

2.1. Plant Material and Extract Preparation

Ripened fruits of *Capparis zeylanca* were collected from the local market at Jangaon, Telangana, India. Fruits were identified and voucher specimens were deposited in the herbarium at Department of Botany, Kakatiya University, Warangal, India.

The dried and powdered plant material was extracted with methanol by cold percolation for 7 days. The extract was filtered and concentrated by using vacuum evaporation and freeze drying.

2.2. *In Vivo* Studies

2.2.1. Animals

Male Wister albino rats of weighing range 180 - 200 g were purchased from Sanzyme Ltd., Hyderabad, India. Animals were housed at standard laboratory conditions with free access to water and food. Institutional Animal Ethics Committee (IAEC) guidelines were followed for the study.

2.2.2 Acute Toxicity and Glucose Tolerance Test Studies

Acute toxicity studies were conducted on normal rats as previously described by Lorke [17]. The CZME treated four groups (n = 6) were administered with 0.25, 0.5, 1.0 and 2.0 g/kg body weight (bw) and vehicle alone (Carboxy methyl cellulose (CMC) 0.5%; 1 ml/kg bw) for control group. The acute toxicity resultant behavioral changes and mortality within the period of 24 hrs was observed.

The study dose of CZME was determined by oral glucose tolerance test (OGTT) in normal male Wister rats by the method of Gireesh *et al*. [18]. The rats were randomly divided in to five groups (n = 6). Rats in the group A received only glucose (2 g/kg bw); CZME at a dose of 50, 100 and 200 mg/kg was given respectively to the groups B, C and D. Group E received glibenclamide (5 mg/kg bw) alone as standard drug. The blood samples were collected at 0, 30, 60, 90 and 120 min after glucose loading and analyzed for glucose by glucose oxidase

method [19].

2.2.3. Experimental Design and Treatment Schedule

For diabetes induction to overnight fasted rats, a fresh solution of Streptozotocin (STZ) in 0.1 M citrate buffer (pH 4.5) at a dose of 50 mg/kg bw was administered intra peritoneally. One week after STZ administration, rats with blood glucose above 250 mg/dL were used in study as diabetic animals.

A total of four groups (n = 8) of rats were used for 4 weeks study period. Group 1 (naïve animals *i.e*., normal control) and group 2 (diabetic control) were received vehicle alone; group 3 and 4 received CZME (200 mg/kg bw) and glibenclamide (5 mg/kg bw), respectively. Rat blood samples were collected and plasma samples were separated and stored at −20˚C until further analysis.

2.2.4. Determination of Body Weight, Plasma Glucose and Insulin Levels

During the study period of 4 weeks, body weight, plasma glucose and plasma insulin levels were determined on the 1st day and 28th day. Body weight and plasma glucose levels were determined on 7th and 15th days of treatment. Plasma glucose levels were estimated as mentioned above. Plasma insulin concentrations were determined by using insulin enzyme-linked immunosorbent assay (ELISA) kit.

2.3. *In Vitro* Studies on Insulin Secretory Activity

2.3.1. MIN6-*β* Cells Culture

MIN6-*β* cells were cultured at 37˚C under atmosphere of 5% CO_2 in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal calf serum, 2 mM glutamine, 10,000 units/mL of penicillin and 10 mg/mL of streptomycin. CZME stock solution was prepared by dissolving extract in Dimethyl sulphoxide (DMSO) and further diluted with Kreb's Ringer buffer (KRB) to prepare working solutions.

2.3.2. Cell Viability Assay (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide (MTT) Assay)

Cell viability assay was performed according to Adam *et al.* with brief modifications [3]. Briefly, 30,000 MIN6-*β* cells per well was seeded in 96 well plates and allowed to attach for overnight. Then the cells were treated with CZME at a concentration range of 5 - 1000 µg/ml and standard drug, glibenclamide (5 - 100 µM/ml), allowed for 72 hrs incubation. Followed by incubation, to each well a 20 µL solution of 3-(4,5-Dime-thylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide (MTT) (5 mg/mL) was added and incubated for 4 hrs. After that, 100 µL of dimethylsulphoxide (DMSO) was added to each well and aspirated to dissolve the formazan crystals formed by reduction of MTT. Further, plates were shaken for 10 seconds for uniform mixing followed by read for absorbance at 570 nm by using Multiskan Ex microplate reader (Thermo scientific, USA).

