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PREVENTIVE EFFECTS OF THE AQUEOUS EXTRACT OF *CINNAMOMUM ZEYLANICUM* BARK ON DEXAMETHASONE INDUCED INSULIN RESISTANCE IN WISTAR ALBINO RATS

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ABSTRACT

Objectives: To evaluate the preventive effects of aqueous extract of *Cinnamomum zeylanicum* bark on dexamethasone induced insulin resistance and to compare it with rosiglitazone. **Methods:** The animals were categorized into two series of dexamethasone (dexamethasone 4mg/kg, dexamethasone 8mg/kg series) with 5 groups in each [plain control, dexamethasone 4/8mg/kg as per series, rosiglitazone 8mg/kg and 16mg/kg, *cinnamon* bark extract (CZE) 250mg/kg BW]. Six animals were studied in each group. In a12 day study period, rosiglitazone and CZE groups received respective drug treatments and dexamethasone dosing (4mg/kg or 8mg/kg) was started from day 7onwards. On day 12, fasting blood, urine and post IPGTT blood samples were collected and processed for glucose, insulin and ketone estimations. **Results:** In both series, CZE 250mg/kg treatment showed significant reduction in mean fasting glucose and insulin compared to rosiglitazone 8mg/kg and 16mg/kg groups and dexamethasone controls (4mg/kg, 8mg/kg groups) (P<0.05). The fall in glucose and insulin levels observed with CZE treatment at 30, 60 min post IPGTT in both series were significant compared to rosiglitazone and dexamethasone treatment groups (P<0.05). Glycosuria and ketonuria were absent in CZE groups, whereas these were reduced significantly in rosiglitazone groups compared to dexamethasone groups (P<0.05)**. Conclusion:** The aqueous extract of *C. zeylanicum* bark prevented the insulin resistance as evidenced by reduced fasting and post IPGTT glucose and insulin levels in steroid induced insulin resistance model.

KEYWORDS: Glucose uptake**,** Cinnamon bark, Rosiglitazone, Hyperinsulinemia, Hyperglycemia.

INTRODUCTION

Insulin resistance is known as a state where normal or elevated insulin level produces a reduced biological response and is commonly associated with type II diabetes mellitus. It is characterized by hyperinsulinemia and hyperglycemia due to reduced overall peripheral glucose utilization in the body. Although biguanides and thiazolidinediones (TZDs) are the mainstay of the drug therapy; certain adverse effects limit their use in long term management.

Cinnamon (*Cinnamomum zeylanicum Nees*), the evergreen tree of tropical area, a member of the family Lauraceae, is being used in day to day routine as a spice and condiment in India. It has good anti-inflammatory, anti-oxidant, anti-ulcer, anti-microbial, hypoglycemic and hypolipidemic potentials. [1] Studies on cinnamon have revealed that chief constituents like cinnamicacid, cinnamaldehyde, MHCP and cinnamate present in the extract are known to be responsible for its anti-hyperglycemic effect. [2, 3] MHCP closely mimics insulin activity and works synergistically with insulin in cells.[4] However, the hypoglycaemic activity of *C. zeylanicum* bark has been studied in rodents, but its effect on steroid induced insulin resistance is yet to be demonstrated in vivo. The purpose of the present study is to investigate the preventive effects of aqueous extract of *C. zeylanicum* bark on dexamethasone induced insulin resistance and compare it with rosiglitazone.

METHODS AND METERIALS

Animals

The study was performed on male Wistar Albino rats weighing around 230-270gms. Prior to the study, all the animals were housed and maintained at 22-24°C temperature, under 12-h light: 12-h dark cycle with free access to food and water. Approval has been taken from the Institutional Animal Ethics Committee (Letter no: 798/2011) and all procedures were conducted according to the revised guidelines of CPCSEA Act, 1960 India.

Grouping of animals

As shown in Table no: 1 all the animals selected for the study were divided into 8 major treatment groups of 6 animals in each group and one plain control. Except plain control, remaining groups were equally suited in to D4 and D8 series.

Table 1. Grouping of animals

Dexamethasone 4mg/kg (D4 Series)	**Dexamethasone 8mg/kg (D8 Series)**
Plain control – (Vehicle)	
Vehicle+Dexamethasone 4mg/kg(Dexa control)	Vehicle+Dexamethasone 8mg/kg (Dexa control)
Rosiglitazone 8mg/kg+Dexa4mg/kg	Rosiglitazone 8mg/kg+Dexa8mg/kg
Rosiglitazone 16mg/kg+ Dexa4mg/kg	Rosiglitazone 16mg/kg+ Dexa8mg/kg
Cinnamonextrct 250mg/kg + Dexa4mg/kg	Cinnamonextract 250mg/kg +Dexa8mg/kg

Plant material and extraction

Cinnamomum zeylanicum (dalchiniin Kannada) is commonly known as cinnamon, the bark was collected from the pharmacy department at KVG Ayurvedic Medical College & Hospital, Sullia, Karnataka, in the month of December 2012. The plant was identified and authenticated by a Botanist from Nehru Memorial College, Sullia, Dakshina Kannada, India and voucher specimen (No. SP-159: 22/1/2013) was preserved for future reference. The bark was finely powdered and then subjected to successive extraction in a Soxhlet apparatus using distilled -water at 80°C temperature. The yield of aqueous extract was concentrated in a rotary evaporator at reduced pressure and the water was allowed to evaporate completely. [5] The total yield was 6.1% and it was picked up and stored in cool and dry bath, which was further employed in the study.

Drugs and doses

All drug doses were selected based on a pilot study conducted in a small group of animals.

Dexamethasone injections 4mg/kg and 8mg/kg body weight/day i.p were chosen. *C. zeylanicum* bark aqueous extract solution was prepared at a concentration of 250mg/ml with distilled water and a dose of 250mg/kg BW orally was given to the respective groups. A pure fine powdered form of rosiglitazone was purchased from Sigma labs, Rajendra traders, Dharwad, Karnataka. Drug solution was prepared by using 2% gum acacia solution. 8mg/kg and 16mg/kg of rosiglitazone were given orally to the respective groups.

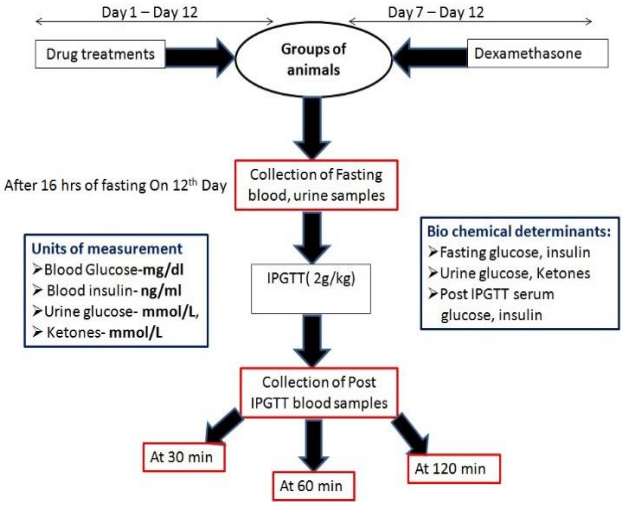

Figure 1. ***Study design***

Except dexamethasone, all the animals in all the groups received respective drugs daily throughout the study period (12 days). Treatment with dexamethasone was started from day 7 to day 12. Each rat was allowed to have 100gm of standard food pellets and 100 ml of water daily up to 11th day evening, followed by overnight fasting with free access to water alone. On 12th day morning, all physical parameters were recorded and drugs were given two hours prior to collecting blood by retro orbital sinus puncture method. The collected blood samples were centrifuged

(4000 RPM/20min) and the serum was processed for biochemical estimations (fasting glucose, insulin) (Figure 1).

***Intra peritoneal (i.p) glucose tolerance test* (IPGTT)**

After 16 hours of fasting, blood samples from all the animals were collected followed by administration of glucose i.p (2gm/kg body weight). The blood samples were collected again at intervals of 30min, 60min and 120 min and then processed for glucose and insulin levels [6].