2.3.3.Bioassay for Insulin secretion

The *β*-Cell insulin secretion assay was conducted as already described with brief modifications [20] [21] by seeding about 30,000 MIN6-*β* cells per well into 96-well plates. During study, cells were incubated for 60 min with only KRB (naïve), KRB containing glucose only at 3 mM (basal) and 11.1 mM (hyperglycemic) conditions. CZME at 5 - 1000 µg/mL dose range was used to evaluate dose dependent effect on insulin secretion. CZME sub maximal dose (500 µg/mL) and glibenclamide (10 µM) were used in the studies. Unless stated, the experiment was conducted at 11.1 mM glucose concentration.

The insulin secretagogue mechanisms of the extract were assessed by using insulin release modulators like diazoxide (*β*-cell K^+-ATP channel opener, 0.5 mM), 3-isobutyl-1-methylxanthine (IBMX) (phosphodiesterase inhibitor, 100 µM) and glibenclamide. Role of K^+-ATP channel and calcium on insulin secretion was evaluated by using calcium chloride ($CaCl_2$, 1.28 mM), ethylene glycol tetra acetic acid (EGTA, 1 mM), nifedipine (20 µM) and potassium chloride (KCl) at depolarizing concentration 30 mM.

After 60 min of incubation, aliquots from each well was collected and centrifuged (4000 g, 5 min, 4˚C) and stored at −20˚C until for further analysis of insulin by using ELISA.

2.4. Statistical Analysis

All the data were expressed as mean ± SD. One-way or two-way analysis of variance (ANOVA) was used upon

suitability. The significance of difference was assessed by using the Dunnett's post hoc test or Bonferroni test. Values with $P < 0.05$ were considered to be significant. Graph Pad Prism (Graph Pad Software, San Diego, CA) was used for all statistical analysis.

3. Results

3.1. *In Vivo* Studies

3.1.1. Acute Toxicity and Glucose Tolerance Test Studies

CZME acute toxicity studies revealed that the extract at given doses did not showed any lethal or toxic effect on the animals. In 24 h observation period, no behavioral changes and mortality were observed as signs of acute toxicity.

In OGTT studies, CZME 200 mg/kg bw treatment significantly reduced blood glucose levels, where 50 and 100 mg/kg bw doses were not effective (**Table 1**). Therefore, CZME at 200 mg/kg bw dose was used in *in vivo* studies for anti diabetic and insulin secretagogue activity.

3.1.2. Body Weight, Blood Glucose and Insulin

After 28 days study period, a significant decrease ($P < 0.001$) was observed in the body weight (142.08 ± 1.33 g) of the STZ induced diabetic rats compared with naïve group (183.28 ± 1.34 g). However, treatment with CZME (200 mg/kg bw), glibenclamide (5 mg/kg bw) in diabetic rats prevented this significant loss in body weight and led to restoration in the body weights to near normal levels *i.e.* 174.71 ± 2.12 g ($P < 0.001$) and 179.79 ± 1.72 g ($P < 0.001$), respectively, when compared with diabetic control group (**Figure 1**).

Table 1. Oral glucose tolerance test of CZME at different doses.