Estimation of serum glucose

GOD-PAP method was employed to determine the serum glucose. The values were measured as mg/dl and were presented as Mean±SD. [7]

Estimation of serum insulin

Rat ultra sensitive ELISA insulin kit [8] was purchased from Crystal Chem labs, New Delhi. A high range assay (1-64ng/ml) was performed by using provided reagents and serum samples to determine the insulin values. To the Elisa frame, the antibody coated micro plates reagent which was marked 'A' were affixed. 95µl of the sample diluent which was marked 'G' were dispensed per each well. 5 µl of the sample was pipetted out into each well. The micro plate was incubated for 2 hours at 4°C. After incubation, each well is washed with wash buffer for 5 times. 100 µl of anti insulin enzyme conjugate was dispensed per well and the micro plate was incubated for 30 min at room temperature. Each well was washed 7 times with wash buffer. 100 µl of enzyme substrate solution which was marked 'E' was dispensed per well. The micro plate was now incubated at room temperature for 10 min in light free area. The enzyme reaction was terminated by adding 100 µl of enzyme reaction stop solution marked 'F' per well. Optical density values were estimated using standard curves. The obtained optical density values were converted into its original insulin values (ng/ml) by subjecting to linear regression equation in MS Excel 2007 version. The values were presented as Mean±SD.

Urine glucose and ketones

The fasting samples of urine were collected on day 12th morning in sample containers and presence of glucose and ketones were determined by (uristix) dip stick method. [9] The amount of glucose and ketones was measured in mmol/L. [10]

STATISTICAL EVALUATION

All the data were represented as Mean ±S.D and was subjected to One-Way ANOVA followed by Scheffe multiple comparison Post Hoc test in SPSS version 19. Level of significance was set at 5% and $P \leq 0.05$ was considered as statistically significant.

RESULTS

Fasting serum glucose and insulin

The comparative effects of the *C. zeylanicum*and rosiglitazoneon hyperinsulinemia and hyperglycemia induced by dexamethasone are shown in Table 2. CZE250mg/kg significantly reduced fasting glucose and insulin levels compared to dexamethasone control and rosiglitazone 8, 16mg/kg groups in both D4 and D8 series ($P<0.05$). These effects were not significant between different doses of standard drug treatment (Rosiglitazone 8,16mg/kg) ($P>0.05$) (Table 2).

Post IPGTT serum glucose and insulin

The post IPGTT values of serum glucose and insulin are shown in Figure 2A-D. CZE 250mg/kg and rosiglitazone treatments improved glucose intolerance compared to dexamethasone control group in both D4 and D8 series ($P<0.05$). On intra-peritoneal injection of glucose (2g/kg body weight) the mean blood glucose levels in plain control and CZE250mg/kg treatment group did not differ from each other in D4 as well as D8 series ($P>0.05$). The mean blood glucose levels in CZE 250mg/kg showed significant differences at 30 and 60 min compared to rosiglitazone 8mg and 16mg/kg treatment in D4 series and CZE250mg/kg treatment in D8 series showed a significant difference at all intervals compared to both doses of rosiglitazone treatment ($P<0.05$). There was no significant difference in glucose values at respective intervals between two standard doses of rosiglitazone in both D4 and D8 series ($P>0.05$) (Table 3A).

The mean insulin levels in CZE250 mg/kg showed significant difference at 30, 120min when compared to plain control in D4 series ($P<0.05$). Nonetheless, there was no significant difference observed in D8 series at respective intervals ($P>0.05$). CZE250 mg/kg showed a significant difference with rosiglitazone 16mg/kg at 60min and both 8,16mg/kg of rosiglitazone at 120 min in D4 series ($P<0.05$). The mean insulin values of CZE250 mg/kg significantly reduced at 30, 60 and 120min when compared with rosiglitazone in D8 series ($P<0.05$). The maximum hypoglycaemic and hypoinsulinic effects were

observed in CZE250mg/kg treatment at 30 min post IPGTT in D4 and D8 series (Table 3B).

Urine glucose and ketones

The description and comparisons of urine glucose and ketones are represented in table 4. Glycosuria and ketonuria were absent in the CZE group in both D4 and D8 series, but there was a significant decrease in urine glucose in rosiglitazone 8, 16mg/kg treatment groups when compared to dexa control group (P<0.05). However, there was a significant decrease of urine glucose in rosiglitazone 16mg/kg compared to 8mg/kg in both D4 and D8 series (P>0.05). Urine ketones were absent in rosiglitazone 8 and 16mg when compared to dexa control group in D4 series. In D8 series rosiglitazone 8 and 16mg significantly lowered the ketonuria compared to dexa control group (P<0.05) (Table 4).

Table.2.Differences in means of fasting glucose (mg/dl) and insulin (ng/ml) values on day 12 in Dexamethasone 4 and 8 mg/kg series

n=6 Group	Fasting Glucose D4 series	Fasting Glucose D8 series	Fasting insulin D4 series	Fasting insulin D8 series
Plain control	77.2±3.6	77.2±3.6	0.9±0.2	0.9±0.2
Dexa control	190.5±2.6	274.7±3.9	14.0±3.0	19.1±4.1
Rosi 8mg/kg	108.7±3.5^{*be}	125.9±4.4^{*abe}	3.4±0.4^{*b}	7.3±0.8^{*abde}
Rosi 16mg/kg	112.6±6.2^{*abe}	122.8±5.8^{*abe}	3.8±0.3^{*be}	5.4±0.5^{*bce}
CZE 250mg/kg	84.6±7.7^{*bcd}	96.3±5.5^{*bcd}	1.1±0.5^{*bcd}	2.3±0.7^{*bcd}

Note: *= significant at 5 % level (P<0.05), a= plain control; b= Dexa control; c= Rosiglitazone 8mg/kg; d= Rosiglitazone 16mg/kg; e= *C. zeylanicum* bark extract 250mg/kg.

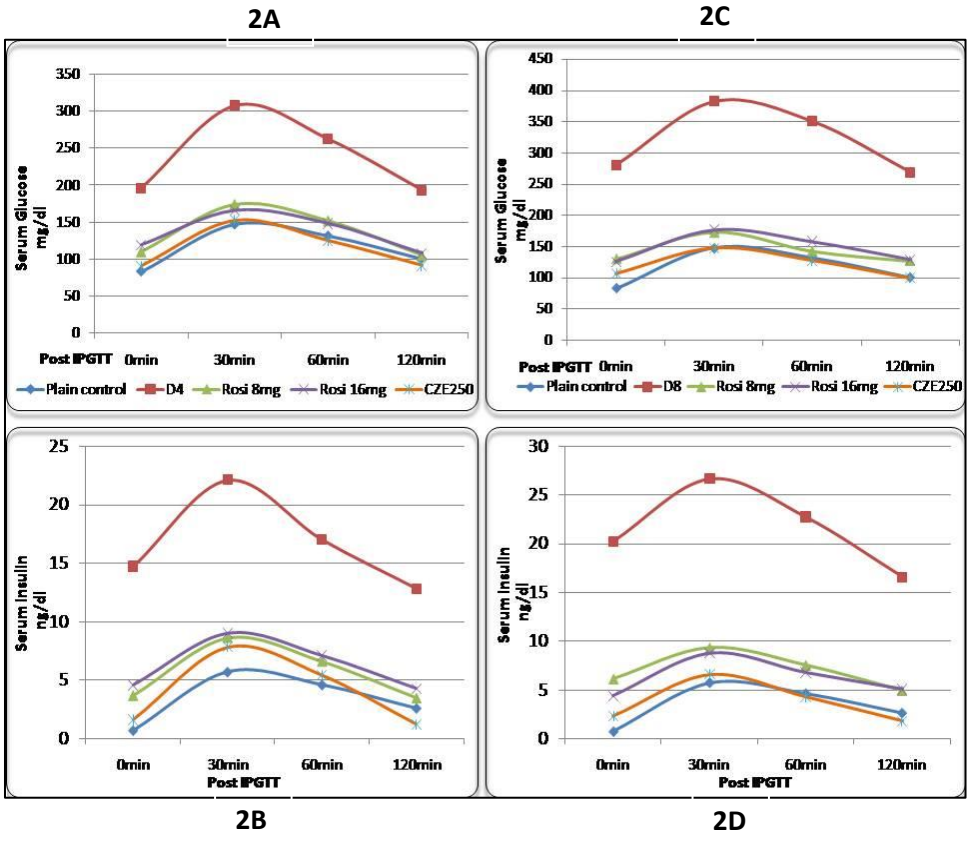

Figure: 2 Post IPGTT glucose and insulin values on day 12 in Dexamethasone 4 and 8 mg/kg series

Note: Figure: 2 Post IPGTT glucose and insulin values on day 12 in Dexamethasone 4mg and 8mg/kg series, (2A) Post IPGTT glucose levels in D4 series, (2B) Post IPGTT insulin levels in D4 series, (2C) Post IPGTT glucose levels in D8 series, (2D) Post IPGTT insulin levels in D8 series.