	Time (min)				
	0 min	30 min	60 min	90 min	120 min
Naïve	75.26 ± 4.04	131.39 ± 6.11	101.26 ± 5.20	89.59 ± 4.43	83.97 ± 5.20
Glibenclamide (5 mg/kg)	70.35 ± 4.51	104.17 ± 4.34$^{\#}$	86.35 ± 3.38$^{\#}$	76.56 ± 3.79$^{\#}$	70.29 ± 3.23$^{\#}$
CZME (50 mg/kg)	81.67 ± 3.70	138.84 ± 4.38	101.35 ± 3.50	88.15 ± 4.36	85.38 ± 1.23
CZME (100 mg/kg)	80.92 ± 5.03	126.96 ± 4.42	96.95 ± 4.60	85.16 ± 4.72	83.98 ± 4.36
CZME (200 mg/kg)	81.49 ± 5.06	122.8 ± 4.70*	90.88 ± 4.31$^{\#}$	83.61 ± 4.63	81.23 ± 4.85

Values indicate mean ± SD. Data was analyzed by two-way ANOVA followed by Bonferroni test (n = 6); $^{\#}P < 0.001$, $^{*}P < 0.01$ as compared to naïve animals at respective time points.

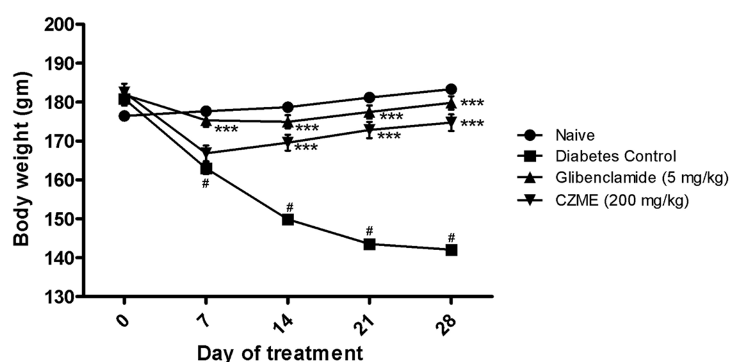

Figure 1. Effect of CZME extract (200 mg/kg) and standard drug glibenclamide (5 mg/kg) on body weight in STZ induced diabetes model in rats (Data was analyzed by two-way ANOVA followed by Bonferroni test (n = 6); $^{\#}P < 0.001$ as compared to naïve animals, $^{***}P < 0.001$ as compared to diabetes control group at respective time points).

The effect of CZME on blood glucose and insulin levels in naïve and diabetic rats presented in **Figure 2**. In diabetic rats, administration of CZME (200 mg/kg bw) significantly (P < 0.01) reduced blood glucose levels by 35.53%, where as the standard drug glibenclamide reduced blood glucose levels by 35.51% (P < 0.01). In untreated diabetic rats, a significant rise (P < 0.01) 24.96% in the blood glucose levels was observed. However, a significant reduction in blood glucose levels were observed in treated animal groups.

The difference in plasma insulin levels in untreated diabetic animals group (0.34 ± 0.01 ng/mL) was significant (P < 0.001) in comparison with naïve animals (0.64 ± 0.01 ng/mL). Though, the plasma insulin levels were about same (0.33 ± 0.01 − 0.34 ± 0.01 ng/mL) on day 0 in groups 2, 3 and 4; the 28 days treatment with CZME (200 mg/kg bw) and glibenclamide (5 mg/kg bw) resulted insulin levels to 0.60 ± 0.01 ng/mL and 0.62 ± 0.02 ng/mL, respectively (**Figure 3**). This is a noteworthy (P < 0.001) difference in plasma insulin levels compared with untreated animals. Therefore, CZME administration restored decreased plasma insulin levels of diabetic rats.

3.2. *In Vitro* Studies on Insulin Secretory Activity

3.2.1. Cell Viability Assay

The effect of CZME on MIN6 β cells viability was shown in **Table 2**. Tested doses the extract and glibenclamide have not shown any significant reduction in the viability in comparison with control. Therefore, the standard drug and extract at studied doses were used in *in vitro* studies.