Table 3A. Differences in means of post IPGTT glucose and insulin levels on day 12 in dexamethasone 4mg/kg series (D4)

Group n=6	0min		30min		60min		120min	
	G	I	G	I	G	I	G	I
PC	83.3±7.9	0.7±0.0	147.8±3.9	5.7±1.4	131.9±9.5	4.6±1.8	100.8±5.4	2.6±0.5
D4/kg	196.5±6.1	14.7±2.7	307.9±18.5	22.1±5.7	262.4±11.2	17.0±4.9	193.5±7.2	12.8±3.8
R8/kg	110.7±8.4 *abe	3.7±1.1 *abe	174.2±13.7 *abe	8.6±2.8 *ab	152.1±6.5 *abe	6.6±2.5 *abe	106±4.3 *b	3.5±1.7 *be
R16/kg	119.8±5.2 *abe	4.6±1.3 *abe	166.4±9.1 *abe	9.0±3.1 *ab	148.6±4.1 *abe	7.1±4.1 *abe	108.4±3.7 *b	4.3±1.4 *abe
CZE 250/kg	91.6±11.3 *bcd	1.6±0.3 *bcd	153.1±7.0 *bcd	7.8±2.2 *ab	125.8±3.6 *bcd	5.4±1.9 *bd	92.2±6.7 *bcd	1.2±0.0 *abcd

Table 3B. Differences in means of post IPGTT glucose and insulin levels on day 12 in dexamethasone 8mg/kg series (D8)

Group n=6	0min		30min		60min		120min	
	G	I	G	I	G	I	G	I
PC	83.3±7.9	0.7±0.0	147.8±3.9	5.7±1.4	131.9±9.5	4.6±1.8	100.8±5.4	2.6±0.5
D8/kg	280.7±23.7	20.2±8.6	382.3±28.8	26.6±7.3	350.7±14.2	22.7±8.6	269.5±12.0	16.6±4.4
R8/kg	130.3±13.2 *abe	6.1±3.1 *abde	173.1±9.5 *abe	9.3±4.1 *abe	142.7±7.3 *be	7.5±2.2 *abe	126.9±6.2 *abe	4.9±0.7 *abe
R16/kg	125.8±6.9 *abe	4.4±1.0 *abce	177±10.7 *abe	8.8±2.3 *abe	153.9±8.4 *be	6.8±2.0 *abe	128.8±7.8 *abe	5.1±1.7 *abe
CZE 250/kg	107.3±6.0 *abcd	2.3±0.9 *abcd	149.6±5.7 *bcd	6.6±2.1 *bcd	127.9±9.1 *bcd	4.3±1.3 *bcd	99.9±5.4 *bcd	1.8±0.0 *bcd

Note: *= significant at 5 % level (P<0.05), PC=plain control, R8=Rosiglitazone 8mg/kg, R16= Rosiglitazone 16mg/kg, G=glucose, I=insulin, a= plain control; b= Dexa control; c= Rosiglitazone 8mg/kg; d= Rosiglitazone 16mg/kg; e= *C. zeylanicum* bark extract 250mg/kg,

Table 4. Differences in means of fasting urine glucose and ketones on day 12 in dexamethasone 4mg and 8mg/kg series

Group n=6	Urine Glucose (mmol/L)		Urine ketones (mmol/L)	
	D4 series	D8 series	D4 series	D8 series
Plain control	Nil	Nil	Nil	Nil
Dexa control	14.1±3.7	76.6±1.2	1.5±0.5	10.6±4.1
Rosi 8mg/kg	4.1±0.8 *bd	20±3.0 *bd	Nil	1.1±0.2 *b
Rosi 16mg/kg	1.6±1.0 *bc	11.6±2.1 *bc	Nil	2.3±1.2 *b
CZE 250mg/kg	Nil	Nil	Nil	Nil

Note: *= significant at 5 % level (P<0.05), a= plain control; b= Dexa control; c= Rosiglitazone 8mg/kg; d= Rosiglitazone 16mg/kg; e= *C. zeylanicum* bark extract 250mg/kg.