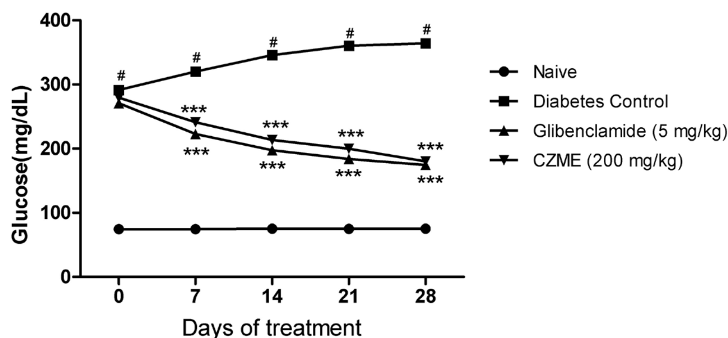

Figure 2. Effect of CZME extract (200 mg/kg) and standard drug glibenclamide (5 mg/kg) on blood glucose levels in STZ induced diabetes model in rats (Data was analyzed by two-way ANOVA followed by Bonferroni test (n = 6); #P < 0.001 as compared to naïve animals, ***P < 0.001 as compared to diabetes control group at respective time points).

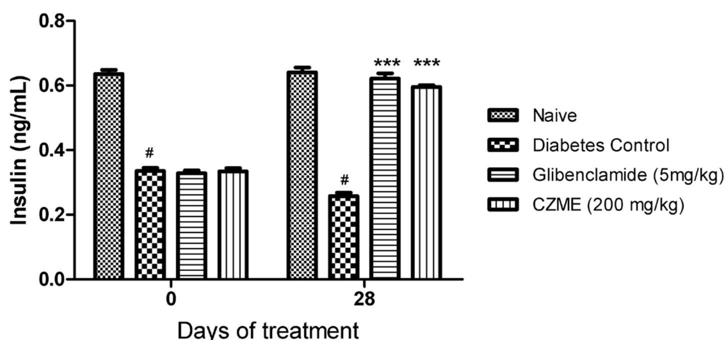

Figure 3. Effect of CZME extract (200 mg/kg) and standard drug glibenclamide (5 mg/kg) on plasma insulin levels in STZ induced diabetes rats on 0th and 28th day of treatment (Data was analyzed by two-way ANOVA followed by Bonferroni test (n = 6); #P < 0.001 as compared to naïve animals, ***P < 0.001 as compared to diabetes control group at respective time points).

3.2.2. Effects of CZME on Insulin Secretion from MIN 6 Beta Cells

A dose dependent stimulation in insulin secretion was exhibited by CZME extract within the dose range of (5 - 1000 µg/mL) at 3 mM and 11.1 mM glucose, compared with respective glucose controls (Figure 4). The insulin release was about two folds at hyperglycemic conditions (11.1 mM) than basal concentration (3 mM). The maximum insulin secretion was observed at 500 µg/mL extract; therefore the same concentration was used in further studies. However, decline in insulin secretion was observed at extract concentration of 1000 µg/mL.

At 3 - 16.7 mM glucose concentration range, the MIN6 cells exhibited a glucose dependent rise in insulin secretion. The glucose dependent insulin release was significantly potentiated in the presence of CZME (500 µg/mL), compared with extract only (Figure 5). Glucose at sub-maximal dose of 11.1 mM was selected for further studies. The extract treatment alone led to an insignificant stimulation on insulin secretion (0.183 - 0.35 ng/mL) in comparison with insulin output ranges of 2.13 - 16.29 ng/mL and 5.30 - 35.24 ng/mL at basal and hyperglycemic conditions, respectively.