DISCUSSION

The present study was designed to investigate the potential effects of *C. zeylanicum* extract on dexamethasone induced insulin resistance emphasizing on its prevention in wistar albino rats. Dexamethasone is well recognized to cause hyperglycemia and whole body insulin resistance. Up to 2.5% of the population takes prescribed glucocorticoids and their side effects represent a considerable clinical burden.[11] In certain clinical conditions, dexamethasone needs to be administered in high doses and in such cases it causes adverse effects such as muscle catabolism, increased adiposity and increased insulin resistance.[12] The insulin resistance is mainly because of decrease in number of GLUT-1 transporter and decrease in GLUT-4 transporter translocation to plasma membrane.[13] Dexamethasone induces insulin resistance whether or not it induces hyperglycemia and whenever hyperglycemia is present, GLUT-2 positive β cell numbers, glucose transport into cells and insulin response to glucose are reduced.[14]

Dexamethasone was chosen in the present study to induce insulin resistance as it is virtually devoid of mineralocorticoid actions.[13] Based on dose response curve of dexamethasone from the pilot study, a dose of 8mg/kg was chosen as it caused optimal insulin resistance which was measured by recording fasting insulin and fasting glucose. 4mg/kg dexamethasone was taken as the secondary dose as 16mg/kg caused severe weakness and intolerability in animals. It was observed that 4mg/kg dexamethasone produced a minimal rise in fasting glucose and insulin levels compared to 8mg/kg dexamethasone treatment groups throughout the study period which confirms that the insulin resistance is dose dependent.

Cinnamon has been reported to have remarkable pharmacological effect in the treatment of insulin resistance. In the present study, 250mg/kg of aqueous extract of cinnamon bark significantly prevented the development of insulin resistance induced by dexamethasone. This was evidenced by a significant fall in fasting insulin and fasting glucose levels in CZE250mg/kg group compared to rosiglitazone and dexamethasone groups in both D4 and D8 series (Table2). Cinnamon bark extract acts probably by up-regulating expression of insulin receptors and promoting glucose metabolism in peripheral tissues in dexamethasone induced insulin resistance in rats as described by JiYeon Kim et al.[15] The primary chemical constituents of cinnamon include cinnamaldehyde, gum, tannin, mannitol, coumarins, essential oils (aldehydes, eugenol, pinene),[16] and it is evident that a substance in cinnamon called MHCP (methyl hydroxyl chalcone polymer) is mainly responsible for its beneficial results. MHCP closely resembles the insulin activity and acts synergistically with insulin in cells and further, MHCP treatment stimulated glucose uptake and glycogen synthesis to a similar level as insulin.[4]

The fasting glucose and insulin in rosiglitazone group were significantly lowered compared to dexamethasone control in both D4 and D8 series (P<0.05) but the levels were significantly higher than CZE 250mg/kg treatment (P<0.05). However, the overall difference found between rosiglitazone 8 and 16mg/kg treatments was insignificant (P>0.05) (Table 2).

IPGTT was performed to assess the overall utilization of glucose and post IPGTT glucose and insulin levels at 30 and 60min intervals in CZE250mg/kg group were reduced markedly compared to rosiglitazone and dexa control groups due to enhanced utilization of glucose at these intervals (Figure 2A-D). In vitro studies have shown that cinnamaldehyde which is an important chemical constituent of *C. zeylanicum* bark produces significant anti-hyperglycemic effect [17] and MHCP isolated from *C. zeylanicum*bark stimulates the autophosphorylation of the insulin receptor, glycogen synthesis and GS activity in 3T3-L1 adipocytes also downregulates the GSK-3_ activity. Glycogen synthesis stimulation is through class I PI-3-K dependent pathway. [18] However, these intracellular actions of CZE250mg/kg favor the utilization of glucose and improve the insulin resistance caused by dexamethasone.

The glycosuria was not completely reversed by rosiglitazone treatment when compared to CZE250mg/kg treatment, but, ketonuria was effectively reversed by both rosiglitazone and CZE250mg/kg in D4 series, not by rosiglitazone in D8 series

(Table 4). It is apparent from this study that rosiglitazone play limited role which may not be sufficient to improve higher degree of insulin resistance caused by dexamethasone.

CONCLUSION

The results found in this study reveal that, the aqueous extract of *C. zeylanicum* bark 250mg/kg has preventive effects on dexamethasone induced insulin resistance probably by enhancing peripheral uptake of glucose in to tissues and causing reduction in fasting glucose and insulin levels. Further evaluation should be undertaken to isolate and standardize these constituents for their efficacy and potency in insulin resistant animal models.

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CONFLICT OF INTEREST

None declared**.**

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