3.2.3. Insulin Secretion Mechanisms of CZME by Employing Insulin Release Modulators

Figure 6 presents the influence of insulin secretion modulators namely diazoxide, IBMX and glibenclamide on insulin secretion by CZME extract. The insulin output of 33.52 ± 1.38 ng/mL was significantly higher ($P < 0.05$) with extract treatment, than insulin secretion of 17.73 ± 0.57 ng/mL by extract in presence of diazoxide. This reduction in insulin enhancement specifies that the extract resulted insulin secretion was not an effect of MIN6 cells damage; K^+-ATP channel blockade directed depolarization led to elevated insulin levels. Extract treatment enhanced insulin release by MIN6 cells in the presence of IBMX (40.35 ± 1.09 ng/mL) than the absence. The glibenclamide significantly potentiated insulin output in the absence (31.98 ± 0.63 ng/mL, $P < 0.001$) and

Table 2. MIN6 *β*-Cell viability assay of Glibenclamide and CZME at different doses.

		Glibenclamide (µM/mL)			
Concentration	1	5	50	100	Control
% Viability	97.84 ± 2.56	96.8 ± 1.45	96.32 ± 1.57	95.84 ± 1.18	100.05 ± 0.08
		CZME (µg/mL)			
Concentration	5	50	500	1000	Control
% Viability	99.75 ± 2.24	98.79 ± 2.49	98.12 ± 2.71	96.78 ± 2.31	100.01 ± 0.02

Effect of glibenclamide and CZME on viability of MIN6 beta cells. (The values were expressed as Mean ± SD); (n = 6).

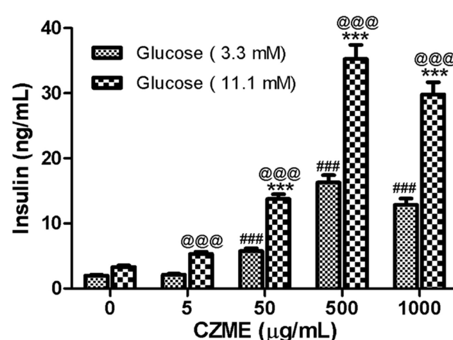

Figure 4. Effect of CZME extract (5 - 1000 µg/mL) on released insulin levels from MIN6 beta cells upon incubation for 60 minutes. All the values are the means ± SD (n = 5) of the insulin released as an effect of response to dose of extract at glucose basal (3.3 mM) and hyperglycemic (11.1 mM) conditions. $^{###}P < 0.001$ respective to control at basal condition. $^{***}P < 0.001$ relative to control at hyperglycemic condition. $^{@@@}P < 0.001$ compared with insulin levels at basal and hyperglycemic conditions at same extract concentration.

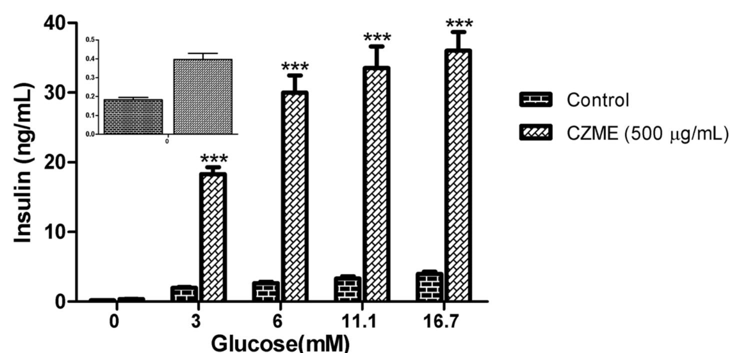

Figure 5. Effect of CZME extract (500 μg/mL) on released insulin levels) at different glucose levels (0 - 16.7 mM) from MIN6 beta cells upon incubation for 60 minutes. All the values are the means ± SD (n = 5) of the insulin released in response to glucose load. $^{***}P < 0.001$ relative to control condition. Graph insert shows insulin released at blank (0 mM glucose) with similar axes titles of main graph.

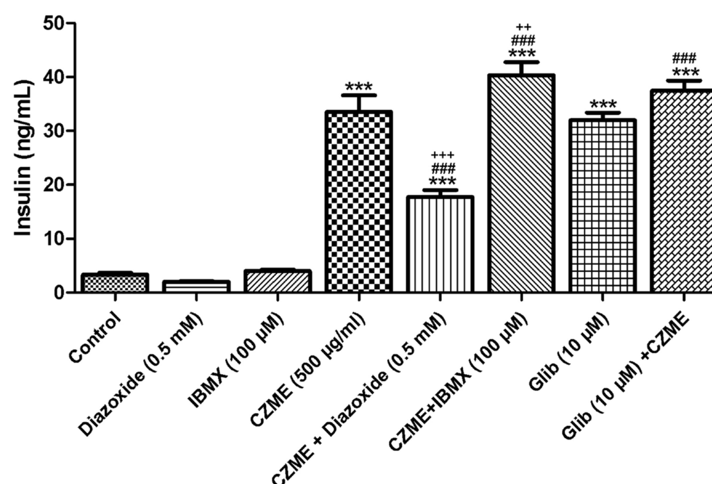

Figure 6. Effect of insulin release modulators (Diazoxide, IBMX and Glibenclamide) on insulin secretion from MIN6 beta cells upon incubation with 11.1 mM glucose for 60 minutes in the presence and absence of CZME (500 μg/mL). All the values are the means ± SD (n = 5). All the data was analyzed by one way ANOVA followed by Dunnet's test. $^{***}P < 0.001$ in comparison with control. $^{+++}P < 0.001$, $^{++}P < 0.01$ in comparison with the extract. $^{\#\#\#}P < 0.001$ in comparison with respective modulator in the absence of CZME.

presence (37.42 ± 0.86 ng/mL, $p < 0.001$) of extract compared with glucose control (3.33 ± 0.13 ng/mL).

3.2.4. Role of K^+-ATP Channels and Calcium (Ca^{2+}) on Insulin Secretion Effects of CZME

The extracts ability to enhance the insulin secretion from MIN6-β cells was retained even at depolarizing concentration of KCl (30 mM). In contrast, the CZME effect on insulin secretion was reduced in the presence of diazoxide. This signifies other than K^+-ATP channel effect on insulin secretion by the extract. The Ca^{2+} dependency of the extract was displayed by stimulated insulin release in the presence of 1.28 mM calcium in incubation medium, compared with extract and glucose treated cells in basal medium. Under elevated extracellular Ca^{2+} conditions, the treatment of cells with nifedipine (calcium channel blocker), EGTA (Ca^{2+} chelator) led to significantly lowered insulin secretion (**Figure 7**). Therefore Ca^{2+} concentrations in extracellular environment and Ca^{2+} influxes affect the insulin release potential of CZME.

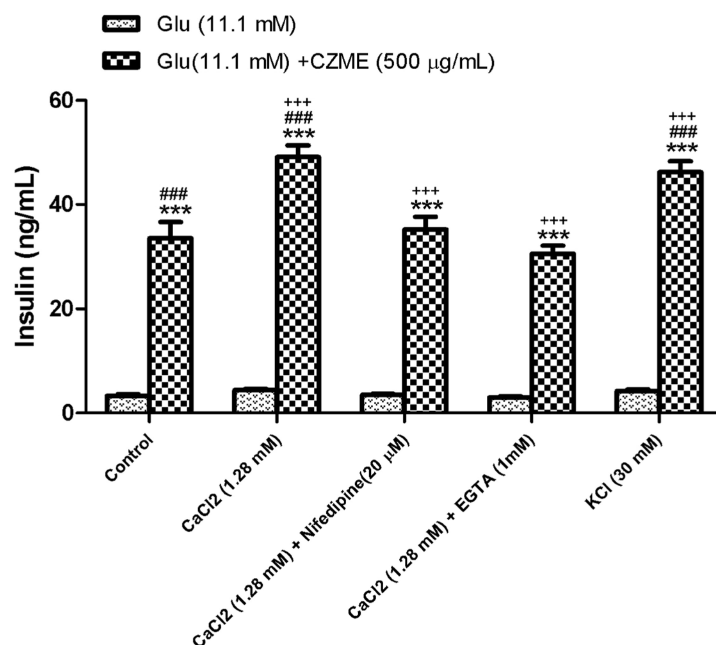

Figure 7. Role of K^+-ATP channels and calcium (Ca^{2+}) on insulin secretion from MIN6 beta cells upon incubation with 11.1 mM glucose in the presence and absence of CZME (500 µg/mL). All the values are the means ± SD (n = 5). All the data was analyzed by one-way ANOVA followed by Dunnet's test. $^{***}P < 0.001$ in comparison with control in the absence of extract. $^{\#\#\#}P < 0.001$ in comparison with control in the presence of extract. $^{+++}P < 0.001$ in comparison with respective control in the absence of CZME.

4. Discussion

The present study has demonstrated that the administration of *Capparis zeylanica* fruit methanolic extract (CZME) at a dose of 200 mg/kg bw reduces elevated blood glucose levels in STZ induced diabetic rats via enhancing insulin release. This is the first report on the anti hyperglycemic activity and insulin secretagogue effects of the edible fruit of *Capparis zeylanica*.

The treatment of diabetic rats with CZME leads to improved body weight, blood glucose and insulin levels in comparison with diabetic control group. Improved body weight in diabetic animals specifies the role of extract in protecting the body tissues from hyperglycemic damage [18] by enhancing glycemic control and structural protein synthesis [22]. CZME antihyperglycemic activity is comparable to the standard drug, glibenclamide. Enhanced circulating insulin levels in the extract treated diabetic animals are analogous to that of standard drug treated diabetic animals. Thus, CZME antihyperglycemic activity could be a result of insulin secretagogue effect [23].

In *in vitro* insulin secretion experiments on MIN6 beta cells, CZME stimulated insulin release in glucose and extract dose dependent manner. However, extract at higher dose (1000 µg/mL) did not show expected insulin secretion, which could be due to the interference from the other substances that were presented in it. Studies confirmed that CZME insulin secretagogue effect was significantly higher at hyperglycemic conditions, which indicated the role of β cell glucose metabolism in insulin secretagogue activity of the extract [24].

K_{ATP} channels in β cell membrane are pivotal in insulin exocytosis from β cell granules [25]. In distinction, K_{ATP} channel openers like diazoxide reduces insulin release. Therefore, present investigations evaluate the role of K_{ATP} channels in the insulin secretagogue effect of CZME. In the presence of Diazoxide, insulin secretion by CZME treatment is reduced significantly. This implies the role of K_{ATP} channels in the insulin release by CZME. However, the extract has also potentiated insulin secretion under depolarizing conditions (KCl 30 mM) which signifies K_{ATP} channel independent effects of the extract [26]. This may be an effect of intracellular actions on exocytosis. CZME treatment along with IBMX resulted increase in insulin secretion might be an effect of in-

crease in intracellular cyclic adenosine monophosphate (cAMP) levels [25] [26].

The insulin secretagogue effect of the CZME was significantly dependent on the calcium. CZME administration significantly enhanced insulin release from beta cells in extracellular media (rich in calcium (1.28 mM)) than the normal media. Lowered insulin release by CZME from β cells in the presence of nifedipine (20 µM) and EGTA elucidates dependency on extracellular calcium and Ca^{2+} influx [25].

Limitation of the present study includes limited experimental sample size and studies in one species of animals. Further investigations have to be carried out to standardize the composition of extract and examine the adverse effects of the drug on large scale for longer duration.

In conclusion, present *in vivo* and *in vitro* studies revealed that *Capparis zeyalnica* fruit methanolic extract showed anti diabetic activity by means of influencing insulin secretion from pancreatic beta cells through physiological mechanisms. This insulin secretagogue effect of the extract was exerted by K_{ATP} channel dependent and independent ways. Hence, *Capparis zeyalnica* could be a natural remedy with anti hyperglycemic potential mainly through augmenting insulin secretion.

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